UNIVERSITÀ
DEGLI STUDI DI MILANO-BICOCCA

COURSE SYLLABUS

Computational Tools for Bioinformatics

2627-1-F0803Q045

Aims

The course aims to explore the main computational strategies employed in molecular modeling and structural bioinformatics, with a focus on the characterization of biological macromolecules. Both the static structural features and the dynamic behavior of biomolecules will be addressed, together with the simulation of molecular interactions, including those between small molecules and biological targets, and the study of the mechanisms underlying their reactivity. The course will also provide an overview of the current state of the art and practical applications of these methodologies in the major computational environments and molecular modeling software platforms currently in use, including recent approaches based on Artificial Intelligence (AI) and Machine Learning (ML) for the investigation of structure–function relationships and molecular simulations.

Knowledge and understanding
At the end of the course, the student will:**

- know the computational strategies generally used to discern structure-function relationships in biological macromolecules.
- comprehend the algorithms on which such computational strategies rely, as well as their modern Artificial Intelligence (AI)-based counterparts.
- understand the differences among computational methods and tools, both from theoretical and practical standpoints, and their role in the study of moelcular systems with biological/industrial relevance.
- choose and use autonomously software and web-server for molecular recognition simulations (protein-ligand, protein-peptide, protein-protein) and for protein design.

Applying knowledge and understanding
At the end of this training activity, the student will be able to apply the gained knowledge, using it to recognize (theoretically and practically) potentialities and (eventual) limits of the computational strategies seen during the course.

Making judgments
At the end of this course, the student will be able to select the most appropriate computational approach to address

molecular problems of biological or industrial relevance. They will also be able to critically evaluate the results of computational simulations and provide an independent interpretation. These skills will be developed through guided exercises, interactive classroom discussions based on case studies, and critical analysis of data obtained using computational tools introduced in the provided teaching materials.

Abilità comunicative
This course will enable students to effectively present the topics covered and the concepts learned using appropriate scientific language. The development of these skills is supported by the preparation and presentation of written reports on classroom activities, based on the analysis and discussion of scientific literature, which constitute an integral part of the final examination.

Learning skills
At the end of the course the student will dispose of all the tools that are necessary to apply his knowledge to address issues others than those presented during the course. He will be able to plan bioinformatic calculations on the basis of his gained knowledge, together with skills of literature reading and understanding.

Contents

- Computational modeling of biomolecule structure
- Relationship between molecular structure and energy in molecular mechanics (MM).
- Hints of relationship between molecular structure and energy in quantum mechanics (QM) and Hybrid techniques (QM/MM).
- Global and local search algorithms, in theory and practice.
- Molecular Docking (protein-ligand, protein-protein, covalent docking, protein-peptide), in theory and practice.
- Simulation techniques (molecular dynamics, Coarse Grained simulations).
- Computational protein design
- AI and ML applications to molecular modeling, structure prediction of proteins and their complexes and protein design (*de novo* and rational).

Detailed program

Fundamentals of Structural Bioinformatics and Molecular Modeling:

- Introduction to molecular modeling: context and fields of application;
- Concept of computability and basic requirements for molecular modeling;
- Evaluation of molecular structure quality and preparation for modeling;
- AI-based approaches for protein structure prediction.

Molecular Structure and Energy:

- Theoretical relationship between structure and energy: degrees of freedom, internal coordinates (Z-matrix), molecular symmetry;
- Topological analysis of the potential energy surface (PES);
- Energy in molecular mechanics: components of a force field (FF), comparison of different FFs (including coarse-grained) and their applications;
- Energy in quantum mechanics (overview) and introduction to hybrid techniques (QM/MM, ONIOM) for the study of reactivity in protein systems (with applications in catalysis and drug design);
- TUTORIAL:

-Example of a QM and QM/MM calculation.

Optimization Algorithms

- Local optimizers: zero-, first-, and second-order algorithms (simplex, grid search, univariate search, steepest descent, conjugate gradients, Newton-Raphson (NR), and quasi-NR); algorithms for transition state search and estimation of rate constants for biochemical processes;
- Global optimizers: comparison of deterministic and stochastic algorithms (multi-start/GOA, Monte Carlo Metropolis, Simulated Annealing, evolutionary algorithms);
- PRACTICAL EXERCISES:
  -Use of different algorithms for local minimum search, to rationalize their performance based on theory;
  -Use of stochastic algorithms for global minimum search and folding of a small peptide.

Molecular Docking

- Molecular docking algorithms: search algorithms (stochastic and systematic) and scoring functions implemented in the most widely used software;
- Potential energy grid and key concepts in pre-processing;
- Covalent docking and macromolecule–macromolecule docking and their applications;
- Survey of the most popular software and web servers, with practical usage guidelines;
- ML in docking and AI for drug design;
- PRACTICAL EXERCISES:
  -Semiflexible docking using different theoretical approaches, to understand the strengths and limitations of the method;
  -Covalent docking for various applications (drug design/industrial);
  -Protein–protein docking and in silico mutagenesis using local software and web servers.

Molecular Dynamics

- Introduction to statistical thermodynamics and canonical ensembles;
- Integration algorithms, thermostats and barostats;
- Trajectory analysis;
- Applications of MD;
- EXERCISE/TUTORIAL:
  -Molecular dynamics simulation with GROMACS.

Introduction to Protein Design

- Fundamental concepts of de novo protein design: physics-based and AI-based approaches;
- Tools and web servers available for protein design;
- Application examples.

Prerequisites

Prerequisites: Specific knowledge of other topics is not required. **All the theory necessary to deal with the various topics will be taken from scratch**. It is preferable **being motivated** and **curios** toward in silico investigations of molecular basis of chemical-biological processes.

Prerequisites. None

Teaching form

-15 two-hour lectures, in person, Delivered Didactics
-2 two-hour lectures, in person, Interactive Teaching
-6 two-hour practical classes, in person, Interactive Teaching

The course will be delivered in Italian.

Textbook and teaching resource

The following materials will be available on the course e-learning platform:

- Video recordings of all lectures
- Video tutorials of practical exercises
- Lecture slides
- Supporting handouts
- Recommended bibliography, including a selection of scientific articles and monographs to complement and deepen the topics covered in class
- Links to seminars for further exploration

Suggested textbooks:
“Bioinformatica” , Stefano Pascarella, Alessandro Paiardini;
"Molecular Modelling", Andrew Leach.
"Introduction to Computational Chemistry", Frank Jensen (chapter 2).

Semester

Second semester

Assessment method

The exam consists in the preparation of a written report on some of the exercises / practical demonstrations carried out in class. This report will then be discussed orally.

Office hours

Contact: on demand by email to the lecturer.

Sustainable Development Goals

RESPONSIBLE CONSUMPTION AND PRODUCTION