Updated 08/16/2024.

CHEM 246: Advanced Statistical Mechanics: Frontiers in Research
Harvard University, Fall 2024

Course Description:
This class is for students who have undergraduate-level background in statistical mechanics but would like to explore how statistical mechanics helps to expand frontiers of research in modern biophysical chemistry, systems biology, and materials science. The course includes regular lectures and journal club style in-depth discussion of current literature. The course starts with introductory lectures with emphasis on statistical mechanics of complex multi-particle systems including theory of phase transitions, statistical mechanics of complex systems and related topics. Next, we proceed with discussion of topics at the forefront of current research. These include but not limited to biomolecular folding and organization including protein and genome folding and assembly of supramolecular complexes, statistical mechanics of liquid-liquid phase separation in living cells, statistical mechanics of biological evolution, thermal and dynamic properties of complex materials (polymers, gels multicomponent solutions). Special emphasis will be placed on current developments that revolutionized life sciences such as application of artificial intelligence in structural biology (AlphaFold2) and AI-based approaches to computational drug discovery.

Prerequisites:
Chem 161 (Statistical Thermodynamics), Physics 181 (Statistical Mechanics and Thermodynamics), MCB 199 (Statistical Thermodynamics and Quantitative Biology) at Harvard, or an equivalent course at another college.

Lectures:
- Time: Tu, Th 3:00pm - 4:15pm
- Location: Mallinckrodt 217
- The first class will be on Tuesday, Sept. 3rd, 2024.

Course Staff
Course Head: Prof. Eugene I. Shakhnovich, shakhnovich@chemistry.harvard.edu, 617-495-4130
Teaching Fellow: Dr. Vaibhav Mohanty, mohanty@hms.harvard.edu

Office Hours:
Prof. Shakhnovich, By appointment
Vaibhav, office hours to be held during problem set weeks, otherwise by appointment

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Course Structure:

	Topics
Part I: Folded Protein	**1.1 Topics in advanced statistical mechanics.** Including but not limited to Landau phase transition theory, spin glass, replica trick, Potts model, and Hopfield network.
	1.2 Statistical mechanics of protein folding (structure space). Apply theory in 1.1 to the protein folding problem.
	1.3 Statistical mechanics of molecular evolution in sequence space. Apply theory in 1.1 to gain molecular-level understanding of evolution. Including but not limited to population genetics, maximum likelihood method of inference.
	1.4 AlphaFold2. The success of AlphaFold2 comes from the combination of machine learning, protein structure database, and protein evolution information. This part includes, but is not limited to, AlphaFold2 and multiple sequence alignment.
Part II: Unfolded Protein	**2.1 Basics of polymer physics.** Including but not limited to spinodal decomposition, Flory-Huggins theory, gelation, Rouse model, and reptation model.
	2.2 Liquid-liquid phase separation (LLPS). Intrinsically disordered proteins and/or RNA can phase-separate into biomolecular condensates to facilitate cellular compartmentalization. We will apply theory in 2.1 to understand the mechanism of LLPS and connect the macroscopic phenomena with molecular details.
Part III: Protein Interactions	**3 Systems biology of proteins.** Including but not limited to protein-protein interactions, metabolon, gene regulation.

References:

Part I:

- Kardar, Statistical Mechanics of Particles, Cambridge University Press, 2007.
- Kardar, Statistical Mechanics of Fields, Cambridge University Press, 2007.

Part II:

- de Gennes, Scaling Concepts in Polymer Physics, Cornell University Press, 1979.
- Rubinstein, Colby, Polymer Physics, Oxford University Press, 2003.
- Doi, Edwards, The Theory of Polymer Dynamics, Clarendon Press, 1988.

Part III:

- To be added.

Other Useful Resources:

- Ken Dill, Molecular Driving Forces: Statistical Thermodynamics in Biology, Chemistry, Physics, and Nanoscience, Garland Science, 2003.
- MIT 8.592J Statistical Physics in Biology, http://web.mit.edu/8.592/www/.

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Course Format:

Each week is divided as follows:

- **Tuesday:** The first lecture introduces key concepts pertinent to the week's topic, providing insights into its application and drawing comparisons with other subjects. This session establishes a foundational understanding for students.
- **Thursday:** The second session revolves around a discussion of significant literature in the field, led by the Professor and a selected student. The chosen student is expected to present a 10-15 minute overview of the key literature. All other students must submit a concise written summary of the central literature before this class.

Note:

- During part 1.1 and 2.1 (see course structure), discussions will not take place. Instead, lectures will be conducted on both Tuesday and Thursday.
- Literature that needs to be discussed will be provided at least two weeks before the discussion class.

Homework (30%)	
Description	There will be 3-4 problem sets assigned throughout the semester, accounting for half of the homework grade. Students not presenting in a given week must submit a concise written summary of the key literature; these summaries will account for half of the homework grade. Each summary, **due before the Tuesday of the same week**, is pivotal to their course participation. It should: ● Outline 3-4 key takeaways from the paper. ● Address any aspects of the paper that were unclear or with which the student disagrees. ● Be between 0.5-1 page single-spaced.
Note	The student presenting that week is **exempt** from submitting the written summary.

Discussion Lead (20%)	
Description	Every Thursday (detailed schedule below), a student will partner with the professor to lead a discussion on the week's chosen literature. To initiate the discussion, the student will give an informal presentation, which: ● Last 10-15 minutes. ● Highlight the main points and significance of the literature. ● Draw any relevant comparisons or contrasts with other materials.
Note	The frequency with which each student leads the discussion will be determined by the total number of enrolled students. Last year, each student only had one presentation.

Final Presentation (50%)	
Description	Students will give a **15-minute presentation** to the class proposing a new physical study of a problem in molecular or cellular biology. The presentation may either propose a new experiment, develop a new physical model for a known phenomenon, or do a combination of the two. The presentation idea is expected to be independently conceived and original. “Original” means that that no work on the selected topic can be found in a published form. Students, especially those concerned about the originality of their projects, are encouraged to seek out advice from the course instructor and TF.
Timeline	● **4 weeks before the assigned final exam date**: project title and a few sentences description are due. We will not strictly hold you to the topic you state here, but the idea is for you to start a dialog with us about your proposal. All students are encouraged to meet with the instructor to discuss their final projects. ● **2 weeks before the assigned final exam date**: revised title and abstract (150-250 words) are due. This will be part of the final presentation grade and your abstract should reflect the final topic that you have chosen. ● **During the last 2-3 class dates**: your presentation slides are due, and your 15-minute presentation will take place. (15 minutes per student, so the presentation is 12 minutes followed by 3 minutes of Q&A.)
Proposal Requirements	The organization of the presentation should be as follows: begin by describing the scientific issue or question you will address, state the significance of solving this issue or answering your question, and then clearly describe your approach to solving this problem, including sufficient technical detail for your audience to evaluate the feasibility of your proposal. It is CRITICAL that you cite literature references that are relevant to your work. Of course, you are expected to develop an original proposal idea, but you must give credit to previous experiments that inspire your work and to sources of ideas or estimates of numerical quantities relevant to your work. ● The importance of the abstract: should get all the main points across. Often this is challenging to write! ● The need for clear figures to illustrate either the proposed experimental design or a schematic of the types of data you might expect from a successful outcome.

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Tentative Course Calendar:

Date	*Lectures*, *Discussion Schedule*, *Proposal Checkpoint*, *Presentations*
Sept. 3-26	Lectures. **Problem set due dates TBD.**
Oct. 1 & 3	Topic: Statistical mechanics of protein folding (structure space) **Summary due Oct. 1.**
Oct. 8 & 10	Topic: Statistical mechanics of molecular evolution in sequence space **Summary due Oct. 8.**
Oct. 15 & 17	Topic: Statistical mechanics of molecular evolution in sequence space **Summary due Oct. 15**
Oct. 22 & 24	Topic: AlphaFold2 and AI for Protein **Summary due Oct. 22**
Oct. 29 & 31	Topic: Liquid-liquid phase separation (LLPS) **Summary due Oct. 29**
Nov. 5 & 7	Topic: Liquid-liquid phase separation (LLPS) **Summary due Nov. 5** **Proposal Checkpoint 1 due Nov. 5: Project title and a few sentences description.**
Nov. 12 & 14	Topic: Protein-protein interaction network (Systems biology of proteins) **Summary due Nov. 12**
Nov. 19	**Proposal Checkpoint 2 due Nov. 19: Revised title and abstract (150-250 words).**
Nov. 21	**Presentation Day 1**
Nov. 26	**Presentation Day 2**
Nov. 28	No class, Thanksgiving.
Dec. 3	**Presentation Day 3**

Policy on the use of AI
Certain assignments in this course may permit or even encourage the use of generative artificial intelligence (GAI) tools such as ChatGPT. The default is that such use is disallowed unless otherwise stated. Any such use must be appropriately acknowledged and cited. It is each student's responsibility to assess the validity and applicability of any GAI output that is submitted; you bear the final responsibility. Violations of this policy will be considered academic misconduct. We draw your attention to the fact that different classes at Harvard could implement different AI policies, and it is the student's responsibility to conform to expectations for each course. Learn more at https://oue.fas.harvard.edu/ai-guidance.

Disability Accessibility Office Statement
Harvard University values inclusive excellence and providing equal educational opportunities for all students. Our goal is to remove barriers for disabled students related to inaccessible elements of instruction or design in this course. If reasonable accommodations are necessary to provide access, please contact the Disability Access Office (DAO). Accommodations do not alter fundamental requirements of the course and are not retroactive. Students should request

accommodations as early as possible, since they may take time to implement. Students should notify DAO at any time during the semester if adjustments to their communicated accommodation plan are needed.