Brandeis UNIVERSITY

BCHM102a

Quantitative Approaches to Biochemical Systems

Instructor Details

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All students can contact me via e-mail at any time and I will reply within the day. In addition, individual Zoom meetings can be setup to answer any questions that have not been answered in the class or during the TA session.
Teaching Assistant: Rishika Baral

Meeting Times

Classes

Monday, Wednesday, 10-11.30 AM

Office Hours

No fixed office hours, zoom meetings can be setup on an individual basis.

Course Description

What this course is about

Understanding biological phenomena often comes down to comprehending the structures of the molecules that participate in biochemical processes and the ways that these molecules work and interact. Biochemistry textbooks are packed to the brim with such information, but where does this knowledge come from in the first place? A great deal of our knowledge about biochemical processes comes from just two basic types of laboratory experiments. First, we explore the ***mechanisms*** of biochemical reactions by measuring the rates of various reaction steps. Second, we infer the ***structures*** and behavior of biological molecules from the ways that they interact with electromagnetic radiation. All such experiments involve making and interpreting quantitative chemical and physical measurements on biochemical systems.

This is not a laboratory course, nor will it teach the details of how to use specific techniques. Instead, the course covers *basic principles* that underlie *a range of quantitative biochemical experiments and phenomena*. Many of these principles arise from physical chemistry (the study of large collections of molecules), and their applications to real systems are worked out via mathematics. The aim here is to equip students with some of the basic attitudes, approaches, and knowledge they will require reading, critically evaluating, and ultimately contributing to original research in macromolecular biochemistry and biophysics.

Another purpose of this course is to gain experience with *mathematical methods* in common use in the quantitative treatment of biochemical problems – linear differential equations in kinetics, concepts of probability, statistics, stochastic processes, and Fourier series. Students have seen most of these before but usually have not had much practice actually using them. My object here is not to torture students but rather to empower them by teaching a few of these tools and demystifying them so that when they are encountered in the biochemical literature later on, they will be seen as useful friends rather than as obscure tormentors.

Learning Goals:

The goal of this course is to equip students with the skillsets and toolkits necessary to critically evaluate and solve biochemical problems they encounter in their own research. It will also allow them to be able to assess the quality of research performed in the literature and allow for them to evolve themselves to original and independent thinkers, who can practice the highest level of biochemistry, a characteristic that will be invaluable for their future career and progress.

Prerequisites

The course requires knowledge of basic biochemistry at the level covered in a good introductory college biochemistry course (e.g., Bchm 100). I will assume that you already are familiar with fundamental chemistry concepts like Gibbs free energy and chemical equilibrium and that you have had at least some previous exposure to basic chemical kinetics. **A *calculus-based introductory physics course is an essential prerequisite.*** You should be *very, very* familiar with the properties of common mathematical functions such as polynomials, logarithms, exponentials, and trig functions. You must also to be able to **solve algebraic equations, differentiate, and integrate with ease** and also to apply univariate calculus to the solution of physical problems stated in words.

Course Requirements

Academic Integrity

Every member of the University community is expected to maintain the highest standards of academic integrity. A student shall not submit work that is falsified or is not the result of the student's own effort. Infringement of academic honesty by a student subjects that student to serious penalties, which may include failure on the assignment, failure in the course, suspension from the University or other sanctions (see section 20 of R&R). Please consult Brandeis University Rights and Responsibilities for all policies and procedures related to academic integrity. Students may be required to submit work to TurnItIn.com software to verify originality. A student who is in doubt regarding standards of academic honesty as they apply to a specific course or assignment should consult the faculty member responsible for that course or assignment before submitting the work. Allegations of alleged academic dishonesty will be forwarded to the Department of Student Rights and Community Standards. Citation and research assistance can be found at Brandeis Library Guides - Citing Sources (https://guides.library.brandeis.edu/c.php?g=301723).

Assignments

The assignments will be sent to me directly electronically (mepandelia@brandeis.edu) and they will be returned in the next class.

Exams/Quizzes

There will be three exams in total. i) on the section of kinetics, ii) on the section of single molecules and diffusion, and iii) on the spectroscopy section.

There will be separate small quizzes that will be posted in LATTE after some of the classes to ensure that you have understood the material and identify any weaknesses in any of the topics. These quizzes will hold a very small percentage of the final grade and their purpose is to assist you in comprehending and mastering the taught material.

Participation

Participation is key to this class. One or two absences can be justified, and the instructor should be notified in advance that a student would not be able to attend the class. The class is small so I will encourage strongly everyone to raise their ***real hand*** and ask questions. If I am in the process of explaining things and I have yet to realize the real hand, please interrupt me. I like conversation! Participation is also taken into account for the final grade of this class.

Evaluation

The grading policy for this class, including percentages allocated to elements such as class participation, exams, homework, papers, and projects is summarized in the Table below and we will briefly go over it in the introduction. All students' work will be graded according to the same standard.

Class Elements	Percentage of Grade
In-class participation	15 %
Quizzes	5 %
Assignments	10 %
Exams	70 %
1st exam	30 %
2nd exam	20 %
3rd exam	20 %

Essential Resources

Required Readings / Optional Readings

The course uses sections from the following texts:

Kuriyan, J. et al. (2013). *The Molecules of Life*. New York, Garland Press
A pretty good general textbook emphasizing physical-chemical principles underlying biochemical analysis. Paperback, worth owning.

Berg, H. C. (1983). *Random Walks in Biology.* Princeton, N.J., Princeton University Press. (This is a cheap paperback and an absolute gem - really worth owning.)

Fersht A. (1977) Enzyme structure and mechanism, New York, W.H. Freeman and Company (some Chapters will be posted)

Other pdfs of relevant books for the course material will be uploaded in LATTE (or just ask if you need more information on a subject and I will gladly provide it to you).

Some of you may already have these texts, but if you don't, you will not need to buy them, as the relevant sections will be posted on LATTE. You should also have available an introductory biochemistry text in case you need to refresh your memory of some of the background material.

For those of you who feel rusty on your introductory calculus, Chris Miller recommends that you buy a sweet little paperback "*Quick Calculus*" by Kleppner and Ramsey. The book emphasizes methods rather than proofs, and it takes you through many practice problems. I have posted the entire book as a pdf on the LATTE site.

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Apps or Tools/Equipment

The use of MATLAB will be required for some sections of the course. All students are strongly encourage to download it from the Brandeis website.
The use of kaleidagraph for fitting of kinetic data is also required and will be provided to all students free of charge via the LATTE website.

LATTE

LATTE is the Brandeis learning management system: http://latte.brandeis.edu. Login using your UNET ID and password.

Remote Teaching

The majority of the class will take place via the Whiteboard. Prior to the beginning of the class and intermittent, a slide will appear to serve as a guideline about the items and activities the students will engage into during the course of each class.

Course Plan

Date: 08.26.2020

Topic:

1. Introduction
2. Study of reaction mechanisms, rates of chemical reactions, introduction of rate constants and reaction velocities.
3. Integrated Rate Equations and derivation of rates (Zero-order, First-order, Second order and pseudo-order reactions).
4. Second order rate constants
5. Reversible reactions and equilibrium constants (K_d and Ka)

Skills:

- We will understand how to define the rate constants of reactions, their units and meaning.
- Equilibrium constants
- This is the basic background for setting the stage to understand more complex kinetics and reaction mechanisms.

Readings for next class

Kinetic Exercise I. No explicit reading is required; you should have the pdf file available, so that we can go over the exercise in real time in the next class.

Installation of the **Kaleidagraph** software from LATTE.

In-class activities:

In half time, we take 10 min in separate breakout rooms and you will answer a small quiz that we will go over at the end of the class.

Date 08.31.2020

Topics:

1. Complex Reactions (Reversible Reactions, Consecutive Reactions A→B→C)
2. Half-life and lifetime in reaction mechanisms
3. Brief Introduction to **Kaleidagraph** software
4. Demonstration of how to use linear regression to fit more complex kinetic data

Skills:

1. We will learn how to derive the rate constants of more complex reactions
2. We will utilize some integrals and derivatives that are extremely useful for subsequent kinetic analyses.
3. We will use a linear regression program to fit real data and extract reaction rates and discuss their meaning.

Readings and focus questions:

Use the **Kaleidagraph** software to go over the question we handled in this section. A manual for the basic use of Kaleidagraph has been posted in LATTE.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the beginning of the second section.

Preparation for next class:

Make sure you are familiarized with the nomenclature of kaleidagraph, because we will use it in next class to fit some more kinetic data.

Date 09.02.2020

* No class in session (there is no holiday, but no classes will take place for BCHM102a on that day). You will receive a first poll to comment on the effectiveness of the class, and the elements that were most useful or problematic.

Date 09.07.2020

* Labor Day. No classes in session

Date 09.09.2020

*class to be done at a later date

Date 09.10.2020

Brandeis Monday: Monday class schedule in effect

Topics:

1. Brief Introduction to **Kaleidagraph** software
2. Demonstration of how to use linear regression to fit more complex kinetic data (Kinetic Exercise I)
3. Kd and Ka and examples

Skills

We will use a linear regression program to fit real data and extract reaction rates and discuss their meaning.

Readings and focus questions:

Use the **Kaleidagraph** software to go over the question we handled in this section. A manual for the basic use of Kaleidagraph has been posted in LATTE.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the beginning of the second section.

Date 09.14.2020

1. Steady-state experiments - Michaelis-Menten (MM) and Briggs and Haldane approximation.
2. Difference between Kd and Km.

3. Brief introduction to diffusion-limited reactions.
4. Meaning of the steady state kinetic parameters, upper limit of kinetic parameters limit of rate constants and kinetic partitioning.

Skills:

1. We will learn how to derive the steady state approximation and what it means for kinetic experiments
2. We will fit real data with the MM equation
3. Familiarization with kcat, Km and kcat/Km

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the rest of the class.

Date 09.16.2020

Topics:

Steady-state Inhibition

1. Competitive inhibition
2. Non-competitive inhibition
3. Mixed inhibition
4. Uncompetitive inhibition (a special case)
5. Practical example on inhibition

Skills:

We will overview the different modes of enzymatic inhibition and we will make a practical exercise to understand the meaning of the inhibition constant Ki.

Assignment:

Model kinetic exercise II in kaleidagraph or in excel and send me the file by 09.21.2020. Right the combined answers in the provided word document. Or also if you prefer hand notes, you can send me those. The answer key will be posted in LATTE after completion of the assignment.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Preparation for next class:

Look through kinetic exercise II (uploaded in LATTE), and have the pdf available for the next class.

Date 09.21.2020

Topics:

1. Kinetic Isotope effects
2. Viscosity Effects
3. Temperature effects on reaction rates
4. Kinetic Exercise III

Skills:

1. Understand and quantify the effects of isotopes, viscosity and temperature on reaction rates
2. Combine elements of previous lectures to understand more complex reaction mechanisms.

Assignment:

Model kinetic exercise III in kaleidagraph and send me the file by 09.24.2020. The answer will be posted in LATTE after completion of the assignment.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 09.23.2020

Topics:

1. Reversible and irreversible one-step binding.
2. Quadratic vs hyperbolic equations.
3. Cooperative binding (Hill)
4. Allosteric activation of enzymes

Skills:

1. Learn to obtain Kd from equilibrium titrations
2. Learn the difference between tight and weak binding of a ligand (protein or molecule)
3. How do enzymes utilize allostery for regulation of their activities.

Quiz:

A small quiz is available in LATTE. Should be completed by 09.30.2020. The answer key will be posted on LATTE.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Preparation for next class:

Look through kinetic exercise IV (uploaded in LATTE), and have the pdf available for the next class.

Date 09.30.2020

Topics:

1. Two-step irreversible binding
2. Differentiation between Kd obtained from equilibrium titrations and transient kinetics
3. Kinetic Exercise IV (kaleidagraph session)

Skills:

1. Learn the difference between true and apparent Kd
2. Think about different experiments to measure Kd
3. Apply linear regression to fit data and obtain the kinetic parameters and equilibrium constants.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 09.28.2020

* Yom Kippur. No classes are in session.

Date 10.05.2020

Topics:

1. Burst kinetics and their importance
2. Single-turnover experiments and why they are a useful alternative to multiple-turnover experiments. Examples and approaches.

Skills:

Mastering some critical aspects of enzymology to delineate reaction mechanisms.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 10.07.2020

In person class @ G-zang 121!

Date 10.12.2020
Time: 10.30 am
Exam on kinetics. It will be open book and in real-time during a class session. It will be 60 min in duration and will go over the aspects we have gone through. You are welcome to have your notes and any textbooks you would like next to you. The exam will be available on LATTE that same day. All students are requested to log in at least 5 min before the exam time to make sure everything goes as planned!

Date 10.14.2020

Topics:

1. Feynman's prediction: Enzymology at the Single Molecule level.
2. The probability density function (PDF)
3. Single ion channels; the first single-molecule experiment in biology.
4. Dwell time distributions, mean, and variance

Skills:

Connect the microscopic parameters with the macroscopic ones and see that we obtain the same behavior as in bulk experiments.
Understand where the exponential in kinetics come from.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Preparation for next class:

Download the single-molecule exercise that has been uploaded in LATTE.

Date 10.19.2020

Topics:

1. In-class assignment: Single-molecule experiment on ion-channels. Open the file single channel exercise in LATTE. You will work for the first 60 min in groups of 2 or 3 in breakout rooms. Please email me the data once you have them so that I can compile them and we can be ready for the next section.
2. We will come back, compile the data and see what they look like and answer a few questions that are as quizzes in the file.

Skills:

Obtain single molecule parameters from experimental data

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 10.21.2020

Topics:

1. The first-passage time problem
2. Problem sets on the white board – Interactive work together to understand elements in single-molecule kinetics.

Skills:

Obtain single molecule parameters from experimental data

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Preparation for next class:

Download the one-dimensional random walk exercise that has been uploaded in LATTE.

Date 10.26.2020

Topics:

1. Diffusion; Microscopic description.
2. One-dimensional Random walk + MATLAB exercise. (you do need to have MATLAB, so that in real time we do the exercise together)
3. Two and three-dimensional random walks (+ MATLAB example)

Skills:

Use of MATLAB to simulate diffusion processes.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Assignment:

Complete the MATALB-based exercise and answer the individual questions.
You will have a week time to submit it.

Date 10.28.2020

Topics:

1. Macroscopic Diffusion; Fick's equations, differential equations that describe changes in concentration as a result of molecular motion.
2. Diffusion equation and diffusion constants.
3. Upper limit of diffusion and diffusion-limited reactions

Skills:

How molecules propagate in 1D, 2D, and 3D and how we quantify this motion.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 11.02.2020

Topics:

1. Diffusion to capture.
2. Problem examples in class.

3. Overview of any questions in single-molecules and diffusion in preparation for the exam.

Skills:

Diffusion constant and rate constants.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 11.04.2020

Time: 10.30 am

Exam on single-molecules and diffusion. It will be open book and in real-time during a class session. It will be 60 min in duration and will go over the aspects we have gone through. You are welcome to have your notes and any textbooks you would like next to you. The exam will be available on LATTE that same day. All students are requested to log in at least 5 min before the exam time to make sure everything goes as planned!

Date 11.09.2020

Topics:

1. Molecules and radiation. Introduction to basic physical parameters.
2. The electromagnetic spectrum (Overview of the spectroscopies and their energy regimes).
3. Ground and Excited States.
4. Absorption Spectroscopy (UV/VIS)

Skills:

The basic language and mathematic tools to understand the different types of spectroscopies, without a deep introduction to quantum mechanics.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 11.11.2020

Topics:

1. Fluorescence
2. Fluoresence spectroscopy and Fluorescence Polarization
3. FRET and applications

Skills:

The basics of fluorescence spectroscopy and its applications.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Quiz:

A quiz on Fluorescence and Absorption spectroscopy will be posted on LATTE. It needs to be returned prior to 11.11.2020.

Date 11.16.2020

Topics:

1. Nuclear Magnetic Resonance Spectroscopy (Basic theory)
2. Larmor Frequency and Boltzmann Distribution
3. One dimensional and two-dimensional NMR spectroscopy (with examples).
4. 19-F NMR

Skills:

The basic experiments of NMR and its applications.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 11.18.2020

Topics:

1. EPR spectroscopy (basic theory)
2. *g*-values and chemical information
3. Hyperfine interactions
4. DEER (distance measurements, alternative to FRET)

Skills:

Understanding of EPR and its potency in the study of paramagnetic molecules.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Date 11.30.2020

Topics:

1. Moessbauer Spectroscopy.
2. Basic theory and analogy to NMR
3. *Examples* of Moessbauer spectra
4. *Exercise* on the ferryl-intermediate of none-hem oxygenases.

Skills:

Understanding of Moessbauer spectroscopy and the diverse chemical and kinetic information we can obtain.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

Assignment:

Problem sets on spectroscopy. You will have the thanksgiving break and can submit them prior to or on 11.30.2020. The answer key will be posted on 11.30.2020.

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Topics: **Date 12.02.2020**

1. Moessbauer, EPR, Fluorescence, and NMR Spectroscopy on [Fe-S] clusters
2. Combination of different spectroscopic methods to interrogate kinetic, thermodynamic and structural parameters.

Skills:

Bring together all the kinds of spectroscopies we have looked at so far.

In-class activities:

In half time, you will have the time to take 10 min in separate rooms by yourselves to write down any questions that arose in the first section, and we will discuss them during the class.

TBD

Time: 10.30 am
Exam on spectroscopic methods. It will be open book and in real-time during a class session. It will be 60 min in duration and will go over the aspects we have gone through. You are welcome to have your notes and any textbooks you would like next to you. The exam will be available on LATTE that same day. All students are requested to log in at least 5 min before the exam time to make sure everything goes as planned!