Syllabus

1. Course Description
    a. Title of a Course

    Computer molecular biology and medicine

    b. Pre-requisites .

    The Course is to be based on the acquisition of the following Courses:
    - General physics;
    - Mathematical analysis;
    - Probability theory and mathematical statistics;
    - Numerical methods;
    - General English

    c. Course Type (compulsory, elective, optional)

    compulsory

    d. Abstract

    The course covers: basic physical principles of molecular simulations, mathematical algorithms and computationalprotocols employed to study supramolecular biological objects in the framework of classicalmechanics and empirical force fields; the methods of molecular mechanics, molecular dynamics, Monte Carlo, structural bioinformatics and molecular docking along with their theoretical foundations and employedphysical models and mathematical algorithms; -Combined approaches to rational design of computational experiments with the help of in silicotechnologies; efficient application of the macroscopic approximation and classical mechanics in detailedanalysis of complex microscopic phenomena – individual molecules and their ensembles.

2. Learning Objectives

The purpose of learning the discipline “Computer molecular biology and medicine” is the students’ introduction into modern methods of computer modeling of complex - multicomponent and mesoscopic - biomolecular systems. The modeling is carried out in the framework of classical Newtonian mechanics, using empirical energy functions - so-called force fields.

3. Learning Outcomes

The student will know:

-Basic computer technologies of the experimental data processing;

-Modern methods of computational analysis and prediction of properties and functioningmechanisms of the studied complex biomolecular systems and constructs;

-Basic physical models describing structural and dynamic properties of biomolecularsystems;

-Basic principles of computer-aided drug design and multiscale modeling;

-State-of-the-art computational techniques to study biomolecular systems incomputational experiments (molecular dynamics, Monte Carlo, molecular docking, and so on);

-Methods of rational interpretation and further design of traditional physicalexperiments in molecular biology;
-Approximations and limitations of physical models and mathematical algorithms used insimulations of biomolecular systems;
-Importance of computer modeling in solving specific biological and medical problems.

The student will be capable of:

-Analyzing scientific problems and physical processes, realizing in practice fundamentalknowledge obtained in the course of training;
-Adaptation new problematics, knowledge, scientific terminology and methodology, topossess the skills of independent learning;
-Application in the given subject area statistical methods of processing experimentaldata, numerical methods, methods of mathematical and computational modeling of complexsystems;
-Understanding meaning of the tasks appearing in the course of professional activity andemployment the related physico-mathematical apparatus for description and solving the abovetasks;
-Using the knowledge of physical and mathematical subjects for further learningaccording to the training profile;
-Practical working with modern software in the field of computer modeling of complexsystems.

The student will get experience in:

-Formulation of computational tasks in studies of complex biomolecular systems;
-Preparing and running computer simulations of various biomolecular systems, includingsmall molecules, proteins, membranes and their complexes;
-Correct processing of modeling results and their comparison with available experimentaland literature data;
-Theoretical analysis of real problems related to atomic-scale studies of molecularsystems and their functioning mechanisms.

4. Course Plan

Section 1. *Introduction: "Classical mechanics and in silico modeling in solving modern biomedical tasks (brief overview)".*

Topic 1.1. The term "in silico". General characteristics of computer molecular modeling techniques based on classical mechanics formalism. Main directions of research. Types of the problems under study. Real and computational experiments.

Topic 1.2. Bioinformatics. Electronic resources of biological information: databases of functional motifs and patterns, biomolecular sequences and spatial structures. Search in databases, alignment of homologous sequences. Delineation of motifs and patterns. Protein secondary structure prediction. Examples of applications to solving biomedical problems.

Topic 1.3. Intermolecular interactions: molecular docking. Principle of the method. Limitations. Docking scoring functions and the problem of finding of correct docking solutions. Ligand- and target-specific scoring functions. Examples of applications in drug design.

Topic 1.4. Homology modeling of protein structure. Principle of the method. Stages of model building. Choice of the structural template. Quality assessment of the resulting models (PROCHECK, D. Eisenberg' 3D_1D profile), and so on. Application of the predicted models. Protein fold recognition techniques.

Section 2. *Biomolecular simulations with empirical force fields.*

Topic 2.1. Modern state-of-the-art. Origination of force fields (foundations of quantum chemistry). Approximate methods of solving Schrodinger equation for many-atom systems. Wave equations for electrons and nuclei.

Topic 2.2. Methods of quantum chemistry. Task formulation and approximations used. Information obtained via quantum chemical calculations. Semi-empirical and ab initio approaches. Examples of applications.

Topic 2.3. Definition of empirical force field. Classical or quantum mechanics: which one to choose? Analytical expressions for potential energy of molecular systems. Physical basis. Bonded and nonbonded energy terms. Definition of energy terms for various types of interactions.

Topic 2.4. Development and application of force fields. Parameterization using experimental and computational data? Approximations used in force field calculations (periodic boundary conditions, cutoff functions, charge groups, constraints and restraints). Energy minimization algorithms. Examples of molecular mechanics applications in solving biomedical problems. Modern force fields, examples of biomolecular simulations. Perspectives of force fields.

Section 3. *Molecular dynamics (MD).*

Topic 3.1. Basic principles. Problem formulation, integrators in MD, preparation of the starting configurations. Choice of the integration timestep, Verlet scheme, requirements to MD integrators.

Topic 3.2. Computational protocols in MD. Concepts of temperature and pressure in MD, thermostat and barostat. Control of systems' equilibration. Thermodynamic ensembles in MD. Algorithms of realization. Examples of MD applications in biomedicine, available software and MD-related resources.

Section 4. *Monte Carlo (MC) technique in biomolecular modeling.*

Topic 4.1. Basic principles, Metropolis criterion. Typical computational schemes in MC simulations of biomolecular systems. Conformational analysis and modeling of equilibrated systems.

Topic 4.2. Comparative analysis of MD and MC methods: advantages and limitations. Examples of MC applications in biomedicine.

Section 5. *Methods of free energy calculations in molecular systems.*

Topic 5.1. Relative free energy. Basic principles and formulation of the problem. Method of thermodynamic integration. Examples of applications.

Section 6. *Solvation effects in biomolecular simulations.*

Topic 6.1. Role of solvation effects in formation and maintenance of biomolecular structure.

Topic 6.2. Implicit solvation models. Simplest dielectric models, solution of Poisson-Boltzmann equation, atomic solvation parameters.

Topic 6.3. Explicit solvent models. Periodic boundary conditions, boundary potential. Comparative analysis of implicit and explicit solvation models.

Section 7. *Molecular modeling of biomembranes.*

Topic 7.1. Structure and physico-chemical properties of biomembranes. Theoretical models of biomembranes. Structure and dynamics of lipid bilayers. Macroscopic parameters, lateral heterogeneities and clusters. Examples of computer simulations of model biomembranes.

Section 8. *Modern computational techniques for assessment of hydrophobic properties of molecular systems.*

Topic 8.1. Hydrophobic effect. Quantitative characterization of spatial hydrophobic/hydrophilic properties of biomolecules. Method of molecular hydrophobicity potential and its application to protein modeling and drug design.

Topic 8.2. Mapping and visualization of hydrophobic/hydrophilic properties of biomolecular surfaces – the Protein Surface Topography method. Examples of modern applications.

Section 9. *Numerical experiment in molecular biology and biophysics: modern possibilities and perspectives.*

Topic 9.1 Recent "breakthrough" results of computational experiments in molecular biophysics.

Topic 9.2. Supercomputing in simulations of mesoscopic biomolecular systems. Challenges and perspectives.

5. Reading List

a. Required

1. Finkelstein A.V., Ptitsyn O.B. Protein Physics: A Course of Lectures. – Academic Press, 2002. – URL: https://ebookcentral.proquest.com/lib/hselibrary-ebooks/detail.action?docID=294665 – ELS: ProQuest Ebook Central - Academic Complete.
2. Snurr, Randall Q, Adjiman, Claire, Kofke, David A. Foundations of Molecular Modeling and Simulation. – Springer, 2006. – URL: https://www.springer.com/gp/book/9789811011269 – ELS: Springer Books.
3. Frenkel D., Smit B. Understanding Molecular Simulation: From Algorithms toApplications. – Elsevier, 2002. – URL: https://ebookcentral.proquest.com/lib/hselibrary-ebooks/detail.action?docID=307221 – ELS: ProQuest Ebook Central - Academic Complete.

b. Optional

1. Rapaport, D. C. The art of molecular dynamics simulation. – Cambridge university press, 2004. – URL: https://ebookcentral.proquest.com/lib/hselibrary-ebooks/detail.action?docID=259878 – ELS: ProQuest Ebook Central – Academic Complete.

6. Grading System

Evaluations of all intermediate forms of control are exhibited by the 10-point scale. The current control consists of the control work (C) and the homework (H). The Control work is conducted as a test of 60 questions with 3-4 variants of answers. Written homework: analysis of a research article in English on the mom of course. Oral defense of the work via interviews on the research topic.

The knowledge assessment is made in accordance with the aggregated sum:

$$K = 0{,}4H+0{,}6E,$$

where H is the accumulated score for intermediate controls:

$$H= 0.5\ (C+D),$$

and E is the score for the final exam (on the 10-points scale). The rating is rounded up.

7. Guidelines for Knowledge Assessment

Sample questions/tasks of the current control

a.1. Question: “Ideology of computational experiment to study biomolecular systems assumesthe following stages:

(Variants of answers)

A. Mathematical model – prediction of properties of new bioobjects;

B.Experimental data – mathematical model – parameterization of the model – model validation– prediction of properties of new bioobjects.

C.Experimental data – mathematical model – parameterization of the model – prediction ofproperties of new bioobjects”.

a.2. Question: “Scoring function used in molecular docking permits:
(Variants of answers)
A. increasing of efficiency of selection of correct solutions.
B.energy relaxation of atoms in molecular system upon analysis of intermolecular interactions.
C.ranking of the resulting intermolecular complexes according to criteria envisaged by the givenscoring function”.

The approximate list of questions for the final exam

1. The term “in silico”. General characteristics of computer molecular modeling techniques based on classical mechanics formalism. Real and computational experiments.
2. Molecular docking: Principle of the method; Limitations; Docking scoring functions and the problem of finding of correct docking solutions; Ligand- and target-specific scoring functions.
3. Main tasks of bioinformatics upon elucidation of protein structure and function. Electronic resources of biological information: databases of functional motifs and patterns, biomolecular sequences and spatial structures. Search in databases, alignment of homologous sequences.
4. Homology modeling of protein structure. Principle of the method. Stages of model building. Choice of the structural template. Quality assessment of the resulting models. Protein fold recognition techniques.
5. Biomolecular simulations with empirical force fields. Approximate methods of solving Schrodinger equation for many-atom systems. Analytical expressions for potential energy of molecular systems. Parameterization of force fields.
6. Approximations used in empirical force field calculations (periodic boundary conditions, cutoff functions, charge groups, constraints and restraints).
7. Energy minimization algorithms for molecular systems. Comparative analysis of the steepest descent and conjugate gradients algorithms. Examples of application of energy minimization techniques in biomolecular simulations.
8. The method of molecular dynamics (MD): basic principles, problem formulation, integrators in MD, choice of the starting conditions and the integration timestep. The Verlet scheme and the requirements to MD integrators.
9. Computational protocols in molecular dynamics (MD). Concepts of temperature and pressure in MD, thermostat and barostat. Control of systems’ equilibration. Thermodynamic ensembles in MD.
10. Solvation effects in biomolecular simulations. Implicit solvation models. Simplest dielectric models, solution of Poisson-Boltzmann equation, atomic solvation parameters. Explicit solvent models. Periodic boundary conditions. Comparative analysis of implicit and explicit solvation models.
11. Monte Carlo (MC) technique in biomolecular modeling. Basic principles, Metropolis criterion. Typical computational schemes in MC simulations of biomolecular systems. Conformational analysis and modeling of equilibrated systems.
12. Methods of free energy calculations in molecular systems. Relative free energy. Method of thermodynamic integration.

8. Methods of Instruction

The training uses the following types of academic work: analysis of practical research tasks in the field of computer modeling of biomolecular systems; familiarization with modern software and self-running a set of test problems of modeling.

9. Special Equipment and Software Support (if required)

Some lectures and practical classes require media-projector. Wireless access to the Internet is obligatory. One laptop per 2-3 students is required for practical exercises.