

**STUDENTS' UNDERSTANDING OF MICHAELIS-MENTEN KINETICS  
AND ENZYME INHIBITION**

by

**Jon-Marc G. Rodriguez**

**A Dissertation**

*Submitted to the Faculty of Purdue University*

*In Partial Fulfillment of the Requirements for the degree of*

**Doctor of Philosophy**



Department of Chemistry

West Lafayette, Indiana

May 2019

**THE PURDUE UNIVERSITY GRADUATE SCHOOL**  
**STATEMENT OF COMMITTEE APPROVAL**

Dr. Marcy H. Towns

Department of Chemistry

Dr. Minjung Ryu

Department of Chemistry, Department of Curriculum and Instruction

Dr. Angeline Lyon

Department of Chemistry

Dr. Adam Wasserman

Department of Chemistry

**Approved by:**

Dr. Christine A. Hrycyna

Head of the Graduate Program

*To My Family*

## ACKNOWLEDGMENTS

This document is the culmination of nearly a decade of post-secondary education. Supported by opportunities and surrounded by people, I am very fortunate. It is with great gratitude, humility, and respect that I write the final words of this dissertation.

To my amazing family, Joseph, Aileen, Alex, David, Jack, Melina, Tiffany, Victoria, and Samuel, thank you. Your love and support push me forward and draw me close. I will be home soon. Mom, thank you for being my first teacher and for investing time in homeschooling me and my siblings, you and Dad have set your children up for success. Thank you to my maternal grandparents, Sammy and Esther, your generosity and warmth set an example worth emulating. Thank you to my paternal grandparents, Johnny (deceased) and Lydia, I am grateful for your faith and reverence.

To my church family in sunny California, whenever I come home during the holidays, I always feel loved. Pastor Sam and Angie, you have been close family friends and one of my biggest supporters, thank you. To my church family in not-always-so-sunny Indiana, what you lack in pleasant weather, you make up for in sincerity and kindness of heart. I am glad I found a place to feel at home during my time as a graduate student. Pastor Tim and Nadine, thank you for welcoming me and allowing me to serve. Shelly and Jeremy, thank you for grafting me into your family, your love is appreciated.

To the best research advisor, Dr. Marcy Towns. You have done an excellent job fostering a community among your graduate students. Thank you for providing the skills and opportunities for me to succeed as a graduate student and develop as a researcher. You are more than a mentor, you are a friend.

To all of the Towns research group members, as well as our other friends that have shared the office space: Kinsey Bain, Jessica Callus, Patrick Chaffin, JR Frey, Sarah Hensiek, Sara Johnson, Franziska Lang, Alex Parobek, Stephanie Santos-Diaz, Carly Schnoebelen, James Towns, and Adam Zabih. Thank you for all the research discussions, the friendship, and the fun. I will always remember sharing an office with you. I would also like to thank the Towns research group alumni, although we never shared an office, we have shared conversations and I appreciate your support: Nicole Becker, Daniel Cruz-Ramirez de Arellano, Brittland DeKorver, Michael Mack, Alena Moon, and Jeff Raker. #evidencebasedliving



A special thank you to Kinsey Bain—together we have published more papers than I thought possible in graduate school. Thank you for mentoring me and helping me navigate through academia. You are a brilliant researcher and a true friend. I am confident we will have many more “Bain and Rodriguez” publications in the future. May the “assessment and cross-disciplinary discussions” flag forever wave.

To my next-door neighbors, Josie Nardo, Casey Wright, and Matt Wu, thank you for being there with me every step of the way. We started this program together and learned to adapt. We have shared classes, ideas, and memories. I look forward to interacting with you in the next stages of our careers, as fellow researchers, colleagues, and long-time friends.

I would also like to thank the undergraduate researchers that worked with me, Nick Hux and Sven Phillips. It has been wonderful having the opportunity to mentor you, I consider you colleagues and I wish you the best in your future endeavors.

To the members of my committee, Dr. Marcy Towns, Dr. Minjung Ryu, Dr. Angeline Lyon, Dr. Adam Wasserman, thank you for your helpful comments and support that have helped me improve as a chemist, researcher, and scholar. Thank you to Dr. Christine Hrycyna for providing feedback for my original proposal and my dissertation proposal.

Thank you to the Chemistry Education Division, it is the community of like-minded graduate students that interested me in coming to Purdue. I am grateful for all the opportunities Purdue has provided for me to grow.

Finally, I would like to thank all of the undergraduate students I have worked with over the past few years, from the students in my research studies to the students in courses I have taught, and the undergraduate researchers I have mentored. It is for you and for future students that we do this work. My interactions with you have inspired me to pursue a career in academia and I believe the future is bright.

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## ABSTRACT

Author: Rodriguez, Jon-Marc, G. PhD

Institution: Purdue University

Degree Received: May 2019

Title: Students' Understanding of Michaelis-Menten Kinetics and Enzyme Inhibition

Committee Chair: Marcy H. Towns

Currently there is a need for research that explores students' understanding of advanced topics in order to improve teaching and learning beyond the context of introductory-level courses. This work investigates students' reasoning about graphs used in enzyme kinetics. Using semi-structured interviews and a think aloud-protocol, 14 second-year students enrolled in a biochemistry course were provided two graphs to prompt their reasoning, a typical Michaelis-Menten graph and a Michaelis-Menten graph involving enzyme inhibition. Student responses were coded using a combination of inductive and deductive analysis, influenced by the resource-based model of cognition. Results involve a discussion regarding how students utilized mathematical resources to reason about chemical kinetics and enzyme kinetics, such as engaging in the use of symbolic/graphical forms and focusing on surface-level features of the equations/graphs. This work also addresses student conceptions of the particulate-level mechanism associated with competitive, noncompetitive, and uncompetitive enzyme inhibition. Based on the findings of this study, suggestions are made regarding the teaching and learning of enzyme kinetics.



## CHAPTER 1. INTRODUCTION

This study seeks to respond to the need for more discipline-based education research that targets improving education for upper-division chemistry courses (Bodner & Weaver, 2008; Singer, Nielson, & Schweingruber, 2012). Biochemistry education research is an interdisciplinary and emerging field and little work has been done in biochemistry education research that seeks to understand how students reason about topics such as enzyme kinetics (Bain & Towns, 2016). Enzymes are biological catalysts that increase the rate of a chemical reaction, and enzyme kinetics involves quantifying the speed or rate of these reactions (Xie, 2013). The Michaelis-Menten model of enzyme kinetics provides a mathematical representation of the process in which enzymes convert substrate molecules into product molecules, reflecting a rich context to explore students' reasoning regarding problem solving and the use of mathematical models.

A review of the education literature reveals that work related to enzyme kinetics involves discussing alternative ways of presenting enzyme kinetics content in lecture (Bearne, 2012, 2014; Cohlberg, 1979; Johnson, 2014; Lawrence & Jaffe, 2008; Ochs, 2000; Waldrop, 2009), using analogies and analogy-based activities (Abel & Halenz, 1992; Asimov, 1959; Junker, 2010; Hinckley, 2012; Hesler, 1991; House, Meades, & Linenberger, 2016; Lechner, 2011; Ochs, 2000; Murkin, 2015; Runge, Hill, & Moran, 2006; Silverstein, 1995; Silverstein, 2011), and framing computer software as a potential teaching tool (Antuch, Ramos, & Alvarez, 2014a, 2014b; Bruist, 1998; Clark, 2004; Frezza, 2011; Gonzalez-Cruz, Rodriguez-Sotres, & Rodriguez-Penagos, 2003; Johnson, 2009; Johnson, Simpson, & Blom, 2009; Potratz, 2018). Additionally, there are a variety of laboratory experiments that allow students to focus on various aspects of enzyme kinetics (Barton, 2011; Bezerra & Dias, 2007; Hamilton, Dobie-Galuska, & Wiestock, 1999; Heinserling, Schrader, & Schanze, 2012; Howard, Herr, & Hollister, 2006; Johnson, 2000; Guerra, 2017).

However, there is lack of evidence-based research that (1) investigates students' understanding of enzyme kinetics or (2) assesses the pedagogical efficacy of the interventions suggested by the literature. Therefore, to help address the understudied nature of enzyme kinetics in education research, this study is situated in the context of enzyme kinetics, focusing on students' graphical reasoning. The overarching aim of this project is to better understand how students reason about enzyme kinetics in order to develop instruction that targets and builds on current student understanding. The results discussed in this dissertation are discussed in two recently submitted publications (Rodriguez, Bain, & Towns, 2019; Rodriguez & Towns, 2019).

### **1.1 Guiding Research Questions**

This study focuses on students' reasoning in the context of enzyme kinetics. In order to narrow the scope of this work, the design of this study and subsequent analysis was informed by the following research questions:

- (1) How do students use mathematical resources to reason about enzyme kinetics?
- (2) How do students reason about the particulate-level mechanism associated with enzyme kinetics and enzyme inhibition?

In short, these research questions were addressed by providing biochemistry students two Michaelis-Menten graphs (one without enzyme inhibition and one with enzyme inhibition) and having them discuss and interpret the graphs. The first research question focuses on students' mathematical reasoning, such as the use of symbolic and graphical forms (i.e., mathematical resources), which are intuitive mathematical ideas about equations and graphs, respectively (Sherin, 2001; Rodriguez, Bain, & Towns, 2019). In the context of this study, emphasis is placed on the intuitive mathematical ideas students use to interpret the graphs provided and reason about ideas related to Michaelis-Menten kinetics. The second research question focuses on student discussions related to the chemistry associated with enzyme kinetics and how the different enzyme

inhibitors (competitive, noncompetitive, uncompetitive) influence the function of enzymes, with the specific mechanism of each inhibitor having implications for the values of the relevant kinetic parameters.

## **1.2 Overview of Chapters**

The second chapter of this work discusses relevant literature that helps situate this study. Following this discussion, in the third chapter an overview is provided of the methodological considerations, discussing the theoretical underpinnings, along with data collection and analysis. Chapter four centers around addressing the first research question regarding students' mathematical reasoning. In chapter five the second research question is addressed regarding students' understanding of the mechanism associated with enzyme kinetics and enzyme inhibition. The sixth (final) chapter concludes this work by discussing the instructional implications and suggestions for future work.

## CHAPTER 2. LITERATURE REVIEW

Here literature that is relevant for this study is presented and synthesized. As mentioned previously, biochemistry content as a context for education research is not well represented in the literature, which is particularly evident for the topic of enzyme kinetics (Bain & Towns, 2016). This chapter will begin with literature that discusses student understanding of enzymes and catalysts (in general terms), followed by suggestions and resources for practitioners, research on graphical reasoning, and this chapter will end with research done related to chemical kinetics.

### 2.1 Enzymes and Catalysts

Looking at research that has investigated student understanding of enzymes and catalysts in more general terms, research indicates that students tend to focus on a surface-level definition of catalysts—catalysts speed up reactions and lower the activation energy—without considering the mechanism or physical interaction between catalysts and reactants (Cakmakci, 2010; Cakmakci & Aydogdu, 2011; Tastan & Boz, 2010; Bain, Rodriguez, & Towns, 2018). Responding to the need to address student understanding of the physical mechanism of catalysts such as enzymes, Bretz and Linenberger (2012) developed a concept inventory related to enzyme-substrate interactions, which they used in subsequent studies (Linenberger & Bretz, 2014; Linenberger & Bretz, 2015). This research trajectory indicated students struggle with the role of charge and shape in mediating enzyme-substrate interactions (Linenberger & Bretz, 2014), and students have difficulty making the connection that related terms such as *active site*, *specificity pocket*, and *allosteric site*, all represent locations in which the enzyme binds and interacts with the substrate (Linenberger & Bretz, 2015). It is also worth noting that research related to representations of proteins (which has relevance for representing enzymes), indicates the importance of clearly describing the limitations of different types of representations (ribbon, vines, hydrophobic/polar

space-filling) and providing opportunities for students to draw their own representations to illustrate their reasoning (Harle & Towns, 2012a, 2012b, 2013).

In a recent study, Halim et al. (2018) used writing-to-learn (WTL) assignments in a biology course to elicit students' alternative conceptions regarding a variety of topics, including protein structure, photosynthesis, enzymes, and recombinant DNA. The WTL assignments used by Halim and colleagues (2018) were developed to emphasize a conceptual understanding, which utilized a peer-review format that required students to think metacognitively and reflect on the material as they read and "corrected" a peer's work. Although this study was not framed around enzymes and enzyme kinetics, some relevant alternative conceptions were identified by the authors: *irreversible inhibition is related to noncovalent binding; a reversible inhibitor only binds to the active site; competitive inhibition is always reversible, while noncompetitive is always irreversible; an irreversible inhibitor only binds to the allosteric site*. Nevertheless, the extent in which these ideas would be identified in subsequent studies is unclear, due to the small sample size ( $n = 26$ ) and the fact that most of the alternative conceptions identified were only present in less than 5% of the total sample, that is, generally, it appears each alternative conception was specific to an individual.

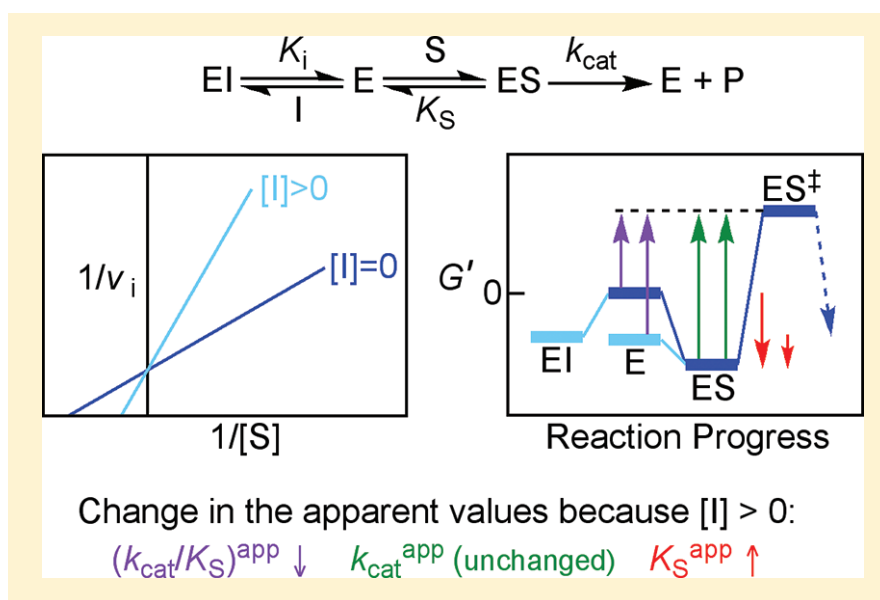
## **2.2 Resources for Practitioners Teaching Enzyme Kinetics**

Although there is a gap in the literature regarding chemistry education research done in the context of enzyme kinetics, a review of previous work elucidated various resources that practitioners can use when discussing enzyme kinetics in their courses. These resources involve instructional alternatives, analogies, technology and software, and a variety of laboratory activities.

### **2.2.1 Alternatives for Framing Content**

One suggestion made about the presentation of enzyme kinetics content was presented in a *Journal of Chemical Education* article by Bearne (2012), in which he outlined the potential utility

of discussing enzyme inhibition using Gibbs energy profiles. In his paper, he drew connections between the Lineweaver-Burke plots, the reaction scheme, and the Gibbs energy profiles, to provide a more holistic conception of different enzyme inhibition types (competitive, uncompetitive, noncompetitive, and mixed). The central tenet of this paper was to use Gibbs energy profiles to visually display the energy changes associated with enzymatic reactions (see **Figure 2.1**); in a different paper, the same author discussed a similar approach for considering the effect of pH on an enzyme's activity (Bearne, 2014). Other suggestions for portraying this content involve conceptualizing  $K_m$  as the apparent steady-state substrate dissociation constant (Colhberg, 1979), contextualizing enzyme kinetics using morphine proteins (Lawrence & Jaffe, 2008) or HIV protease (Johnson, 2014), and a more qualitative presentation of enzyme kinetics that focuses on mechanistic reasoning (Ochs, 2000; Waldrop, 2009).

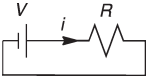

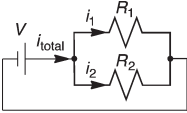
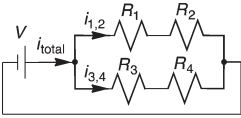
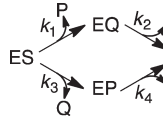


**Figure 2.1** Example of Gibbs energy profile that could potentially be used for instruction on enzyme kinetics, reproduced from Bearne (2012).

### 2.2.2 Using Analogies and Analogy-based Activities

There were a surprising number of discussions in the literature regarding analogies that could be used to explain features of enzyme kinetics, such as the temperature-dependence of rate,

the influence of substrate concentration, and the role of inhibitors (Abel & Halenz, 1992; Asimov, 1959; Junker, 2010; Hinckley, 2012; Hesler, 1991; House, Meades, & Linenberger, 2016; Lechner, 2011; Ochs, 2000; Murkin, 2015; Runge et al., 2006; Silverstein, 1995; Silverstein, 2011). The variety of analogies available in the literature is an indication of the complexity of enzyme kinetics as a topic and the desire for instructors to provide support for their students in understanding these ideas. Nevertheless, instructors should be aware of the challenges associated with using analogies. Analogies have the potential to support student learning, but there are many factors to consider when using analogies in biochemistry education, such as whether or not students are able to make connections between the analog domain and the target domain (Orgill & Bodner, 2004, 2006, 2007; Orgill, Bussey, & Bodner, 2015). For example, Murkin (2015) discussed using Ohm's Law and electric circuits as an analogy to describe the relationship between rate constants in a multi-step enzymatic reaction scheme (as shown in **Figure 2.2**), but if students are not familiar with the analog domain (electrical circuits and Ohm's Law), this is unlikely to improve student understanding of the target domain (enzyme kinetics); thus, the analogy will only create more confusion and students will view the analogy as additional content they have to learn. A summary of analogies related to enzyme kinetics that are discussed in the literature are provided in **Appendix A**.

Case	Circuit	Enzymatic reaction <sup>a</sup>
1	One resistor 	One step $ES \xrightarrow{k} E + P$
	Total resistance $R$	Total transit time $\tau$
	Total current $i = \frac{V}{R}$	Net rate constant $k$
2	Two resistors in series 	Two linear steps $ES \xrightarrow{k_1} EP \xrightarrow{k_2} E + P$
	Total resistance $R_{total} = R_1 + R_2$	Total transit time $\tau_{total} = \tau_1 + \tau_2$
	Total current $i = \frac{V}{R_1 + R_2}$	Net rate constant $\frac{1}{k_{net}} = \frac{1}{k_1} + \frac{1}{k_2}$
3	Two resistors in parallel 	Two parallel steps $ES \xrightarrow{k_1} E + P$ $ES \xrightarrow{k_2} E + Q$
	Total resistance $\frac{1}{R_{total}} = \frac{1}{R_1} + \frac{1}{R_2}$	Total transit time $\frac{1}{\tau_{total}} = \frac{1}{\tau_1} + \frac{1}{\tau_2}$
	Total current $i_{total} = \left(\frac{1}{R_1} + \frac{1}{R_2}\right) V$	Net rate constant $k_{net} = k_1 + k_2$
4	Two resistors in series in parallel to two resistors in series 	Two linear steps in parallel to two linear steps 
	Total resistance $\frac{1}{R_{total}} = \frac{1}{R_1 + R_2} + \frac{1}{R_3 + R_4}$	Total transit time $\tau_{total} = \frac{1}{k_1 + k_3} + \frac{k_1}{k_1 + k_3} \tau_2 + \frac{k_3}{k_1 + k_3} \tau_4$
	Total current $i_{total} = \left(\frac{1}{R_1 + R_2} + \frac{1}{R_3 + R_4}\right) V$	Net rate constant $k_{net} = \frac{k_1 + k_3}{1 + k_1/k_2 + k_3/k_4}$
		Initial steady-state rate $v_0 = \frac{k_1 + k_3}{1 + k_1/k_2 + k_3/k_4} [E]_t$

<sup>a</sup>The enzymatic schemes here are arbitrarily shown as starting from the ES complex, in which case,  $k_{net}$  is the turnover number,  $k_{cat}$ , but any other enzyme form could be used.

**Figure 2.2** Electric circuits and analogous reaction schemes, reproduced from Murkin (2015).

### 2.2.3 Technological Resources

The availability of technological resources in the literature were also noted (Antuch et al., 2014a, 2014b; Bruist, 1998; Clark, 2004; Frezza, 2011; Gonzalez-Cruz et al., 2003; Johnson, 2009; Johnson et al., 2009; Potratz, 2018). These papers tended to make similar instructional suggestions, using computer software to aid in the generation of data to simulate and model enzyme kinetics (take note of publication years; the differences between these papers are a product of technological advances). The most recent publication, Portraz (2018), allows instructors to display plots (concentration vs. time, velocity vs. substrate), modify variables, and view real-time changes,



affording students a dynamic representation of the effect associated with manipulating different factors. As discussed by Portraz (2018), one of the strengths of this software is that it supports students in understanding the specific conditions and assumptions necessary in order to have a system characterized by the Michaelis-Menten model of enzyme kinetics.

#### **2.2.4 Laboratory Experiments**

Laboratory experiments placed in the context of enzyme kinetics were common in the literature, with older laboratory experiments typically involving collecting spectrophotometric data and calculating kinetics parameters from Lineweaver-Burke plots (Bezerra & Dias, 2007; Hamilton et al., 1999; Howard et al., 2006; Johnson, 2000). More recent laboratory experiments build on these protocols by incorporating additional data analysis methods, in which students determine the kinetics parameters from Eadie-Hofstee and/or Hanes plots in addition to using the Michaelis-Menten and Lineweaver-Burk plots (Barton, 2011; Guerra, 2017). Moreover, there was an enzyme kinetics laboratory experiment that made use of commercial blood glucometers as a low-cost alternative to using spectrophotometers to collect data to calculate kinetic parameters (Heinserling et al., 2012).

#### **2.2.5 Summary of Practitioner Resources**

The papers discussed above vary in the extent in which they incorporated evidence-based practices, utilized research methodology and data to support claims, and evaluated the pedagogical efficacy of suggestions made—in some cases reflecting the “personal empiricism” discussed by Cooper and Stowe (2018). This limits the ability to make claims regarding the impact of this work on learning. Nevertheless, the ideas discussed in these papers are worth considering, in part because they reflect how the biochemistry community approaches the topic of enzyme kinetics. Although it is beyond the scope of the study discussed herein, examining the pedagogical efficacy of these resources would be useful to the community.

### 2.3 Graphical Reasoning

Context for this study is provided by looking at research on graphical reasoning in general. As discussed previously, graphs, such as those used in enzyme kinetics, communicate large amounts of information. However, it has been noted that when representations summarize more information, they often become increasingly abstract, making it difficult to connect it to the phenomena it models (Becker & Towns, 2012; Lunsford, Melear, Roth, Perkins, & Hickok, 2007). Within chemistry this problem is further compounded because students are asked to reason about processes that occur at a scale that is not readily observable (Kozma & Russell, 1997). Thus, instructors are faced with the challenge of using abstract representations to describe abstract processes. The implications of this problem have been documented in the literature; for example, chemical kinetics studies show that students have difficulty connecting the graphical representation to the particulate-level description of the process (Bain & Towns, 2016; Cakmaci & Aydogu, 2011; Cakmakci, Leach, & Donnelly, 2006; Kolomuc & Tekin, 2011; Tastan & Boz, 2010). Taken together, the literature indicates the need for more work that investigates students' graphical reasoning to help provide insight into how instructors can support students in their understanding and use of graphs.

### 2.4 Chemical Kinetics

In the section that follows, previous work placed in the context of chemical kinetics is described, beginning with a general review of relevant studies and then focusing in more detail on work completed in this context by the author. This section is not intended to be exhaustive, and for a more comprehensive review, readers are directed to published literature reviews by Bain and Towns (2016) and Justi (2002), which indicate that research related to chemical kinetics has typically focused on identifying and cataloguing students' alternative conceptions (primarily at the level of general chemistry). However, recent work has focused on analyzing students' reasoning

during problem solving and eliciting detailed descriptions of students' ideas related to the nature of mathematical models (Becker, Rupp, & Brandriet, 2017; Brandriet, Rupp, Lazenby, & Becker, 2018).

One of the relevant ideas related to chemical kinetics that has been investigated in detail is students' conceptions of rate laws and reaction order, with previous work indicating students have difficulty recognizing the empirical nature of the rate law expression and the order parameter (Becker et al., 2017; Brandriet et al., 2018; Cakmakci & Aydogdu, 2011; Cakmakci et al., 2006; Turanyi & Toth, 2013). In addition, because of surface similarities, (e.g., rate laws and equilibrium expressions,  $k$  and  $K$ ), studies situated in chemical kinetics often involve students conflating kinetics and equilibrium ideas (Becker et al., 2017; Cakmakci, 2010; Tastan, Yalcinkaya, & Boz, 2010).

As mentioned previously, research related to graphical reasoning in the context of chemical kinetics indicates students have difficulty drawing connections to the process indicated in a graph, such as how rate changes over time (Cakmakci et al., 2006; Cakmakci, 2010; Tastan et al., 2010; Cakmakci & Aydogdu, 2011; Kolomuc & Tekin, 2011). Moreover, research indicates that the presentation of chemical kinetics in textbooks (including graphical representations) does not adequately support students in making conceptual connections and may be a source of confusion (Gegios, Salta, & Koinis, 2017; Quisenberry & Tellinghuisen, 2006; Seethaler, Czworkowski & Wynn, 2018). Further complicating the problem, in the context of chemical kinetics, research suggests that students' anxiety increases when working with graphical representations (Secken & Seyhan, 2015).

#### **2.4.1 Our Previous Work Contextualized in Chemical Kinetics**

The primary focus of this section is to review previous research completed by the author and colleagues in the context of chemical kinetics, which helps situate the current work involving

enzyme kinetics. The chemical kinetics project described in this section is also summarized in a recent ACS Symposium Series book chapter (Bain, Rodriguez, & Towns, 2019).

#### **2.4.1.1 “Characterizing the cognitive processes involved in chemical kinetics using a blended processing framework” (Bain, Rodriguez, Moon, & Towns, 2018)**

This paper reflected a larger project that was interested in analyzing how students integrated chemistry and mathematics while solving problems in chemical kinetics. This larger qualitative project involved interviews with students as they worked through chemical kinetics prompts and yielded multiple manuscripts that focused on various aspects of this dataset (with the exception of the two final papers in the list presented here, the papers in this list share the same data corpus). Utilizing a framework from cognitive science called blended processing (Fauconnier & Turner, 1998; Coulson & Oakley, 2000) to characterize engagement in modeling, this study focused on how students combined ideas from different knowledge spaces, chemistry and mathematics. Analysis focused on different features of student engagement in modeling, such as the specific context and the directionality. Findings indicate that specific topics commonly served as the context for participants to engage in modeling, suggesting that combining a chemical and mathematical understanding about reaction order, catalysts, and how concentration changes, may be more accessible for students, serving as an opportune context to support students in engaging in modeling. In addition, in the dataset, students indicated a preference for thinking mathematically, and when engaging in modeling it tended to involve students anchoring their reasoning in mathematics and assigning chemical meaning to equations or representations (the reverse was less common in the data, in which mathematical implications were attributed to a chemical system), implying that students needed more support in mathematizing chemical phenomena.

#### **2.4.1.2 “Zero-order chemical kinetics as a context to investigate student understanding of catalysts and half-life” (Bain, Rodriguez, & Towns, 2018)**

In this paper student responses were analyzed that were related to an interview prompt that involved asking students about the half-life of a zero-order reaction that occurred in the presence of a catalyst. Although it was not the primary intention of the overarching project, the zero-order chemical kinetics prompt yielded rich data regarding student conceptions of zero-order reactions. Students in the sample held a primarily algorithmic understanding of zero-order reactions and had difficulty reasoning about the chemical implications of this reaction type. In addition, students’ reasoning about half-life was often characterized by inappropriately applying first-order kinetics ideas, such as associating half-life with radiometric dating, stating half-lives are constant, and attempting to use these ideas to solve the zero-order prompt. Taken as a whole, in order for students to have a more holistic and comprehensive understanding of ideas such as zero-order reactions and half-life, students must be exposed to a variety of contexts and examples (Bussey, Orgill, & Crippen, 2013; Gilbert, 2006). As opposed to only using first-order and second-order examples, zero-order reactions provide a unique opportunity for students to reason about chemical phenomena.

#### **2.4.1.3 “Productive features of problem solving in chemical kinetics: More than just algorithmic manipulation of variables” (Rodriguez, Bain, Hux, & Towns, 2019)**

For this paper an emphasis was placed on analyzing the problem-solving approaches used by students in the sample, characterizing different problem-solving routes based on how productive they were for moving students closer to the final answer. Generally speaking, students had difficulty reasoning about data and unproductively attempted to plug values into algorithms. The findings emphasized the importance of incorporating conceptual reasoning during problem solving, such as answering the question conceptually and engaging in reflection by evaluating the feasibility of an answer or approach. Findings suggest that unproductive problem-solving routes

could be made more productive by reasoning conceptually; however, instruction must be intentional in supporting students with this skill.

#### **2.4.1.4 “Investigating student understanding of rate constants: When is a constant ‘constant’?” (Bain, Rodriguez, & Towns, Submitted)**

This study focused on how students conceptualized the rate constant, which is an important feature of chemical kinetics (Holme, Luxford, & Murphy, 2015). Findings for this study indicate students have a variety of conceptions regarding the nature of the rate constant and its relationship to rate, and in some cases, students conflated rate and rate constants. In addition, consistent with previous work, conflation between rate laws and equilibrium expressions were observed (e.g., Becker et al., 2017). Furthermore, student conceptions of the rate constant varied in terms of how they reasoned about the conditions under which the rate constant was “constant”. Findings involve a discussion of student conceptions based on the sophistication associated with their reasoning.

#### **2.4.1.5 “Mathematics in a chemistry context: Implications for mathematics instruction and research on undergraduate mathematics education” (Rodriguez, Bain, & Towns, Submitted)**

Based on the scope of the larger project that was centered on students’ understanding and use of mathematics, paired with continued interest and engagement with research on the teaching and learning of mathematics, this paper focused on communicating the results of the larger study to the mathematics community. The general sentiment of this paper is that chemistry is a rich context to prompt students’ mathematical reasoning in both instructional and research contexts. Thus, it is argued that students in calculus courses should be exposed to chemistry examples; similarly, researchers interested in undergraduate mathematics education should take advantage of contexts such as chemical kinetics to situate their work and investigate students’ ideas about problem-solving, differentials, and integrals. Findings from the larger project are used to illustrate the utility of chemistry as a context for mathematics instruction and research, such as students’

conceptualization of equations in algebraic terms (simply using an equation to solve for values) and students' discussion of the relationship between the rate law and an integrated law, both of which suggest students compartmentalize mathematics and chemistry knowledge. Furthermore, a call is made for more discussion between faculty across disciplines to better understand the ways in which students in calculus courses will be expected to apply mathematics in the physical sciences.

#### **2.4.1.6 “Using symbolic and graphical forms to analyze students’ mathematical reasoning in chemical kinetics” (Rodriguez, Santos-Diaz, Bain, & Towns, 2018)**

During the process of data analysis for the larger project, it was observed that students used reasoning that was reminiscent of Sherin's (2001) symbolic forms. This framework is expanded upon further in the Methods section, but the general idea is that reasoning using symbolic forms involves assigning mathematical ideas to a pattern in an equation (Sherin, 2001). These intuitive mathematical ideas emerged from the data, but there were also instances in which students engaged in reasoning about graphs in a way that was analogous to symbolic forms. This led to the exploration of this idea further and a small subset of the data was analyzed to better understand how the symbolic forms framework could be adapted to characterize graphical reasoning. This adaption of symbolic forms was presented at the 2018 Conference on Research on Undergraduate Mathematics Education; the work received warmly along with feedback, and it was decided to call this construct that involved assigning intuitive ideas to patterns in graphs, *graphical forms*. In the dataset, students that utilized more symbolic and graphical forms had a better understanding of chemical phenomena, evidenced by their ability to integrate chemistry and mathematics in their reasoning.

#### **2.4.1.7 “Graphical forms: The adaption of Sherin’s symbolic forms for the analysis of graphical reasoning across disciplines” (Rodriguez, Bain, & Towns, Submitted)**

In this work, a comprehensive review of the different symbolic forms that have been identified in the literature is presented along with the adaption of the framework to analyze graphical reasoning. This piece was more theoretical in nature, although the use of the framework is illustrated by analyzing the presentation of graphs in textbooks. In order to illustrate the utility of the framework for thinking about graphical reasoning across disciplines, graphs from different introductory textbooks were analyzed, including chemistry, biology, physics, and calculus. The text descriptions that accompanied each graph were analyzed and the graphical forms used in the textbooks to describe graphical representations were characterized. This analysis revealed that graphical forms reflected a shared set of resources utilized by experts (i.e., textbook authors) to describe and interpret graphs across the different disciplines. The discussion of symbolic and graphical forms is discussed further in the Methods section, since it is relevant for examining students’ mathematical reasoning in the context of enzyme kinetics.

#### **2.4.1.8 “Covariational reasoning and mathematical narratives: Investigating students’ understanding of graphs in chemical kinetics” (Rodriguez, Bain, Towns, Elmgren, & Ho, 2019)**

This work involved an international collaboration with researchers at Uppsala University in Sweden. In this project the graphical forms framework was utilized to analyze how students reasoned about a concentration vs. time graph, sampling from a non-major general chemistry course at a university in Sweden. For this work modeling was framed as engaging in mathematical narratives, which provided the language to describe how students reasoned about the “story” communicated by the graph provided (Nemirovsky, 1996). The findings indicated that students had a variety of productive resources for interpreting graphs and providing explanations for the “story” communicated by the chemical kinetics graph. However, in some cases students used chemistry ideas in non-normative ways or focused on surface features of the graph, attending only



to the general shape of the graph without considering the implications of the values represented on the axes (concentration vs. time). In these instances, students seemed to view the graph as an “object”, with which they associated ideas, limiting their understanding of the phenomena modeled.

#### **2.4.1.9 Summary of our previous work**

Looking across the different studies we have completed related to investigating students’ understanding of chemical kinetics, a common thread resonates: students tend to perform better at reasoning algorithmically and algebraically, and students find it challenging to reason conceptually and integrate conceptual reasoning as they solve problems, which is consistent with previous work across different chemistry contexts (Cracolice, Deming, & Ehlert, 2008; Nakhleh, 1993; Nakhleh, Lowrey, & Mitchell, 1996; Nakhleh & Mitchell, 1993; Nurrenbern & Pickering, 1987; Pickering, 1990; Sanger, Vaughn, & Binkley, 2013; Sawrey, 1990; Stamovlasis, Tsaparlis, Kamilatos, Papaoikonomou, & Zaratiadou, 2005; Zoller, Lubeszky, Nakhleh, Tessier, & Dori, 1995). Furthermore, focusing on the specific context of chemical kinetics, the highly quantitative nature of this topic makes it ideal for investigating students’ mathematical reasoning, engagement in modeling, and integration of chemistry and mathematics. In the studies discussed above students had nuanced conceptions regarding kinetic parameters (such as the rate constant), limited views regarding reaction order, and in some cases, a static understanding of graphical representations. It is within the context of this previous work that the current work is situated, investigating students’ conceptions about ideas related to enzyme kinetics graphs.

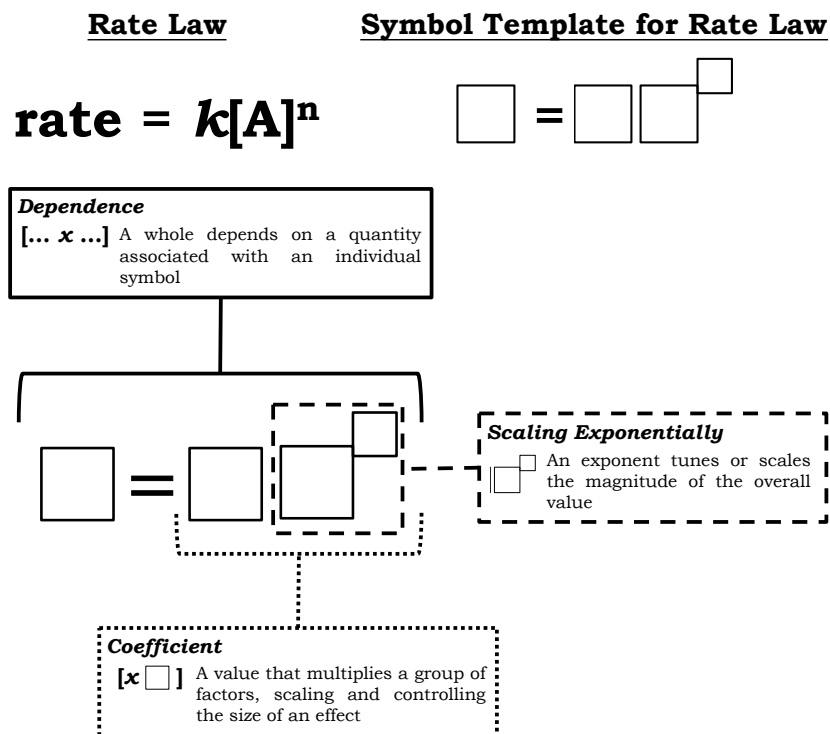
## CHAPTER 3. METHODS

### 3.1 Theoretical Underpinnings

The central focus of this study is to better understand how students reason about ideas related to enzyme kinetics. The approach toward addressing this aim was influenced by the resource-based model of cognition, which conceptualizes knowledge as a complex network of connections between different cognitive units (i.e., resources) (Hammer & Elby, 2002; Hammer & Elby, 2003; Hammer, Elby, Scherr, & Redish, 2005). These cognitive units can be characterized as procedural, epistemological, or conceptual in nature, representing the variety of types of knowledge constructed by individuals (Becker et al., 2017). For example, procedural resources could involve information regarding the process of estimating the  $K_m$  value from the Michaelis-Menten plot, epistemological resources could involve beliefs relating to the type of knowledge or conclusions that can be reached from data (e.g., graphs), and conceptual resources could involve ideas related to how a competitive inhibitor interacts with an enzyme. The resources perspective has its roots in constructivism, which asserts that knowledge is constructed in the mind of the learner based on experiences (Bodner, 1986; Bodner & Klobuchar, 2001), and encompasses diSessa's (1993) "knowledge-in-pieces" view of cognition, which accounts for the context-dependence of ideas and the observed lack of consistency with an individual's responses to different tasks. Analysis guided by the resources perspectives acknowledges that even if the resources used by students do not move them toward the answer for a specific prompt, those same resources may be useful in a different context; thus, the goal of instruction should be to help build on students' current knowledge and help students use their knowledge productively (Heisterkamp & Talanquer, 2015; Becker et al., 2017).

### 3.1.1 Symbolic Forms

In the context of this study, emphasis is placed on better understanding the different resources used by students in the sample to reason about enzyme kinetics. One category of resources can be broadly described as “mathematical resources”, which includes symbolic and graphical forms. Symbolic forms represent intuitive ideas about patterns in an equation and were developed as an analytic framework by Sherin (2001) to characterize students’ mathematical reasoning while they were working through physics problems. According to Sherin (2001), symbolic forms consist of a symbol template (a recognizable pattern in an expression or equation) and a conceptual schema (an intuitive idea that is assigned to the symbol template). For example, consider the zero-order integrated rate law from chemical kinetics ( $[A] = [A]_0 - kt$ ), which expresses the final concentration of a reactant as the difference between the (1) initial concentration and (2) the product of the rate constant and time. This can be conceptualized as the symbolic form *base – change*, where the symbol template is written as  $\square - \Delta$  and the conceptual schema involves ideas related to having an initial value that is altered by another value (in this representation the box indicates a term or group of terms and the delta symbol indicates change). **Figure 3.1** provides an additional example of the meaning encoded in equations, in which a rate law can be conceptualized as representing a combination of multiple intuitive mathematical ideas, including the symbolic forms *dependence*, *coefficient*, and *scaling exponentially*.



**Figure 3.1** Illustration of the symbolic forms associated with a generic rate law, along with the symbol template for a rate law, reproduced from Rodriguez, Bain, and Towns (2019).

The importance of reasoning involving symbolic forms is that students may recognize patterns in equations and associate ideas that are productive even if they are not familiar with the context. For example, students may have ideas related to how values change and how this is represented mathematically—which is important for reasoning about chemical kinetics—even if students are not familiar with the content associated with this topic. Furthermore, it has been previously reported that being able to engage in reasoning characterized by a variety of different symbolic forms affords a more comprehensive understanding of chemical phenomena, because it allows students to consider the system from multiple perspectives and integrate conceptual and mathematical reasoning (Rodriguez, Santos-Diaz, Bain, & Towns, 2018), with similar assertions made in physics education research (Kuo, Hull, Gupta, & Elby, 2013).

It is worth noting Sherin (2001) acknowledged the initial list of symbolic forms he published was incomplete, and researchers across discipline-based education fields have since

added to Sherin's (2001) list of symbolic forms (Dreyfus, Elby, Gupta, & Sohr, 2017; Dorko & Speer, 2015; Hu & Rubello, 2013; Izak, 2004; Jones, 2013, 2015a, 2015b; Rodriguez, Santos-Diaz, Bain, & Towns, 2018; Sherin, 2001; Schermerhorn & Thompson, 2016; Von Korff & Rubello, 2014). An abridged list of symbolic forms is provided in **Table 3.1**, with a more comprehensive list of symbolic forms identified in the literature provided in **Appendix B**.

**Table 3.1** Examples of symbolic forms, adapted or reproduced from Sherin (2001) and Rodriguez, Santos-Diaz, Bain, and Towns (2018).

Symbolic Form	Symbol Template	Conceptual Schema
Base $\pm$ change	$\square \pm \Delta$	A change increases or decreases an initial value
Coefficient	$[x\square]$	A value that multiplies a group of factors, scaling and controlling the size of an effect
Dependence	$[...x...]$	A whole depends on a quantity associated with an individual symbol
No dependence	$[...]$	A whole does not depend on a quantity associated with an individual symbol
Prop-	$\left[\frac{\dots}{\dots x \dots}\right]$	Indirectly proportional to a quantity, $x$ , appears as an individual symbol in the denominator
Scaling	$[n\square]$	Similar to coefficient, but the coefficient is unitless; a scaling coefficient is seen as operating on the rest of the factors to produce an entity of the same sort that is larger or smaller than the original
Scaling exponentially	$\square^{\square}$	Similar to scaling, but in this case an exponent is tuning or scaling the magnitude of the overall value
<b>Template Key</b> $[...]$ Expression in brackets corresponds to an entity in the schema $x$ Individual symbols in an expression $\square$ A term or group of terms $...$ Omitted portions of an expression that are inconsequential or continue a pattern		

### 3.1.2 Graphical Forms

In his discussion of symbolic forms, Sherin (2001) briefly mentioned the potential to adapt this framework to characterize reasoning about graphical representations, a sentiment that was later reiterated by Lee and Sherin (2006). Over the course of analyzing the data from the larger

study discussed in Bain, Rodriguez, Moon, and Towns (2018), instances were noted in which students engaged in reasoning that could be characterized by symbolic forms, but analogous graphical reasoning also emerged from the data, prompting the consideration of how the symbolic forms framework could be expanded to characterize graphical reasoning. In a recent paper, an overview of the symbolic forms framework is discussed, and the conceptualization of *graphical forms* is provided (Rodriguez, Bain, & Towns, 2019). Graphical forms reflect intuitive mathematical ideas about graphs, involving assigning a conceptual schema to a *registration*. The term *registration* is used similarly as Roschelle (1991), describing a feature of a representation to which an individual attends. Thus, when an individual attributes or *registers* mathematical ideas to a region in a graph, they are reasoning using graphical forms. For example, consider the graphical form *steepness as rate*, which involves attributing ideas related to rate to the relative steepness of a region in a graph (note the descriptive names given to each of the graphical forms indicate the relationship of interest). In **Table 3.2**, a list of graphical forms identified in previous work is provided (Rodriguez, Bain, & Towns, 2019; Rodriguez, Bain, Elmgren, Towns, & Ho, 2019).

**Table 3.2** Examples of graphical forms, adapted or reproduced from Rodriguez, Bain, and Towns, (2019) and Rodriguez, Bain, Elmgren, Towns, and Ho (2019).

<b>Graphical Form</b>	<b>Registration and Conceptual Schema</b>
<b>Steepness as rate</b>	Varying levels of steepness in a graph correspond to different rates
<b>Straight means constant</b>	A straight line indicates a lack of change/constant rate
<b>Curve means change</b>	A curve indicates continuous change/changing rate
<b>Trend from shape directionality</b>	The general shape of the graph suggests information regarding the graph's tendency to increase or decrease

As was the case with symbolic forms, graphical forms afford the ability to draw inferences and make connections between ideas, which aids the integration of mathematical and conceptual reasoning (Rodriguez, Bain, Elmgren, Towns, & Ho, 2019; Rodriguez, Santos-Diaz, Bain, & Towns, 2018). Building on this idea, the presentation of graphs from various college-level introductory textbooks were analyzed (biology, calculus, chemistry, and physics), resulting in the assertion that experts from different disciplines use a shared set of mathematical resources (i.e., graphical forms) to support their understanding and explanation of phenomena modeled (Rodriguez, Bain, & Towns, 2019). In other recent work, the graphical forms framework has been found to be productive for analyzing students' graphical reasoning in the United States (Rodriguez, Santos-Diaz, Bain, & Towns, 2018) and in Sweden (Rodriguez, Bain, Elmgren, Towns, & Ho, 2019).

### 3.2 Research Design

It is within the context of the research questions and the theoretical perspectives discussed above that this study was designed. As discussed in more detail later, the prompt used in the interview was developed to elicit students' conceptions of enzyme kinetics, including the mathematical ideas (symbolic and graphical forms) students used to describe concepts related to enzyme kinetics.

### 3.2.1 Sampling

The participants for this study were second-year undergraduate students recruited from an introductory undergraduate biochemistry course for life science majors (offered by a chemistry department), which is part of a recently revised and condensed chemistry curriculum (Schnoebelen, Towns, Chmielewski, & Hrycyna, 2018). Recruitment of students began before instruction on enzyme kinetics and students were given a \$20 gift card for their involvement in the project. All data collection took place during the spring of 2018 after the students were tested on enzyme kinetics. In order to protect the identities of the participants, pseudonyms were assigned. This project was conducted in accordance with the guidelines of the university's Institutional Review Board.

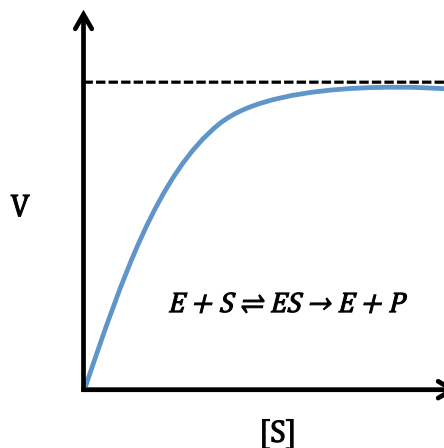
### 3.2.2 Interview Prompts

The primary data source for this study was semi-structured interviews using a think-aloud protocol (Becker & Towns, 2012). Two interview prompts were developed to elicit students' ideas about enzyme kinetics, both of which contain graphs that students are asked to interpret as part of the interview. The graphs and accompanying interview prompts are provided in **Figure 3.2**, and the complete interview prompt with sample follow-up questions are provided in **Appendix C** and **Appendix D**. In the first prompt students were provided a graph and a reaction scheme that they were asked to explain and in the second prompt students were provided an enzyme inhibition graph and they were asked to discuss the types of inhibition represented in the graph.

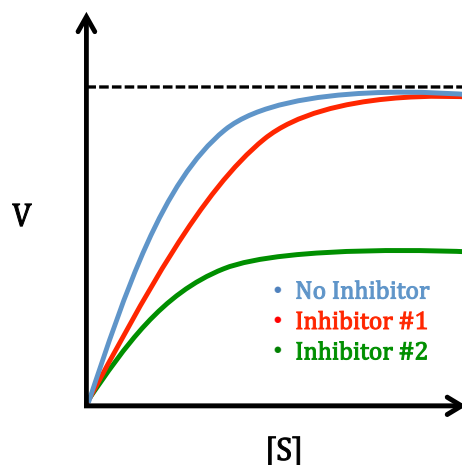


**Interview Prompt #1**

Here's a graph and a reaction scheme you may have seen in class to describe enzyme kinetics. How would you explain these to a friend from class? How would you explain these on an exam?

**Interview Prompt #2**

Multiple experiments were run in which kinetics data were collected for a reaction involving an enzyme. The first reaction was run without an enzyme inhibitor, the second reaction was run with an enzyme inhibitor, and the third reaction was run with a different enzyme inhibitor. The results are shown below. Explain the types of inhibition observed.



**Figure 3.2** Enzyme kinetics interview prompts used in this study. The first interview prompt has the students explain a typical Michaelis-Menten plot and the second interview prompt asks the students to draw conclusions from the graph showing enzyme inhibition.

In order to validate the content assessed in each prompt, the prompts were discussed with two biochemistry professors that had experience teaching undergraduate and/or graduate courses that involved instruction on enzyme kinetics. The primary concern was with the second prompt, namely, whether or not it was clear how the parameters of the graph ( $K_m$  and  $V_{max}$ ) varied between the three different curves (*No Inhibitor*, *Inhibitor #1*, and *Inhibitor #2*). However, both content experts stated the relevant relationships could be determined from the data given (i.e., *Inhibitor #1* is a competitive inhibitor because the  $V_{max}$  is unaffected and the  $K_m$  increases; *Inhibitor #2* is a

noncompetitive inhibitor because the  $V_{\max}$  decreases and the  $K_m$  is unaffected). For clarity, our use of *noncompetitive inhibition* in this work is in reference to an inhibitor that binds the free enzyme and the enzyme-substrate complex with equal affinity. After discussing the prompts with the content experts, minor edits were made to the wording of the prompt and the first prompt was simplified (in its original version the students were provided the graph, the reaction scheme, and the Michaelis-Menten equation, but the Michaelis-Menten equation was removed from the prompt to reduce cognitive load).

The primary researcher attended the course lectures related to enzymes and enzyme kinetics and collected the relevant exams in order to ensure that the content assessed in the interview prompts was within the scope of what was emphasized in the course. Based on reviewing the content discussed in lecture and assessed on exams, in combination with feedback from the content experts, it was determined that the prompts developed for this study were reasonable in terms of the content assessed and the nature of the questions asked in the interview. In an effort to confirm that the interview prompt would result in data that would help address the research, the interview prompt was piloted with four students from the target sample population. No changes were made to the prompt following the pilot study and an additional 10 students were interviewed, resulting in a final sample of 14 students.

### **3.2.3 Data Collection and Analysis**

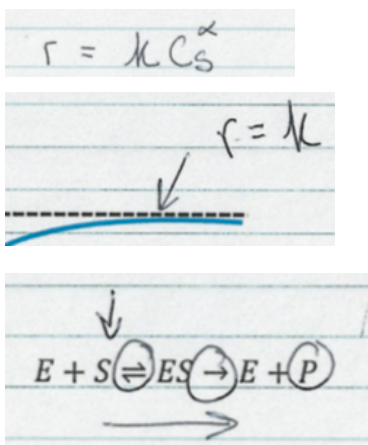
During the interviews the students were asked to reason through two prompts involving enzyme kinetics graphs and follow-up questions were asked to make students' reasoning more explicit. Data was collected using a Livescribe™ smartpen, which records and digitally synchronizes students' audio and written work (Linenberger & Bretz, 2012; Harle & Towns, 2013; Cruz-Ramirez de Arrellano, & Towns, 2014). Immediately following each interview, the researcher engaged in memoing (reflective journaling) by listening to the audio recording of the

interview and taking initial notes regarding each student's responses to the prompts provided (Birks, Chapman, & Francis, 2008; King & Horrocks, 2010).

### **3.2.3.1 Coding interview transcripts**

Following transcription of the interviews, the data went through an additional processing step to construct “interpretative narratives” for each interview (Bain, Rodriguez, Moon, & Towns, 2018; Page, 2014). In this context, interpreted narratives were used differently than Page (2014), with more emphasis on organizing and restructuring the data to aid the multimodal analysis, involving students' verbal discussions and written work (see **Table 3.3** for an example). The modified interpreted narratives involve: (1) a “refashioned transcript”, which contains the students' verbatim response to the interview prompts (with some of the interviewer's questions/comments when relevant for context) and (2) students' written work. Using the software associated with the Livescribe™ smartpen it could be determined what the student was saying while they were writing or drawing. This information is conveyed in the interpreted narratives by having the students' written work directly to the right of the corresponding text (along with some additional notes in brackets for clarity). After organizing the data into interpreted narratives, the interpreted narratives were open-coded and coded using considerations of the symbolic and graphical forms frameworks, using a constant comparison methodology (Strauss & Corbin, 1990). Based on the emergence of no additional codes and adequate representation of themes, it was determined that data saturation was reached (Saunders et al., 2018). For the sake of transparency, the codes and accompanying descriptions that compose the coding scheme are provided in **Appendix E**.

**Table 3.3** Example of an interpreted narrative.

Refashioned Transcript	Students' Written Work
<p><b>Interviewer:</b> "Okay, and what do you mean by rate law?"</p> <p><b>Ellie:</b> "Rate law is what governs your rate. For example, that could be your rate law if it was a first order [draws rate law, without alpha], up here when you hit your V-max it's a zero order [labels graph], so it has nothing to do with the substrate concentration. Yeah, so your rate law is usually governed by your reactants and not necessarily your products. Especially if it's irreversible like it is here [circles forward arrow], so the concentration of your products supposedly has something to do with your rate law because it's irreversible. Here because it is reversible [circles equilibrium arrow] it could depend on the concentration of your products as well."</p>	

With respect to considerations of inter-rater reliability, Kappa values were calculated using the NVivo qualitative analysis software, which has an algorithm that incorporates percent agreement and percent disagreement between two coders (QSR International, 2018). Using the developed coding scheme, an additional researcher coded two interviews (~14% of the dataset), yielding a Cohen's Kappa of 0.88. A second Cohen's Kappa of 0.95 was calculated following the discussion of the code assignments, which involved refining and modifying code descriptions and code assignments. The changes made to the coding scheme was then utilized to recode the full data corpus (Charmaz, 2006).

### 3.2.3.2 Resource Graphs

As part of the data analysis related to students' understanding of competitive, noncompetitive, and uncompetitive enzyme inhibition, this work utilizes *resource graphs* to represent the data. Resource graphs provide a way to visually depict the connections observed between students' resources (Wittmann, 2006; Sayre & Wittmann, 2008). In a resource graph,

*resources* are represented by circles and a line connecting the resources indicates that a student made a connection between these ideas. As discussed by Wittman (2006), resources are emergent and fractal in nature which makes it difficult for analysis, thus, this work focused on identifying resources that were large enough to be identified in the context of the interview, along with supporting evidence to be able to draw conclusions regarding the connectivity of resources. In **Table 3.4** an example of a resource graph is provided for one of the participants (Malcolm), illustrating his conception of noncompetitive inhibition. Also provided in **Table 3.4** is information regarding how the resource graphs were constructed in terms of the evidence that links students' resources. A resource graph was constructed for competitive, noncompetitive, and uncompetitive inhibition for each of the participants, which were collectively used to frame the themes discussed (see **Appendix F** for a compilation of all of the students' resource graphs).

Note that for the resource graphs used in this work, the general structure is the same, which is a result of the interview prompt; for each inhibition type, each of the students were asked about the influence on the reaction scheme, interaction with enzyme, and the kinetic parameters. The variation observed in the sample is in regard to how the students discussed these resources and the connections students made between the resources. Since each of the students' resource graphs involves the same general structure, students' reasoning can be compared, with a special emphasis on the observed connectivity between resources. For example, one student may have stated that in relation to the kinetic parameters,  $K_m$  decreases with a noncompetitive inhibitor, whereas another student may have stated that  $K_m$  is unaffected, or one student may have drawn a connection between a changing parameter and its interaction with the enzyme, whereas another student may not have made this connection.

**Table 3.4** Example of how resource graphs were constructed (Malcolm's resource graph for noncompetitive inhibition).

Passage	Student Discussion and Written Work	Resource Graph
A	"And then noncompetitive would have the same $K_m$ , but a smaller $V_{max}$ ..."	
B	<p>"Non-competitive, your inhibitor [shaded circle] binds to an allosteric site that's not the active site and it just changes the conformation slightly so that the substrate [unshaded circle] can still bind, but it just doesn't produce product [triangles] as quickly. And it keeps the same <math>K_m</math> because, since it doesn't bind to the enzyme active site, you can still have half of your enzymes bound at that concentration. It's just as you increase concentration, since it has the changed confirmation, it's not as effective, and you're never gonna reach that same <math>V_{max}</math> as you had uninhibited."</p>	
C	<p>"Competitive inhibitor, it kind of prevents this portion happening [underlines left side of reaction, enzyme and substrate forming enzyme-substrate complex], while noncompetitive inhibitor kind of prevents this portion from happening [draws a line above right side of reaction, enzyme-substrate complex forming enzyme and product]. So, a competitive inhibitor will produce enzyme-competitive inhibitor complex, which means that you can't form your enzyme-substrate complex, whereas your noncompetitive inhibitor will still allow for your enzyme-substrate complex to happen. It just makes your enzyme-product happen a lot slower, so your competitive inhibits things harder. ... Uncompetitive binds here [downward arrow], so it kind of makes this reaction happen [left side of reaction], so it makes that go to that [curved arrow on left]. But since it binds here, it kinda also prevents that from happening [curved arrow on right]. It still happens, but it just happens a lot slower."</p>	

## CHAPTER 4. MATHEMATICAL RESOURCES

The focus of this chapter centers on discussion of the data that provided insight into addressing the first research question, *How do students use mathematical resources to reason about enzyme kinetics?* Here we focus primarily on the first interview prompt related to the presentation of the Michaelis-Menten plot, and within the sample, student use of mathematical resources was often in the context of a discussion about reaction order and rate laws. In most cases, students focused on the surface features of the relevant equations and graphs, with a primarily algebraic discussion of rate laws and a discussion of reaction order that emphasized graphs as “objects”, which limited students’ ability to reason about the provided Michaelis-Menten graph. Nevertheless, instances were noted where students productively combined mathematical resources with chemistry ideas, affording a more comprehensive understanding of enzyme kinetics.

### 4.1 Rate Law as a Symbol Template

Among the sample, four students reflected reasoning that emphasized an algebraic understanding of the rate law, which often involved non-normative ideas, as shown in **Table 4.1**. From the perspective of Sherin’s (2001) symbolic forms, it appears that Tim, Claire, and Alan’s representation of the rate law was an attempt to map terms onto a specific pattern. Using the notation of symbolic forms, for Tim and Claire, this can be viewed as having the symbol template  $\square = \square \square \square$ , which reflects the general form of a rate law (e.g.,  $\text{rate} = k[A]^2$ ). This type of reasoning was particularly evident in Tim’s discussion when he mentioned the two “boxes” associated with first-order reactions (i.e.,  $\text{rate} = k[A]$ ) and the single box associated with zero-order reactions (i.e.,  $\text{rate} = k$ ). This over-emphasis on the overall pattern and surface features of the equation was not productive, because Tim then generalized his conception of the rate law by stating

that the reaction between the enzyme and substrate must be first-order, since this would fill both boxes. In a study that involved calculus students working through problems involving area and volume, Dorko and Speer (2015) observed similar “box-filling” tendencies. Students in their sample made use of the *measurement* symbolic form, which represents the idea that a measured value should have units ( $\square\square$ , magnitude and units), but in some instances the students did not carefully consider what belongs in the “units box” (e.g., writing  $144\pi$  and considering it to be adequate to fill both boxes, despite it representing a single magnitude value, not a magnitude with units). Although Claire did not explicitly discuss “boxes”, as in the case of Tim, her reasoning was similar, in which she assigned values to a similar pattern of symbols. Looking closer at Claire’s discussion, the “rate law” equations she wrote were part of her discussion about reaction order, and when asked about rate laws, she drew an expression that is more reminiscent of the equilibrium expression. This is similar to Alan’s reasoning, which represents mapping values onto a different symbol template. Placing these results in the context of previous work, the conflation between kinetics and equilibrium ideas is well-documented in the literature (Bain & Towns, 2016; Becker et al., 2017).



Table 4.1 Student reasoning about rate laws.

Student	Transcript and Written Work
Tim	<p>"I think if I remember right, like <math>k</math> and then you can do it to like the first order here and then, there was <math>a</math>, yeah, so there was a rate or something was equal to the <math>k</math> to the first order ... If I remember right ... [the rate law] had two boxes for here, but I think zero only had one ... because there's two, there's two things that are multiplied here, essentially, you have the enzyme and you have the substrate. And so, for the rate you have the enzyme, I think if I remember right for first order you had something multiplied by something else ... which would lead for me to think it's a first-order, first-order rate reaction."</p> $Rate = [ ] [k]^1$
Claire	<p>"This is second order. ... 'Cause it's a hyperbola graph and so the substrate is gonna be like, the order would be substrate, to the second, squared, and then first is just a linear line and then zero is just a horizontal straight across line. ... Yeah. So this is zero order. That's a straight line. I think it's <math>k</math> equals the substrate concentration to the zero, so you're just gonna have the straight line. And then this is gonna be first order and it's just gonna be a linear line, to the one."</p> $k = [S]^2 \quad k = [S]^0 \quad k = [S]^1$ <p><b>Interviewer:</b> "And what about in terms of writing a rate law for this reaction?"  <b>Claire:</b> "Goodness. Is that like products over reactants? I can't remember. If what I'm thinking is right, it was, you do the products over the reactants. I think that was, it's like the equilibrium equation."</p> $\frac{[E][P]}{[E][S]}$
Alan	<p>"So, rate law, if I remember right, is something like concentration of C plus concentration of D over concentration of A plus concentration of B. Where A plus B yields C plus D. So, for this I believe it would be E plus P over E plus S. I believe. ... So, that tells us essentially the rate at which the reaction is taking place. So you're using concentrations here but those concentrations cancel out, and so they're going to tell you, essentially the speed, or kind of the ratio of the products to the reactants ... which has something to do with the speed."</p> $Rate = \frac{[C] + [D]}{[A] + [B]} \quad \frac{E + P}{E + S}$
Carrie	<p>"... if your rate law, if it's like second order, so you have like <math>kA</math> squared, and then if that happens, and that means whenever you double the concentration of whatever your solution, your, if you are saying A, if you double the concentration of A, then you would see a jump to like times four of your rate, and that's what we learned. We learned zero, first, and second rate laws in gen chem, yeah."</p>

In comparison to the other participants in this group, Carrie correctly identified the relationship between the terms in the rate law, reasoning about the rate law by focusing on the concentration dependence associated with different reaction orders. This reasoning is rooted in the symbolic form *scaling exponentially*, which involves describing how exponents scale or tune a value (Rodriguez, Santos-Diaz, Bain, & Towns, 2018). This is distinct from the other students because they simply focused on the symbol template associated with the rate law, but they did not make use of the relevant mathematical ideas associated with the pattern of symbols. Although Carrie's reasoning helped her provide a reasonable description of the rate law, her understanding, like the other students, was primarily algorithmic in nature, which limited her ability to draw connections and reason about enzyme kinetics.

## 4.2 Graph as an Object

Discussions related to reaction order typically revolved around assigning specific graphical shapes to different orders (zero-order, first-order, second-order reactions), framed here as *viewing the graph as an object*, that is, associating ideas with a graphical pattern. This is distinct from reasoning using graphical forms, because graphical forms involve associating *mathematical* ideas with a graph. When viewing the graph as an object, students see the graph more as a picture or static image that has associated properties. Similar reasoning was described in a previous study involving non-major students in a general chemistry course at a Swedish university (Rodriguez, Bain, Elmgren, Towns, & Ho, 2019). In Rodriguez, Bain, Elmgren, Towns, and Ho (2019), the prompt provided for the students involved a concentration vs. time graph with a curve that had an S-shape and the students were asked to provide reasonable particulate-level explanations for the graph shape, to which some students discussed ideas related to acid-base chemistry and titrations. In this instance, the students were focusing on the surface-level similarities between the

concentration vs. time curve and the sigmoidal shape of a titration curve, which was not productive for reasoning about the prompt.

As shown in **Table 4.2**, seven students in the sample had reasoning that involved focusing on the graph as a static object, five of which were more explicit with their reasoning, drawing graphs to illustrate their ideas. Viewing graphs as objects is similar to what was previously reported with students' discussion of rate laws; however, in this case, students focused on surface-level features of patterns in a graph rather than patterns in an equation. In the student discussions shown in **Table 4.2**, the students associated reaction orders with specific shapes, and in some cases, the students then used this type of reasoning to draw a conclusion about the order of the reaction in the provided Michaelis-Menten graph, making note of which of the graphs looked like the Michaelis-Menten plot. In addition, for the students that drew the graphs, although the "shapes" were technically correct for the zero-order and first-order graphs, none of the students drew the correct shape for the second-order graph; instead these students focused more the fact that the second-order graph needed to be curved. Furthermore, it is worth noting that when drawing the graphs, the students did not label their axes, and it was only after some prompting from the interviewer that students added titles for the axes, suggesting that the shape of the graph was the salient feature focused on by students.

Table 4.2 Student reasoning about reaction order.

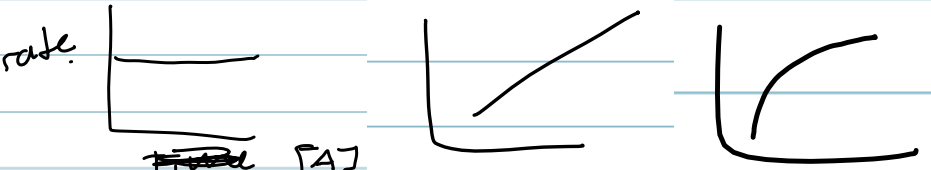
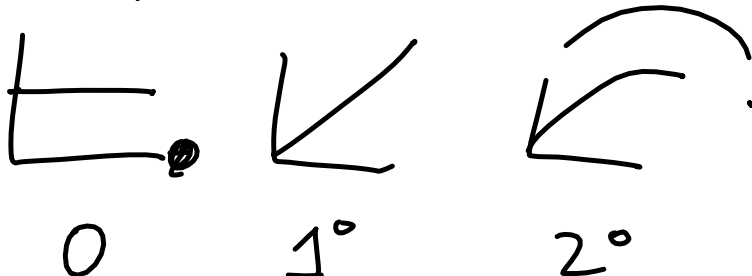
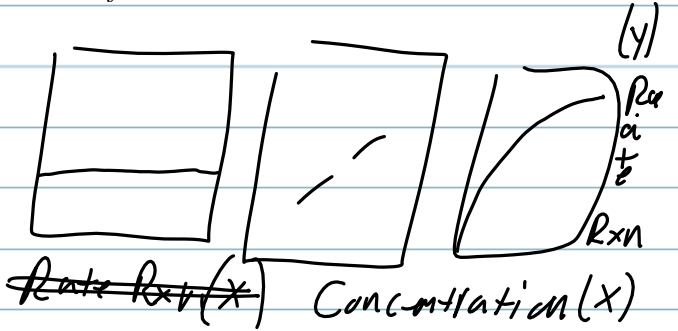
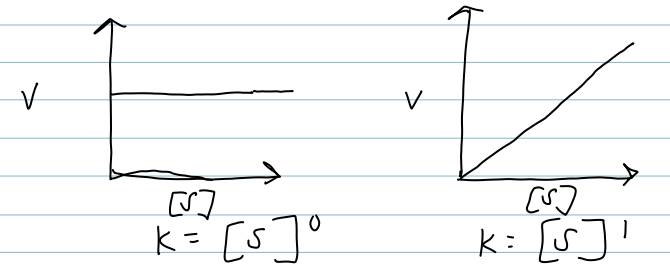
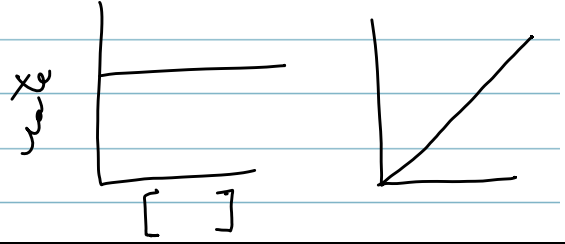
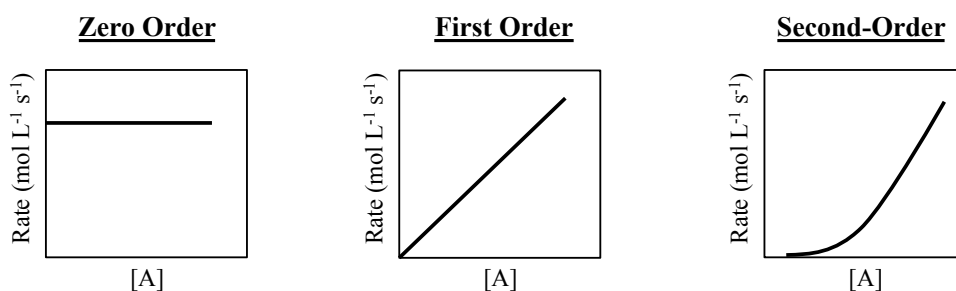
Student	Transcript and Written Work
Malcolm	<p>"I think zero looks like that [draws first plot], I think. First is maybe a little straight line [draws second plot] and second is curved somehow [draws third plot]. I just don't know how, but it's curved ... X is time and Y is ... No, that's not time [crosses out time on x-axis]. ... so that would be reactant concentration and this would be rate, I think."</p> 
Karen	<p>"There was first order, second ... Wasn't that when you have zero order, first order and second order. Zero is like, first order, and second order, something like that [draws graphs below]. I think x is time, or wait, no, no, no. For one of them, maybe, x is time. Sorry, I don't remember."</p> 
Tim	<p>"... I think a zeroth order was just a straight line, if I remember right [draws first plot]. And then I, and then I thought first order might have been more linear [draws second plot], while as the second line might be more curved [draws third plot]? I honestly don't remember. ... If I had to guess, maybe that is concentration, maybe this is the rate of reaction, so actually, if I may [crosses out rate on x-axis and writes concentration]. ... Okay, I want to say that maybe this is concentration and then this is ... rate of reaction."</p> 

Table 4.2 continued

Claire	<p>"This is second order [Michaelis-Menten graph provided in prompt]. ... 'Cause it's a hyperbola graph and so the substrate is gonna be like, the order would be substrate, to the second, squared, and then first is just a linear line and then zero is just a horizontal straight across line. ... Yeah. So this is zero order. That's a straight line. I think it's <math>k</math> equals the substrate concentration to the zero, so you're just gonna have the straight line. And then this is gonna be first order and it's just gonna be a linear line, to the one."</p> 
Carrie	<p>"As it is right now, so this is not first rate. This would be second maybe, I don't know. ... Because I don't think it's first. So, rate laws, didn't we usually take the logarithmic, like didn't we take the log functions of the graphs to look at them more clearly. If you have a straight line, I think that would just be zero, if you had ... "Yeah if you had like this, I think that's just zero [draws first graph], versus if you have, I don't remember. It's just like really just glimpses of freshman year, but something like this I think was a first-order rate law [draws second graph]. Then I don't know what second would be. ... Maybe it was, so this I would say is probably still concentration, maybe. I don't know. Then this would be your rate in terms of, yeah your rate."</p> 
Amanda	<p>"I believe that's first order, second order, and if it's linear then it's first order or something. If it's just a straight line, it's zero order. Something like that. ... I'm gonna take a straight guess and say it's second order [Michaelis-Menten graph provided in prompt]. ... Because it's curved, and it's a ... is it an exponential ... maybe it's a log function, something like that, but I just remember it from the picture that it might be a second order one."</p>
Vivian	<p>"I wanna say that this, I feel like zero order is when it's at this top part when adding more substrate doesn't matter, but I don't, I'm not 100% sure. ... I just remember that from studying, but I guess I don't really know what the orders mean, I just kind of, I memorized what they were associated with. I guess I don't really know what they mean. But I'm pretty sure, I think it's related to what format the line's in. So like I remember like with the Lineweaver-Burk plot I remember it's a straight line, and I think that's a different type of order than this kind of graph is. ... I have a picture, like a mental picture of the slides in my mind, I can't really recall what it was saying, but from what I remember I believe the order has something to do with how the equation of the line is kind of oriented on a graph. But I'm not sure."</p>

Based on the observation that multiple students seemed to have the same image in mind regarding reaction order (and Amanda explicitly mentioned trying to remember a “picture”), this prompted a closer look at the course materials, and ultimately, a lecture slide was found that graphically illustrated reaction order, see **Figure 4.1**. Unfortunately, most of the students did not connect order to enzyme kinetics in a productive way, and even when students were able to make connections between reaction order and enzyme kinetics it was clear the students were relying on rote memorization, such as Vivian’s discussion associating order with different regions of the Michaelis-Menten graph, without considering the deeper meaning of these relationships.



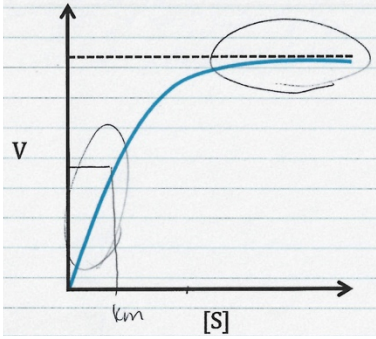
**Figure 4.1** Kinetics graphs (concentration vs. rate), adapted from the lecture slides provided for the students as part of the unit on enzyme kinetics.

### 4.3 Rate Law and Reaction Order: Drawing Connections to Enzyme Kinetics

Nevertheless, for two of the students in the sample, Lex and Ellie, more normative reasoning was observed, in which the students were able to connect rate laws and reaction order to enzyme kinetics. **Table 4.3** and **Table 4.4** illustrates how Lex and Ellie used a combination of symbolic and graphical forms to draw connections between relevant ideas. Lex and Ellie’s discussion of rate laws began in a way that was similar to the previously discussed students, discussing the symbol template that is relevant for the rate law. However, in addition to correctly writing the rate law, they both reasoned about the implications of having a zero-order rate law, namely, that the reaction rate is constant. The key point is that Lex and Ellie then connected this

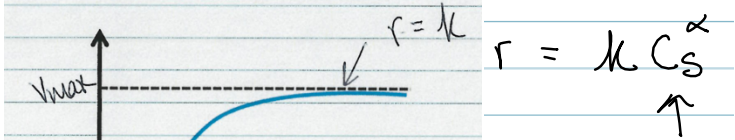
to the region of the Michaelis-Menten graph that has a constant rate (the “plateau”). Both students then provided reasonable explanations regarding the order of the reaction before the graph levels off. Lex stated that the reaction must be first-order or second-order, since the graph shows some concentration dependence, and Ellie discussed how order is empirically determined, so some experimentation would be needed to determine the order. As discussed previously, reasoning involving graphical and symbolic forms affords the ability to combine mathematical and conceptual knowledge; these mathematical resources support understanding of phenomena by allowing individuals to draw inferences from representations (such as the straight region of the graph has a constant rate), and then meaningfully connect these inferences to conceptual ideas.

**Table 4.3** Lex's reasoning, which involves graphical forms (GF) and symbolic forms (SF).

Transcript and Written Work	Reasoning
<p><b>Lex:</b> <i>"Well, I know that when if you're looking at the rate of a reaction or how quickly it occurs, your rate is equal to some constant for that enzyme times like the actual concentration of that compound that you have in the reaction, and there are different forms of this rate reaction that you can have. So you can have rate equals k times A to the zero power, or you can have it to be first order power or to the second order."</i></p> <p>...</p> <p><i>And basically what these show are that if, for example you had your rate to the zero power or your concentration to the zero power, then that would just convert that to one [crosses out concentration and writes k].</i></p> <p><i>So that means your rate is just dependent on like the constant and not necessarily on your substrate concentration. But as your order increases, the rate of the reaction depends more and more on your substrate concentration,</i></p> <p><i>which relates to this because up here where you have a plateau, this means that you don't have your rate depending on the substrate concentration anymore,</i></p> <p><i>whereas down here [circles first region in Michaelis-Menten plot] where you do have like an actual increase in your graph, you have either like a first- or second-order reaction because it's actually dependent on your concentration."</i></p> <p><b>Interviewer:</b> <i>"Okay. I see. So you're saying like the first part is first or second and the second part would be. ..."</i></p> <p><b>Lex:</b> <i>"Yeah. Zero-order."</i></p>	<p><b>Recall:</b> symbol template for rate law</p> <p><b>SF:</b> scaling exponentially</p> <p><b>SF:</b> dependence</p> <p><b>GF:</b> straight means constant</p> <p><b>GF:</b> trend from shape <b>SF:</b> directionality</p> <p><b>SF:</b> dependence</p> <p><b>Summary:</b> different regions of the graph correspond to different reaction orders</p>
 $r = k[A]^0 = k$ $k[A]^1$ $k[A]^2$	



**Table 4.4** Ellie's reasoning, which involves graphical forms (GF) and symbolic forms (SF).

Transcript and Written Work	Reasoning
<p><b>Ellie:</b> "Rate law is what governs your rate. For example, that could be your rate law if it was a first order [draws rate law, without alpha], up here when you hit your V-max it's a zero order [labels graph], so it has nothing to do with the substrate concentration. ...</p> <p>It's zero order once you get up to your maximum because, or once you hit your V-max supposedly because your substrate concentration should no longer have any effect on your rate</p> <p>because your enzymes are saturated, so you have so much substrate and a finite number of enzymes that adding more substrate won't make your reaction happen any faster because all of your enzymes are busy.</p> <p>Which effectively makes this CS right here [draws arrow], which I guess it should put alpha [draws alpha], the CS right here, it wouldn't matter if you added more, if this number went up, which means it's only dependent on your reaction rate constant, which is the k. ...</p> <p>Before zero order, it'd probably be, I think most of the time we've gone with first order. I would have to do a whole new set of experiments for me to say, from a chemical engineering stand point, the way we've been taught, you do a whole lot of other things to figure that out."</p> 	<p><b>Recall:</b> symbol template for rate law</p> <p><b>GF:</b> straight means constant</p> <p><b>SF:</b> dependence</p> <p><b>Recall:</b> biochemistry ideas</p> <p><b>SF:</b> dependence</p> <p><b>Recall:</b> experimentally determined order</p> <p><b>Summary:</b> different regions of the graph correspond to different reaction orders</p>

## CHAPTER 5. ENZYME INHIBITION

In this section the second research question is addressed, focusing on students' understanding of competitive, noncompetitive, and uncompetitive enzyme inhibition—*How do students reason about the particulate-level mechanism associated with enzyme kinetics and enzyme inhibition?* In the context of the interview prompts provided, the second interview prompt that students were given serves as the focus for this chapter, in which students were asked to draw conclusions about enzyme inhibition from the provided graph. This served as a context to investigate students' conceptions of each of the inhibition types. In response to this prompted, students typically attended to how relevant kinetic parameters changed and correctly identified the observed types of inhibition; however, students tended to have difficulty discussing how the mechanism associated with each inhibitor related to the changing parameters.

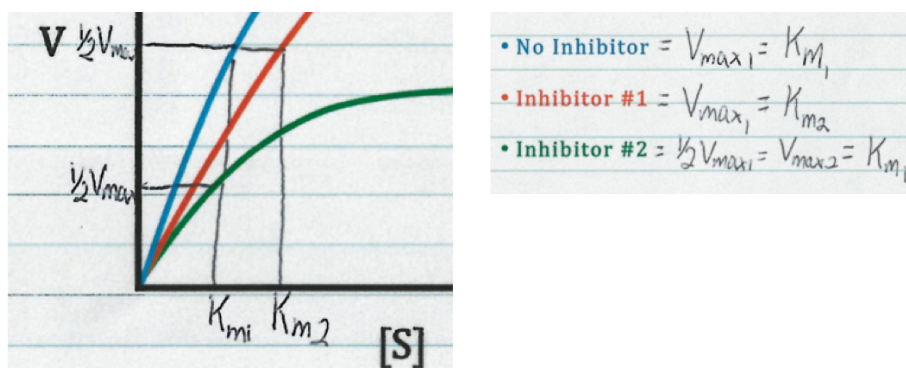
### 5.1 Attending to Relevant Parameters in the Graph

Generally, when provided the graph displaying enzyme inhibition, students focused on how the  $K_m$  value and the  $V_{max}$  value changed as a result of the inhibitor. For example, Alan stated:

**Alan:** “So, this graph has a blue line with no inhibitor, a red line with inhibitor one, the red line with inhibitor one has the same  $V_{max}$ , so we're going to say that no inhibitor has  $V_{max1}$ . Inhibitor number one also has  $V_{max1}$ , however it takes a little bit longer for it to reach  $V_{max1}$ . It doesn't take longer, it takes more substrate to reach  $V_{max1}$ . And inhibitor number two, we're going to say that's roughly one-half  $V_{max1}$ , or  $V_{max2}$ . ... And, with the no inhibitor [blue curve], so what you've got is the  $K_m$  goes forward a little bit, so we're going to say that no inhibitor has  $K_{m1}$ , inhibitor number one [red curve] has  $K_{m2}$ , and inhibitor number two [green curve] has  $K_{m1}$ .”

In Alan's discussion above, he discussed the differences between *Inhibitor #1* (red curve) and *Inhibitor #2* (green curve) in comparison to *No Inhibitor* (blue curve), more explicitly illustrated with Alan's written work provided in **Figure 5.1**. The importance of being able

to identify how these kinetic parameters change is due to the fact that it has implications for the type of inhibitor, and later in Alan's interview, based on his analysis of the provided data (i.e., the graph), Alan correctly concluded that *Inhibitor #1* involved competitive inhibition and *Inhibitor #2* involved noncompetitive inhibition.



**Figure 5.1** Alan's written work.

In **Table 5.1**, a summary is provided that shows how the students in the sample discussed the  $K_m$  and  $V_{max}$  values of *Inhibitor #1* and *Inhibitor #2* in comparison to the *No Inhibitor* reference curve, along with the conclusion made by the students regarding the identity of the associated enzyme inhibitor. Most students correctly indicated how the kinetic parameters changed and associated it with the correct type of inhibition, and in comparison to *Inhibitor #2*, more students correctly characterized *Inhibitor #1* as a competitive inhibitor that exhibited an increased  $K_m$  and an unchanged  $V_{max}$ . As will be discussed in the next sections, students also tended to have a better understanding of competitive inhibition.

**Table 5.1** Conclusions reached by students when interpreting the enzyme inhibition graph; incorrect responses are bolded.

Student	Inhibitor #1 (Red Curve)			Inhibitor #2 (Green Curve)		
	$K_m$	$V_{max}$	Conclusion	$K_m$	$V_{max}$	Conclusion
Sarah	higher	same	competitive	same	lower	<b>uncompetitive</b>
Ellie	higher	same	competitive	same	lower	noncompetitive
Kelly	higher	same	competitive	<b>lower</b>	lower	<b>uncompetitive</b>
Alan	higher	same	competitive	same	lower	noncompetitive
Amanda	higher	same	competitive	same	<b>higher</b>	noncompetitive
Cathy	higher	same	<b>noncompetitive</b>	same	lower	<b>competitive</b>
Lex	higher	same	competitive	same	lower	noncompetitive
Malcolm	higher	same	competitive	same	lower	noncompetitive
Zara	higher	same	competitive	same	lower	noncompetitive
Vivian	higher	same	competitive	<b>lower</b>	lower	noncompetitive
Karen <sup>a</sup>	-	-	-	same	lower	<b>competitive</b>
Tim	higher	same	competitive	same	lower	noncompetitive
Claire	higher	same	competitive	<b>higher</b>	lower	<b>mixed</b>
Carrie	higher	same	competitive	same	lower	noncompetitive

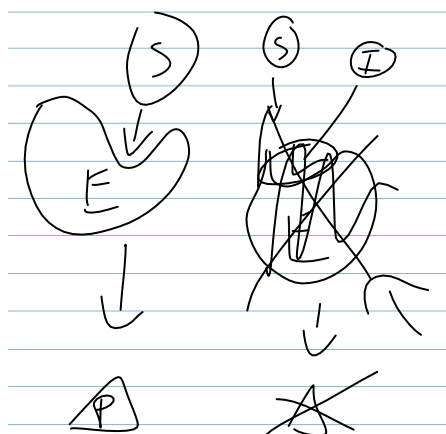
<sup>a</sup>Student had difficulty interpreting the graph, did not provide a response regarding how the parameters change for Inhibitor #1, and did not reach a conclusion regarding the identity of Inhibitor #1, "I don't remember how to determine what type of inhibition. I can tell you the mechanisms for the different types of inhibition, and that's it." (Karen).

## 5.2 Competitive Inhibition

In the previous section it was discussed how students attended to the changing parameters in the graph and concluded what type of inhibition was observed; upon prompting, students were then able to describe the mechanism associated with each inhibition type. When describing competitive inhibition, all the students mentioned that the competitive inhibitor binds the active site instead of the substrate. This is illustrated in Sarah's description of competitive inhibition:

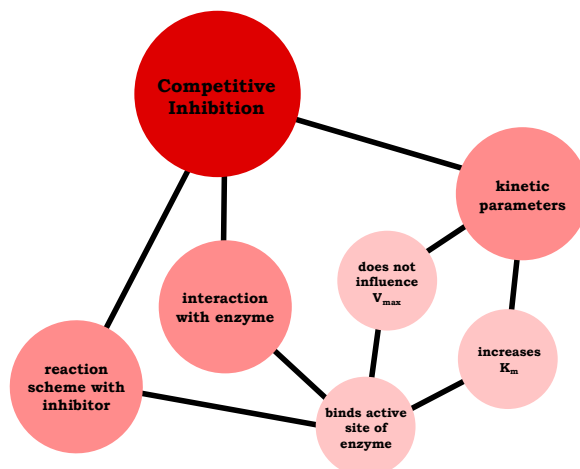
**Sarah:** "So it's still, like the way competitive inhibitors work is that say you have XYZ, you know, enzyme or whatever. And normally you got this substrate that comes in, and it binds to it, and then you get, you know, product. How the competitive inhibitor works is that you, you got your enzyme right here ... Enzyme right here. And so instead of the sub-, normal substrate coming in you got inhibitor comes in, blocks up that binding site, so substrate can't bind. And then it might, you know, muck up the enzymes that you don't make any product, like nothing happens. It just, binds up the enzyme and takes it up and so no substrate can be bind so than nothing can be produced."

In addition to her discussion above, Sarah drew a picture to illustrate her reasoning, depicted in **Figure 5.2**. Taken together, Sarah's description and the accompanying illustration reflect a clear understanding of how a competitive inhibitor interacts with enzymes, which was representative of the larger sample. However, further insight is gained by focusing on the resource graphs constructed for each of the students.



**Figure 5.2** Sarah's written work describing competitive inhibition; in the image,  $S$ ,  $E$ ,  $P$ , and  $I$ , represent the substrate, enzyme, product, and inhibitor, respectively.

In **Figure 5.3**, Ellie's resource graph for competitive inhibition is provided, summarizing the ideas she expressed about competitive inhibition—the competitive inhibitor influences the reaction scheme (i.e.,  $E + S \rightleftharpoons ES \rightarrow E + P$ ), binds the active site, increases  $K_m$ , and does not influence  $V_{max}$ . Although these ideas were discussed by students across the sample, the primary utility of the resource graphs is to characterize the extent in which students made connections between these related ideas, which is particularly useful to draw conclusions regarding where students may need more instructional support. Here it is argued that one of the important connections is *why* a specific inhibitor influences  $K_m$  and  $V_{max}$  in the way that it does (e.g., *Why does a competitive inhibitor increase  $K_m$ , but not change  $V_{max}$ ?*).



**Figure 5.3** Ellie's resource graph for competitive inhibition.

Making these types connections is important because it requires students to move beyond simply *memorizing ideas* to being able to *construct explanations* that are consistent with observations:

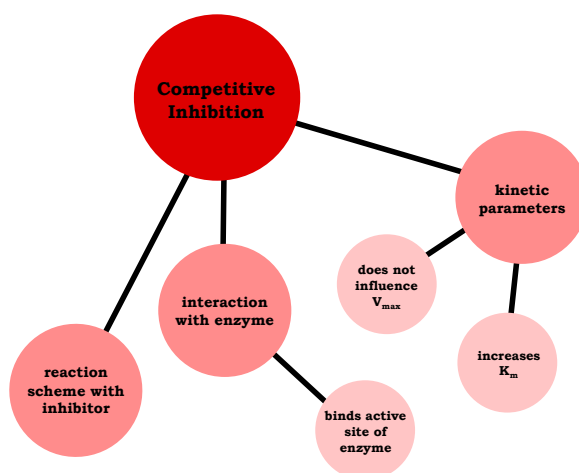
**Ellie:** *"It's competitive because basically what's happening is the inhibitor is binding to the enzyme active site, so it's blocking the substrate from binding with the enzyme as well. That's meaning that it's changing the affinity for the enzyme for the substrate, but it's not changing the maximum rate. Because if you add more substrate, then you will saturate the enzyme ... and reach the same maximum rate that you would have gotten without the inhibitor."*

In the example above, Ellie displayed a sophisticated type of reasoning that afforded her a more complete understanding that involved connecting the competitive inhibitor's mechanism with its changing parameters. However, even though students tended to correctly identify that competitive inhibitors increase  $K_m$  and do not influence  $V_{max}$ , and all students indicated competitive inhibitors bind the active site, connecting these ideas was less common:

**Interviewer:** *"And then why is it that they change these specific parameters? So why does competitive change  $K_m$ , but not  $V_{max}$ ?"*

**Amanda:** *"I think it's because the amount of substrate actually being taken in or being binded to the enzyme it increases but it's inhibited ... So, yeah, I think it's the amount of substrate that's being taken in is just ... it shouldn't be increased, but it is. Do you know what I mean? ... I know this is wrong, but I'm just going to say the amount of substrate being taken in is increased. Yeah. ... But the  $V_{max}$  stays the same so the amount ... I don't know. You know what? I'm just going to end it there."*

Students such as Amanda were unsure how to connect the changing parameters to the mechanism of the inhibitor, suggesting a less coherent and more fragmented understanding, which is reflected in Amanda's resource graph (**Figure 5.4**). Comparing Ellie's resource graph in **Figure 5.3** with Amanda's resource graph in **Figure 5.4**, it can be seen that Amanda has some missing connections. Even though Amanda was able to describe how the inhibitors influenced the kinetic parameters (**Figure 5.5**), the additional connections were absent.



**Figure 5.4** Amanda's resource graph for competitive inhibition.

	$K_m$	$V_{max}$
C	↑	—
NC	—	↑
UC	↓	↓

**Figure 5.5** Amanda's written work that describes how competitive (C), noncompetitive (NC), and uncompetitive (UC) inhibitors influence  $K_m$  and  $V_{max}$ .

### 5.3 Noncompetitive and Uncompetitive Inhibition

As stated previously, students tended to correctly associate the changing parameters with each inhibition type. Looking closely at student conceptions of noncompetitive and uncompetitive inhibition, a majority of students discussed that these inhibitors *bind an allosteric site*, but there was less agreement regarding what differentiated the two inhibition types in terms of the mechanism and how the inhibitors physically interact with the enzyme, as shown in **Table 5.2**. The intention with the examples provided is not to characterize each of the students' ideas as correct or incorrect, but to highlight the variety of ideas discussed by the students, some of which are productive for reasoning about enzyme interactions in general (e.g., binding resulting in conformational/geometric changes). It is worth noting that among the students in **Table 5.2**, it is clear that some of the student discussions simply involve misapplying the term to a particular mechanism. For example, Vivian's description of "noncompetitive inhibition"—involving only binding the enzyme-substrate complex, decreasing  $K_m$ , and decreasing  $V_{max}$ —is consistent with uncompetitive inhibition; similarly, the mechanism and changing parameters described for "uncompetitive inhibition" is consistent with noncompetitive inhibition, indicating Vivian switched the vocabulary terms, likely due to the similarity between the phrases. Sarah exhibited similar conflation of terms, as did Carrie (although to a lesser extent than Vivian and Sarah).

In order to summarize the results in **Table 5.2**, the ideas students associated with each inhibition type are provided in **Figure 5.6**. The difference between **Table 5.2** and **Figure 5.6** is that **Figure 5.6** illustrates the ideas discussed by all of the students, including the six students that expressed a clear distinction between noncompetitive and uncompetitive inhibition (i.e., students that stated noncompetitive inhibitors can bind the free enzyme or the enzyme substrate-complex, whereas uncompetitive inhibitors can only bind the enzyme-substrate complex).



**Table 5.2** Student discussions regarding the distinction between noncompetitive and uncompetitive inhibition.

<p><b>Cathy:</b> “[Noncompetitive inhibition involves] Binding to an allosteric site other than the active site, so the substrate can still bind, it just has a lower affinity for the active site. ... With competitive it binds directly to the active site, so no binding can occur. ... And with the uncompetitive, it can bind to the allosteric site, or ... It binds to an allosteric site under certain conditions, I can't remember what conditions.”</p>
<p><b>Interviewer:</b> “So if the competitive inhibitors bind to an active site, what is happening with non-competitive?”</p> <p><b>Amanda:</b> “It binds to an allosteric site and I feel like ... I know the uncompetitive one is the one that distorts it. I think the noncompetitive one just makes a new conformation of the enzyme. So it's just less efficient.”</p> <p><b>Interviewer:</b> “So what happens with the uncompetitive?”</p> <p><b>Amanda:</b> “It also binds to an allosteric site, but I know I just said it. Oh yeah. It distorts it so it becomes less, less efficient than the noncompetitive one.”</p> <p><b>Interviewer:</b> “Okay. So noncompetitive doesn't distort it, but uncompetitive does?”</p> <p><b>Amanda:</b> “There you go. Mm-hmm [affirmative].”</p>
<p><b>Tim:</b> “Yeah, if I remember right it's uncompetitive. ... because there's one that binds on a completely different side of the enzyme, but still changes its configuration, but there's also, one of the inhibitors binds, kind of, it doesn't actually bind in the active site, but it binds off to the side of the active site, thus preventing the enzyme from, the substrate from actually getting into the enzyme's active site. So, maybe I got that wrong. So perhaps this is non-competitive, it actually binds off to the side, whereas uncompetitive actually changes the enzyme, substrate, the actual geometry of the enzyme itself. ... Okay, I was, I was originally thinking, and once I said it was uncompetitive, but I would almost think it's non-competitive now, 'cause I, if I remember uncompetitive actually changes the geometry while the non-competitive does not. It still doesn't compete within the active site, but still inhibits and blocks the substrate from getting into the enzyme complex.”</p>
<p><b>Karen:</b> “Yeah. Then you have uncompetitive, and that one, it binds to, I think, a site other than the active site. Okay. I always get this one mixed up with non-competitive, which also binds allosteric site. ... It's just a site other than ... that. One of them changes the shape of the enzyme so that it is unable to bind substrate because the shape ends up being wrong. Then the other one ... Sorry, I don't remember. ... Then there's another type of noncompetitive which is mixed, and it does something else, and they all have different effects on <math>K_m</math> and <math>V_{max}</math>. I can't tell you what they are.”</p> <p><b>Interviewer:</b> “That's okay. So how are you distinguishing between these two? Because they both bind to an allosteric site.”</p> <p><b>Karen:</b> “That's the thing, I don't remember.”</p>
<p><b>Alan:</b> “For noncompetitive and uncompetitive, they're going to bind to the allosteric sites, which are just any sites separate from the active site, and when those inhibitors bind to the allosteric site the enzyme changes its shape, which keeps the substrate from binding to it as efficiently. Noncompetitive keeps it from binding all together, uncompetitive makes it less efficient.”</p>
<p><b>Interviewer:</b> “Okay, so noncompetitive and uncompetitive binds some place?”</p> <p><b>Carrie:</b> “Other than the active site.”</p> <p><b>Interviewer:</b> “Then what was the difference between those two?”</p> <p><b>Carrie:</b> “I'm just scared that I'm mixing them up now. non-competitive, it binds, I do know what I said earlier about the uncompetitive being able to bind before or after the substrate complex has been made is right. That's something it can do that noncompetitive inhibition doesn't do. Noncompetitive inhibition, I'm pretty sure, only binds before the substrate, changing its confirmation and then the substrate cannot bind to the enzyme. ... Either way they are inhibiting it.”</p>

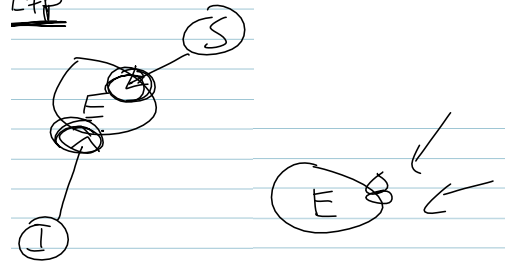
Table 5.2 continued

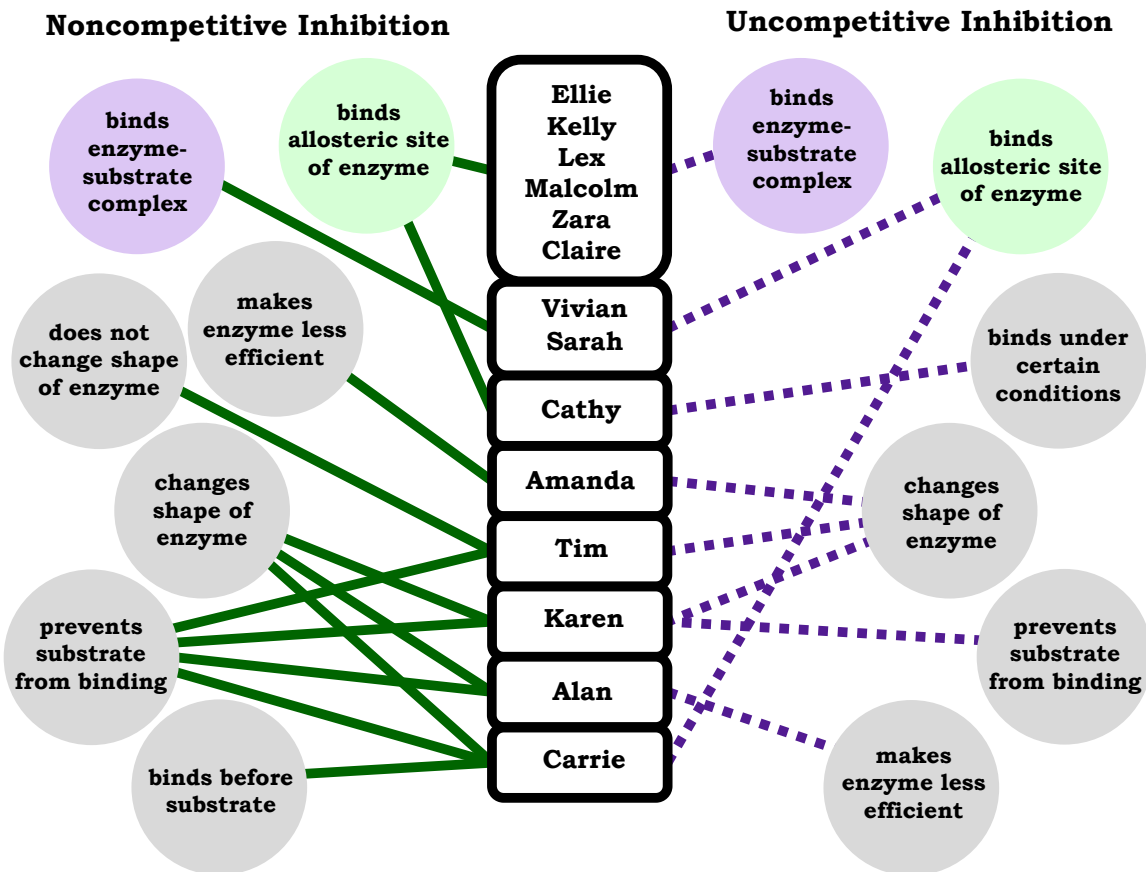
**Vivian:** "With noncompetitive the inhibitor will only bind to the enzyme-substrate complex only if the enzyme and substrate are bound. In the noncompetitive, it binds to the enzyme-substrate complex and I'm not really sure after that why exactly, I think maybe it lowers the, yeah because the  $K_m$  is smaller in a non-competitive because it will bind more tightly to the enzyme substrate complex rather than if it wasn't complex. And then it lowers the  $V_{max}$  because ... I'm not really sure why it lowers the  $V_{max}$  but I'm pretty sure it does. Yeah, I'm not really sure why."

...

"Uncompetitive is when, okay let's see, the inhibitor will bind on the enzyme somewhere other than the active site, so it doesn't always affect the  $K_m$  but if it's a mix inhibitor it can affect, or it will affect the  $K_m$  if it is a mixed inhibitor. But for uncompetitive it just, I think it combines to either just the substrate or the substrate, or sorry, just the enzyme or the enzyme-substrate complex. I think it can bind to either one of those. But a true uncompetitive won't affect the  $K_m$  but it will decrease the  $V_{max}$ ."

**Sarah:** "And, so then this is the part that I'm most likely going to get wrong because I, again, get them mixed up every other sentence. And so what the uncompetitive one does is that, so you've got enzyme right here [draws image on left]. And typically, and what happens is that substrate comes, binds right there. And then, what your inhibitor's gonna do is it's gonna come up and it's go to an allosteric site. So it's not gonna go to the active site, it's gonna go somewhere else. And it's basically gonna make it so that the enzyme is just super inefficient. So, even though it's still binding substrate at the same rate, like the  $K_m$ 's the same, it's not producing as much product. ... 'Cause it just, is super inefficient so that's why the  $V_{max}$  goes down. And so, that would make this uncompetitive I'm pretty sure. Or noncompetitive, one of those two. I'm pretty sure it's uncompetitive, though. I think noncompetitive the one where, if you have enzyme, then it comes in, substrate binds here but then also inhibitor comes in and it binds like right next to it and it, it just makes a conformational change, and it makes the enzyme not function very well. And it makes the  $V_{max}$  and the  $K_m$  both change [draws image on the right] ."





**Figure 5.6** Summary of student discussions regarding the distinction between noncompetitive and uncompetitive inhibition. On the left are the ideas students attributed to noncompetitive inhibition and on the right are the ideas students attributed to uncompetitive inhibition. The shaded green and purple circles indicate the primary and salient features associated with noncompetitive and uncompetitive inhibition, respectively. Reproduced from Rodriguez and Towns (2019).

As discussed in the section about competitive inhibition, one of the ideas that is foundational to have a more comprehensive understanding of enzyme inhibition is the connection between the mechanism of an inhibition type and the relevant changing parameters. Only six students in the sample discussed the primary and salient features that distinguishes noncompetitive and uncompetitive inhibition—whether the inhibitor’s binding is independent (noncompetitive) or dependent (uncompetitive) of the binding of the substrate—and of these students all six connected the noncompetitive mechanism to the associated changing parameters, whereas only four of these students correctly connected the uncompetitive mechanism to the associated changes in both kinetic parameters. To illustrate this, consider Zara’s description of noncompetitive inhibition:

**Zara:** *“The  $K_m$  value's unchanged because in noncompetitive it's bonding to a site other than the active site, allosteric, I think to it. So it can't reach  $V_{max}$  because even if you saturate it with substrate you have like another site where the inhibitor's gonna bind so it doesn't really matter. But yeah, the  $K_m$  stays the same because you have two separate sites that the substrates bind to and where the inhibitor's binding to.”*

In this instance, Zara explained why  $K_m$  does not change and why the  $V_{max}$  decreases for a noncompetitive inhibitor, demonstrating more than simply memorizing changing parameters. As part of this description, Zara reasoned about  $K_m$  and  $V_{max}$  as more than simply “the substrate concentration at half the maximum velocity” and the “dotted line”. Although these ideas may be useful for interpreting the graph, framing  $K_m$  as related to binding, for example, is important for mediating the connection between the kinetic parameters and the molecular-level mechanism of the inhibitors, and in some cases, students may need support in making these connections:

**Lex:** *“So no matter how much concentration of substrate you put in, it doesn't matter because it's not competing for it at the active site. So that's why your  $V_{max}$  decreases, but I don't understand why the  $K_m$  does. I just know it does.”*

In the passage above Lex was initially unsure about the relationship between the  $K_m$  decreasing and the binding of the uncompetitive inhibitor; however, after some prompting from the interviewer, she exhibited sophisticated reasoning:

**Interviewer:** “And so before you had also talked about  $K_m$  as like thinking in terms of affinity, right?”

**Lex:** “Yeah.”

**Interviewer:** “Or like binding?”

**Lex:** “Yes.”

**Interviewer:** “How might that explain why this value changes when the inhibitor binds for uncompetitive?”

**Lex:** “I guess maybe, this is total ballpark. There might be something on the actual inhibitor that does bind to both the enzyme and the substrate. No, well, I don't know. There just might be something [draws line protruding from inhibitor, see **Fig. 5.7**] on the inhibitor that can maybe help the substrate bind to the enzyme so that the inhibitor can inhibit the enzyme. I don't know if that's possible with molecules but there might be something on the actual inhibitor itself that encourages the substrate to bind in the active site so then the inhibitor can fully bind to the enzyme-substrate complex and inhibit it. ... So either that or the inhibitor could maybe bind partially to the enzyme without a substrate inside of it, and that itself also encourages maybe more substrate to interact with the enzyme, and then once both of those two have bound then it can actually fully inhibit the enzyme. So like, yeah. ... 'Cause then that would end up decrease the  $K_m$  but then also decreasing the  $V_{max}$ .”

After being prompted by the interviewer regarding her previous discussion of  $K_m$ , Lex constructed an explanation to account for the increased affinity observed between the substrate and enzyme with uncompetitive inhibition (see **Figure 5.7** for Lex's written work).



**Figure 5.7** Lex's written work related to uncompetitive inhibition

## 5.4 Mixed Inhibition

Student conceptions of mixed inhibition was not explicitly addressed in the interview protocol, which focused primarily on competitive, noncompetitive and uncompetitive inhibition; however, eight of the students in the sample discussed mixed inhibition during their interview. Most of these students discussed mixed inhibition in a way that was very similar to how they discussed competitive, noncompetitive, and uncompetitive inhibition, in which they listed the

changing parameters:

**Kelly:** *“Mixed inhibitors confused me. Anyway. So that one's like the worst one in my opinion because it's not increasing binding affinity, it's decreasing binding affinity, so it's increasing the  $K_m$ . ... And it's decreasing the  $V_{max}$ . So that one's like the worst one 'cause it's not only decreasing the binding affinity, but it's decreasing  $V_{max}$  as well. So, it's like ... the most inhibiting inhibitor.”*

Although her discussion of the changing parameters in mixed inhibition was consistent with what was discussed in the course, Kelly (along with the other students that discussed mixed inhibition) did not make the connection discussed in the textbook associated with the course (Appling et al., 2016) that noncompetitive inhibition is a special case of mixed inhibition; however, two of the students framed mixed inhibition as a type of noncompetitive inhibition:

**Karen:** *“Then there's another type of noncompetitive which is mixed, and it does something else, and they all have different effects on  $K_m$  and  $V_{max}$ . I can't tell you what they are. ... It increases one of these [ $V_{max}$  or  $K_m$ ], I think, slightly, and then it decreases the other one. Something like that. If there's a slight increase anywhere, it's mixed.”*

Confusion regarding mixed inhibition is understandable, partly because of its presentation in textbooks. Berg et al. (2015, p.235) only briefly discusses mixed inhibition and Voet and Voet (2011, p.495) seem to interchangeably use the terms *mixed* and *noncompetitive*:

*“If both enzyme and the enzyme-substrate complex bind the inhibitor ... Both of the inhibitor-binding steps are assumed to be at equilibrium, but with different dissociation constants ... This phenomenon is alternatively known as mixed inhibition or noncompetitive inhibition.”*

This statement seems to imply that *noncompetitive* and *mixed* are synonymous, however, the authors later clarify that “in ambiguity of nomenclature” noncompetitive can be used to describe the special case when an inhibitor has equal affinity for the free enzyme and enzyme-substrate complex. Similarly, due to the potential for confusion, in education literature, authors tend to be explicit regarding how they operationalize *mixed* and *noncompetitive* in their discussions, as shown

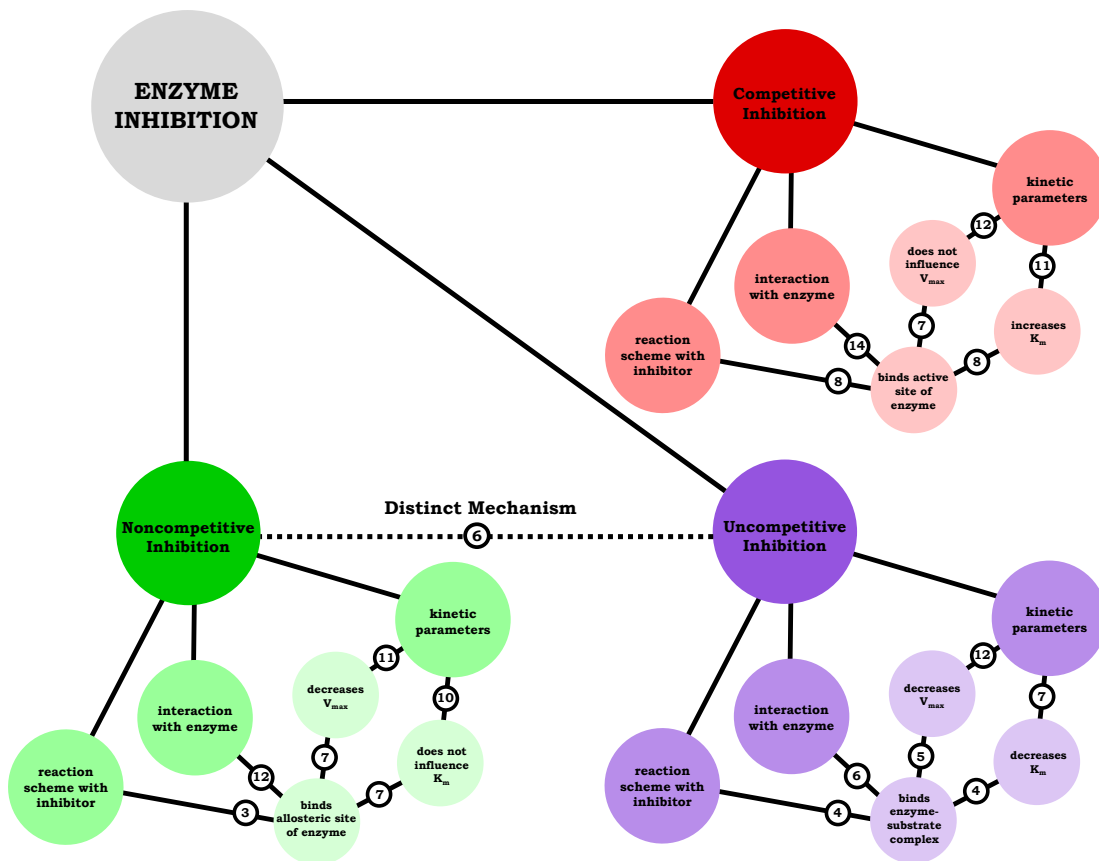
in the footnotes in Ochs (2000) and Waldrop (2009).

### 5.5 Summary of Enzyme Inhibition

Students in the sample tended to correctly indicate how the kinetic parameters,  $V_{\max}$  and  $K_m$ , changed in the graph, and subsequently draw a connection to enzyme inhibition. Although the students tended to associate the correct changing parameters with an inhibition type, they needed more support with reasoning about the molecular-level mechanism of the enzyme inhibitors, such as why a specific inhibitor-enzyme interaction results in the observed change in  $V_{\max}$  and  $K_m$ . This was particularly true for noncompetitive and uncompetitive inhibition, in which students were unsure about what distinguished these two types of inhibition in terms of the physical interaction with the enzyme. This sentiment is nicely summarized with Ellie's discussion below:

**Ellie:** *"These names are confusing. ... We took a quiz. I knew it wasn't competitive and I knew that it wasn't non but I couldn't think what the last word was and my brain just kept telling me it was uncompetitive and I kept thinking those are synonyms, that can't be it ... That can be confusing."*

Ellie's discussion highlights the similarly named inhibition types, which makes them prone to confusion, or perhaps may result in using the incorrect term to describe an inhibitor (as seen in this dataset). In **Figure 5.8** a summary of students' reasoning about the different inhibition types is provided (see **Appendix F** for a list of all of the students' resource graphs). The numbers indicate the students in the sample that drew a connection between the resources provided (e.g., all fourteen students indicated that competitive inhibitors interaction with the enzyme by binding the active site, six students discussed distinct mechanisms between noncompetitive/uncompetitive inhibition, seven students stated an uncompetitive inhibitor decreases the  $K_m$ , etc.).



**Figure 5.8** Summary of student conceptions of competitive, noncompetitive, and uncompetitive inhibition, constructed by combining students' resource graphs; the numbers indicate the amount of students that exhibited a particular connection. Reproduced from Rodriguez and Towns (2019).

## 5.6 Limitations

As is the case with qualitative studies, the small sample size limits the generalizability of results; however, the intention is not to discuss how the results apply to broad categories of students, but to provide insight to inform instruction. Furthermore, not all of the students in the sample were able to discuss rate law and reaction order, stating that they did not remember these ideas (i.e., the students skipped the topic). Rate laws and reaction order are one of the key topics assessed in general chemistry, and although it was discussed in the biochemistry course associated



with this study, it was not the focus of assessment. This is an issue retention, the implications of which are discussed in the next section.

It is also important to note that in order to construct the resource graphs some decisions were made regarding the characterization of students' conceptions and how they discussed these ideas. In order to construct a composite representation like the one provided in **Figure 5.8** an emphasis was placed on ideas that were more productive for reasoning about enzyme kinetics. This allowed more direct comparisons between students across the sample. A disadvantage of this approach is that it does not showcase the variety of conceptions exhibited by students, particularly when their reasoning deviated from ideas that were more scientifically normative. However, some of this variation is reflected in individual students' resource graphs in **Appendix F**, as well as **Figure 5.6**, which summarizes the different conceptions regarding how students distinguished noncompetitive and uncompetitive inhibition. Furthermore, all the students in the sample had ideas that were productive, allowing them to be mapped onto the structure of the resource graphs, and based on the analysis, this yielded rich insight regarding the specific connections with which students need more support. In addition, a distinction was not made between students based on the strict use of the terms "active site" and "allosteric site", focusing instead on the students' reasoning. Not all of the students explicitly used "active site" and "allosteric site" when describing the binding of substrate and inhibitors, instead students used equivalent descriptive phrases (e.g., Tim described how the noncompetitive inhibitor binds someplace other than "where the catalysis actually occurs"); notably, student difficulty with terminology related to enzyme interactions is consistent with previous work (Linenberger & Bretz, 2015).

## CHAPTER 6. CONCLUSION AND IMPLICATIONS

This work was situated within the resource-based model of cognition, motivating the analysis to focus on resources, connections between resources, and a cognitive structure that reflects more sophisticated reasoning. The resources perspective acknowledges student challenges are complex and cannot simply be categorized as alternative conceptions, a stance that supports inquiry related to skills and tasks that move beyond rote memorization. According to Becker et al. (2017),

“Framing students’ difficulties in terms of alternative conceptions provides some insight into how to address these difficulties through instruction. However, overall, this research direction provides relatively little insight as to how instructors can scaffold students’ engagement in more complex and authentic tasks.”

As mentioned above by Becker and colleagues (2017), research framed using a manifold ontology of cognitive structure provides insight regarding how to better support students. Within the context of the first research question, most of the students had difficulty using mathematical resources such as symbolic and graphical forms to reason about enzyme kinetics. This does not necessarily imply that students are unable to engage in this type of reasoning, but it does build on previous work that indicates students’ reasoning tends to be compartmentalized and they need more support in order to integrate chemistry and mathematical ideas (Rodriguez, Santos-Diaz, Bain, & Towns, 2018). These results suggest the need for more cross-disciplinary discussions between instructors across disciplines, so that mathematics instructors are more aware of how students are expected to use mathematics and chemistry instructors have a better idea regarding the presentation of mathematics in mathematics courses. Ideally, opening such a dialogue would help improve curricular alignment and get students to utilize productive mathematical resources in contexts outside of mathematics courses.

In addition, the results were contextualized around ideas such as rate law and reaction order, which are more explicitly taught and assessed in general chemistry (Holme et al., 2015), suggesting the importance of retention. Previous research has indicated that retention associated with general

chemistry ideas is higher when concepts are discussed, reinforced, and assessed over the course of the undergraduate chemistry curriculum (Schnoebelen, 2018). Thus, if instructors want students to develop a clear understanding of chemistry ideas *and* retain these ideas, it is important to not only draw connections between concepts discussed in previous courses, but also require students to make these connections on assessments. For example, prompting students to draw connections between reaction order, concentration dependence, and the observed shape of the enzyme kinetics graph (similar to the description provided by Lex and Ellie). In some cases, this may involve more explicit prompting on exams to encourage students to attend to relevant details in the graph and activate the appropriate resources.

With respect to the second research question, centered on enzyme inhibition, overall, students excelled at analyzing and interpreting the graph and drawing conclusions about the relevant inhibition type, suggesting the utility of Michaelis-Menten graphs as an assessment tool and context to probe students' reasoning. Moreover, it is worth noting that the students also reflected productive resources for reasoning about enzyme-substrate interactions (e.g., ideas regarding geometric changes resulting from binding), but focusing on the group as a whole using the resource graphs revealed some fragmented ideas, particularly for noncompetitive and uncompetitive inhibition. The findings reported herein suggest students tended to simply associate changing parameters with inhibition types, rather than reason through why an inhibitor results in specific changes in  $V_{\max}$  and  $K_m$ . From the perspective of practitioners, in order to create the space for students to reason deeply about enzyme inhibition, here it is argued that instructional learning objectives and assessment should focus specifically on competitive and noncompetitive inhibition, as opposed to requiring students to memorize competitive, noncompetitive, uncompetitive, and mixed inhibition. The argument in favor of focusing on competitive and noncompetitive inhibition is due to the relative simplicity in terms of graphical representation—only one parameter changes

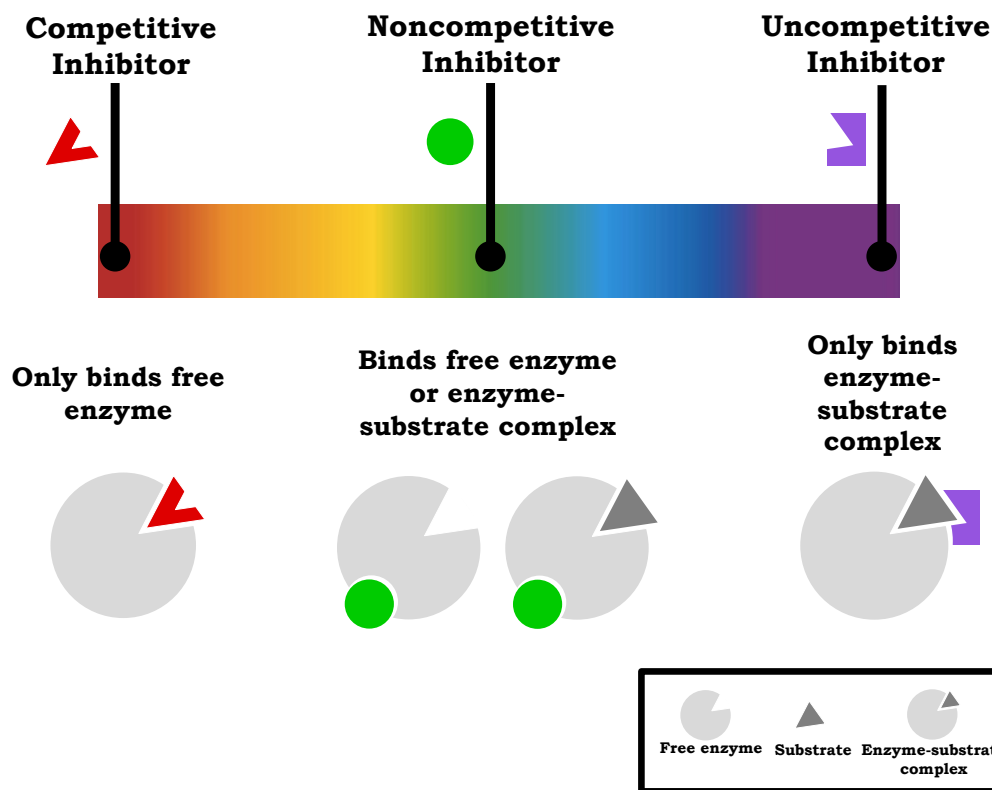
for each, which is associated with the x-intercept and y-intercept in a Lineweaver-Burk plot. Thus, instructors can use graphical representations as a context to prompt students to qualitatively describe the molecular-level mechanism and its relationship to the changing kinetic parameters. Diving deeply into these types of mechanistic explanations is simply not feasible when students are responsible for a whole array of different inhibition types. Furthermore, focusing on competitive and noncompetitive inhibition removes the potential non/un confusion observed in this study.

For clarification, reframing enzyme kinetics primarily around competitive and noncompetitive inhibition is not an argument in favor of completely removing other inhibition types from the curriculum. On the contrary, discussing other inhibition types is important to provide context. The key is communicating to students clear learning objectives and the implications for assessment—students will only be responsible for understanding the details of competitive and noncompetitive inhibition—since students focus on and study what is assessed (Cooper, 2015). As a means to more explicitly describe how the different enzyme inhibition types are connected, one potential suggestion is for instructors to present enzyme inhibition as a spectrum as shown **Figure 6.1**. In this sense, all inhibitors reflect some tendency to bind to the free enzyme and the enzyme-substrate complex, with competitive and uncompetitive being extreme cases on opposite ends of the spectrum, and everything in between these extremes is mixed inhibition (noncompetitive inhibition being the special case of mixed inhibition where the inhibitor binds the free enzyme and enzyme-substrate complex with equal affinity):

*“Another way of looking at reversible inhibition is that all three types of inhibition—competitive, uncompetitive, and mixed with equal affinities for (E) and (ES) [pure noncompetitive]—are just limiting cases of a single more general type in which the inhibitor has some affinity for both enzyme forms.” (Ochs, 2000).*

This conceptualization of enzyme inhibition serves as a potential way to organize the different inhibition types, clarify how they are related to one another, and frame them as specific cases of a

more general phenomenon.



**Figure 6.1** Suggested figure to use in instruction to illustrate the connection between each of the inhibition types, framing enzyme inhibition as a spectrum in which inhibitors vary in terms of their affinity for the free enzyme and the enzyme-substrate complex. Reproduced from Rodriguez and Towns (2019).

There are plenty of avenues for future work related to enzyme kinetics, particularly in relation to the various resources available for enzyme kinetics instruction. For example, building on the enzyme kinetics analogies in the literature, it would be useful to develop an analogy that specifically addresses students' challenges discussed in this work (e.g., noncompetitive and uncompetitive conflation). Other areas of inquiry involve further investigating student (and faculty) conceptions of mixed inhibition, since there seemed to be some competing ideas among students. Furthermore, more work is needed to characterize student use and conception of alternative representations of kinetic data, such as Lineweaver-Burk plots, which some students discussed in the interview, but was not explicitly part of the interview prompt in this study.

As discussed previously, little work has been done in the context of research on the teaching

and learning of enzyme kinetics, with the work discussed serving the purpose of providing insight regarding *how* concepts should be taught and implications regarding *what* concepts should be taught. In this sense, chemistry education research affords the opportunity to move beyond “personal empiricism” to make informed decisions that incorporate evidence resulting from research efforts (Cooper and Stowe, 2018). This is particularly useful because there seems to be lack of consensus among faculty regarding what topics should be taught in biochemistry (Lang, 2018), and although recent work by the American Chemical Society’s Exam Institute (ACS-EI) has outlined the concepts that are relevant for general chemistry, organic chemistry, inorganic chemistry, and physical chemistry (Holme & Murphy, 2012; Holme et al., 2015; Holme, Reed, Raker, & Murphy, 2018; Marek, Raker, Holme, & Murphy, 2018; Murphy, Holme, Zenisky, Caruthers, & Knaus, 2012; Raker, Holme, & Murphy, 2013), there is not yet a report regarding the relevant biochemistry concepts. As a side note, the biology community has released “threshold concepts” for biochemistry (Loertscher et al., 2014), but are more analogous to “core ideas” (Cooper, Posey, and Underwood, 2017), and thus are intended to be used as foundational ideas that are present throughout a discipline. Therefore, echoing the call of the National Research Council more research is needed that is contextualized in the context of upper-division courses, such as biochemistry, to further provide insight regarding how to improve instruction and determine the appropriate scope of the concepts covered in a course (Singer et al., 2012).

## REFERENCES

- Abel, K. & Halenz, D. (1992). Enzyme Activity: A Simple Analogy. *Journal of Chemical Education*, 69(1), 9.
- Antuch, M., Ramos, Y., & Alvarez, R. (2014). Simulated Analysis of Linear Reversible Enzyme Inhibition with SCILAB. *Journal of Chemical Education*, 91, 1203-1206.
- Antuch, M., Ramos, Y., & Alvarez, R. (2014). Addition to Simulated Analysis of Linear Reversible Enzyme Inhibition with SCILAB, *Journal of Chemical Education*, 91, 2221-2221.
- Asimov, I. (1959). Enzymes and Metaphor. *Journal of Chemical Education*, 36(11), 535-538.
- Bain, K., Rodriguez, J. G., Moon, A., & Towns, M. H. (2018). The characterization of cognitive processes involved in chemical kinetics using a blended processing framework. *Chemistry Education Research and Practice*, 19, 617-628.
- Bain, K., Rodriguez, J. G., Moon, A., & Towns, M. H. (2019). Mathematics in Chemical Kinetics: Which is the Cart and Which is the Horse? In Towns, M. H., Bain, K., & Rodriguez, J. G., (Eds.), *It's Just Math: Research on Students' Understanding of Chemistry and Mathematics*, Vol. 1316. American Chemical Society, Washington, DC (in press).
- Bain, K. & Towns, M. H. (2016). A Review of Research on the Teaching and Learning of Chemical Kinetics. *Chemistry Education Research & Practice*, 17(2), 246-262.
- Bain, K., Rodriguez, J. G., & Towns, M. H. (2018). Zero-Order Chemical Kinetics as a Context To Investigate Student Understanding of Catalysts and Half-Life. *Journal of Chemical Education*. <http://doi.org/10.1021/acs.jchemed.7b00974>
- Bain, K., Rodriguez, J. G., & Towns, M. H. (2019). Investigating Student Understanding of Rate Constants: When is a Constant 'Constant'? *Journal of Chemical Education*, Submitted.
- Barton, J. A Comprehensive Enzyme Kinetics Exercise for Biochemistry, *Journal of Chemical Education*, 88(9), 1336-1339.
- Bearne, S. (2012). Illustrating Enzyme Inhibition Using Gibbs Energy Profiles. *Journal of Chemical Education*, 89(6), pp.732-737.
- Bearne, S. (2014). Illustrating the effect of pH on Enzyme Activity Using Gibbs Energy Profiles. *Journal of Chemical Education*, 91(1), pp.84-90.
- Becker, N. & Towns, M. (2012). Students' understanding of mathematical expressions in physical chemistry contexts: An analysis using Sherin's symbolic forms. *Chemistry Education Research and Practice*, 13, 209-220.
- Bezerra, R. & Dias, A. (2007). Utilization of Integrated Michaelis-Menten Equation to Determine Kinetic Constants. *Biochemistry and Molecular Biology Education*, 35(2), 145-150.

- Becker, N. M., Rupp, C. A., & Brandriet, A. (2017). Engaging Students in Analyzing and Interpreting Data to Construct Mathematical Models: an analysis of students' reasoning in a method of initial rates task, *Chemistry Education Research and Practice*, 18, 798–810.
- Birks, M., Chapman, Y., & Francis, K. (2008). Memoing in qualitative research: Probing data and processes. *Journal of Research in Nursing*, 13(1), 68-75.
- Bodner, G. M. (1986). Constructivism: A Theory of Knowledge. *Journal of Chemical Education*, 63(10), 873–878.
- Bodner, G. & Klobuchar, M. (2001). The Many Forms of Constructivism. *Journal of Chemical Education*, 78(8), 1107.
- Bodner, G. M. & Weaver G. (2008). Research and Practice in Chemical Education in Advanced Courses, *Chemistry Education Research and Practice*, 9, 81-83.
- Brandriet, A., Rupp, C., Lazenby, K., & Becker, N. (2018). Evaluating Students' Abilities to Construct Mathematical Models from Data Using Latent Class Analysis. *Chemistry Education Research & Practice*, 19, 375-391.
- Bretz, S. L. & Linenberger, K. J. (2012). Development of the Enzyme-Substrate Interactions Concept Inventory. *Biochemistry and Molecular Biology Education*, 40(2), 229-233.
- Bruist, M. (1998). Use of a Spreadsheet to Simulate Enzyme Kinetics. *Journal of Chemical Education*, 75(3), 372-375.
- Cakmakci, G. (2010). Identifying Alternative Conceptions of Chemical Kinetics Among Secondary School and Undergraduate Students in Turkey. *Journal of Chemical Education*, 87, 449–455.
- Cakmakci, G. & Aydogdu, C. (2011). Designing and Evaluating an Evidence-informed Instruction in Chemical Kinetics, *Chemistry Education Research & Practice*, 12(1), 15–28.
- Cakmakci, G., Leach, J., & Donnelly, J. (2006). Students' Ideas About Reaction Rate and its Relationship with Concentration or Pressure, *International Journal of Science Education*, 28(15), 1795–1815.
- Charmaz, K. (2006). Constructing grounded theory: A practical guide through qualitative analysis. Thousand Oaks, CA: Sage Publications.
- Clark, A. (2004). Lucenz Simulator: A Tool for the Teaching of Enzyme Kinetics. *Biochemistry and Molecular Biology Education*, 32(3), 201-206.
- Cohlberg, J. (1979). Km as Apparent Dissociation Constant. *Journal of Chemical Education*, 56(8), 512-514.
- Cooper, M. (2015). Why ask why? *Journal of Chemical Education*, 92(8), 1273-1279.
- Cooper, M, M., Posey, L. A., Underwood, S. M. Core Ideas and Topics: Building Up or Drilling Down? *Journal of Chemical Education*, 94(5), 541-548.



- Cooper, M. M. & Stowe, R. L. (2018). Chemistry Education Research—From Personal Empiricism to Evidence, Theory, and Informed Practice. *Chemical Reviews*, 118, 6053-6087.
- Cracolice, M. S., Deming, J. C., & Ehlert, B. (2008). Concept learning versus problem solving: A cognitive difference. *Journal of Chemical Education*, 85(6), 873-878.
- Cruz-Ramirez de Arellano, D., & Towns, M. H. (2014). Students' understanding of alkyl halide reactions in undergraduate organic chemistry. *Chemistry Education Research and Practice*, 15, 501–515. <http://doi.org/10.1039/C3RP00089C>
- Dorko, A. & Speer, N. (2015). Calculus Students' Understanding of Area and Volume Units. *Investigations in Mathematics Learning*, 8(1), 23-46.
- Dreyfus, B. W., Elby, A., Gupta, A., & Sohr, E. R. (2017). Mathematical sense-making in quantum mechanics: An initial peek. *Physical Review Physics Education Research*, 13, 020141.
- diSessa, A. A. (1993). Toward an Epistemology of Physics. *Cognition and Instruction*, 10(2–3), 105–225. <http://doi.org/10.1080/07370008.1985.9649008>
- Frezza B. M., Michaelis-Menten Enzyme Kinetics and the Steady-State Approximation, <http://demonstrations.wolfram.com/MichaelisMentenEnzymeKineticsAndTheSteadyStateApproximation/>, Wolfram Demonstrations Project, Published: March 7, 2011.
- Gegios, T., Salta, K., & Koinis S. (2017). Investigating High-school Chemical Kinetics: the Greek Chemistry Textbook and Students' Difficulties. *Chemistry Education Research & Practice*, 18(1), 151–168.
- Gonzalez-Cruz, J., Rodriguez-Sotres, R., & Rodriguez-Penagos, M. (2003). On the Convenience of Using a Computer Simulation to Teach Enzyme Kinetics to Undergraduate Students with Biological Chemistry-related Curricula. *Biochemistry and Molecular Biology Education*, 31(2), 93-101.
- Guerra, N. P. (2017). Enzyme Kinetics Experiment with the Multienzyme Complex Viscozyme L and Two Substrates for the Accurate Determination of Michaelian Parameters. *Journal of Chemical Education*, 94(6), 795-799.
- Hamilton, T., Dobie-Galuska, A., & Wiestock, S. (1999). The o-Phenylenediamine-Horseradish Peroxidase System: Enzyme Kinetics in the General Chemistry Laboratory. *Journal of Chemical Education*, 76(5), 642-644.
- Hammer, D. & Elby, A. (2002). On the Form of a Personal Epistemology. In B. K. Hofer & P. R. Pintrich (Eds.), *Personal Epistemology: The Psychology of Beliefs about Knowledge and Knowing* (pp. 169–190). Mahwah, NJ: Erlbaum.
- Hammer, D. & Elby, A. (2003). Tapping Epistemological Resources for Learning Physics. *Journal of the Learning Sciences*, 12(1), 53–90.

- Hammer, D., Elby, A., Scherr, R. E., & Redish, E. F. (2005). Resources, Framing, and Transfer. In J. P. Mestre (Ed.), *Transfer of Learning from a Modern Multidisciplinary Perspective* (pp. 89–119). Greenwich, CT: IAP.
- Harle, M. & Towns, M. H. (2012). Students' Understanding of External Representations of the Potassium Ion Channel Protein Part I: Affordances and Limitations of Ribbon Diagrams, Vines, and Hydrophobic/Polar Representations. *Biochemistry and Molecular Biology Education*, 40(6), 349-356.
- Harle, M. & Towns, M. H. (2012). Students' Understanding of External Representations of the Potassium Ion Channel Protein Part II: Structure Function Relationships and Fragmented Knowledge. *Biochemistry and Molecular Biology Education*, 40(6), 357-363.
- Harle, M. & Towns, M. H. (2013). Students' understanding of primary and secondary protein structure: drawing secondary protein structure reveals student understanding better than simple recognition of structures. *Biochemistry and Molecular Biology Education*, 41(6), 369–376.
- Heinzerling, P., Shrader, F., & Schanze, S. (2012). Measurement of Enzyme Kinetics by Use of a Blood Glucometer: Hydrolysis of Sucrose and Lactose. *Journal of Chemical Education*, 89(12), 1582-1586.
- Heisterkamp, K. & Talanquer, V. (2015). Interpreting Data: The Hybrid Mind. *Journal of Chemical Education*, 92 (12), 1988–1995.
- Helser, T. (1991). Enzyme Activity: The Ping-Pong Ball Torture Analogy. *Journal of Chemical Education*, 68, 286-287.
- Hinckley, G. (2012). A Method for Teaching Enzyme Kinetics to Nonscience Majors. *Journal of Chemical Education*, 89(9), 1213-2014.
- Holme, T., Luxford, C., & Murphy, K. (2015). Updating the General Chemistry Anchoring Concepts Content Map. *Journal of Chemical Education*, 92, 1115-1116.
- Holme, T. & Murphy, K. (2012). The ACS Exams Institute Undergraduate Anchoring Concepts Content Map I: General Chemistry, *Journal of Chemical Education*, 89, 721-723.
- Holme, T. A., Reed, J. J., Raker, J. R., & Murphy, K. L. (2018). The ACS Exams Institute Undergraduate Chemistry Anchoring Concepts Content IV: Physical Chemistry. *Journal of Chemical Education*, 95 (2), 238-241.
- House, C., Meades, G., & Lineberger, K. (2016). Approaching Conceptual Understanding of Enzyme Kinetics and Inhibition: Development of an Active Learning Inquiry Activity for Prehealth and Nonscience Majors. *Journal of Chemical Education*, 93(8), 1397-1400.
- Howard, R., Herr, J., & Hollister, R. (2006). Using Trypsin & Soybean Trypsin Inhibitor. *The American Biology Teacher*, 68(2), 99-104.

- Hu, D. & Rubello, N. (2013). Using conceptual blending to describe how students use mathematical integrals in physics. *Physical Review Special Topics - Physics Education Research*, 9(2), 1-15.
- Izak, A. (2004) Students' Coordination of Knowledge When Learning to Model Physical Situations. *Cognition and Instruction*, 22(1), 81-128.
- Johnson, K. (2000). A Simple Method for Demonstrating Enzyme Kinetics Using Catalase from Beef Liver Extract. *Journal of Chemical Education*, 77(11), 1451-1452.
- Johnson, K. A. (2009). Fitting Enzyme Kinetic Data with KinTek Global Kinetic Explorer. *Methods in Enzymology*, 467, 601-626.
- Johnson, K. A., Simpson, Z. B., & Blom, T. (2009). Global Kinetic Explorer: A new computer program for dynamic simulation and fitting of kinetic data. *Analytical Biochemistry*, 387, 20-29.
- Johnson, R. (2014). Teaching Foundational Topics and Scientific Skills in Biochemistry Within the Conceptual Framework of HIV Protease. *Biochemistry and Molecular Biology Education*, 42(4), 299-304.
- Jones, S. (2013). Understanding the integral: Students' symbolic forms. *Journal of Mathematical Behavior*, 32(2), 122-141.
- Jones, S. (2015). The prevalence of area-under-a-curve and anti-derivative conceptions over Riemann sum-based conceptions in students' explanations of definite integrals. *International Journal of Mathematics Education in Science and Technology*, 46(5), 721-736.
- Jones, S. (2015). Areas, anti-derivatives, and adding up pieces: Definite integrals in pure mathematics and applied science contexts. *Journal of Mathematical Behavior*, 38, 9-28.
- Junker, M. (2010). A Hands-on Classroom Simulation to Demonstrate Concepts in Enzyme Kinetics. *Journal of Chemical Education*, 87(3), 294-295.
- Justi, R. (2002). Teaching and learning chemical kinetics. In Gilbert, J. K., De Jong, O., Justi, R., Treagust, D., & Van Driel, J. H. (Eds.), *Chemical Education: Towards Research-based Practice*, 293-315. Dordrecht, Kluwer.
- King N. and Horrocks C. (2010). Interviews in qualitative research, London: SAGE Publications, Ltd.
- Kolomuc, A. & Tekin, S. (2011). Chemistry Teachers' Misconceptions Concerning Concept of Chemical Reaction Rate. *Eurasian Journal of Physics and Chemistry Education*, 3(2), 84-101.
- Kuo, E., Hull, M., Gupta, A., & Elby, A., (2013) How students blend conceptual and formal mathematical reasoning in solving physics problems. *Science Education*, 97(1), 32-57.

- Kozma, R. B. & Russell, J. (1997). Multimedia and Understanding: Expert and Novice Responses to Different Representations of Chemical Phenomena, *Journal of Research in Science Teaching*, 24(9), 949-968.
- Lang, F. K. (2018). Understanding Perceptions and Beliefs Biochemistry Instructors Hold and the Influence These Factors Have on Their Personal Style of Teaching. Purdue University: Unpublished doctoral dissertation.
- Lawrence, S. & Jaffe, E. K. (2008). Expanding the Concepts in Protein Structure-Function Relationships and Enzyme Kinetics: Teaching Using Morpheesins. *Biochemistry and Molecular Biology Education*, 36(4), 274-283.
- Lechner, J. (2011). More Nuts and Bolts of Michaelis-Menten Enzyme Kinetics. *Journal of Chemical Education*, 88(6), 845-846.
- Lee, V. R. & Sherin, B. (2006). Beyond transparency: How students make representations meaningful. In Proceedings of the 7th international conference on Learning sciences (pp. 397-403). International Society of the Learning Sciences.
- Linenberger, K. J. & Bretz, S. L. (2012). A Novel Technology to Investigate Students' Understandings. *Journal of College Science Teaching*, 42(1), 45-49.
- Linenberger, K. J. & Bretz, S. L. (2014). Biochemistry Students' Ideas About Shape and Charge in Enzyme-Substrate Interactions. *Biochemistry and Molecular Biology Education*, 42(3), 203-214.
- Linenberger, K. J. & Bretz, S. L. (2015). Biochemistry Students' Ideas About How an Enzyme Interacts with a Substrate. *Biochemistry and Molecular Biology Education*, 43(4), 213-222.
- Loertscher, J., Green, D., Lewis, J. E., Lin, S., & Minderhout, V. (2014). Identification of Threshold Concepts for Biochemistry. *CBE—Life Sciences Education*, 13, 516-528.
- Lunsford, E., Melear, C., Roth, W., Perkins, M., & Hickok, L. (2007). Proliferation of Inscriptions and Transformations Among Preservice Science Teachers Engaged in Authentic Science. *Journal of Research in Science Teaching*, 4, 538-564.
- Marek, K. A., Raker, J. R., Holme, T. A., Murphy, K. L. (2018). The ACS Exams Institute Undergraduate Chemistry Anchoring Concepts Content Map III: Inorganic Chemistry. *Journal of Chemical Education*, 95, 223-237.
- Murkin, A. Commentary: Ohm's Law as an Analogy for Enzyme Kinetics. (2015). *Biochemistry and Molecular Biology Education*, 43(2), 139-141.
- Murphy, K., Holme, T., Zenisky, A., Caruthers, H., & Knaus, K. (2012). Building the ACS Exams Anchoring Concept Content Map for Undergraduate Chemistry. *Journal of Chemical Education*, 89 (6), 715-720.
- Nakhleh, M. B. (1993). Are Our Students Conceptual Thinkers or Algorithmic Problem Solvers? Identifying Conceptual Students in General Chemistry. *Journal of Chemical Education*, 70(1), 53-55.

- Nakhleh, M. B., Lowrey, K. A., & Mitchell R. C. (1996). Narrowing the Gap between Concepts and Algorithms in Freshmen Chemistry. *Journal of Chemical Education*, 70(8), 758-762.
- Nakhleh, M. B. & Mitchell R. C. (1993). Concept Learning versus Problem Solving: There is a Difference. *Journal of Chemical Education*, 70(3), 191-192.
- Nemirovsky, R. (1996). Mathematical Narratives, Modeling, and Algebra. In Bednarz, N., Kiernan, C., & Lee, L. (Eds.), *Approaches to Algebra: Perspectives for Research and Teaching*, 197-223. Dordrecht, The Netherlands: Kluwer Academic Publishers.
- Nurrenbern, S. C. & Pickering, M. (1987). Concept Learning versus Problem Solving: Is There a Difference? *Journal of Chemical Education*, 64(6), 508-510.
- Pickering M. (1990). Further studies on concept learning versus problem solving, *Journal of Chemical Education*, 67(3), 254-255.
- Page, J. M. (2014). Childcare Choices and Voices: Using Interpreted Narratives and Thematic Meaning-Making to Analyze Mothers' Life Histories. *International Journal of Qualitative Studies in Education*, 27 (7), 850–876.
- Potratz, J. (2018). Making Enzyme Kinetics Dynamic via Simulation Software. *Journal of Chemical Education*, 95(3), 482-486.
- Ochs, R. S. (2000). Understanding Enzyme Inhibition. *Journal of Chemical Education*, 77(11), 1453-1456.
- Orgill, M. & Bodner, G. (2004). What Research Tells Us About Using Analogies to Teach Chemistry. *Chemistry Education Research & Practice*, 5(1), 15-32.
- Orgill, M. & Bodner, G. (2006). An Analysis of the Effectiveness of Analogy Use in College-level Biochemistry Textbooks. *Journal of Research in Science Teaching*, 43(10), 1040-1060.
- Orgill, M. & Bodner, G. (2007). Locks and Keys: An Analysis of Biochemistry Students' Use of Analogies. *Biochemistry and Molecular Biology*, 35(4), 244-254.
- Orgill, M., Bussey, T., & Bodner, G. (2015). Biochemistry Instructors' Perceptions of Analogies and Their Classroom Use. *Chemistry Education Research and Practice*, 16, 731-746.
- QSR International. Running a Coding Comparison Query. Retrieved November 16, 2018, from [http://help-nv11.qsrinternational.com/desktop/procedures/run\\_a\\_coding\\_comparison\\_query.htm](http://help-nv11.qsrinternational.com/desktop/procedures/run_a_coding_comparison_query.htm)
- Quisenberry, K. & Tellinghuisen J. (2006). Textbook Deficiencies: Ambiguities in Chemical Kinetics Rates and Rate Constants. *Journal of Chemical Education*, 83(3), 510–512.
- Raker, K., Holme, T., & Murphy, K. (2013). The ACS Exams Institute Undergraduate Chemistry Anchoring Concepts Content Map II: Organic Chemistry. *Journal of Chemical Education*, 90 (11), 1143-1145.

- Rodriguez, J. G., Bain, K., Hux, N. P., & Towns, M. H. (2019). Productive Features of Problem Solving in Chemical Kinetics: More Than Just Algorithmic Manipulation of Variables. *Chemistry Education Research and Practice*, 20, 176-186, DOI: 10.1039/C8RP00202A.
- Rodriguez, J. G., Bain, K., & Towns, M. H. (2019). Graphs as Objects: Analysis of the Mathematical Resources Used by Undergraduate Biochemistry Students to Reason About Enzyme Kinetics. In Towns, M. H., Bain, K., & Rodriguez, J. G., (Eds.), *It's Just Math: Research on Students' Understanding of Chemistry and Mathematics*, Vol. 1316. American Chemical Society, Washington, DC (in press).
- Rodriguez, J. G., Bain, K., & Towns, M. H. (2019). Graphical Forms: The Adaption of Sherin's Symbolic Forms for the Analysis of Graphical Reasoning Across Disciplines. *International Journal of Research in Undergraduate Mathematics Education*, Submitted.
- Rodriguez, J. G., Bain, K., Towns, M. H., Elmgren, M., & Ho, F. M. (2019). Covariational Reasoning and Mathematical Narratives: Investigating Students' Understanding of Graphs in Chemical Kinetics. *Chemistry Education Research and Practice*, 20, 107-119, DOI: 10.1039/c8rp00156a.
- Rodriguez, J. G., Bain, K., & Towns, M. H. (2019). Mathematics in a Chemistry Context: Implications for Mathematics Instruction and Research on Undergraduate Mathematics, *International Journal of Research in Undergraduate Mathematics Education*, Submitted.
- Rodriguez, J. G., Santos-Diaz, S., Bain, K., & Towns, M. H. (2018). Using Symbolic and Graphical Forms to Analyze Students' Mathematical Reasoning in Chemical Kinetics. *Journal of Chemical Education*, 95, 2114-2125, DOI: 10.1021/acs.jchemed.8b00584.
- Rodriguez, J. G. & Towns, M. H. (2019). Analysis of student reasoning about Michaelis-Menten enzyme kinetics: mixed conceptions of enzyme inhibition. *Chemistry Education Research and Practice*, Submitted.
- Roschelle, J. (1991). Students' construction of qualitative physics knowledge: Learning about velocity and acceleration in a computer microworld. University of California, Berkley: Unpublished doctoral dissertation.
- Runge, S., Hill, B., & Moran, W. (2006). A Simple Classroom Teaching Technique to Help Students Understand Michaelis-Menten Kinetics. *CBE – Life Science Education*, 5, 348-352.
- Sanger, M. J. Vaughn, C. K., & Binkley, D. A. (2013). Concept learning versus problem solving: Evaluating a threat to the validity of a particulate gas law question, *Journal of Chemical Education*, 90(6), 700-709.
- Saunders, B., Sim J., Kingstone, T., Bakjer, S., Waterfield, J., Bartlam, B., Burroughs, H., & Jinks, C. (2018). Saturation in qualitative research: exploring its conceptualization and operationalization, *Quality and Quantity*, 52(4), 1893-1907.
- Sawrey, B. A. (1990). Concept learning versus problem solving: Revisited. *Journal of Chemical Education*, 67(3), 253-254.

- Sayre, E. C. & Wittmann M. C. (2008). Plasticity of mechanics students coordinate system choice. *Physical Review Special Topics – Physics Education Research*, 4, 020105, 1-14.
- Schermerhorn, B. & Thompson, J. (2016). Students' use of symbolic forms when constructing differential length elements. Paper presented at Physics Education Research Conference 2016, Sacramento, CA.
- Schnoebelen, C. (2018). Evaluation of a Redesigned Chemistry Course Sequence for Undergraduate Life Science Majors. Purdue University: Unpublished doctoral dissertation.
- Secken, N. & Seyhan, H. (2015). An Analysis of High School Students' Academic Achievement and Anxiety Over Graphical Chemistry Problems About the Rate of a Reaction: The Case of the Sivas Province. *Procedia – Social and Behavioral Sciences.*, 174, 347–354.
- Seethaler, S., Czworkowski, J., & Wynn, L. (2018). Analyzing General Chemistry Texts' Treatment of Rates of Change Concepts in Reaction Kinetics Reveals Missing Conceptual Links. *Journal of Chemical Education*, 95(1), 28–36.
- Sherin, B. L. (2001). How Students Understand Physics Equations. *Cognition and Instruction*, 19(4), 479-541.
- Singer, S. R., Nielson, N. R., & Schweingruber, H. A. (2012). *Discipline-Based Education Research: Understanding and Improving Learning in Undergraduate Science and Engineering*. Washington, DC: National Academies Press. <http://doi.org/10.17226/13362>
- Silverstein, T. (1995). Breaking Bonds Versus Chopping Heads: The Enzyme as Butcher. *Journal of Chemical Education*, 72(7), 645-646.
- Silverstein, T. (2011). The Nuts and Bolts of Michaelis-Menten Enzyme Kinetics: Suggestions and Clarifications. *Journal of Chemical Education*, 88(2), 167-168.
- Stamovlasis, D., Tsaparlis, G., Kamilatos, C., Papaoikonomou, D., & Zarotiadou, E. (2005). Conceptual understanding versus algorithmic problem solving: Further evidence from a national chemistry examination. *Chemistry Education Research & Practice*, 6(2), 104-118.
- Strauss, A. & Corbin J. (1990). *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*. Newbury Park, CA: SAGE Publications, Ltd.
- Tastan, O., Yalcinkaya, E., & Boz, Y., (2010), Pre-service chemistry teachers' ideas about reaction mechanism, *J. Turk. Sci. Educ.*, 7, 47–60.
- Tastan, O. & Boz, Y. (2010). Pre-service Chemistry Teachers' Ideas About Reaction Mechanism. *Journal of Turkish Science Education*, 7, 47-60.
- Turanyi, T. & Toth, Z. (2013). Hungarian University Students' Misunderstandings in Thermodynamics and Chemical Kinetics. *Chemistry Education Research & Practice*, 14, 105–116.

- Von Korff, J. & Rubello, N. (2014). Distinguishing between “change” and “amount” infinitesimals in first-semester calculus-based physics. *American Journal of Physics*, 82, 695-705.
- Waldrop, G. (2009). A Qualitative Approach to Enzyme Inhibition. *Biochemistry and Molecular Biology Education*, 37(1), 11-15.
- Wittmann, M. C. (2006). Using resource graphs to represent conceptual change, *Physical Review Special Topics – Physics Education Research*, 2, 020105, 1-17.
- Xie, X. S. (2013). Enzyme Kinetics, Past and Present. *Science*, 342, 1457–1458.
- Zoller, U., Lubezky, A., Nakhleh, M. B., Tessier, B., & Dori, Y. J. (1995). Success on algorithmic and LOCS vs. conceptual chemistry exam questions. *Journal of Chemical Education*, 72(11), 987-989.



## APPENDIX A. ENZYME KINETICS ANALOGIES

**Appendix Table 1** Features of enzyme kinetics addressed in each analogy, ordered in terms of frequency.

Type	Publication	Enzyme	Substrate	Catalytic Event	Competitive inhibition	Substrate concentration	$V_{max}$ (saturation)	Noncompetitive inhibition	Irreversible inhibition	Specificity	Reaction scheme	Enzyme concentration	Temperature	Uncompetitive inhibition
Narrative-Based Analogy	Asimov, 1959	lock	key	unlocking the lock	X					X				
	Helser, 1991	person	ping-pong ball	crushing the ping-pong ball	X	X	X	X				X	X	
	Abel and Halenz, 1992	child holding a pin	balloon	popping the balloon	X	X	X	X	X			X	X	
	Silverstein, 1995	butcher with knife and chopping block	goose	Cutting off the goose's head	X	X	X	X	X	X		X		
	Ochs, 2000	bear	honey	- <sup>a</sup>										X
		suspect	contraband	- <sup>a</sup>										X
Activity-Based Analogy	Runge et al., 2006	student	marble	moving the marble from one container to another		X	X				X			
	Junker, 2010; Lechner, 2011; Silverstein, 2011		nut screwed onto a bolt	unscrewing the nut from the bolt	X	X	X	X			X	X		
	Hinckley, 2012		bean	removing the bean from the paper bag	X	X	X							
	House et al., 2016	student holding a falcon tube	penny	placing the penny in the falcon tube	X	X	X	X	X	X	X		X	X

<sup>a</sup>Ochs (2000) did not clearly specify the catalytic event, primarily using analogies to describe uncompetitive inhibition in general terms.

## APPENDIX B. COMPREHENSIVE LIST OF SYMBOLIC FORMS

**Appendix Table 2** Comprehensive list of symbolic forms identified in the literature.

Cluster	Symbolic Form <sup>a</sup>	Symbol Template	Brief Description of Conceptual Schema
Competing terms	1. Competing terms	$\square \pm \square \pm \square \dots$	Influences in competition
	2. Opposition	$\square - \square$	Two terms, separated by a minus sign, associated with influences that work against each other
	3. Balancing	$\square = \square$	Two influences, each associated with a side of the equation, in balance so the system is in equilibrium
	4. Canceling	$0 = \square - \square$	Two influences that precisely cancel so there is no net outcome
Terms are amounts	5. Parts-of-a-whole	$\square + \square + \square \dots$	Amounts of a generic substance, associated with terms, that contributes to a whole
	6. Base $\pm$ change	$\square \pm \Delta$	Two terms contribute to a whole but play different roles; one is a base value, the other is a change to that base
	7. Whole - part	$[\square - \square]$	A new net amount is produced by taking away a piece of an original whole
	8. Same amount	$\square = \square$	Two amounts, each associated with a side, are the same
Dependence	9. Dependence	$[\dots x \dots]$	A whole depends on a quantity associated with an individual symbol
	10. No dependence	$[\dots]$	A whole does not depend on a quantity associated with an individual symbol
	11. Sole dependence	$[\dots x \dots]$	A whole depends only on one particular quantity associated with an individual symbol

Appendix Table 2 continued

Coefficient	12. Coefficient	$[x\Box]$	A product of factors is broken into two parts and one part is identified with an individual symbol, the coefficient
	13. Scaling	$[n\Box]$	Similar to coefficient, but the coefficient is unitless; a scaling coefficient is seen as operating on the rest of the factors to produce an entity of the same sort that is larger or smaller than the original
Multiplication	14. Intensive-extensive	$x \times y$	A product of an intensive quantity and an extensive quantity (an intensive quantity is an amount of something per unit of something else, an extensive property is a number of units)
	15. Extensive-extensive	$x \times y$	A product of two quantities, both associated with extensiveness
Proportionality	16. Prop+	$\left[\frac{\dots x \dots}{\dots}\right]$	Directly proportional to a quantity, $x$ , which appears as an individual symbol in the numerator
	17. Prop-	$\left[\frac{\dots}{\dots x \dots}\right]$	Indirectly proportional to a quantity, $x$ . appears as an individual symbol in the denominator
	18. Ratio	$\left[\frac{x}{y}\right]$	Comparison of a quantity in the numerator and the denominator
	19. Cancelling ( $b$ )	$\left[\frac{\dots x \dots}{\dots x \dots}\right]$	Identical symbols appear in the numerator and denominator cancel
Other	20. Identity	$x = \dots$	A single symbol that appears alone on one side of an equation has the same properties as the expression on the other side
	21. Dying away	$[e^{-x} \dots]$	A whole dies away with some parameter that appears raised to a negative power in the exponent of an exponential
	22. Measurement	$\Box \Box$	Values involving units, with the larger term corresponding to the magnitude and the smaller term corresponding to the
	23. Nuanced measurement	$\Box \Box^2$	Similar to the <i>measurement</i> symbolic form, but accounts for the fact that units can have exponents

Appendix Table 2 continued

Calculus	24. Intermediate catching up + total catching up	$ \square \pm \square $	Describes the distance between weights attached to spools as a you turn the crank on a winch; one term is associated with intermediate states in the catching-up process and the other term is associated with the total amount that one weight had to catch up to the other; the absolute value symbols indicate that the distance has to be positive (Note: this seems very specific to a particular problem, modeling a specific physical system, winch)
	25. Scaling exponentially	$\square^{\square}$	Similar to scaling, but in this case an exponent is tuning or scaling the magnitude of the overall value
	26. Adding up pieces (multiplicatively-based summation concept)	$\int_{\square}^{\square} \square d\square$	The integrand and the differential create rectangles, each with a small piece of the resultant quantity; the integrand is an active (infinite) totaling of these pieces; the limits are the starting and stopping point of the running total; a similar notion is discussed with Hu & Rubello's (2013) idea of <i>integral as a sum/differential as a small part</i> and Von Korff & Rubello's (2014) idea of the <i>amount infinitesimal</i>
	27. Adding up the integrand (miscompilation)	$\int_{\square}^{\square} \square d\square$	The differential determines a partition, where a small quantity of the <i>integrand</i> exists in each piece; these small quantities of the <i>integrand</i> are added up and the result is multiplied by the variable of the differential
	28. Perimeter and area	$\int_{\square}^{\square} \square d\square$	The integrand, differential, and limits of integration construct the physical boundaries (perimeter) of a whole, fixed region; the integral represents the area of this region; the region is taken as a static whole
	29. Function matching	$\int_{\square}^{\square} \square d\square$	The integrand comes from some "original function"; the differential indicates the relationship between them; the integral seeks to find this "original function"; the limits represent a measurement between values
	30. Generic answer	$\int \square d\square$	The integral yields a "generic" version of a result; the generic result is "waiting" for limits to be attached in order for a more specific result to be determined; the generic result can take in a range of possible inputs
	31. Function matching (no limits)	$\int \square d\square$	See <i>function matching</i> ; no limits are attached to this, though, creating no need for a measurement between values; the integral only seeks to find the "original function"

Appendix Table 2 continued

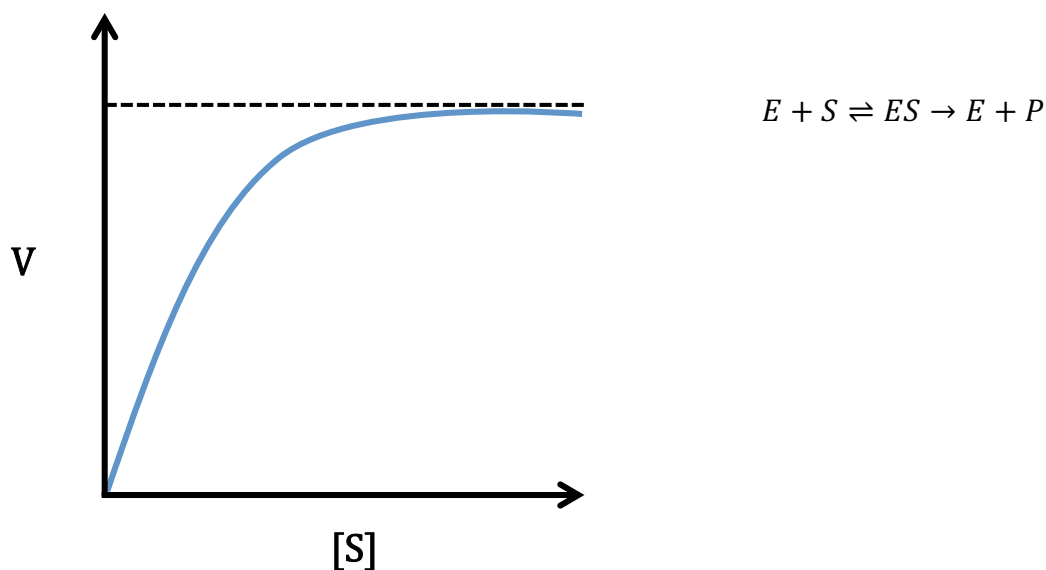
32. Area in between	$\int_a^b (f(x) - g(x)) dx$	See <i>perimeter and area</i> ; however, the unique structure of the integrand suggests that the fixed area is situated in between two curves in the plane
33. Stretch or flip	$\int$	The integral is taken to be a single entity and the front multiplier has the effect of physically manipulating this entity; for example, a fixed region might be stretched out or flipped over the x-axis
34. Mends with integrand	$\int$	The front multiplier can be combined with the integrand function in such a way that the front multiplier and the integrand are no longer distinguishable; they are blended into creating a new integral
35. Symmetric graph	$\int_0^x$	The front multiplier represents a symmetry in the graph of the integrand; thus, the integration is actually occurring over a larger area than that given by the limits of integration
36. Multiplies the result	$\int$	The front multiplier is seen as a value to be multiplied with the value of the integral; this may reduce to symbolic forms for simple multiplication
37. Region in space	$\int$	The subscript symbol is seen as representing a region in multi-dimensional space
38. Differential as a shape	$dx$	The differential is thought of as a shape in space; this shape may be dependent on either the function of integrand, the coordinate used, or the shape of the domain
39. Differential as variable of integration	$dx$	The differential term describes the variable integration is done with respect to
40. Differential as an operation	$d$	The differential term indicates the operation of taking the derivative
41. Change infinitesimal	$f(x) - f(x + \Delta x) = \Delta$	The differential term, " $\Delta$ ", (e.g., $dx$ ) represents the difference between two finite terms that result an infinitesimally small quantity
42. Product infinitesimal	$f(x) \cdot \Delta$	The product of a finite term and an infinitesimally small quantity

Appendix Table 2 continued

Vectors, operators, eigenvectors, & eigenvalues	43. Magnitude-direction	$\hat{\square\square}$	Used to denote a vector expression including the magnitude of a quantity (having units) and a unit vector to indicate a specific direction
	44. Transformation	$\hat{\square} \rangle$	$\hat{\square}$ is an operator and $ \rangle$ is a state, represented as a vector, function, or abstract ket; associated with this symbolic form is the idea of reshaping or the notion that the operator acting on a vector results in another vector that in general points in a different direction (e.g., an operator acting on a wave function “spits out” a new function with a different shape)
	45. Eigenvector eigenvalue	$\hat{\square} \rangle = C \rangle$	The state vector or function is the same on both sides and $C$ is a constant (with or without units); transformation that reproduces the original; a potentially transformative process has a net effect of reproducing the original state of affairs; for a given operator there are a particular set of values $C$ and $ \rangle$ that satisfy this condition of equality and are solutions to the eigenvalue equation; note that this is a compound symbolic form that is composed of multiple symbolic forms (both sides of the equation are symbolic forms with the left side being the <i>transformation</i> symbolic form and the right side being the <i>coefficient</i> symbolic form)
<p><sup>a</sup>Symbolic Forms and their descriptions are adapted or reproduced from the following literature: 1-21 (Sherin, 2001); 22, 23 (Dorko &amp; Speer, 2015); 24 (Izak, 2004); 25 (Rodriguez, Santos-Diaz, Bain, &amp; Towns, 2018); 26-38 (Jones, 2013, 2015a, 2015b); 39, 40 (Hu &amp; Rubello, 2013); 41, 42 (Von Korff &amp; Rubello, 2014); 43 (Schermerhorn &amp; Thompson, 2016); 44, 45 (Dreyfus, Elby, Gupta, &amp; Sohr, 2017)</p> <p><b>Template Key</b></p> <p>[...] Expression in brackets corresponds to an entity in the schema</p> <p><math>x, y, n</math> Individual symbols in an expression</p> <p><math>\square</math> A term or group of terms</p>			

## APPENDIX C. GRAPH AND REACTION SCHEME (PROMPT #1)

*Here's a graph and a reaction scheme you may have seen in class to describe enzyme kinetics. How would you explain these to a friend from class? How would you explain these on an exam?*



### **Possible Follow-up Questions**

*Do you have any questions for me?*

*Are you taking the accompanying laboratory course?*

*Explain the axes on the graph (velocity and substrate)? What is velocity? What is substrate?*

*What information does the graph tell you?*

*What chemistry is happening?*

*What does the dotted line represent?*

*If they write equation:*

*How does the graph relate to the equation?*

*What do each of the terms in the equation mean? How is  $V$  different from  $V_{max}$ ?*

*Does this equation apply to all substrate-enzyme interactions? Why or why not?*

*Under what conditions does this equation not apply?*

*What assumptions are with this equation?*

*Explain the reaction scheme.*

*What is an enzyme? What is a substrate?*

*How is this graph different/similar as graphs in general chemistry kinetics?*

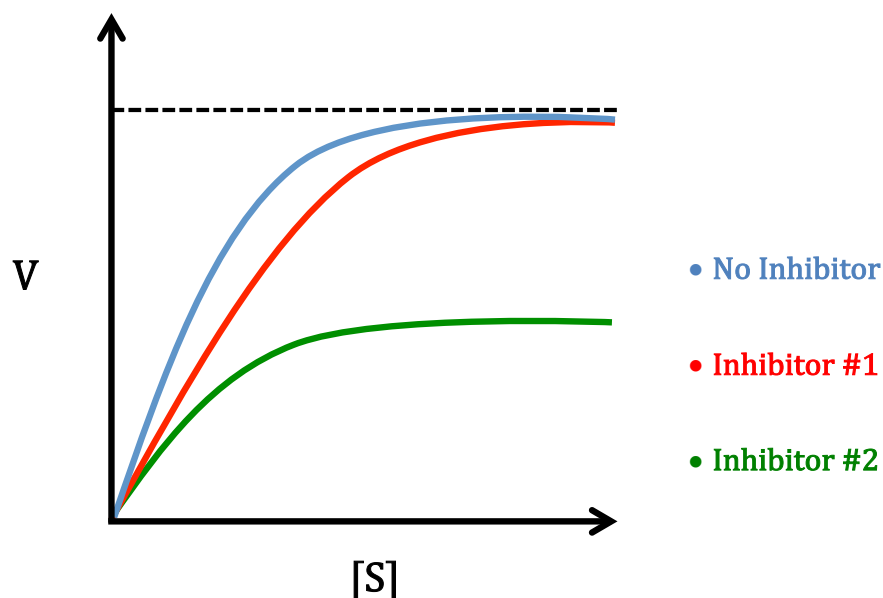
*What is would the rate law be for this reaction?*

*What is the order of this reaction?*

*Is there anything else you would like to add?*

## APPENDIX D: ENZYME INHIBITION GRAPH (PROMPT #2)

Multiple experiments were run in which kinetics data were collected for a reaction involving an enzyme. The first reaction was run without an enzyme inhibitor, the second reaction was run with an enzyme inhibitor, and the third reaction was run with a different enzyme inhibitor. The results are shown below. Explain the types of inhibition observed.



### Possible Follow-up Questions

*What is enzyme inhibition? What does it change? What does it inhibit? How?*

*Describe the different types of inhibition (competitive, non-competitive, uncompetitive)*

*How does inhibition change the equation (and reaction scheme) from the previous prompt?*

*What information does the graph tell you?*

*What chemistry is happening?*

*Is there anything else you would like to add?*

*Do you have any questions for me?*



## APPENDIX E: CODE DESCRIPTIONS

**Appendix Table 3** Code descriptions relevant for addressing the first research question: *How do students use mathematical resources to reason about enzyme kinetics?*

<b>Symbolic Forms</b>	
dependence	A value is dependent or not dependent on another value; for simplicity, this code encompasses Sherin's <sup>33</sup> "dependence cluster" ( <i>dependence, no dependence, sole dependence</i> ).
scaling exponentially	A value raised to a particular power tunes the size or magnitude of an entity.
<b>Graphical Forms</b>	
straight means constant	A straight line is associated with a lack of change or something being constant.
trend from shape directionality	Associating a graph with its overall tendency to increase or decrease (positive or negative trend).
<b>Chemistry Content</b>	
rate law	Discussion of rate laws (equation), which often involved a discussion of reaction order.
reaction order	Discussion of reaction order, which often involved the graphical representation of order.

**Appendix Table 4** Code descriptions relevant for addressing the second research question: *How do students reason about the particulate-level mechanism associated with enzyme kinetics and enzyme inhibition?*

<b>Enzyme Inhibition</b>	
competitive, Vmax & Km	Student discusses how this inhibitor influences the V-max and Km values of the velocity vs. substrate graph; this is normally in a general sense and in response to prompting from the interviewer and the student does not necessarily explain why this inhibitor causes these changes.
competitive, mechanism	Student discusses what physically happens with this inhibitor in a general sense or at the molecular level; often combined with other codes such as when student is discussing the reaction or scheme or reasoning about the inhibitor's influence on V-max and Km (to consider why the inhibitor influences these kinetic parameters).
non-competitive, Vmax & Km	Student discusses how this inhibitor influences the V-max and Km values of the velocity vs. substrate graph; this is normally in a general sense and in response to prompting from the interviewer and the student does not necessarily explain why this inhibitor causes these changes.

**Appendix Table 4** continued

non-competitive, mechanism	Student discusses what physically happens with this inhibitor in a general sense or at the molecular level; often combined with other codes such as when student is discussing the reaction or scheme or reasoning about the inhibitor's influence on V-max and Km (to consider why the inhibitor influences these kinetic parameters).
uncompetitive, Vmax & Km	Student discusses how this inhibitor influences the V-max and Km values of the velocity vs. substrate graph; this is normally in a general sense and in response to prompting from the interviewer and the student does not necessarily explain why this inhibitor causes these changes.
uncompetitive, mechanism	Student discusses what physically happens with this inhibitor in a general sense or at the molecular level; often combined with other codes such as when student is discussing the reaction or scheme or reasoning about the inhibitor's influence on V-max and Km (to consider why the inhibitor influences these kinetic parameters).
non vs. un confusion	Student states that they are confused by the distinction between noncompetitive and uncompetitive, or they express confusion with the similar-sounding names.
<b>Interpreting Inhibition Graph</b>	
inhibitor #1 (red)	Paired with one of the other codes to describe what feature of the inhibitor #1 (red) curve they are discussing.
inhibitor #2 (green)	Paired with one of the other codes to describe what feature of the inhibitor #2 (green) curve they are discussing.
competitive, identifies curve as	Paired with "inhibitor #1 (red)" or "inhibitor #2 (green)"; student states that the curve represents a competitive inhibitor.
non-competitive, identifies curve as	Paired with "inhibitor #1 (red)" or "inhibitor #2 (green)"; student states that the curve is a noncompetitive inhibitor.
uncompetitive, identifies curve as	Paired with "inhibitor #1 (red)" or "inhibitor #2 (green)"; student states that the curve represents an uncompetitive inhibitor.
higher Km	Paired with "inhibitor #1 (red)" or "inhibitor #2 (green)"; student discusses how in comparison to the no-inhibitor (blue) curve, the Km is higher; in some cases the student only says the Km "changes" or is "different" without explicitly saying how, although this is often clarified based on what they drew on the graph).
higher Vmax	Paired with "inhibitor #1 (red)" or "inhibitor #2 (green)"; student discusses how in comparison to the no-inhibitor (blue) curve, the V-max is higher; not common in data.
inhibitor #1 (red)	Paired with one of the other codes to describe what feature of the inhibitor #1 (red) curve they are discussing.
inhibitor #2 (green)	Paired with one of the other codes to describe what feature of the inhibitor #2 (green) curve they are discussing.
lower Km	Paired with "inhibitor #1 (red)" or "inhibitor #2 (green)"; student discusses how in comparison to the no-inhibitor (blue) curve, the Km is lower.

**Appendix Table 4** continued

lower Vmax	Paired with “inhibitor #1 (red)” or “inhibitor #2 (green)”; student discusses how in comparison to the no-inhibitor (blue) curve, the V-max is lower; in some cases the student only says the V-max “changes” or is “different” without explicitly saying how, although this is often clarified based on what they drew on the graph.
same Km	Paired with “inhibitor #1 (red)” or “inhibitor #2 (green)”; student discusses how in comparison to the no-inhibitor (blue) curve, the Km is the same.
same Vmax	Paired with “inhibitor #1 (red)” or “inhibitor #2 (green)”; student discusses how in comparison to the no-inhibitor (blue) curve, the Vmax is the same.

## APPENDIX F: RESOURCE GRAPHS

**Appendix Table 5** Resource graphs for students' conceptions of competitive, noncompetitive, and uncompetitive enzyme inhibition.

	Competitive Inhibition	Noncompetitive Inhibition	Uncompetitive Inhibition
<b>Sarah</b>			
<b>Ellie</b>			
<b>Kelly</b>			
<b>Alan</b>			
<b>Amanda</b>			

Appendix Table 5 continued

Cathy			
Lex			
Malcolm			
Zara			
Vivian			
Karen			

Appendix Table 5 continued

Tim			
Claire			
Carrie			
Summary for each inhibitor			
Summary for all inhibitors			

## APPENDIX G: PARTICIPANT RECRUITMENT INFORMATION

### Initial E-mail

Are you interested in...

*...participating in research at Purdue University?*  
*...improving chemistry courses at Purdue University?*  
*...leaving a legacy for future students?*

Please consider participating in a **one-on-one confidential interview** regarding topics in biochemistry! As a student in CHM 339, you are a perfect candidate! Your participation is voluntary, and you must be 18 years or older. Those who complete an interview will receive a **\$20 gift card!**

If you are interested, please use the link below to indicate your availability:

[https://purdue.ca1.qualtrics.com/jfe/form/SV\\_d0GRPX5YgGVTj7f](https://purdue.ca1.qualtrics.com/jfe/form/SV_d0GRPX5YgGVTj7f)

**Interviews will be arranged according to your schedule and can start as early as next week.** Any questions you have about this study or our research can be directed to Johnny Rodriguez ([rodri461@purdue.edu](mailto:rodri461@purdue.edu)) or Marcy Towns, the Principal Investigator on this project ([mtowns@purdue.edu](mailto:mtowns@purdue.edu)).

You are being contacted based on previously expressing interest when I gave a brief description of this research project during a CHM 339 lecture. If you are no longer interested, please discard this e-mail. Thank you for your time.

Best,

Johnny

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*Jon-Marc G. Rodriguez  
Graduate Student & Research Assistant  
Towns Research Group  
Purdue University, Department of Chemistry  
560 Oval Drive  
West Lafayette, IN 47907*

**Follow-up E-mail:**

Hi [student name],

I hope all is going well with your studies. Thank you so much for responding to the survey. Based on your response, it appears this week at

**[time, date, room (WTH 107 or WTH 229)]**

would be a great time to meet for the interview. You do not need to bring anything, and it will probably take about an hour. Thank you so much for your participation. If you have any questions, feel free to contact me.

**Please reply to this e-mail stating whether or not you are able to make this appointment.**

Best,

Johnny

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*Jon-Marc G. Rodriguez  
Graduate Student & Research Assistant  
Towns Research Group  
Purdue University, Department of Chemistry  
560 Oval Drive  
West Lafayette, IN 47907*



## PUBLICATIONS

### Peer-Reviewed Publications

- Rodriguez, J. G.** & Towns, M. H. (2019). Investigating Student Understanding of Michaelis-Menten and Lineweaver-Burk Plots. Manuscript in preparation.
- Rodriguez, J. G.** & Towns, M. H. (2019). Catalyzing student learning: Using analogies to teach enzyme kinetics. *Journal of Chemical Education*, Submitted.
- Rodriguez, J. G.**, Bain, K., & Towns, M. H. (2019). Mathematics in a chemistry context: Implications for mathematics instruction and research on undergraduate mathematics education. *International Journal of Research in Undergraduate Mathematics Education*, Submitted.
- Bain, K., **Rodriguez, J. G.**, & Towns, M. H. (2019). Investigating Student Understanding of Rate Constants: When is a Constant “Constant”? *Journal of Chemical Education*, Submitted.
- Rodriguez, J. G.** & Towns, M. H. (2019). Analysis of student reasoning about Michaelis-Menten enzyme kinetics: mixed conceptions of enzyme inhibition. *Chemistry Education Research and Practice*, Submitted.
- Rodriguez, J. G.**, Bain, K., & Towns, M. H. (2019). Graphical forms: The adaption of Sherin’s symbolic forms for the analysis of graphical reasoning across disciplines. *International Journal of Research in Undergraduate Mathematics Education*, Submitted.
- Rodriguez, J. G.**, Bain, K., Hux, N. P., & Towns, M. H. (2019). Productive features of problem solving in chemical kinetics: more than just algorithmic manipulation of variables. *Chemistry Education Research and Practice*, 20, 176-186, DOI: 10.1039/c8rp00202a.
- Rodriguez, J. G.**, Bain, K., Elmgren, M., Towns, M. H., & Ho, F. M. (2019). Covariational reasoning and mathematical narratives: Investigating students’ understanding of graphs in chemical kinetics. *Chemistry Education Research and Practice*, 20, 107-119, DOI: 10.1039/c8rp00156a.
- Rodriguez, J. G.** & Towns, M. H. (2018). Modifying laboratory experiments to promote engagement in critical thinking by reframing pre-Lab and post-Lab questions. *Journal of Chemical Education*, 95, 2141-2147.
- Rodriguez, J. G.**, Santos-Diaz, S., Bain, K., & Towns, M. H. (2018). Using symbolic and graphical forms to analyze students’ mathematical reasoning in chemical kinetics. *Journal of Chemical Education*, 95, 2114-2125.
- Rodriguez, J. G.**, Hensiek, S., Meyer, J. R., Harwood, C. J., & Towns, M. H. (2018). Buffers in context: Baby wipes as a buffer system. *Journal of Chemical Education*, 95, 1816-1820.
- Bain, K., **Rodriguez, J. G.**, & Towns, M. H. (2018). Zero-order chemical kinetics as a context to investigate student understanding of catalysts and half-life. *Journal of Chemical Education*, 95, 716-725.
- Bain, K., **Rodriguez, J. G.**, Moon, A., & Towns, M. H. (2018). The characterization of cognitive processes involved in chemical kinetics using a blended processing framework. *Chemistry Education Research and Practice*, 19, 617-628.

**Rodriguez, J. G.**, Bain, K., Moon, A., Mack, M. R., DeKorver, B. K., & Towns, M. H. The citation index of chemistry education research in the Journal of Chemical Education from 2008 to 2016: A closer look at the impact factor. *Journal of Chemical Education*, 94, 558-562.

#### **Peer-Reviewed Book Chapters**

**Rodriguez, J. G.**, Bain, K., & Towns, M. H. (2019). Graphs as Objects: Analysis of the Mathematical Resources Used by Undergraduate Biochemistry Students to Reason About Enzyme Kinetics. In Towns, M. H., Bain, K., & Rodriguez, J. G., (Eds.), *It's Just Math: Research on Students' Understanding of Chemistry and Mathematics*, Vol. 1316. American Chemical Society, Washington, DC.

Bain, K., **Rodriguez, J. G.**, Moon, A., & Towns, M. H. (2019). Mathematics in Chemical Kinetics: Which is the Cart and Which is the Horse? In Towns, M. H., Bain, K., & Rodriguez, J. G., (Eds.), *It's Just Math: Research on Students' Understanding of Chemistry and Mathematics*, Vol. 1316. American Chemical Society, Washington, DC.

Towns, M. H., Bain, K., & **Rodriguez, J. G.** (2019). How did we get here? Using and applying mathematics in chemistry. In Towns, M. H., Bain, K., & Rodriguez, J. G., (Eds.), *It's Just Math: Research on Students' Understanding of Chemistry and Mathematics*, Vol. 1316. American Chemical Society, Washington, DC.

Ho, F. M., Elmgren, M., **Rodriguez, J. G.**, Bain, K., & Towns, M. H. (2019). Student Understanding of Graphs in Chemical Kinetics – Covariational Reasoning and Mathematical Narratives. In Towns, M. H., Bain, K., & Rodriguez, J. G., (Eds.), *It's Just Math: Research on Students' Understanding of Chemistry and Mathematics*, Vol. 1316. American Chemical Society, Washington, DC.

## Using Symbolic and Graphical Forms To Analyze Students' Mathematical Reasoning in Chemical Kinetics

Jon-Marc G. Rodriguez,<sup>†</sup> Stephanie Santos-Diaz,<sup>†</sup> Kinsey Bain,<sup>‡</sup> and Marcy H. Towns<sup>\*,†</sup>

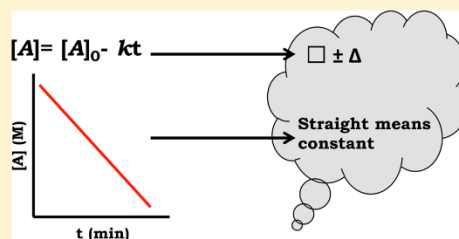
<sup>†</sup>Department of Chemistry, Purdue University, West Lafayette, Indiana 47907, United States

<sup>‡</sup>Department of Chemistry, Michigan State University, East Lansing, Michigan 48824, United States

**ABSTRACT:** This work is part of a larger project that seeks to understand how students blend (integrate) chemistry and mathematics as they work through chemical kinetics problems. Here we focus on four students from our larger sample: two students that demonstrated more instances of blending chemistry and mathematics in their interviews ("high-frequency blenders") and two students that did not have any instances of blending chemistry and mathematics in their interviews ("nonblenders"). In this study, we characterized the intuitive mathematical ideas the students associated with equations (symbolic forms) and graphs (graphical forms), focusing on how the students' mathematical reasoning influenced their understanding of chemical phenomena. The findings suggest that, in order for students to integrate chemistry and mathematics in a way that supports their understanding of the chemical processes in chemical kinetics, they must be able to reason using symbolic and graphical forms.

**KEYWORDS:** First-Year Undergraduate/General, Upper-Division Undergraduate, Chemistry Education Research, Kinetics, Interdisciplinary/Multidisciplinary

**FEATURE:** Chemical Education Research



Chemistry is inherently a multidisciplinary field in part due to the foundational role mathematics plays in modeling and describing chemical processes. This is particularly the case for the topic under consideration: chemical kinetics, a branch of study in chemistry that is related to modeling the rate of change of species in a chemical reaction, which readily lends itself to being described using mathematical formalisms such as those afforded by differential calculus. Moreover, there is a rich body of literature that correlates mathematical ability with success in undergraduate chemistry.<sup>1–9</sup> For example, low scores on the math portion of standardized exams such as the SAT have been used in general chemistry courses to identify at-risk students and determine topics in chemistry that are particularly challenging.<sup>10,11</sup> While it has been reported that performance in high school mathematical subjects is a better predictor of success in college (as measured by GPA),<sup>12</sup> SAT scores are still relevant as these influence the students' decisions on which college to attend and which career to pursue.<sup>13</sup> Since mathematics is often the language used to describe chemical phenomena, it is important to analyze how students think and reason about mathematical expressions so that we can scaffold their understanding in a way that is productive for learning.<sup>2,14</sup>

We define scientific modeling as a process that involves students engaging in developing, evaluating, and working with models that reflect empirical data, as well as the ability to consider ideas regarding the nature of models, such as their roots in experimental data and their limitations.<sup>15,16</sup> Furthermore, the process of engaging in modeling can be described as

a scientific practice (a noncontent skill that moves beyond discipline-based ideas), the importance of which has been stated by faculty and national-level organizations, such as the American Chemical Society and the National Research Council.<sup>17–23</sup> The study we describe in this work is part of a larger project with the aim of investigating students' understanding and use of chemistry and mathematics. We have previously published results from this project,<sup>24</sup> focusing on students' engagement in modeling using the blended processing framework.<sup>25,26</sup> In this paper, using the shared data corpus of the larger project, we build on our prior work by characterizing students' mathematical reasoning and analyzing the extent in which it influenced students' abilities to engage with chemical kinetics concepts, a subject that has previously been identified as understudied in the literature.<sup>27,28</sup> To this end, the research question that guided this study is *How does student understanding of equations and graphs influence their understanding of phenomena modeled in chemical kinetics?*

### LITERATURE REVIEW

According to published literature reviews, chemical kinetics is currently not well represented in the chemistry education research literature, with most studies focusing on identifying and cataloging alternative conceptions (misconceptions),

Received: July 20, 2018

Revised: September 10, 2018

Published: October 8, 2018

suggesting the need for more work to be done within this context; we direct readers to these reviews for a more comprehensive review of studies placed in the context of chemical kinetics.<sup>27,28</sup> A more recent study by Becker, Rupp, and Brandriet<sup>14</sup> influenced this work, which, along with Cooper and Stowe,<sup>29</sup> suggested the need to move beyond discussing alternative conceptions to focus on student reasoning and how we can guide students to use their knowledge productively. The review that follows focuses primarily on work that relates to students' mathematical reasoning, adopting more of an interdisciplinary perspective to provide context for this study.<sup>30</sup>

### Research on Mathematical Reasoning

Due to the heavy reliance in chemistry on mathematics, it is important for chemistry education researchers to broaden their familiarity with research to encompass fields that discuss related areas of concern. For example, a review of the literature in undergraduate mathematics education reveals that students have difficulty with concepts related to the derivative and rate, which helps explain why students have difficulty applying calculus in other contexts such as chemistry.<sup>2,31–33</sup>

Since we will be analyzing both mathematical expressions and graphical representations, we will adopt the general term *inscription*, which encompasses equations, expressions, and graphs, as well as a variety of other nontextual representations.<sup>2,34</sup> It has been noted that inscriptions are more powerful when they communicate more information, but as the inscriptions become encoded with more information, they also become more abstract and distant from the related physical phenomena, which increases student difficulties associated with making connections between equations and their meaning.<sup>2,24,34</sup>

**Symbol Sense.** Particularly relevant for this study, research on undergraduate mathematics education has emphasized the importance of *symbol sense*, which involves a deep understanding of the versatility and utility of symbols.<sup>35,36</sup> Having roots in the idea of *number sense*, when students have symbol sense they are able to algebraically manipulate equations and expressions to solve a problem, but they are also able to move beyond algorithmic problem-solving approaches to think more globally in terms of the meaning and implications of symbols and symbolic relationships.<sup>35–37</sup> It is important to note that the construct of symbol sense is a purely mathematical idea in which students are encouraged to be very reflective and aware of their algebraic manipulations. In the context of physical science problem solving, there is an additional layer of conceptual knowledge that needs to be incorporated as students model physical phenomena. Symbols mediate the connection between the physical world and how we think about phenomena, a process that is not trivial, due to the complexity of symbolic notations and the abstract relationship between mathematical expressions and the phenomena they reflect.<sup>2,34,38,39</sup>

Understanding based on the construct of symbol sense is closely related to Gray and Tall's<sup>40</sup> conceptualization of successful mathematics thinkers that are able to view mathematical expressions and representations as both a process and a concept, dynamically moving between both conceptualizations when necessary. According to Tall et al.,<sup>41</sup> "Symbols occupy a pivotal position between processes to be carried out and concepts to be thought about. They allow us both to *do* mathematical problems and to *think* about mathematical relationships [emphasis in the original]." Building on the idea of the duality of purposes communicated by symbols in mathematics, Rubenstein and Thompson<sup>42</sup> discussed a more complex,

nuanced understanding, in which symbols serve a myriad of functions that can be verbalized, read, and written in different ways, providing challenges for student engagement with symbolic representations. This reflects a level of higher-order thinking that is reflective and aware of additional factors, such as how context can influence the meaning of variables and when particular approaches and representations are better suited for a problem-solving scenario.<sup>35</sup>

**Graphical Reasoning.** As articulated by Johnstone,<sup>43</sup> although not all aspects of science, technology, engineering, and mathematics-related knowledge or skills are necessary or relevant for the average modern citizen (e.g., a particulate-level understanding of acid–base titrations), arguably some skills are fundamental to have an informed citizenry. In a review paper about students' ability to interpret graphs, Glazer<sup>44</sup> framed graphical reasoning as critical for students to be able to engage with modern social issues. Similar sentiments have been echoed by researchers, who have discussed the importance of getting students to think about data, how it is represented, and the limits associated with data collection.<sup>20,45–48</sup> However, being able to reason about the trends and the information a graph communicates is a complex competency to master; research shows that students have difficulty reasoning about graphs, even when devoid of the additional dimension of conceptual reasoning associated with discipline-specific topics.<sup>49</sup> Thus, when placed in the context of physical sciences, students have increased difficulty with reasoning about graphs.<sup>50,51</sup> Chemistry, for example, can be particularly challenging for students, because it deals largely with abstract ideas on a scale not readily observable to students, making graphical reasoning and modeling even more challenging for novices.<sup>52</sup> This is troubling because students are being asked to utilize abstract mathematical formalisms to represent abstract processes. It is increasingly important to study students' understandings and use of mathematics in fields such as chemistry, so instructors can learn how to better provide support for students as they engage in modeling.

## ■ THEORETICAL PERSPECTIVES

### Resources Framework

The resources perspective conceptualizes the cognitive structure of knowledge as a system of interacting fine-grained components, generally referred to as "resources".<sup>53,54</sup> These resources are constructed by individuals and activated in specific contexts, encompassing procedural knowledge, epistemological ideas, or conceptual knowledge.<sup>14</sup> One example of constructed student ideas that are deeply rooted in experience is the conceptualization of "phenomenological primitives" or "p-prims", which are simple and intuitive ideas developed on the basis of observations and experiences.<sup>55</sup> In Sherin's "How Student's Understand Physics Equations",<sup>56</sup> he discussed symbolic forms as an analytic framework that describes a unique category of p-prims, which characterizes students' intuitive ideas regarding equations and expressions. It is within the symbolic forms framework (and the closely related graphical forms framework) that this study is situated.

**Symbolic and Graphical Forms.** Reasoning involving symbolic forms occurs when an individual assigns mathematical ideas ("conceptual schema") to a pattern in an equation ("symbol template").<sup>56</sup> To illustrate this notion using chemical kinetics as a context, consider the zero-order integrated rate law which is listed as item (1) below. According to

Table 1. Examples of Symbolic Forms Adapted or Reproduced from Sherin<sup>56</sup>

Symbolic Form	Symbol Template	Conceptual Schema
Base $\pm$ change	$\square \pm \Delta$	A change increases or decreases an initial value
Canceling	$0 = \square - \square$	Two influences that precisely cancel so there is no net outcome
Canceling (b)	$\frac{[\dots x \dots]}{[\dots x \dots]}$	Identical symbols that appear in the numerator and the denominator cancel
Coefficient	$[x]\square$	A value that multiplies a group of factors, scaling and controlling the size of an effect
Dependence	$[\dots x \dots]$	A whole depends on a quantity associated with an individual symbol
Identity	$x = \dots$	A single symbol that appears alone on one side of an equation has the same properties as the expression on the other side
No dependence	$[\dots]$	A whole does not depend on a quantity associated with an individual symbol
Scaling	$[n]\square$	Similar to coefficient, but the coefficient is unitless; a scaling coefficient is seen as operating on the rest of the factors to produce an entity of the same sort that is larger or smaller than the original
Prop-	$\frac{[\dots]}{[\dots x \dots]}$	Indirectly proportional to a quantity, $x$ , which appears as an individual symbol in the denominator
Template Key		
[ ... ] Expression in brackets corresponds to an entity in the schema		
$x$ Individual symbols in an expression		
$\square$ A term or group of terms		
... Omitted portions of an expression that are inconsequential or continue a pattern		

Sherin,<sup>56</sup> when students see the right side of the equation with the  $[A]_0 - kt$  group of terms, they may be cued to think about an initial value or base,  $[A]_0$ , that is altered by another value,  $kt$ . Within Sherin's framework, this is described as the *base – change* symbolic form, which is shown in general terms in item 2, where  $\square$  can be substituted for any variable/term and  $\Delta$  signifies a change.

- (1)  $[A] = [A]_0 - kt$  (zero-order integrated rate law)
- (2)  $\square - \Delta$  (symbol template for *base – change* symbolic form)

The importance of symbolic forms is the extent to which this mathematical reasoning supports an understanding of phenomena, particularly in the physical sciences. To continue building on the example provided, before learning any chemical kinetics content, when students read an equation such as item 1, they may bring in ideas about the system being modeled due to recognition of the specific symbolic pattern (such as ideas regarding how a value changes, a central tenet of chemical kinetics). More examples of symbolic forms, with symbol templates and corresponding conceptual schema are provided in Table 1.

Sherin's symbolic forms was originally conceptualized to analyze reasoning about equations, but since we are interested in student use of inscriptions, not just equations, for this study, we also employ the graphical forms framework, which affords the ability to analyze students' graphical reasoning in a way that is analogous to symbolic forms. We have previously utilized the graphical forms framework to analyze students' graphical reasoning,<sup>57</sup> and in a forthcoming paper we describe the framework in more detail, demonstrating its utility across discipline-based education fields.<sup>58</sup> The general idea of graphical forms is the same as symbolic forms, in which mathematical ideas are assigned to a pattern, but in the context

of graphical reasoning, the pattern (i.e., registration) focused on by students is a region in a graph or an entire graph. For example, the graphical form *steepness as rate* involves registering or associating ideas related to rate with the relative steepness of the graph. See Table 2 for examples of the graphical forms we previously identified.

Table 2. Summary of Graphical Forms Reproduced or Adapted from Rodríguez et al.<sup>57,58</sup>

Graphical Form	Registration and Conceptual Schema
Steepness as rate	Varying levels of steepness in a graph correspond to different rates
Straight means constant	A straight line indicates a lack of change/constant rate
Curve means change	A curve indicates continuous change/changing rate

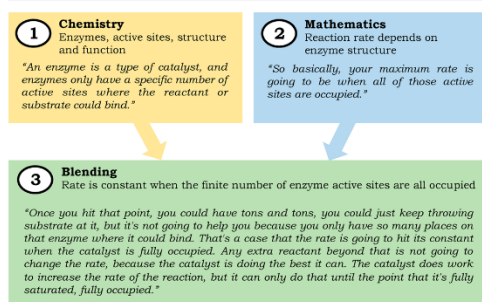
As discussed by Rodríguez and colleagues,<sup>57,58</sup> it is useful to pair the graphical forms framework with Nemirovsky's<sup>57</sup> description of mathematical narratives, which describes modeling as considering the "story" represented in a graph. In Nemirovsky's study,<sup>59</sup> students noted different regions of the graph and associated specific ideas with each distinct region of the graph (the reverse case was also noted in which students focused on specific aspects of a process and discussed how this would be represented graphically). Returning to our chemical kinetics example, if we think of a standard concentration vs time graph, the shape of the graph implies a specific particulate-level mechanism, with different regions of the graph communicating different parts of the story that compose the overall process. Thus, when students combine graphical forms (i.e., intuitive mathematical reasoning about graphs) with content-specific knowledge (e.g., chemistry concepts), they are engaging in discussing mathematical narratives, which can



be considered a special case of engaging in blended processing.

### Blended Processing

Blended processing as a framework has its roots in cognitive science and describes the integration or *blending* of ideas from different knowledge spaces.<sup>25,26</sup> According to Bing and Reddish,<sup>60</sup> a knowledge space can be conceptualized as a group of related resources that are activated together; thus, blending involves integrating different clusters of knowledge (e.g., when individuals combine ideas from mathematics and chemistry). In our previous work, we utilized blended processing to describe how students integrated chemistry and mathematics when they worked through chemical kinetics problems, conceptualizing blended processing as a framework that allowed for a fine-grain analysis of student engagement in modeling.<sup>24</sup> To illustrate and summarize our previous characterization of blending, consider the quote in Figure 1 where Blair (a student



**Figure 1.** Example of blended processing, in which the student combined chemical and mathematical ideas by (1) discussing chemistry concepts related to enzymes, (2) quantifying this conceptualization, and (3) considering the implications for rate; figure adapted from Bain et al.<sup>24</sup> with permission. Copyright 2018 Royal Society of Chemistry.

enrolled in physical chemistry for life sciences) discussed an enzyme–substrate system and how that relates to rate; she discussed enzyme structure and function considerations and related this to the influence of concentration on rate, a connection that was mediated by quantifying the relationship between rate and enzyme structure. In this example, Blair blended chemistry and mathematics ideas, which provided a more holistic understanding of the phenomena. Thus, blended processing derives its importance from its synergistic properties that affords students insight about phenomena, and instruction should create opportunities to promote meaningful connections between physical science concepts and mathematics.<sup>24,60–62</sup> Blended processing is particularly relevant for this study, because our selection of students from the larger sample was based on their ability to blend chemistry and mathematics; this is described in more detail in the [Methods](#) section.

## METHODS

### Student Participants

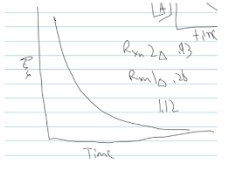
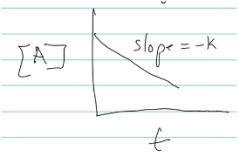
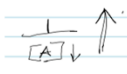
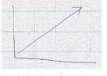

This study is part of a larger project implemented in the context of chemical kinetics that focuses on the interaction between chemical and mathematical knowledge. For the larger

project, a total of 48 students were sampled across two semesters (fall 2015 and spring 2016) from introductory and upper-level chemistry courses, with all aspects of this project implemented in accordance with our university's Institutional Review Board. Using this data set, we previously reported our characterization based on student ability to blend chemistry and mathematics concepts by attributing physical (chemical) meaning to equations or mathematizing physical scenarios.<sup>24</sup> Here, the goal is to utilize the same data corpus and focus on students' intuitive mathematical concepts, ideas that are largely independent of a science discipline, but are useful for understanding science concepts.

For this study, our intention with sampling was to compare students on the basis of their ability to blend chemistry and mathematics. In the study described by Bain et al.,<sup>24</sup> students characterized as "high-frequency blenders" displayed more frequent instances of the integration of mathematics and chemistry ideas (which is an indication of more expert-like thinking in physical science fields<sup>57</sup>); in contrast, students characterized as "nonblenders" displayed no instances of integrating mathematics and chemistry ideas. Thus, our aim is to compare the mathematical reasoning of high-frequency blenders and nonblenders. However, in selecting interviews from our larger sample to analyze, we considered additional criteria. All student interviews were selected from the students sampled in spring of 2016 from a second-semester general chemistry course intended for engineering majors. We intentionally selected interviews where the students had the correct final answer for both chemistry prompts (interview prompts discussed in the section to follow). The rationale for selecting interviews where students solved the prompts correctly was to further investigate students' reasoning, emphasizing that the goal for instruction should not be to simply get students to answer a question correctly; rather, we want students to have a deeper, more meaningful understanding of chemistry principles. In addition, each student interview was "math-first", meaning students received the "math prompt" before the "chemistry prompt", as opposed to the converse. This is relevant in order to account for the priming effects associated with prompt order (as reported in Bain et al.<sup>24</sup>).

On the basis of our selection criteria, four students' interviews (Steven, Howie, Louis, and Isabel) were intentionally chosen for analysis from the larger sample. According to our previous analysis discussed in Bain et al.,<sup>24</sup> Steven and Howie were characterized as high-frequency blenders, whereas Louis and Isabel were characterized as nonblenders. In [Table 3](#), we provide examples to describe how the selected high-frequency blenders discussed contexts in comparison to the selected nonblenders. For example, Steven and Louis both discussed how the variable  $[A]$  changes with time; however, Louis' discussion of a zero-order reaction was dominated by mathematical reasoning, without considering the physical meaning encoded in this representation. This is in contrast to Steven's discussion of a second-order reaction, which more explicitly utilized knowledge of the system and combined this with mathematical reasoning to describe the shape of the curve in relation to the reaction. Blending is also exemplified in Howie's explanation regarding why the second-order integrated rate law has a positive  $k$  ( $\frac{1}{[A]} = kt + \frac{1}{[A]_0}$ ), as opposed to the zero-order integrated rate law, which has a negative  $k$  ( $[A] = -kt + [A]_0$ ). In this instance, Howie was able to reason more deeply than Isabel, making use of the idea that the reactant,  $A$ , decreases

Table 3. Student Discussions Highlight the Differences between Student Responses That Involve Blending

High-Frequency Blenders	Non-Blenders
<p><b>How does [A] change over time?</b></p> <p><b>Steven:</b> "Since, if you graph it out, the slope would be, if you just graph it out like, concentration over time [student later clarified that y-axis on graph should say 'concentration'], pretty sure it would kind of be like half of a parabola, because it's going to be starting off fast because there's a high concentration, okay. Then if it goes on, in a sense it's a more heavily dependent on concentration, I guess you could say, since it's the second order. That means that the rate's going to kind of steeply drop off as time goes on, just by the fact that there's fewer reactants."</p>  <p>(second-order chemistry prompt)</p>	<p><b>Louis:</b> "I guess the coordinates would be t comma concentration of A, yeah . . . Yeah, so you'd have your concentration of A and then t and then this should be a straight line."</p>  <p>(zero-order math prompt)</p>
<p><b>Why is the sign of k different for the second-order and zero-order integrated rate laws?</b></p> <p><b>Howie:</b> "Concentration of A almost always goes down as long as it's a reactant, unless you're dealing with the reverse of an equilibrium something. Molarity of A almost always goes down, but if it's one over the molarity of A, this is why that's positive [k in the second-order integrated rate law], if it's one over the molarity of A, then as A gets smaller, one over the molarity, this whole thing is going to get bigger. As the concentration of A goes down, the y of the integrated second-order rate law goes up."</p>  <p>(zero-order math prompt)</p>	<p><b>Isabel:</b> "It's the slope. All I know is that one, if you graph that equation, it's going to look like this, like the line will go up. Then this equation, the line's going to go this way."</p>  <p>I think that's why, because the k is the slope and if it's a negative slope, it's going to go towards this way . . .</p>  <p>I'm not sure about that [difference in signs]."</p> <p>(zero-order math prompt)</p>

over the course of the reaction, which is consistent with the mathematical expression. In the examples of blending shown in Table 3, the reasoning of the high-frequency blenders involved the use of graphical and symbolic forms, whereas the responses from the nonblenders did not, suggesting a relationship between graphical/symbolic and engaging in blending, a sentiment that will be discussed in more detail later. This discussion of blending helps serve as a foundation for the remainder of the study, which is centered on investigating students' mathematical reasoning and the extent to which it supported their understanding of physical systems.

#### Data Collection and Analysis

The primary source of data for the larger project was collected through semistructured interviews using a think-aloud protocol in which students' written and audio responses were collected using a Livescribe smartpen, which provides a real-time digital recording of student work.<sup>63–65</sup> During the interviews, students were provided four prompts to work through: two prompts that involved textbook-style chemical kinetics problems (a second-order and a zero-order "chemistry prompt") and two prompts that involved students explaining a provided integrated rate law equation (a second-order and zero-order "math prompt"). The prompts are provided in Table 4. Following transcription of the student interviews, the transcripts were then coded to yield the themes described in Bain et al.<sup>24</sup> Here we report the results from an additional layer

of analysis using the analytic frameworks described by Sherin<sup>56</sup> and Rodriguez et al.,<sup>57,58</sup> this process involved deductive analysis to characterize Steven, Howie, Louis, and Isabel's mathematical reasoning using the descriptions provided by the symbolic forms (Table 1) and graphical forms (Table 2) frameworks. Throughout the entire data analysis process, two researchers coded the interviews in tandem using a constant-comparison methodology to refine and modify the coding scheme, only assigning codes once 100% intercoder agreement was met.<sup>24,66,67</sup>

#### RESULTS AND DISCUSSION

Across the math and chemistry prompts, we noted variation in the graphical and symbolic forms employed by Steven, Howie, Louis, and Isabel. Generally, different symbolic and graphical forms were paired with specific contexts, suggesting their utility in reasoning about particular concepts. Here we describe the range of student responses, followed by a discussion of the relationship between symbolic/graphical forms and engagement in blending chemistry with these mathematical ideas.

##### Symbolic Forms Used by Students

We found that most of the observed range of responses fit within the symbolic forms framework developed by Sherin.<sup>56</sup> In total we identified eight symbolic forms that reflected those previously discussed by Sherin,<sup>56</sup> along with one symbolic form

Table 4. Second-Order and Zero-Order Math and Chemistry Prompts

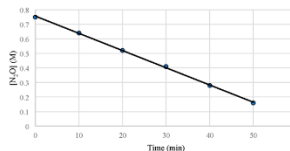
Second-Order Math Prompt	Zero-Order Math Prompt																																																
Here is another equation you've probably seen in class: $\frac{1}{[A]} = kt + \frac{1}{[A]_0}$ How would you explain this equation to a friend from class? How would you explain this on an exam?	Here is another equation you've probably seen in class: $[A] = -kt + [A]_0$ How would you explain this equation to a friend from class? How would you explain this on an exam?																																																
Second-Order Chemistry Prompt	Zero-Order Chemistry Prompt																																																
<p>A second-order reaction</p> $2 \text{C}_4\text{H}_6(\text{g}) \rightarrow \text{C}_8\text{H}_{12}(\text{g})$ <p>was run first at an initial concentration of 1.24 M and then again at an initial concentration of 2.48 M. They were run under the same reaction conditions (e.g., same temperature). Data collected from these reactions are provided in the table. Is the rate constant for reaction 2 (1.24 M) greater than, less than, or equal to the rate constant for reaction 1 (2.48 M)?</p> <table><thead><tr><th>Time (hrs)</th><th>[C<sub>4</sub>H<sub>6</sub>] (M)</th><th>R<sub>run 1</sub></th><th>R<sub>run 2</sub></th></tr></thead><tbody><tr><td>0</td><td>1.24</td><td>2.48</td><td></td></tr><tr><td>1</td><td>0.960</td><td>1.55</td><td></td></tr><tr><td>2</td><td>0.775</td><td>1.13</td><td></td></tr><tr><td>3</td><td>0.655</td><td>0.89</td><td></td></tr><tr><td>4</td><td>0.560</td><td>0.73</td><td></td></tr><tr><td>5</td><td>0.502</td><td>0.62</td><td></td></tr><tr><td>6</td><td>0.442</td><td>0.54</td><td></td></tr><tr><td>7</td><td>0.402</td><td>0.48</td><td></td></tr><tr><td>8</td><td>0.365</td><td>0.43</td><td></td></tr><tr><td>9</td><td>0.335</td><td>0.39</td><td></td></tr><tr><td>10</td><td>0.310</td><td>0.35</td><td></td></tr></tbody></table>	Time (hrs)	[C <sub>4</sub> H <sub>6</sub> ] (M)	R <sub>run 1</sub>	R <sub>run 2</sub>	0	1.24	2.48		1	0.960	1.55		2	0.775	1.13		3	0.655	0.89		4	0.560	0.73		5	0.502	0.62		6	0.442	0.54		7	0.402	0.48		8	0.365	0.43		9	0.335	0.39		10	0.310	0.35		<p>Below is a zero-order rate plot for the reaction</p> $\text{N}_2\text{O}(\text{g}) \rightarrow \text{N}_2(\text{g}) + \frac{1}{2}\text{O}_2(\text{g})$ <p>where <math>[\text{N}_2\text{O}]_0 = 0.75 \text{ M}</math> and <math>k = 0.012 \text{ M/min}</math>. The reaction is conducted at <math>575^\circ\text{C}</math> with a solid platinum wire, which acts as a catalyst. If you were to double the concentration of <math>\text{N}_2\text{O}</math> and run the reaction again, how would the half-life change? At the half-lives for each reaction run, how do the chemical systems compare?</p> 
Time (hrs)	[C <sub>4</sub> H <sub>6</sub> ] (M)	R <sub>run 1</sub>	R <sub>run 2</sub>																																														
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Table 5. Frequency of Symbolic Form Codes and Common Contexts

Symbolic Form <sup>a</sup>	High-Frequency Blenders		Nonblenders		Context
	Steven	Howie	Louis	Isabel	
Base $\pm$ change	4	1	0	0	Integrated rate laws
Canceling ( <i>b</i> )	1	1	0	0	First-order half-life equation; discussing conversion factors
Coefficient	0	0	1	0	$k$ in the integrated rate laws
Dependence	8	2	9	10	Factors that affect $k$ , rate of the reaction, half-life, and order
Identity	3	0	1	1	Relationship between slope and $k$
No dependence	9	2	3	5	Factors that affect $k$ , rate of the reaction, and half-life
Scaling	0	0	1	0	Factors that affect half-life
Scaling exponentially <sup>b</sup>	5	1	2	0	Factors that affect rate of the reaction
Prop.	0	1	0	0	Second-order integrated rate law

<sup>a</sup>A description of the symbolic forms is provided in Table 1. <sup>b</sup>This symbolic form was unique to our data set and has not yet been reported in the literature (the remaining symbolic forms were identified by Sherin<sup>56</sup>).

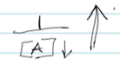
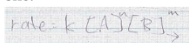
that was unique to our data set; these results are presented in Table 5. The specific context of our prompt involving values with exponents (e.g., students describing the reaction order in a rate law), as well as a discussion of zero-order reactions, led to the identification of a symbolic form not yet noted in the literature. We noted that students made use of the mathematical

notion of raising a value to a particular power, specifically to describe the rate laws. For example, doubling  $[A]$  in the rate law described by  $\text{rate} = k[A]^2$  quadruples the rate of the reaction. We characterized this symbolic form as *scaling exponentially* (symbol template,  $\square^{\square}$ ); this is similar to the symbolic form identified by Sherin,<sup>56</sup> *scaling*, which describes how a value tunes the size or magnitude of an entity. Describing a value raised to the zeroth power is a special case of *scaling exponentially*, and in our data set, this involved a student stating that the term raised to the zero power (e.g., concentration in the zero-order rate law) “goes away” or that it is “just one”. This is important because understanding the nature of this relationship is not trivial.<sup>68</sup> Beyond Steven, Howie, Louis, and Isabel, within the larger data corpus, it was noted that not all students correctly made this connection, with three of our students in our larger sample stating that a value to the zeroth power is zero.

Results indicate symbolic forms involving ideas related to what Sherin<sup>56</sup> referred to as the “dependence cluster” were used more frequently by the students; this includes the *dependence* and *no dependence* symbolic forms, with some examples of dependence-cluster symbolic forms provided in Table 6. As shown in Table 5, there were often specific contexts in which specific symbolic forms were used. For example, *no dependence* was one of the more common symbolic forms we identified, which all four students used to describe the fact that the rate of zero-order reactions does not depend on the concentration of reactants. In most cases a specific context was tied to a specific symbolic form, but in some cases, students used various symbolic forms; for example, Louis discussed half-life using the *scaling* symbolic form (Table 6), which is in contrast to Steven, Howie, and Isabel, who used *dependence/no dependence* symbolic forms in this context. Other examples observed were Howie and Steven’s description



Table 6. Student Reasoning and Use of Symbolic Forms

Student	Transcript and Written Work	Symbolic Form
Steven	<p>"Well, the concentrations other than the initial and final, they don't affect the rate at all. It's just basically the rate changes the amount with time, or the <math>k</math> constant, not the rate. The rate constant just changes with time, and it's not being multiplied by concentration. It reminds me of a physics equation, <math>v_f</math> equals <math>v_i</math> plus <math>at</math>. Basically saying, this is where you start off, this is the amount of change you have, and so, here's what your final is." (zero-order math prompt)</p>	<p>No dependence</p> <p>Dependence</p> <p>Base <math>\pm</math> change</p>
Howie	<p>"Concentration of A almost always goes down as long as it's a reactant, unless you're dealing with the reverse of an equilibrium something. Molarity of A almost always goes down, but if it's one over the molarity of A, this is why that's positive [<math>k</math> in the second-order integrated rate law], if it's one over the molarity of A, then as A gets smaller, one over the molarity, this whole thing is going to get bigger. As the concentration of A goes down, the <math>y</math> of the integrated second-order rate law goes up."  (zero-order math prompt)</p>	Prop-
Louis	<p>"I guess, if you had 0.1 moles of <math>N_2O_2</math>, it would take just 5 minutes to get to that half-life, but if you had 0.2 moles of <math>N_2O_2</math>, it would take 10 minutes to get to that." (zero-order chemistry prompt)</p>	Scaling
Isabel	<p>"Yeah, and <math>m</math> would be the <math>k</math> value. ... Because for each order of reaction, the order's different, so the power that goes on top of the concentration would be different, so the zero order, the power of it would be zero, which means one."  (zero-order math prompt)</p>	<p>Identity</p> <p>Scaling exponentially</p>

of the integrated rate laws using the *base  $\pm$  change* symbolic form, with Steven taking it a step further and drawing a comparison between the chemistry equation and an equation with the same pattern in physics (see Table 6).

#### Graphical Forms Used by Students

In our data set, students used the three graphical forms previously discussed in the literature (see Table 7): curve means change, steepness as rate, and straight means constant.<sup>57,58</sup> It is important to note that graphical forms were mostly used by Steven and Howie, the high-frequency blender participants. For example, they sketched plots to describe the rate of reactions, specifically how concentration changes over time depending on the order of the reaction or other related factors. In addition, Steven and Howie both used graphical forms to describe the graph provided in the zero-order chemistry prompt. As shown in Table 7, Howie made a reference to the shape of the graph to explain how a catalyst would influence different aspects of the reaction. According to Howie, the rate of an uncatalyzed reaction is represented as a curve, while a straight line represents the rate of a catalyzed reaction.

Steven sketched two plots of concentration versus time. In the first graph, Steven drew a curve (see Table 7) to portray a reaction that initially had a high concentration, subsequently associating the steepness of this curve with a decreasing reaction rate. For the second plot, Steven drew a straight, horizontal line to portray how the rate of a zero-order reaction is not dependent on concentration. Steven's horizontal line mathematically implies that the *concentration* of the reactant is

constant as opposed to the *rate*. In this sense, Steven associated *straight* with *constant*, but did not consider that when talking about a physical system (which involves the concentration decreasing over the course of the reaction), the line should be straight and should also have a downward slope. This suggests that in this instance Steven was not utilizing the additional layer of chemistry knowledge (i.e., discussing the mathematical narrative) to reason about this graph. Nevertheless, graphical forms served to support how Steven and Howie were reasoning about the chemistry prompts.

Graphical forms were not identified in Isabel's responses, and only one instance was identified for Louis, who utilized the graphical form *straight means constant*. When discussing a zero-order reaction and a linear plot of concentration versus time, Louis stated, "That would just say that the rate is constant throughout, it doesn't depend on the concentration, so the reactant, it'll still go as fast or slow as the original ..." The use of this graphical form indicates Louis associated a constant rate of reaction with a straight line, adding that rate is independent of concentration.

#### High-Frequency Blenders vs Nonblenders

Comparison between the patterns observed for the high-frequency blenders (Steven and Howie) and nonblenders (Louis and Isabel) helps address how students' mathematical reasoning influenced their understanding of chemistry. Given the varied contexts in which Steven and Howie used symbolic and graphical forms (see Table 8), we have reason to believe that access to more symbolic/graphical forms, and their use in

Table 7. Student Reasoning and Use of Graphical Forms

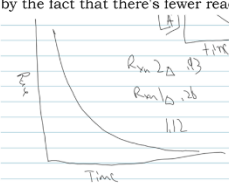
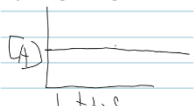
Student	Transcript and Written Work	Graphical Form
Howie	<p><b>Interviewer:</b> "What do you think would happen if you change the amount of catalyst in there, like you added more catalyst? Would it do anything to the reaction or the rate?"</p> <p><b>Howie:</b> "Not in this case. If it was more curved, it would. It would make it look more straight like this. I mean, it may change <math>k</math>."</p> <p><b>Interviewer:</b> "What would happen if you started taking some of the catalyst away?"</p> <p><b>Howie:</b> "Then it would slowly unslope and then I think it would bend into a curve." (zero-order chemistry prompt)</p>	Curve means change
Steven	<p>"Since, if you graph it out, the slope would be, if you just graph it out like, concentration over time [student later clarified that y-axis on graph should say 'concentration'], pretty sure it would kind of be like half of a parabola, because it's going to be starting off fast because there's a high concentration, okay. Then if it goes on, in a sense it's a more heavily dependent on concentration, I guess you could say, since it's the second order. That means that the rate's going to kind of steeply drop off as time goes on, just by the fact that there's fewer reactants."</p>  <p>(second-order chemistry prompt)</p>	Steepness as rate
Steven	<p>"... Well, you have a zero order reaction. I remember that from the book, it's a big part of it. A zero-order reaction, you have time, okay, and then, since it's zero order and concentration doesn't affect change ... You're going to have a line like that, it's just going to go straight across without adjusting in height at all because it's constant."</p>  <p>(second-order chemistry prompt)</p>	Straight means constant

Table 8. Contexts Discussed by Participants When Using Symbolic and Graphical Forms

High-Frequency Blenders	Nonblenders
Factors that affect rate constant	Factors that affect rate constant
Factors that affect rate of reaction	Factors that affect rate of reaction
Factors that affect half-life	Factors that affect half-life
Factors that affect the order of reaction	Factors that affect the order of reaction
Slope is rate constant	Slope is rate constant
Relating slope-intercept form of linear equation to integrated rate law	Rate constant "scales" the rate of reaction (rate law)
Rate law and order of reaction	Rate is dependent on concentration (rate law)
Describing integrated rate law	
Unit conversion	
Solving for the first order half-life equation	
Second-order integrated rate law	
Concentration vs time graphs	
Describing/interpreting provided graph	

varied contexts, allows for a more thorough understanding of chemical phenomena. Steven and Howie were able to use

different symbolic and graphical forms to discuss the prompt from different perspectives. For example, Steven used the *canceled* symbolic form to explain how dimensional analysis plays a role in determining the units of variables in the integrated rate laws, and Howie used the symbolic form *prop-* to solve for the first-order half-life equation. However, the non-blender participants did not use these symbolic forms, and they did not use symbolic forms in these contexts. This suggests that students who use varied symbolic and graphical forms engage in more frequent blending, affording students the ability to reason and make connections between mathematical and chemical ideas.

#### Mathematical Reasoning and Blending

Consistent with the findings of Kuo et al.,<sup>62</sup> we found that the ability to engage in reasoning characterized by symbolic forms (and in our case, graphical forms) supported students engagement in blended processing. Considering the high-frequency blenders, out of the eight times that Steven blended chemistry and mathematics in his interview, five of those instances involved symbolic or graphical forms; similarly, out of the five instances in which Howie blended, three instances involved

symbolic or graphical forms. For example, consider Steven's description of the second-order concentration vs time graph previously discussed in Table 7. In Steven's explanation, he associated the steepness or slope of the curve with rate, drawing the graph to illustrate his reasoning. This is an example of the graphical form *steepness as rate*, in which the registration attended to is the steepness of the curve, and the conceptual schema that is being associated with it are ideas regarding rate or the degree/extent of speed. It is interesting to note that Steven also mentioned the reason why the curve slopes more is because the reaction depends more on the concentration of the reactant, meaning in comparison to a first-order reaction (i.e.,  $\text{rate} = k[A]$ ); since there is a quadratic relationship between rate and the concentration of the reactants for a second-order reaction (i.e.,  $\text{rate} = k[A]^2$ ), rate will change to a much larger extent in response to changing amounts of reactants. Steven then took this idea a step further, blending the graphical form with chemistry ideas, discussing the story or mathematical narrative associated with the graph he drew, in which Steven discussed how reactants are depleted over time, which has implications for the steepness of curve. In this sense, Steven discussed a physical scenario, the story, and then graphically indicated how to communicate this narrative.

Another example in which symbolic and graphical forms promoted blending can be seen in Howie's discussion of the second-order integrated rate law (Table 6). Here, Howie made sense of the sign of the equation, by using the *prop-* symbolic form, which is related to thinking about inversely proportional relationships. He reasoned that as the value in the denominator,  $[A]$ , decreased, the value of the whole term increased. This mathematical reasoning is paired with chemistry understanding, in which he identified that  $[A]$ , the concentration of reactant A, should decrease as it is used up over the course of the reaction. This provides insight into Howie's earlier discussion of the second-order integrated rate law, where he provided a graphical representation (Figure 2). He had previously noted the

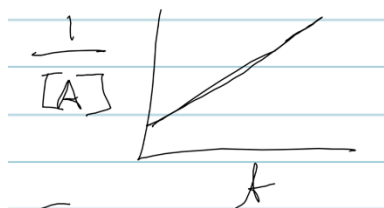


Figure 2. Howie's graphical representation of the second-order integrated rate law.

upward slope of the graph, and here he reasoned why that makes sense by incorporating chemistry ideas regarding how  $[A]$  changes with time and combining this with mathematical reasoning regarding inverse relationships.

### LIMITATIONS

It is important to note that the study reported in this paper is an attempt to apply analytic frameworks to an existing data set; the interview protocol was not framed around the symbolic/graphical forms frameworks. However, when analyzing the data, we noticed reasoning that could be characterized as symbolic and graphical forms, prompting us to investigate students' mathematical reasoning more closely. In retrospect, the graphs

related to the equations provided in the prompts tell a rather straightforward "story" — The graphs associated with the integrated rate laws are linear, and so the narrative is the same for the entire graph. In designing a prompt to elicit graphical reasoning, it would be useful to have a prompt with multiple regions, distinct shapes, and varying slopes, each with chemical implications. Examples in chemistry could involve reaction coordinate diagrams, titration curves, phase diagrams, or heating curves, to name a few. Additionally, in choosing student interviews to analyze for this study, we intended for this work to be more exploratory in nature, intentionally choosing students that we previously characterized as having more or less sophisticated reasoning in terms of their integration of chemistry and mathematics during problem-solving in chemical kinetics. This limits the generalizability of results, suggesting the need to investigate the extent in which other populations of students engage in reasoning using symbolic and graphical forms.

### CONCLUSION AND IMPLICATIONS

In order to analyze student understanding in chemistry, the analysis we outlined utilized frameworks and ideas from education research situated in physics and mathematics, and we encourage researchers from a variety of contexts across disciplines to adopt a similar interdisciplinary approach to better understand students' mathematical reasoning to improve instruction and curriculum development. In our study, we observed instances in which students engaged in reasoning using symbolic and graphical forms when thinking about inscriptions, such as equations and graphs. Often when students used symbolic and graphical forms, it aided in their understanding of the physical phenomena being modeled, leading the students to discuss the mathematical narrative represented in the graph. We view mathematical storytelling as the target for instruction, which involves an integration of mathematical ideas with chemistry content, and we assert that reasoning using symbolic and graphical forms supports students in discussing mathematical narratives.<sup>57</sup>

Nevertheless, being able to integrate chemistry and mathematics knowledge is not trivial, and it requires students to move beyond simply solving for the correct answer. As mentioned previously, Louis and Isabel correctly solved the two chemistry prompts, and we have discussed the symbolic forms they used to reason about the prompts; however, there was no interaction between their mathematical reasoning and their knowledge of chemistry. That is not to say that Louis and Isabel never discussed chemistry concepts, but it does suggest that their knowledge is compartmentalized. Our intention with selecting students that all got the "correct answer" to the chemistry prompts was to illustrate that although we want students to get the correct answer on assessments or exercises, our objectives for students in chemistry courses should move beyond algorithmic manipulation of variables to involve making connections between equations and concepts, allowing them to apply their knowledge to other contexts.<sup>18,69</sup> However, evaluating students and assessing their ability to think deeply about chemistry is challenging. The interviews conducted with the participants afforded the opportunity to gain rich insight regarding students' reasoning in a way that is not possible for courses with large enrollment sizes. However, one way to make students' reasoning more explicit and provide an idea regarding how students reason about these ideas is to have students engage in problem-solving in a collaborative setting. As discussed

by Becker and Towns,<sup>2</sup> when students work in groups and verbalize their reasoning, their conceptions can be communicated to instructors and addressed in a way that is not feasible for typical formative and summative assessments. Furthermore, by having students engage in collaborative problem-solving, instructors can promote metacognitive skills, such as engaging in reflection.<sup>70</sup>

On a related note, we encourage collaboration between faculty from different disciplines in order to better support students with making connections between disciplines such as chemistry and mathematics. The same content is often presented to students in different ways depending on the course and context, requiring students to engage in “interdisciplinary reconciliation”, in which they try to make sense of the seemingly disparate conceptualizations of the same concept,<sup>71–75</sup> for example, reconciling the macroscopic discussion of energy in introductory physics with the microscopic discussion of energy in introductory biology and chemistry.<sup>72</sup> Similarly, mathematics is presented and used differently in purely mathematics/calculus courses in comparison to the physical sciences, as discussed by Redish,<sup>76</sup> “It’s not just the way we read and use our equations that are different from math. Our goals are different. We don’t just want to explore ways of solving equations, we want to describe, learn about, and understand physical systems.” Mathematicians and physical scientists have different goals for the use of mathematics, and the latter group accomplishes these goals by utilizing and assigning meaning to constants, variables, and symbols in a way that is distinct from mathematicians.<sup>76,77</sup> Consequently, we assert that if students view concepts as overly context-dependent and compartmentalized, they will not be able to effectively integrate ideas (i.e., unable to engage in blending). Thus, it is the role of instructors to communicate with faculty from different disciplines and become aware of how students are expected to operationalize concepts and skills across different courses and fields of study.

## AUTHOR INFORMATION

### Corresponding Author

\*E-mail: mtowns@purdue.edu.

### ORCID

Jon-Marc G. Rodriguez: 0000-0001-6949-6823

Kinsey Bain: 0000-0003-0898-1862

Marcy H. Towns: 0000-0002-8422-4874

### Notes

The authors declare no competing financial interest.

## ACKNOWLEDGMENTS

The National Science Foundation under the Graduate Research Fellowship Program DGE-1333468 and Grant DUE-1504371 supported this work. Any opinions, conclusions, or recommendations expressed in this article are those of the authors and do not necessarily reflect the views of the National Science Foundation. We wish to thank Tom Holme and the Towns research group for their support and helpful comments on the manuscript.

## REFERENCES

(1) Bain, K.; Moon, A.; Mack, M. R.; Towns, M. H. A review of research on the teaching and learning of thermodynamics at the university level. *Chem. Educ. Res. Pract.* **2014**, *15* (3), 320–335.

(2) Becker, N.; Towns, M. Students’ understanding of mathematical expressions in physical chemistry contexts: An analysis using Sherin’s symbolic forms. *Chem. Educ. Res. Pract.* **2012**, *13*, 209–220.

(3) Hahn, K. E.; Polik, W. F. Factors Influencing Success in Physical Chemistry. *J. Chem. Educ.* **2004**, *81* (4), S67–S72.

(4) House, J. D. Noncognitive predictors of achievement in introductory college chemistry. *Research in Higher Education*. **1995**, *36* (4), 473–490.

(5) Spencer, H. E. Mathematical SAT Test Scores and College Chemistry Grades. *J. Chem. Educ.* **1996**, *73* (12), 1150–1153.

(6) Nicoll, G.; Francisco, J. S. An investigation of the factors influencing student performance in physical chemistry. *J. Chem. Educ.* **2001**, *78* (1), 99–102.

(7) Derrick, M. E.; Derrick, F. W. Predictors of success in physical chemistry. *J. Chem. Educ.* **2002**, *79* (8), 1013–1016.

(8) Wagner, E. P.; Sasser, H.; DiBiase, W. J. Predicting Students at Risk in General Chemistry Using Pre-semester Assessments and Demographic Information. *J. Chem. Educ.* **2002**, *79* (6), 749–755.

(9) Tsapalis, G. Teaching and Learning Physical Chemistry: A Review of Educational Research. In *Advances in Teaching Physical Chemistry*; Ellison, M. D., Schoolcraft, T. A., Eds.; American Chemical Society: Washington, DC, 2007; pp 75–112.

(10) Lewis, S. E.; Lewis, J. E. Predicting at-risk students in general chemistry: comparing formal thought to a general achievement measure. *Chem. Educ. Res. Pract.* **2007**, *8* (1), 32–51.

(11) Ralph, V. R.; Lewis, S. E. Chemistry topics posing incommensurate difficulty to students with low math aptitude scores. *Chem. Educ. Res. Pract.* **2018**, *19*, 867.

(12) Vulperhorst, J.; Lutz, C.; de Kleijn, R.; van Tartwijk, J. Disentangling the predictive validity of high school grades for academic success in university. *Assessment & Evaluation in Higher Education*. **2018**, *43* (3), 399–414.

(13) Bond, T. N.; Bulman, G.; Li, X.; Smith, J. Updating Human Capital Decisions: Evidence from SAT Score Shocks and College Applications. *Journal of Labor Economics*. **2018**, *36* (3), 807–839.

(14) Becker, N. M.; Rupp, C. A.; Brandriet, A. Engaging students in analyzing and interpreting data to construct mathematical models: An analysis of students’ reasoning in a method of initial rates task. *Chem. Educ. Res. Pract.* **2017**, *18*, 798–810.

(15) Schwarz, C.; Reiser, B.; Davis, E.; Kenyon, L.; Archer, A.; Fortus, D.; Shwartz, Y.; Hug, B.; Krajcik, J. Developing a Learning Progression for Scientific Modeling: Making Scientific Modeling Accessible and Meaningful for Learners. *J. Res. Sci. Teach.* **2009**, *46* (6), 632–654.

(16) Schwarz, C.; Reiser, B. J.; Acher, A.; Kenyon, L.; Fortus, D. MoDeLS: Challenges in Defining Learning Progressions for Scientific Thinking. In *Learning Progressions in Science: Current Challenges and Future Directions*; Alonzo, A. C., Gotwals, A. W., Eds.; Sense Publishers, 2012; pp 101–136.

(17) Brandriet, A.; Reed, J.; Holme, T. A. Historical Investigation into Item Formats of ACS Exams and Their Relationships to Science Practices. *J. Chem. Educ.* **2015**, *92* (11), 1798–1806.

(18) Cooper, M.; Caballero, M.; Ebert-May, D.; Fata-Hartley, C.; Jardeleza, S.; Krajcik, S.; Laverty, J.; Matz, R.; Posey, L.; Underwood, S. Challenge faculty to transform STEM learning. *Science* **2015**, *350* (6258), 281–282.

(19) Holme, T.; Luxford, C.; Brandriet, A. Defining Conceptual Understanding in General Chemistry. *J. Chem. Educ.* **2015**, *92* (9), 1477–1483.

(20) National Research Council. *A Framework for K-12 Science Education: Practices, Crosscutting Concepts, and Core Ideas*; National Academies Press: Washington, DC, 2012. <https://doi.org/10.17226/13165>.

(21) Reed, J.; Brandriet, A.; Holme, T. Analyzing the Role of Science Practices in ACS Exam Items. *J. Chem. Educ.* **2017**, *94* (1), 3–10.

(22) Taber, K. Straw Men and False Dichotomies: Overcoming Philosophical Confusion in Chemical Education. *J. Chem. Educ.* **2010**, *87* (5), 552–558.



- (23) Wenzel, T.; McCoy, A.; Landis, C. An Overview of the Changes in the 2015 ACS Guidelines for Bachelor's Degree Programs. *J. Chem. Educ.* **2015**, *92* (6), 965–968.
- (24) Bain, K.; Rodriguez, J. G.; Moon, A.; Towns, M. H. The characterization of cognitive processes involved in chemical kinetics using a blended processing framework. *Chem. Educ. Res. Pract.* **2018**, *19*, 617–628.
- (25) Coulson, S.; Oakley, T. Blending basics. *Cognitive Linguistics*. **2001**, *11* (3–4), 175–196.
- (26) Fauconnier, G.; Turner, M. Conceptual Integration Networks. *Cognitive Science*. **1998**, *22* (2), 133–187.
- (27) Bain, K.; Towns, M. H. A review of research on the teaching and learning of chemical kinetics. *Chem. Educ. Res. Pract.* **2016**, *17*, 246–262.
- (28) Justi, R. Teaching and Learning Chemical Kinetics. In *Chemical Education: Towards Research-Based Practice*; Gilbert, J. K., de Jong, O., Justi, R., Treagust, D. F., van Driel, J. H., Eds.; Kluwer: Dordrecht, 2002; pp 293–315.
- (29) Cooper, M. M.; Stowe, R. L. Chemistry Education Research From Personal Empiricism to Evidence, Theory, and Informed Practice. *Chem. Rev.* **2018**, *118*, 6053.
- (30) Singer, S. R.; Nielson, N. R.; Schweingruber, H. A. *Discipline-Based Education Research: Understanding and Improving Learning in Undergraduate Science and Engineering*; National Academies Press: Washington, DC, 2012.
- (31) Orton, A. Students' Understanding of Differentiation. *Educational Studies in Mathematics*. **1983**, *14*, 235–250.
- (32) Rasmussen, C.; Marrongelle, K.; Borba, M. C. Research on calculus: what do we know and where do we need to go? *ZDM Mathematics Education*. **2014**, *46*, 507–515.
- (33) White, P.; Mitchelmore, M. Conceptual Knowledge in Introductory Calculus. *Journal for Research in Mathematics Education*. **1996**, *27* (1), 79–95.
- (34) Lunsford, E.; Melear, C.; Roth, W.; Perkins, M.; Hickok, L. Proliferation of Inscriptions and Transformations Among Preservice Science Teachers Engaged in Authentic Science. *J. Res. Sci. Teach.* **2007**, *44* (4), 538–564.
- (35) Arcavi, A. Symbol Sense: Informal Sense-Making in Formal Mathematics. *For the Learning of Mathematics* **1994**, *14* (3), 24–35.
- (36) Arcavi, A. Developing and Using Symbol Sense in Mathematics. *For the Learning of Mathematics* **2005**, *25* (2), 42–47.
- (37) Sowder, J. Estimation and Number Sense. In *Handbook of Research on Mathematics and Learning: A Project of the National Council of Teachers of Mathematics*; Grouws, D., Ed.; Macmillan, New York, NY, 1992.
- (38) Skemp, R. Communicating Mathematics: Surface Structures and Deep Structures. *Visible Language* **1982**, *16* (3), 281–288.
- (39) Quinnell, L.; Carter, M. Greek or not: The use of symbols and abbreviations in mathematics. *Australian Mathematics Teacher* **2012**, *68* (2), 34–41.
- (40) Gray, E.; Tall, D. Duality, Ambiguity, and Flexibility: A Proceptual View of Simple Arithmetic. *Journal for Research in Mathematics Education*. **1994**, *25* (2), 116–140.
- (41) Tall, D.; Gray, R.; Ali, M.; Crowley, L.; DeMarois, P.; McGowen, M.; Pitta, D.; Thomas, M.; Yusof, Y.; Pinto, M. Symbols and the Bifurcation Between Procedural and Conceptual Thinking. *Canadian Journal of Science, Mathematics and Technology Education*. **2001**, *1* (1), 81–104.
- (42) Rubenstein, R.; Thompson, D. Learning Mathematical Symbolism: Challenges and Instructional Strategies. *Mathematics Teacher* **2001**, *94* (4), 265–271.
- (43) Johnstone, A. Macro- and microchemistry. *School Science Review* **1982**, *64* (227), 377–379.
- (44) Glazer, N. Challenges with graph interpretation: a review of the literature. *Studies in Science Education*. **2011**, *47* (2), 183–210.
- (45) Driver, R.; Asoko, H.; Leach, J.; Mortimer, E.; Scott, P. Constructing Scientific Knowledge in the Classroom. *Educational Researcher*. **1994**, *23* (7), 5–12.
- (46) Driver, R.; Leach, J.; Millar, R.; Scott, P. Why does understanding the nature of science matter? In *Young People's Images of Science*; Open University Press: Philadelphia, 1996.
- (47) Grassian, V. H.; Meyer, G.; Abruña, H.; Coates, G. W.; Achenie, L. E.; Allison, T.; Brunschwig, B.; Ferry, J.; Garcia-Garibay, M.; Gardea-Torresdey, J.; Grey, C. P.; Hutchison, J.; Li, C. J.; Liotta, C.; Raguskas, A.; Minter, S.; Mueller, K.; Roberts, J.; Sadik, O.; Schmehl, R.; Schneider, W.; Selloni, A.; Stair, P.; Stewart, J.; Thorn, D.; Tyson, J.; Voelker, B.; White, J. M.; Wood-Black, F. Viewpoint: Chemistry for a Sustainable Future. *Environ. Sci. Technol.* **2007**, *41* (14), 4840–4846.
- (48) Matlin, S. A.; Mehta, G.; Hopf, H.; Krief, A. One-World Chemistry and Systems Thinking. *Nat. Chem.* **2016**, *8* (5), 393–398.
- (49) Potgieter, M.; Harding, A.; Engelbrecht, J. Transfer of Algebraic and Graphical Thinking between Mathematics and Chemistry. *J. Res. Sci. Teach.* **2008**, *45* (2), 197–218.
- (50) Phage, I. B.; Lemmer, M.; Hitge, M. Probing Factors Influencing Students' Graph Comprehension Regarding Four Operations in Kinematics Graphs. *African Journal of Research in Mathematics, Science, and Technology Education*. **2017**, *21* (2), 200–210.
- (51) Planinic, M.; Ivanjek, L.; Susac, A.; Milin-Sipus, Z. Comparison of university students' understanding of graphs in different contexts. *Physical Review Special Topics – Physics Education Research*. **2013**, *9*, No. 020103, DOI: 10.1103/PhysRevSTPER.9.020103.
- (52) Kozma, R. B.; Russell, J. Multimedia and Understanding: Expert and Novice Responses to Different Representations of Chemical Phenomena. *J. Res. Sci. Teach.* **1997**, *34* (9), 949–968.
- (53) Hammer, D.; Elby, A. Tapping Epistemological Resources for Learning Physics. *Journal of the Learning Sciences*. **2003**, *12* (1), 53–90.
- (54) Hammer, D.; Elby, A. On the Form of a Personal Epistemology. In *Personal Epistemology: The Psychology of Beliefs about Knowledge and Knowing*; Hofer, B. K., Pintrich, P. R., Eds.; Erlbaum: Mahwah, NJ, 2002; pp 169–190.
- (55) diSessa, A. A. Toward an Epistemology of Physics. *Cognition and Instruction*. **1993**, *10* (2–3), 105–225.
- (56) Sherin, B. L. How Students Understand Physics Equations. *Cognition and Instruction*. **2001**, *19* (4), 479–541.
- (57) Rodriguez, J. G.; Bain, K.; Towns, M. H.; Elmgren, M.; Ho, F. M. Covariational Reasoning and Mathematical Narratives: Investigating Students' Understanding of Graphs in Chemical Kinetics. *Chem. Educ. Res. Pract.* **2018**, DOI: 10.1039/C8RP00156A.
- (58) Rodriguez, J. G.; Bain, K.; Towns, M. H. Graphical forms: The adaptation of Sherin's symbolic forms for the analysis of graphical reasoning across disciplines. Submitted.
- (59) Nemirovsky, R. Mathematical Narratives, Modeling, and Algebra. In *Approaches to Algebra: Perspectives for Research and Teaching*; Bednarz, N.; Kiernan, C.; Lee, L., Eds.; Kluwer Academic Publishers: Dordrecht, The Netherlands, 1996; pp 197–223.
- (60) Bing, T. J.; Redish, E. F. The cognitive blending of mathematics and physics knowledge. *AIP Conf. Proc.* **2006**, *883*, 26.
- (61) Hu, D.; Rebello, N. S. Using conceptual blending to describe how students use mathematical integrals in physics. *Physics Review Special Topics – Physics Education Research* **2013**, *9*, 020118.
- (62) Kuo, E.; Hull, M.; Gupta, A.; Elby, A. How Students Blend Conceptual and Formal Mathematical Reasoning in Solving Physics Problems. *Sci. Educ.* **2013**, *97* (1), 32–57.
- (63) Cruz-Ramirez de Arellano, D.; Towns, M. H. Students' understanding of alkyl halide reactions in undergraduate organic chemistry. *Chem. Educ. Res. Pract.* **2014**, *15*, 501–515.
- (64) Harle, M.; Towns, M. H. Students' Understanding of Primary and Secondary Protein Structure: Drawing Secondary Protein Structure Reveals Student Understanding Better Than Simple Recognition of Structures. *Biochem. Mol. Biol. Educ.* **2013**, *41* (6), 369–376.
- (65) Linenberger, K. J.; Lowery Bretz, S. A. Novel Technology to Investigate Students' Understandings. *Journal of College Science Teaching* **2012**, *42* (1), 45–49.

- (66) Campbell, J. L.; Quincy, C.; Osseman, J.; Pedersen, O. K. Coding In-depth Semistructured Interviews: Problems of Unitization and Intercoder Reliability and Agreement. *Sociological Methods & Research*. **2013**, *42* (3), 294–320.
- (67) Strauss, A.; Corbin, J. *Basics of Qualitative Research: Grounded Theory Procedures and Techniques*; SAGE Publications, Ltd.: Newbury Park, CA, 1990.
- (68) Levenson, E. Teachers' knowledge of the nature of definitions: The case of the zero exponent. *Journal of Mathematical Behavior*. **2012**, *31* (2), 209–219.
- (69) Rodriguez, J. G.; Bain, K.; Hux, N. P.; Towns, M. H. Productive Features of Problem Solving in Chemical Kinetics: More than Just Algorithmic Manipulation of Variables. *Chem. Educ. Res. Pract.* **2018**, DOI: 10.1039/C8RP00202A.
- (70) Sandi-Urena, S.; Cooper, M. M.; Stevens, R. H. Enhancement of metacognition use and awareness by means of a collaborative intervention. *International Journal of Science Education* **2011**, *33* (3), 323–340.
- (71) Bain, K.; Towns, M. H. Investigation of Undergraduate and Graduate Chemistry Students' Understanding of Thermodynamic Driving Forces in Chemical Reactions and Dissolutions. *J. Chem. Educ.* **2018**, *95* (4), 512–520.
- (72) Dreyfus, B. W.; Redish, E. F.; Watkins, J.; et al. Students' Views of Macroscopic and Microscopic Energy in Physics and Biology. *AIP Conf. Proc.* **2011**, *1413*, 179–182.
- (73) Geller, B. D.; Dreyfus, B. W.; Gouvea, J.; Sawtelle, V.; Turpen, C.; Redish, E. F. "Like Dissolves Like": Unpacking Student Reasoning About Thermodynamics Heuristics. *AIP Conf. Proc.* **2013**, *027*, 157–160.
- (74) Kohn, K. P.; Underwood, S. M.; Cooper, M. M. Energy Connections and Misconceptions Across Chemistry and Biology. *CBE Life Sciences Education* **2018**, *17* (1), ar3.
- (75) Redish, E. F.; Cooke, T. J. Learning Each Other's Ropes: Negotiating Interdisciplinary Authenticity. *Cell Biology Education* **2013**, *12*, 175–186.
- (76) Redish, E. F. Problem Solving and the Use of Math in Physics Courses. Paper presented at the *World View on Physics Education in 2005: Focusing on Change Conference, New Delhi, India August 21–26, 2005*.
- (77) Redish, E. F.; Gupta, A. Making meaning with math in physics: A semantic analysis. *GIREP-EPEC & PHEC 2009* **2009**, 244.