UNIVERSITÀ
DEGLI STUDI DI MILANO-BICOCCA

COURSE SYLLABUS

Ligand-Macromolecule Interactions

2425-1-F0802Q046

Aims

To learn the main molecular modeling techniques that can be used in the modeling of the interactions between a macromolecule and a ligand for the study and rationalization of biological processes.

Knowledge and understanding:

At the end of the course the student knows:

1. the nature of interactions between molecules

2. the concepts of molecular geometry and PES (Potential Energy Surface).

3. the Molecular Mechanics method for calculating molecular energies and interaction.

4. the main methods of molecular simulation

5. the applications of the Molecular Docking for the study of the interactions between macromolecule and ligand.

6. 3D-QSAR techniques for the design of ligands with increased activity with specific targets.

Ability to apply knowledge and understanding:

At the end of the course the student is able to:

1. obtain minimum energy ligand geometries

2. handle the structure of macromolecules deposited in the PDB database

3. set up a Molecular Dynamics simulation and analyze the results

4. build quantitative models

Making judgements

At the end of the course the student is able to:

choose the most appropriate simulation method for studying the system of interest;

Communication skills

To be able to describe in a technical report in a clear and concise way (and to explain orally with a suitable language) the objectives, the procedure and the results of the elaborations carried out in the lab.

Learning skills

Be able to apply the acquired knowledge to different contexts from those presented during the course, and to understand the topics covered in the scientific literature concerning the modeling aspects of computational chemistry.

Contents

Nature of molecular interactions: electrostatic forces; interaction between dipoles; induced and transient dipoles; intermolecular interaction potential (Lennard-Jones), long and short-range forces, dispersive forces.

Molecular geometry and PES (Potential Energy Surface).

The Molecular Mechanics method for the calculation of molecular and interaction energies .

Molecular simulation methods: the Monte Carlo Metropolis method for the estimation of molecular properties at equilibrium; Molecular Dynamics for the study of macromolecules.

Molecular Docking for the study of interactions between macromolecule and ligand.

3D-QSAR techniques for the design of ligands with increased activity with specific targets.

Laboratory experiences.

Detailed program

3D structures of biological macromolecules. PDB database.

Electrostatic nature of molecular interactions : forces exerted between point charges; forces exerted between charges and dipoles and dipole-dipole; dipoles and instantaneous dipoles (transients).

Intermolecular interaction potential (Lennard-Jones potential), long and short-range forces, dispersive forces.

Definition of molecular geometry and PES (Potential Energy Surface). Search for minimum points on PES: Newton-Raphson method and approximate methods. Problem of the many minima: systematic and deterministic research.

The Molecular Mechanics method for the calculation of molecular and interaction energies . Classical description of molecular systems. Force Fields. "Natural" values ??of the geometric parameters and transferability of the parameters. Formulation of interactions in the MM; harmonic force field and its limits; generalized Hooke law. Harmonic stretching, bending and strecth-bend potentials; Torsion potentials; Non-binding potentials. Calculation of interaction energy.

Molecular simulation methods: Characteristics of real molecular systems; calculation of properties of a macroscopic set of particles as a mean value, weighted on energy, of the properties of the single molecules. System status and phase space.

The Monte Carlo Metropolis method for the estimation of molecular properties at equilibrium.

Molecular Dynamics for the study of macromolecules, processes and phenomena of biological interest.

Calculation of properties of a macroscopic set of particles as temporal mean of instantaneous values ??(ergodic hypothesis).

Logical scheme of a molecular dynamics simulation. Setting up a simulation and analysis of the trajectories.

Extensions of the molecular dynamics method: REMD, Steered Dynamics, Meta Dynamics, Free Energy Perturbation.

Molecular Docking for the study of interactions between macromolecule and ligand. Posing and scoring functions. Limits of the docking methods. Systematic analysis of different score functions.

3D-QSAR techniques for the design of ligands with increased activity with specific targets.

Construction of a QSAR model. Molecular properties and molecular descriptors as variables of the model.

3D WHIM and G-WHIM descriptors. COMFA method and subsequent modifications. Pre-selection of model variables.

Fitting (R2) and prediction (Q2) methods. Genetic algorithm for the selection of model variables.

Prerequisites

Background. Knowledge of classical physics: forces, energies, electrostatic interactions.
Knowledge of biochemical processes.
Prerequisites. None

Teaching form

Teaching language: italian.

14 2 hours-lectures composed by:

- a section of delivered didactics (Didattica erogativa, DE) focused on the presentation-illustration of contents by the lecturer.
- a section of interactive teaching (Didattica Interattiva, DI) including teaching interventions supplementary to

delivered didactic activities and case studies.

All didactic activities are conveyed by means of face-to-face lectures

5 laboratory activities lasting 4 hours delivered by interactive teaching carried out directly by the students.

Attendance is compulsory.

Textbook and teaching resource

Slides, and handouts available at the e-learning platform of the course.
Bibliography. Selected scientific papers about the different topics available at the e-learning platform of the course.

Semester

Second semester

Assessment method

The assessment of learning takes place with a final oral examination.

The student must prepare a technical report on the experiences made in the laboratory, clearly explaining the procedure adopted, the results obtained and the analysis of the same.
The examination will be based on what was presented in the report making the necessary connections with the theoretical concepts learned during the lessons. Student responses should always be motivated and linked to broader concepts.

In itinere tests are not planned.

In the final examination, as far as possible, the student will be evaluated on the basis of the following criteria:

1. knowledge and ability to understand;
2. ability to connect different concepts;
3. reasoning autonomy;
4. ability to correctly use scientific language

Office hours

Contact. On demand by email to the lecturer.

Sustainable Development Goals

QUALITY EDUCATION