Rational Drug Design: Principles and Applications

Department of Biomedical Engineering
University of Alberta, Edmonton
BME630
Class periods: W from 02:00 PM to 04:50 PM
Location: GSB 8-11
Academic Term: Winter 2023

Instructor:

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Office hours: *To be announced*
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Course Description:

Principles and applications of rational drug design. An overview of the drug design and development process. Bioinformatic databases and tools. Working with protein sequences and structures. Homology modeling. Force fields and molecular dynamics simulations. Solvation in molecular modelling. Binding free energy prediction. Protein–ligand docking and virtual screening. Ligand-based screening and pharmacophore modelling. Retrosynthesis. Quantitative structure activity relationship (QSAR) modelling. A brief overview of pharmacokinetic modeling and absorption, distribution, metabolism, excretion and toxicity (ADMET) prediction. A brief discussion of systems biology.

Course Objectives and General Content:

This course is primarily intended for graduate students in the Department of Biomedical Engineering accelerated Master of Engineering (M.Eng.) Program in Biomedical Engineering (BME). It will also be available to qualified graduate students in other faculties (for example, Science), and undergraduate students with the permission of the instructor.

Rational drug design to treat a variety of diseases plaguing humans is a vision that is fast becoming a practically achievable goal of computer-aided drug discovery research. This course will expose the student to methods and applications of computational drug design with an in-depth introduction to present-day methods. The objective of this course is to introduce strategies for the rational design of drug candidates. The main focus will be placed on both structure-based and ligand-based computer-aided design of an active compound. There will be an introduction to and training on the bioinformatic data sources and tools that are essential for rational drug design. Specific topics to be discussed include molecular dynamics, molecular docking, computational analysis of drug-receptor interactions, and lead modification for improved biochemical activity. Quantitative structure activity relationship (QSAR) modelling, include both theory and practical examples will be covered. Pharmacokinetics and absorption, distribution, metabolism, excretion and toxicity (ADMET) prediction will also be discussed as well. Lastly, there will be a brief introduction to the field of systems biology with applications to drug discovery.

Students who enter this course should possess a familiarity with the fundamentals of organic chemistry, molecular biology and biochemistry.

Learning Outcomes:

By the end of the course the student will be able to:
1. Retrieve information from bioinformatics and cheminformatic database.
2. Create homology models of proteins.
3. Understand molecular modeling approaches and force fields applied to drug-target systems, and run molecular dynamics simulations.
4. Employ structure-based drug screening/discovery/design algorithms, with a particular focus on drug–target docking simulations and fast binding affinity predictions.
5. Understand ligand-based drug screening/discovery/design algorithms and develop pharmacophore models.
6. Create QSAR models.
7. Understand the basis of pharmacokinetic modeling; use software for ADMET prediction.
8. Appreciate the systems biology approach to combination therapy.

Marking Scheme:

Assignment	**Topic**	**Deadline**	**Percentage of Final Grade**
Assignment 1	Homology Modelling	Assignment 1 due Wed Feb 8 8:00 am	10%
Assignment 2	Molecular Dynamics Simulations	Assignment 2 due Wed Mar 1 8:00 am	10%
Assignment 3	Molecular Docking and Virtual Screening	Assignment 3 due Wed Mar 15 8:00 am	10%
Assignment 4	QSAR	Assignment 4 due Wed Mar 29 8:00 am	10%
Group project	*To be announced*	Oral presentation: April 12 Written report: April 12 6:00 pm	60%

There will be four individual assignments and one group project.

Each individual assignment will correspond to hands-on tutorials covered in class. There will be a total of four assignments with the deadlines listed in the course schedule. Detailed marking rubrics for the assignments will be provided on eClass.

There will be a final group project due at the end of the course. The project will be an applied problem on rational drug design to be solved by a student team. The project may include the following components: bioinformatics database information retrieval, homology modelling, molecular dynamics simulations, drug–protein docking, ligand-based screening, pharmacophore modelling and/or QSAR modelling. A suggested topic will be assigned by the instructor; students

may select an alternate topic with the approval of the instructor. The project will require three components to be submitted: (1) a presentation during the last week of classes; (2) a written report detailing the problem, the methods used, and a discussion of the results; and (3) an archive containing all data files. Detailed requirements and marking rubrics for the final project will be provided on the course eClass.

There will be no final exam.

Textbook and Course Materials:

Recommended textbook:
No available books fully meet the needs of the course. The material necessary to the study of this course will be provided by the professor.

Required software:
The course will require the Molecular Operating Environment (MOE) package, which will be provided for students.

Other course materials:
eClass will contain all lecture presentation slides, tutorials, data files, and all other course files.

Course Content:

Note: The course schedule might be subject to change.

Week (Date)	Subject	Hands-on Tutorial	Deadlines
1 (Jan 11)	Introduction to Drug Design; A Historical Overview of the Evolution of Drug Design and Development	Installing the Molecular Operating Environment (MOE)	
2 (Jan 18)	Drug Development and Disease Targets: An Overview of Medicinal Chemistry; Bioinformatic Databases and Tools	Introduction to MOE	
3 (Jan 25)	Protein Structure Prediction and Homology Modelling	Homology Modelling	
4 (Feb 1)	Force Fields and Molecular Dynamics Simulations; Introduction to the Group Project Topic	Homology Modelling Continued	
5 (Feb 8)	Force Fields and Molecular Dynamics Simulations Continued	Molecular Dynamics Simulations	Assignment 1 due Wed Feb 8 8:00 am

6 (Feb 15)	Electrostatics and Solvation in Biomolecular Systems; Binding Free Energy Predictions	Molecular Dynamics Simulations Continued	
Reading Week (Feb 22)	No Class		
7 (Mar 1)	Protein–Ligand Interactions and Molecular Docking; Virtual Screening and Structure-Based Drug Design	Molecular Docking and Virtual Screening	Assignment 2 due Wed Mar 1 8:00 am
8 (Mar 8)	Ligand-based Screening and Retrosynthesis Issues; Pharmacophore Modelling	Molecular Docking and Virtual Screening Continued	
9 (Mar 15)	Quantitative Structure Activity Relationship (QSAR)	QSAR	Assignment 3 due Wed Mar 15 8:00 am
10 (Mar 22)	Introduction to Pharmacokinetics; Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Prediction	QSAR Continued	
11 (Mar 29)	Introduction to Systems Biology with Applications to Drug Discovery		Assignment 4 due Wed Mar 29 8:00 am
12 (Apr 5)	Additional topic selected by instructor		
13 (Apr 12)	Student project presentations		Oral presentation: April 12 during class Written report: April 12 6:00 pm

Week 1: Introduction to Drug Design; A Historical Overview of the Evolution of Drug Design and Development

An overview of the methods and tools used in modern drug discovery. The drug design and development process. Issues and challenges in drug development. Historical context and recent approaches.

Week 2: Drug Development and Disease Targets: An Overview of Medicinal Chemistry; Bioinformatic Databases and Tools

Common chemical functional groups. Examples of drug chemical structures. Examples of anticancer chemotherapeutic drugs. Examples of drug resistance. Online data sources on chemical compounds, drugs, targets and interactions. File formats for compounds and target structures. Tools for converting, manipulating and viewing data

Week 3: Protein Structure Prediction and Homology Modelling

Protein structure: primary, secondary, tertiary and quaternary. Working with protein sequence data: searching and alignment. Homology modelling.

Week 4: Force Fields and Molecular Dynamics Simulations; Introduction to the Group Project Topic
A discussion of force fields and examples of force field equation terms. Molecular dynamics simulations: algorithms, issues and limitations. Properties of molecular dynamics ensembles. An introduction to the group project topic.

Week 5: Force Fields and Molecular Dynamics Simulations Continued
A continuation of the force fields and molecular dynamics discussion.

Week 6: Electrostatics and Solvation in Biomolecular Systems; Binding Free Energy Predictions
Incorporating solvent effects in modelling. Implicit versus explicit solvent models. Binding free energy predictions.

Week 7: Protein–Ligand Interactions and Molecular Docking; Virtual Screening and Structure-based Drug Design
Molecular docking: purpose, methods and issues. The workflow of virtual screening and structure-based drug design.

Week 8: Ligand-based Screening and Retrosynthesis Issues; Pharmacophore Modelling
Ligand-based screening: purpose and methods. Small-molecule data formats. Chemical retrosynthesis issues. Generating pharmacophore models and pharmacophore-based virtual screening.

Week 9: Quantitative Structure Activity Relationship (QSAR)
Background on QSAR. Molecular descriptors. QSAR methods.

Week 10: Introduction to Pharmacokinetics; Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) Prediction
An introduction to pharmacokinetics. ADMET prediction. Modeling pharmacokinetics.

Week 11: Introduction to Systems Biology with Applications to Drug Discovery
What is systems biology? An introduction to biological networks. Types of biological networks. Generating and analyzing biological networks. Applications to drug discovery.

Week 12: Additional topic selected by instructor
To be announced.

Week 13: Student project presentations
Time allocated for student project presentations.

Policies and Student Responsibilities:

Attendance Policy, Assignment Expectations, and Make-Up Policy
Attendance in classes is optional. Assignments are due on the deadlines listed in the course schedule. **No late assignments will be accepted.** Missed assignments can only be made up for in extraordinary circumstances with prior approval of the instructor.

Students Requiring Accommodations
Accommodations are available by contacting Academic Success Center (https://www.ualberta.ca/current-students/academic-success-centre/accessibility-resources/index.html) and by providing appropriate documentation. Once registered, an eligible student will receive an accommodation letter which must be presented to the instructor when requesting accommodation. Students with disabilities should follow this procedure as early as possible in the semester.

Academic Success Centre
The Academic Success Centre (https://www.ualberta.ca/current-students/academic-success-centre/index.html) provides professional academic support to help students strengthen their academic skills and achieve their academic goals. Individual advising, appointments, and group workshops are available year-round in the areas of Accessibility, Communication, Learning, and Writing Resources. Modest fees apply for some services.

Commitment to a Safe and Inclusive Learning Environment
The Faculty of Engineering values broad diversity within our community and is committed to individual and group empowerment, inclusion, and the elimination of discrimination. It is expected that every person in this class will treat one another with dignity and respect regardless of gender, sexuality, disability, age, socioeconomic status, ethnicity, race, and culture. Resource Center (https://policiesonline.ualberta.ca/policiesprocedures/policies/discrimination-harassment-and-duty-to-accommodate-policy.pdf) and (https://www.ualberta.ca/human-resources-health-safety-environment/employment-information/ethical-conduct/discrimination-and-harassment.html) by providing appropriate documentation). If you feel like your performance in class is being impacted by discrimination or harassment of any kind, please contact your instructor or any of the following: For more information about disclosures, contact OSDHR by email at osdhr@ualberta.ca or telephone at 780-492-7357. More information about Office of Safe Disclosure and Human Rights (OSDHR) (https://www.ualberta.ca/services/provost/disclosing-discrimination-harrassment-and-other-misconduct.html).

Academic Integrity
According to the International Centre for Academic Integrity, University of Alberta's students are bound by academic integrity which states "a commitment to five fundamental values: honesty, trust, fairness, respect, and responsibility," (Fishman, 2013, p. 16). Students should obey the academic integrity on all work they submit for credit. The academic integrity source (https://www.ualberta.ca/centre-for-teaching-and-learning/teaching-support/assessment/academic-integrity.html) explains the behaviors that are in violation of this code and the possible sanctions. Furthermore, you are obligated to report any condition that facilitates academic misconduct to appropriate personnel. If you have any questions or concerns, please consult with the instructor or TAs in this class. Check academic integrity during COVID-19 (https://www.ualberta.ca/current-students/academic-resources/academic-integrity/index.html)/

Software Use

All faculty, staff, and students of the University are required and expected to obey the laws and legal agreements governing software use. Failure to do so can lead to monetary damages and/or criminal penalties for the individual violator. Because such violations are also against University policies and rules, disciplinary action will be taken as appropriate. Resource: https://policiesonline.ualberta.ca/policiesprocedures/policies/information-technology-use-and-management-policy.pdf