BIOCHEMISTRY AND MOLECULAR BIOLOGY EDUCATION
Vol. 39, No. 1, pp. 10–16, 2011

Article

Using Research to Teach an "Introduction to Biological Thinking"*

Received for publication, March 15, 2010, and in revised form, July 13, 2010

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A course design for first-year science students is described, where the focus is on the skills necessary to do science. The course uses original research projects, designed by the students, to teach a variety of skills including reading the scientific literature, hypothesis development and testing, experimental design, data analysis and interpretation, and quantitative skills and presentation of the research in a variety of formats.

Keywords: Teaching science skills, quantitative skills, teaching introductory biology.

In the last 10–15 years, there has been an increased focus on teaching science at the undergraduate level [1, 2]. This has been in response to a number of issues including a perception that we train very few science students, very few science students consider going on to graduate work in the sciences, science does not reflect our national diversity, and the general public does not understand enough about science and what it takes to do science that were raised in Bio2010 [3]. Much has been written about reforming undergraduate science education [4], with much of the discussion centering on enhancing active learning opportunities for our students [5–9]. In particular, much has been written about incorporating a "research" focus into our classrooms, often by incorporating project-based laboratory experiences [10–12].

There has been much talk of "Teaching Science the Way You Do Science" in a policy forum article published in Science in 2004 by Jo Handelsman *et al*. [13]. There is mounting evidence that supplementing or replacing lectures with active learning strategies and engaging students in discovery and scientific process improves learning and retention of knowledge. More recently, because of conversations started by the National Science Foundation [14], there has been renewed emphasis on introductory courses for science students [15, 16].

Several years ago, the University of Richmond Biology department made the decision to teach "Introduction to Biological Thinking" courses as a prerequisite to introductory biology classes such as genetics or cell biology. The goal was to expose students to the ways that biologists think and prepare them to ask questions and get involved in research activities at an earlier stage of their undergraduate career than they might otherwise have done. A group of faculty each teach one or more sections of a BIO 199: "Introduction to Biological Thinking" course during the year providing sufficient opportunity for incoming first year students interested in a biology or a biochemistry and molecular major [whose SAT scores are in the 590–690 range for the middle 50% of the first year class] to take one of the sections. The sections have similar overall goals but vary significantly in content.

WHAT ARE THE GOALS FOR THE COURSE?

There are three main goals for my sections of the course: the primary goal is to allow students to learn about the process of science, how to design an experiment, collect data, and interpret the data, how to test a hypothesis, and how to communicate both why and how the research was done. The second goal was to put some introductory biology, chemistry, and physics into a "real world" context—in this case, a research project, with the expectation that they would both understand in more detail what they learned and better appreciate why they needed to understand their introductory courses. Finally, I hoped that students taking this course would get more excited about continuing with their science and getting involved in research at an early stage in their undergraduate career.

THE CATALOG DESCRIPTION OF THE COURSETHAT IS TITLED "BIO 199: BIOCHEMSITRY IN THE REAL WORLD"

"Proteins, which play a central role in virtually all biological processes, have one property in common: the ability to specifically bind another molecule. A second property, which many proteins have, is the ability to catalyze a chemical reaction, that is, they are enzymes. Understanding what principles govern their structure and stability is a key to understand these functions and how defects in proteins can lead to a variety of diseases as well as playing a critical role in drug design. This course will use current research to illustrate these principles. Students taking the course, during the semester, will be grouped into pairs and expected to pose a question about one of the pro-

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*This work is supported by NSF-MCB-0448905.

TABLE I
Lecture outline for the course

- Lecture 1: Proteins: The big picture
- Lecture 2: Reactions and Enzymes
  - What is a rate of a reaction, how do you measure it?
  - What is Coulomb's Law?
- Lecture 3: Noncovalent forces, protein structure, and dynamics I
  - What is a hydrogen bond?
  - What is a hydrophobic interaction?
- Lecture 4: Noncovalent forces, protein structure and dynamics II
  - What are the properties of a peptide bond?
  - What are the different types of amino acid side chains?
- Lecture 5: The chemical reaction
  - Plot the Arrhenius Plot of your data from laboratory 1
  - Calculate the Activation energy of the reaction
- Lecture 6: Protein structure–Function relationships/molecular evolution
  - What types of metabolism is malate dehydrogenase involved with?
  - Where is malate dehydrogenase found in the cell?
- Lecture 7: What is unknown about these systems
  - Plot your Michaelis–Menton plot from laboratory 2
  - What are the K_m and V_{max} values?
- Lecture 8: Reading the scientific literature
  - Read the assigned paper
- Lecture 9: Developing a Hypothesis I
  - What question will your project address?
  - What is your "specific aim?"
- Homework 2: Proposal background
- Lecture 10: Designing experiments to test a hypothesis
  - What solutions do you need to perform the kinetics experiments you propose?
  - How would you prepare them?
- Lecture 11: Designing experiments: Quantitative details to test activity
  - If your hypothesis is correct, what do you expect your data to look like?
  - How would you know whether it is different from the control?
- Lecture 12: Designing experiments: to test structure and stability
  - If your hypothesis is correct, what do you expect your data to look like?
  - How would you know whether it is different from the control?
- Lecture 13: Proteases
  - What types of proteases are there?
  - How does nature control the activity of proteases?
- Lecture 14: Critique of draft proposals
  - Read two to three draft proposals
  - Prepare brief comments on one proposal
- Lecture 15: Drug design and HIV
  - What types of HIV drugs are currently used?
  - Choose one and find out how it was discovered/developed
- Lecture 16: Seminar speaker
  - What are "Toll" receptors?
  - What do they look like?
- Lecture 17: Molecular immunology—Adaptive immune system
  - What is the structure on an "Antibody?"
  - What governs the specificity of an antibody?
- Lecture 18: Proteomics
  - What is the proteome?
  - When does the proteome change?
- Lecture 19: Protein folding and dynamics
  - How can you study protein folding?
  - How can you study the "dynamics" of a protein structure?
- Lecture 20: Folding defects and diseases
  - Find a disease where a defect in protein folding is thought to occur
  - How might this disease be treated?
- Lecture 21: Preparing to present the results
  - A 10-min talk versus a poster
  - How to present the background information?
- Lecture 22: Understanding data analysis I
  - Presenting data: Graphs versus tables
  - How to show the "errors" associated with your data?
- Lecture 23: Understanding data analysis II
  - Interpreting the data
  - Drawing appropriate conclusions
- Lecture 24: Multimedia visual presentations I
- Lecture 25: Seminar speaker
  - Key points of the presentation: introduction, data, interpretation
  - How is Science different in Industry?
- Lecture 26: Current ethical issues in science
- Lecture 27: Ethical issues in experiment design and development
- Lecture 28: Ethical issues in data presentation

teins under study, design one or more experiment(s) to interrogate the question, conduct the research, focusing on the collection of quantitative data to address the hypothesis, and analyze the data including the use of appropriate statistics and equation fitting [this will also entail understanding ways to establish that the correct model for analysis is being used] and the design of follow-up experiments. As an integral part of this process, students will learn how to construct a proposal, how to maintain appropriate documentation of their work, and how to present their work, in visual, written, and oral formats. During the course of the semester, ethical issues related to the conduct of research are also addressed."

Each year my section of the course has rapidly filled during freshman registration, and I usually end up with a wait list, but unfortunately without adding an additional lecture session and laboratory section, it is not possible to accommodate more students.

THE STRUCTURE OF THE COURSE

The course meets for two 75-min "lecture" periods plus a 3-hour "Laboratory" each week for the 14-week semester, and each section is limited to 16 students. [I teach two sections for a total of 32 students.]

During the semester, there are series of blocks each with a particular focus. There are four blocks of lecture material and four blocks of laboratory material, although the number of weeks for each lecture and laboratory block are not necessarily the same. An overall outline of the lecture component of the course is given in Table I.

Briefly, during lecture Block 1, Weeks 1–3, we cover the basics: fundamentals of protein structure and dynamics and their roles in binding and catalysis and the central dogma and basics of molecular evolution. The first block of laboratories, Weeks 2–5, the students learn fundamental techniques necessary for the project phase of the semester, working with the native protein—this involves learning how to assay the activity [including activation energy, K_m and V_{max}], measure protein concentrations, and assess protein stability using guanidine hydrochloride or heat denaturation. In Lecture Block 2, Weeks 4–6, the focus is on the various skills necessary to write a research proposal: developing questions: reading and understanding the literature. Deciding on

TABLE II
Laboratory components

Week	Laboratory focus	Relationship to lecture material
1	Measuring activity: The effects of temperature	Concepts of reactions and energy barriers
2	Measuring activity: The effects of substrate concentration	Concept of saturation
3	Molecular visualization and bioinformatics	Concepts of evolution and structure–function
4	Measuring conformation and stability	Dynamic aspects of noncovalent interactions
5	Presenting the proposal	
6	Making mutants	Central dogma and information flow
7-12	Project	
13	Presentations	

experiments and experimental design, which culminates in the laboratory block of Week 6, where the students have to present their research proposal. During the third block of material, Weeks 7–10, the focus is on applied aspects of protein structure and function during lecture and discussion time and on the laboratory project during laboratory time. I usually try to get someone from industry to come in and give an overview of their work during this block, and we often discuss the differences of approach to science between industry and academia. In the final block, Weeks 11–15, lecture time is devoted to data presentation and critical analysis of others work, and the laboratory continues the research project and preparation for the final presentations.

In the class, the focus is on a combination of lectures and guided discussions as described in the lecture outline [Table I], focusing on both basic theory and potential applications. Laboratory time for the first four laboratories, summarized in Table II, focuses on learning basic experimental techniques that are necessary for them to conduct their project, and each week culminates in a "group meeting" discussion of the techniques and so forth. Laboratory 5 includes an extended discussion where each group will present key aspects of their planned experiments. Laboratories 6–10 will involve conducting the experiments and again each week there will be a "group meeting" type presentation at the end of the laboratory where students will present aspects of what they are doing. Laboratories 11 and 12 are devoted to any necessary follow-up experiments and data analysis, and during Laboratory 13 they make their presentation.

TABLE III
Rubric for dissecting a paper

Step	Topic for student to identify
1	What is the context of the paper?
2	What work by others is critical to the current paper?
3	Identify three critical background references.
4	Summarize the big picture aspect of the work.
5	What is the central hypothesis that is to be tested?
6	Identify preparative experiments.
7	What are the critical experiments that test the hypothesis?
8	Which is the most important figure in the paper?
9	What are the major conclusions reached?
10	What evidence are the major conclusions based upon?
11	What is the reproducibility of the experimental data and how might this affect the conclusions that will be reached for each experiment?
12	What are the controls that are used?
13	What are the potential pitfalls of the techniques used?
14	What is the next logical step suggested by the authors?
15	What other experiments do these results suggest to you?

OUTCOMES

During this course, there are a number of student-centered outcomes. These include becoming familiar with foundational concepts in biology [including energy, structure–function relationships, and the central dogma and evolution], foundational concepts in chemistry [including energy and energy barriers, rates and equilibria, covalent and noncovalent bonding, acid-base chemistry, pK, and oxidation–reduction reactions], and foundational concepts of physics [including Coulomb's Law and Newton's Laws of Motion].

These are all things that they will see, or are seeing, in other courses, the major point being that they are seeing them in a more interdisciplinary and "real-life," that is, research, context.

In addition, they become familiar with current research in protein structure and function, and they learn how to develop a hypothesis driven experiment as well as appreciating that some hypotheses are data driven. Quickly in the course, they begin to learn how to read and interpret scientific literature and to develop quantitative skills involved in data analysis and model fitting. In the later parts of the course, they learn a variety of presentation skills. Throughout the course, they learn how to be a "team player" in a research context, and they are continually developing critical thinking and analysis skills.

STYLE OF THE COURSE

This course is designed to allow in-depth discussion of approaches to research problems, illustrated by structure function relationships in malate dehydrogenase, and current topics in research. In addition, there is a focus on the underlying principles that are the foundation of the molecular life sciences. In any given week, the Tuesday class time will usually be used to discuss basic concepts behind the topics, whereas Thursday class time will be more flexible: Thursday lecture times will often end with a 30-min recap and discussion of topics related to the following week's laboratory. In the class, often there will be quizzes or graded work assignments.

They write a proposal—the proposal becomes the basis for the introduction and aims section of their final report/presentation.

We discuss below what it takes to write a proposal.

Familiarity with the Literature

Familiarity with the literature starts in class—we go through how to read a paper and use a rubric [Table III]

to go through a couple of foundational papers about the research topic—malate dehydrogenase in my case. This gets them out of the "google for facts" approach and lets them learn how to search for appropriate literature using PubMed and so forth. They are expected to find appropriate literature for themselves, they use both the provided papers [all 5–6 years old] and PubMed searches that they conduct and, particularly once they have identified a potential mutant to make and have developed their hypothesis, are expected to conduct a more thorough literature search to make sure that no one else has asked/answered the question or made the mutant they are proposing to make.

A Hypothesis

The students work in pairs, that means there are eight different hypotheses per laboratory section. Developing a hypothesis is tied in with a lot of basic chemistry and biology. Coming up with a residue to mutate involves them doing clustal analysis with sequences they select from the protein sequence data base—we work with watermelon glyoxasomal malate dehydrogenase, and they can select to run its sequence with a plethora of different types of sequences—cytoplasmic versus organelle, plant versus bacterial, and so forth, and this shapes the questions they can ask. From the sequence alignments, they identify amino acid residues that appear to play important roles [*i.e*. are conserved—either completely, structurally, or functionally]. Together with the crystal coordinates they can locate the various conserved residues, using molecular visualization with VMD and PyMol, and develop a hypothesis as to the role of a given residue—to do this, they have to find out something about what is known, where the active site is, and so forth.

IDEAS ABOUT HOW IT CAN BE TESTED

Some detail about experiments that can be done—this they get from the more structured experiments in the first part of the course—they are learning how to do the experiments that they will adapt later to test their hypothesis. Each student has to develop their own hypothesis and each student has to think about what the outcomes of a given experiment might be in relationship to their hypothesis.

The proposal writing itself is spread over several weeks and involves critiques and revisions just as you or I would write a proposal. We use peer critiquing, we use drafts that they submit and they get feedback in one on one session with me. This takes time but it is time well invested. We are talking about research that is ongoing in my research group, its giving the student a real insight into the dialog that takes place in real research—after all, it is real research. A mentoring relationship is developed with each student in the class, a far more meaningful one than is usually the case when a student comes to ask questions after class about some point they did not understand in the lecture. By the time the proposal is submitted for grading, the student really understands far more about the project and has taken ownership of the project for the rest of the semester.

Over the next 8–10 weeks, the laboratory sessions are dedicated for doing the various experiments that they have proposed—most of the experiments involve some sort of initial rate kinetics, binding studies, or protein stability studies; although usually no two groups are doing the same experiment for the same purpose, as no two groups are testing the same hypothesis, they learn that they have to depend on their own data and that there is no right answer to come up with. Although they have done the preliminary experiments in the first few weeks with the native protein, they are now working with the mutant protein that they designed, created using QuikChange mutagenesis, and purified using Nickel-NTA affinity chromatography. The mutants may range in activity and stability very significantly, and they learn to troubleshoot the experiments on the fly. Once they have collected the data, a frequent question at the start of the project is "is this right?" They soon get used to the fact that I have no clue whether it is right and my answer is usually "do you trust the data?" and "what is the data telling you?" They learn the importance of reproducible data, and they learn to think.

During the lecture times through this part of the course, we discuss a series of current topics in the discipline and this varies from class to class—we have covered such topics as proteases and drug design, the innate immune system, HIV, and molecular evolution—all the time building on the basics covered in the first several weeks and expanding them to include approaches to examine the structure of a protein. We also cover topics related to data analysis and equation fitting.

The last block of the course is focused on the presentations that they make and a variety of ethical issues. Because we have talked about HIV, which raises all sorts of ethical issues in science, we have a movie night with popcorn and pretzels and watch the film "And the Band Played On," which we talk about during the last few classes of the semester. During the last laboratory week, the students make their poster presentations. I usually bring in some faculty from other institutions to talk with the students about their work and have them grade the students on a variety of aspects of their presentation. Each student is graded twice by outside faculty using a provided rubric [Table IV], and the outside faculty assessments are the grade on that part of their project. They rarely disagree with my own assessment.

IN-CLASS QUIZZES

During the course of the semester, there were a series of quizzes focusing on important concepts [the central dogma, amino acid side chain structures and properties, and kinetics and equilibria] and abilities [quantitative data analysis] as well as on specific background to malate dehydrogenase. These are usually straightforward quizzes that only take 10–20 min of the class period [for example, the "Mathematical Background" quiz is given in Appendix] and are easily graded—I grade by putting a simple score on each question with no other com-

TABLE IV
Rubric for grading the presentations

1	Could the student put the project in the context of "big picture" questions about protein structure and function?
2	Was the specific background to the project clearly described and appropriately referenced?
3	Was the central hypothesis clearly articulated?
4	Could the student relate the background and hypothesis to the appropriate fundamentals of biology, chemistry and physics?
5	Were the experiments proposed and their potential outcomes discussed in relationship to the hypothesis.
6	Did the student understand the fundamentals of the experimental approaches they used?
7	Could the student articulate the quantitative aspects of the data analysis?
8	Did the student understand the limitations and sources of error in the experimental approaches they used?
9	Did the student connect the data and its analysis to conclusions that related to the hypothesis appropriately? Was the student able to articulate how the outcomes of the experiment might modify the hypothesis?
10	Did the student articulate follow-up experiments and relate them to the conclusions and hypothesis.

ments—the student has time until the next class period to correct their answers and resubmit so that they can earn back 50% of whatever they missed.

GRADED ASSIGNMENTS

During the course of the semester, in addition to turning in drafts of their proposal and final presentation, they have a few graded assignments—an analysis of a paper using the rubric in Table I, turning in a graph and data analysis that they will use in their final presentation, a couple of quantitative skills problem sets, and just as with the quizzes, these are graded in the same style and they have an opportunity to revise their answers.

PREPARATION FOR PRESENTATION

Throughout the semester, they are honing their presentation and critical thinking skills—much of this is done during class group discussions where a small group—usually four students, will discuss an aspect of the project background, for example, and will have to present to the rest of the class in visual and oral form. By starting this approach literally in the first couple of weeks of class, the "fear factor" of making a presentation in front of a group of people quickly evaporates and by the time the students have to make their final presentations they are usually looking forward to the experience. To get them involved in critiquing each others work at least twice during the semester there is a "round robin" class where each group has to put up on a white board an assigned topic such as "big picture of the projects," "essential biology background," "the chemistry of the reaction," or "critical aspects of protein structure"—they get 15 min to do this and then have to rotate to the next white board and spend the next 15 min discussing and critiquing what the previous group has put up for a different topic. Then they rotate again—by the end of the class they have thought about and critiqued all four topics and class closes with a general discussion of the good and bad points of each "presentation." Feedback from the students is that they really feel that these sessions are the most productive in terms of them understanding the material and getting confidence in their ability to talk about science.

ASSESSMENT OF OUTCOMES

One of the major goals of the course has been to help students understand how science is done and what constitutes a good project. As such hypothesis testing and experimental design are critical outcomes of the course. To assess the effectiveness of the course I have been using "the experimental design ability test (EDAT)" developed by Karen Sirum et al. (in preparation) as a pretest and post-test.[1] They get the pretest at the start of the very first class and have no idea that it is a pretest where a different form but assessing the exact same abilities will come back on the last day of class. Few students score more than 30–40% on the pretest, almost every student scores 80–90% on the post-test. This tool is unrelated to the actual research they are conducting and assesses their ability to think about experimental design in general. Furthermore the outcomes of the pretest are not discussed in class and the test is not returned to the student. The students at the end of the semester fill out typical student evaluation of teaching questionnaires, and to date, it appears that the students clearly enjoy the class and are not frustrated by the relative lack of formal structure and expectations of the course compared with other courses they are taking.

The other major goal is to get the students interested in getting involved in research with a faculty member. Although only anecdotal at this point as the class is only 2 years old, more than half of the students taking the course have found faculty mentors by the start of the following semester, with the majority of those students then staying for a summer research experience. Feedback from their faculty mentors—again only anecdotal—is that the students are not only excited about getting involved in research but also have much better critical thinking skills and proposal writing ability than other students, even those who are more "experienced" with research.

From my perspective, another goal has been to encourage an environment where quantitative skills are not feared. The mathematical background quiz in Appendix is an example of introducing quantitative skills early in the course that will then form the basis of much of the subsequent data analysis. When they take the quiz they have had no exposure in the course to the content of the quiz so it assesses their prior knowledge and skills in this area. We discuss the quiz thoroughly after it has been "graded" [they are pleased to find that the grade does not contribute to their overall grade in the course], and as they collect and analyze data as the course progresses repeatedly come back to the quiz and start to put the various aspects of it into both a more practical and theoretical context.

Finally, because the students are engaged in original research projects, are they making a contribution to the science that I am interested in—in this case, that funded by the National science Foundation: NSF-MCB-0448905

[1]The information of experimental design ability test (EDAT) is available at ksirum@bgsu.edu (Karen Sirum).

"RUI: The Role of Protein Dynamics in Catalysis and Subunit Cooperativity," of which I am the PI. To date, the students have designed, created, and done preliminary experiments on over 30 new mutants of malate dehydrogenase, a number of which are now the focus of ongoing projects in my laboratory and have led to three presentations at national meetings. Two sets of mutants are in the process of being written up for submission for publication in the peer reviewed scientific literature. Interestingly one of the coauthors on one of the manuscripts will be, of course, the student who started the project but is now working in a colleague's laboratory—I do not feel that I can recruit students for my laboratory during the course, and by the time I approached the student at the end of the course to see if she would be interested in continuing the project she had already lined up a position in another laboratory.

From my perspective, the course is productive and successful on all levels and is certainly my favorite course to teach. Could the course be taught to nonscience majors? Enrollment has permitted several upper class students majoring in a nonscience subject to take the course, and in terms of their enthusiasm for the course and performance in the course, they have been indistinguishable from the first-year science majors. I suspect that they come out of the course with a far better idea of what is involved in science and the discovery of new information than if they had taken a survey course for nonscience majors. Could the course be scaled up to larger numbers? With the type of research that I do, I think the answer is no—32 students working on 16 independent research projects throughout the semester keeps me pretty busy. The way to scale up would be to encourage more faculty to teach this style of course. I would suggest that it is readily adaptable to almost anyone's research.

Finally, I would like to suggest that this type of approach to a course could fruitfully be adapted to almost any group of students and that by exposing students to "doing science" we could provide them with useful skills that would carry into later courses.

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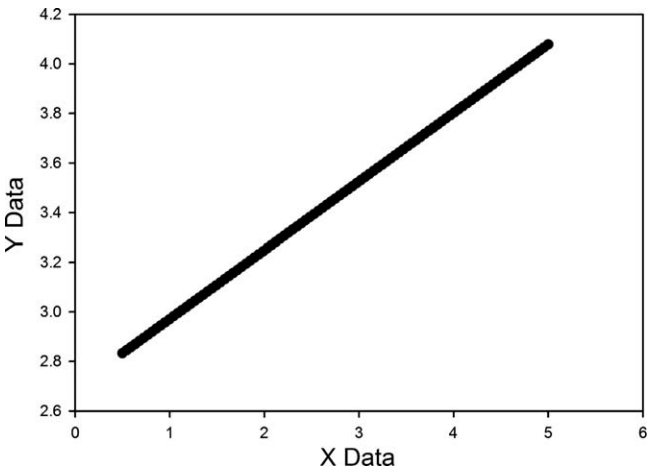
APPENDIX: QUIZ: MATHEMATICAL BACKGROUND

(a) 5 points—For the accompanying graph write down the mathematical expression that describes the line shown.



(b) 15 points—The following expressions represent exponential functions:

$$Y = \mathrm{A} \cdot e^{-kt}$$

And

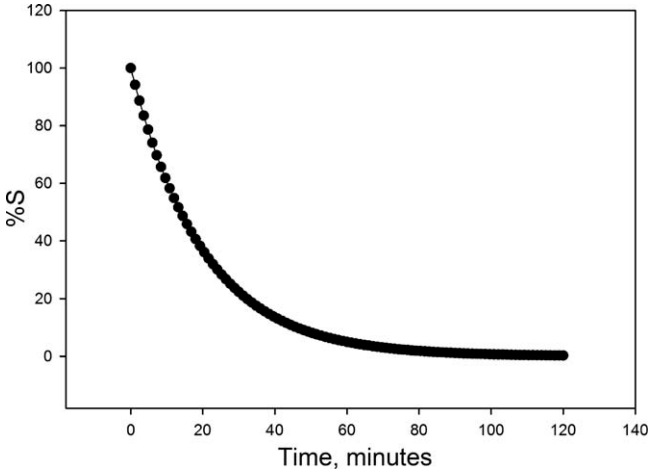
$$Y = \mathrm{A}(1 - e^{-kt})$$

Where t is time and k is the exponential rate constant.

What is the significance of A?

Briefly describe how you would decide whether a process, such as S → R, should be described by an exponential function.

For the graph shown which of the above exponential functions would you use to analyze the data?



(c) 10 points—For the process:

$$A + B \longleftrightarrow C$$

With k_1 being the rate constant of formation of C from A and B, and k_2 being the rate constant for the breakdown of C back to A and B.

Derive an expression for the equilibrium constant K_{eq} in terms of k_1 and k_2 given that

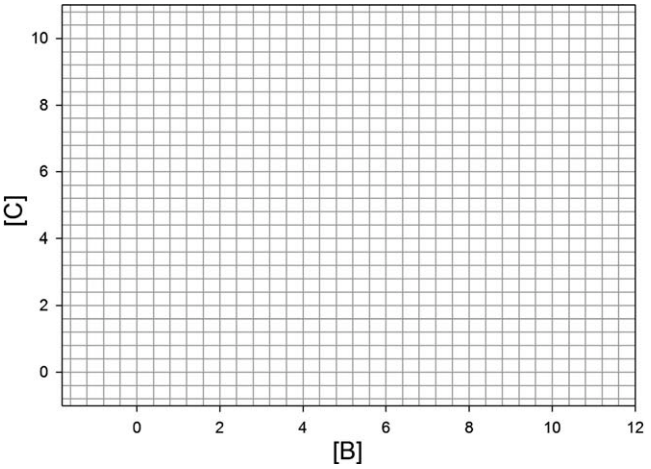
$$K_{eq} = [C]_{eq}/([A]_{eq} \cdot [B]_{eq})$$

The equation

$$[C] = m \cdot [B]/(K + [B])$$

describes the equilibrium of a fixed total concentration of A with varying concentrations of B.

Using the accompanying template, sketch a graph that represents the dependency of [C] on the concentration of B for a high value of K and a low value of K



(d) 10 points—Briefly outline the basis of a "least squares" method of fitting data to an equation.

What information comes from analyzing a plot of the "residuals?"