

COURSE OUTLINE

1. GENERAL

SCHOOL	APPLIED BIOLOGY AND BIOTECHNOLOGY		
DEPARTMENT	BIOTECHNOLOGY		
STUDY LEVEL	Undergraduate-Elective		
COURSE CODE	XXX	SEMESTER	6 th , 8 th ?
COURSE TITLE	BIOMOLECULAR SIMULATIONS		
INDEPENDENT TEACHING ACTIVITIES <i>if credits are awarded for separate components of the course, e.g. lectures, laboratory exercises, etc. If the credits are awarded for the whole of the course, give the weekly teaching hours and the total credits</i>		WEEKLY TEACHING HOURS	ECTS
Theory		3	3
Laboratory exercises		2	2
TOTAL		5	5
COURSE TYPE <i>general background, special background, specialised general knowledge, skills development</i>	General Knowledge		
PREREQUISITES	Recommended knowledge of curriculum courses: Physics, Computer Programming and Applications, Biophysics, Physics of Life.		
LANGUAGE	Greek		
IS THE COURSE OFFERED for ERASMUS STUDENTS?	No		
COURSE WEB PAGE			

2. LEARNING OUTCOMES

Learning Outcomes

The course learning outcomes, specific knowledge, skills and competences of an appropriate level, which the students will acquire with the successful completion of the course are described.

Consult Appendix A

- Description of the level of learning outcomes for each qualifications cycle, according to the Qualifications Framework of the European Higher Education Area
- Descriptors for Levels 6, 7 & 8 of the European Qualifications Framework for Lifelong Learning and Appendix B

Guidelines for writing Learning Outcomes

The course **Biomolecular Simulations** is a specialized interdisciplinary course that offers a comprehensive, first view of classical Computational Chemistry/Biology. The objective of the course is to delve into the theory and practice of biomolecular simulations, resulting in a qualitative and quantitative understanding of critical microscopic mechanisms associated with the (mis)function of the cell and pharmaceutical discovery at a preclinical level. The course offers students a comprehensive overview of the operating principles and applications provided by advanced computational techniques, enabling the study of biological systems at the level of microscopic structure, thermodynamics, and kinetics of individual biomolecules up to more complex cellular processes, such as the formation of liquid droplets. Finally, it examines fundamental issues such as the relationship between microscopic interactions and macroscopic properties of biomolecules, as well as the bridging temporal and spatial scales through biomolecular simulations.

Cognitive Outcomes (Knowledge & Understanding)

- Understand the connection between microscopic interactions and the macroscopic properties of biomolecules.

- Understand the different models of molecular interactions in molecular mechanics forcefields (AMBER, CHARMM) and their specificity to different types of biomolecules.
- Understand the fundamental theory and application of Molecular Dynamics (MD) and Monte Carlo (MC) simulations.
- Distinguish between different mechanisms of protein folding and protein conformational changes in proteins of biotechnological interest.
- Recognize the capabilities and limitations of atomistic Molecular Dynamics biomolecular simulations: A) The timescale problem B) The lengthscale problem.
- Understand the principles of molecular kinetics and Enhanced Sampling Molecular Dynamics (MD) simulations.
- Understand the mechanism of interaction and the release kinetics of an anti-cancer drug from a protein target.
- Understand the operating principles of Coarse-Grained Molecular Dynamics (CGMD) Simulations that provide access to micro-scale biomolecular mechanisms. Through CGMD applications in the literature, distinguish the mechanisms and thermodynamics of liquid droplet and lipid bilayer formation in the presence of membrane proteins.

Application Skills

- Design, execute, and analyze molecular dynamics simulations using the Molecular Dynamics packages GROMACS and OpenMM, and the Python programming language.
- Construct Markov State Models (MSM) for analysing the equilibrium kinetics and thermodynamics of protein folding.
- Apply Enhanced Sampling Molecular Dynamics techniques to study the kinetics and thermodynamics of biomolecular transitions, such as the (un)binding of an anti-cancer drug from its target protein.
- Use coarse-grained models (CALVADOS) for micro-scale Molecular Dynamics simulations with applications in the formation of liquid droplets and lipid bilayers in the presence of membrane proteins.

Analysis & Synthesis Skills

- Analyze simulation trajectories to extract thermodynamic and kinetic properties of biomolecular mechanisms.
- Evaluate the quality and reliability of simulation types and select appropriate methods.
- Compare different methodological approaches and propose optimal strategies for specific biological problems.
- Interpret simulation results in relation to experimental data and biological function.

Evaluation & Creation Skills

- Design research protocols for the study of specific biomolecular phenomena (protein folding, conformational changes, phase separation).
- Combine different computational techniques to understand biological mechanisms at the atomistic level.
- Present results in a scientifically rigorous manner.

Critical Thinking and Collaboration Skills

- Develop critical thinking regarding the limitations and possibilities of computational methods.
- Collaborate effectively in computational biology projects.

General Competencies

Taking into consideration the general competences that the degree-holder must acquire (as these appear in the Diploma Supplement and appear below), at which of the following does the course aim?

Search for, analysis and synthesis of data and information, with the use of the necessary technology
Adapting to new situations

Decision-making
Working independently
Team work
Working in an international environment
Working in an interdisciplinary environment
Production of new research ideas
Project planning and management
Respect for differences and multiculturalism
Respect for the natural environment
Showing social, professional and ethical responsibility and sensitivity to gender issues
Criticism and self-criticism
Production of free, creative and inductive thinking

The students develop skills related to:

- Acquisition of terminology knowledge and correct description skills.
- Development of analytical & critical abilities.
- Development of problem-solving skills.
- Searching, analyzing, and creating data and information, including the use of necessary technologies.
- Connecting knowledge with reality and applications.
- Development of skills for decision-making, effective teamwork, and adaptation to new situations.
- Demonstration of social, professional, and ethical responsibility.
- Respect for the work and natural environment.
- Promotion of free, creative, and inductive thinking.

3. COURSE CONTENT

I. Theory

Introduction. Biomolecular dynamics: Levinthal's paradox. Prediction of biomolecular structures using artificial intelligence algorithms: AlphaFold, RosettaFold, basic operating principles. The importance of biomolecular simulations as a tool to connect microscopic interactions and statistical thermodynamics with the prediction of macroscopic kinetic and thermodynamic properties.

Connecting Thermodynamics and Statistical Thermodynamics as the Theoretical Background of Biomolecular Simulations. Basic thermodynamic equations. Criteria for thermodynamic equilibrium. Statistical ensembles. Statistical interpretation of entropy. Thermal equilibrium and the Boltzmann distribution. Partition function.

Modeling Molecular Interactions. Molecular mechanics model of molecular interactions. Overview of optimal molecular mechanics models for different types of biomolecules (folded proteins, transmembrane proteins, intrinsically disordered proteins, DNA, RNA, lipids): AMBER, CHARMM.

Molecular Dynamics (MD). Newton's equation of motion and time evolution of the molecular trajectory. Molecular simulations at constant energy (NVE), temperature/pressure (NVT, NPT). Efficient calculation of intermolecular interactions. Calculation of macroscopic properties. Example of a Molecular Dynamics protocol applied to the folding of a biotechnologically relevant protein.

Monte Carlo (MC). Principles of the method: Markov chains and detailed balance. The Metropolis sampling algorithm. Examples of conformational space sampling for the

folding and aggregation of intrinsically disordered proteins on a lattice model, under constant temperature (NVT).

Rare Events. The problem of slow sampling in Molecular Dynamics. Kinetic equilibrium analysis of biomolecular systems via Markov State Models (MSM). Steps for constructing an MSM. Example of protein folding for a protein of biological interest, extraction of the atomistic mechanism, thermodynamics, and kinetics of folding.

Multiscale Simulations I: Crossing the Time Scale. Overview of enhanced sampling methods. The reaction coordinate. Techniques for finding the reaction coordinate. Examples of applications of enhanced sampling methods for characterizing the kinetics and thermodynamics of the molecular mechanism of anti-cancer drug (un)binding from its target.

Multiscale Simulations II: Crossing the Length Scale. Coarse-Grained (CG). Models of molecular mechanics. The Martini force field. The CALVADOS force field. Advantages and disadvantages of CG models. Examples of using CG models in molecular dynamics simulations for the prediction of the liquid-liquid phase diagram of intrinsically disordered proteins and the formation of lipid bilayer in presence of transmembrane proteins.

II. Laboratory: 1) Introduction to Python. 2) Molecular dynamics simulation of lysozyme using Gromacs and OpenMM. 3) Sampling the conformational ensemble of folding and aggregation of the intrinsically disordered protein Tau on a lattice, using Monte Carlo. 4) Construction of a Markov State Model (MSM) to extract the atomistic mechanism, thermodynamics, and equilibrium kinetics of the chignolin mini-protein folding. 5) Enhanced sampling simulation using Metadynamics to study the mechanism of conformational change in a dipeptide. 6) Use of the CALVADOS coarse-grained model in Molecular Dynamics simulations for predicting the liquid-liquid phase diagram of the FUS protein and the microscopic mechanism of liquid droplet formation.

4. TEACHING and LEARNING METHODS - EVALUATION

TEACHING METHOD <i>Face-to-face, Distance learning, etc</i>	In suitably equipped teaching rooms.	
USE OF INFORMATICS and COMMUNICATION TECHNOLOGIES <i>Use of ICT in teaching, laboratory education, communication with students</i>	Use of PowerPoint slides, videos of molecular dynamics and Monte Carlo simulations, etc. in the lectures; use of the e-class website system for information, interactive education (quiz), distribution of educational material, submission & grading of lab exercises, and communication with students.	
TEACHING ORGANISATION <i>Lectures, Seminars, Laboratory Exercises, Field Exercise, Literature Study & Analysis, Tutorial, Internship, Clinical Exercise, Interactive Teaching, Educational Visits, Study Preparation (Project), Written assignments, Independent study</i> <i>The student's study hours for each learning activity are listed, so that the total workload at the semester level corresponds to ECTS standards.</i>	Activity	Work Load
	Lectures	39 hr
	Laboratory exercises	12 hr
	Assignments	20 hr
	Independent study	48 hr
	Optional Progress assignment series (quiz)	4 hr
	Final exam	2 hr
	Course total <i>(25 hours of student work load per ECTS)</i>	125 hr (5 ECTS)
STUDENT EVALUATION <i>Evaluation Methods, Formative or Inferential, Multiple Choice Test, Short Answer Questions,</i>	I. Theory (50% of Total Grade)	

<i>Essay Development Questions, Problem Solving, Written Assignment, Report / Report, Oral Examination, Public Presentation, Laboratory Work, Other / Others</i> <i>Expressly specified assessment criteria are stated and whether and where they are accessible to students.</i>	Written final examination (70%–100% of the Theory component) which includes: • Multiple-choice questions • Short answer/critical thinking questions • Long-form problem solving Optional progress assignment for positive evaluation (maximum 30% of the Theory component). II. Laboratory (50% of Total Grade) (a) 6 Group Assignments (2–3 people) involving the analysis of simulation data (70%), with submission of written weekly reports. (b) Final Individual Project (30%)
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5. BIBLIOGRAPHY

Greek literature

1) Tutor notes.

2) Α. Κολοκούρης. Υπολογιστική Χημεία – Μοριακές Προσομοιώσεις: Θεωρίες, Μέθοδοι και Εφαρμογές. Εκδόσεις Παρισιανού.

3) P. Atkins, J. De Paula, J. Keeler. Φυσικοχημεία, Πανεπιστημιακές εκδόσεις Κρήτης, 12^η εκδ. 2025.

E-books:

4) Chontzopoulou, E., Kiriakidi, S., Zoumpoulakis, P., & Mavromoustakos, T. (2022). Principles in Computational Chemistry. Kallipos, Open Academic Editions.

5) Koutselos, A. (2015). Statistical Thermodynamics. Kallipos, Open Academic Editions.

Complementary international literature

6) Frenkel, Daan, Berend Smit Understanding Molecular Simulation: From Algorithms to Applications, Academic Press 3rd edition, 2023.

7) Allen, M. P., & Tildesley, D. J. Computer Simulation of Liquids, Clarendon Press, Oxford 1987.

8) Peters, Baron, Reaction Rate Theory and Rare Events, Elsevier, 2017.

Laboratory:

1) Tutor notes.