**MASTER IN BIOINFORMATICS (2019-2020)**

**University Paris Diderot**

**M2 ISDD Research Course: Modelling of macromolecules**

**SEMESTER 3 (30 ECTS)**

**EU 0 UPGRADE**

**Coordinator: AC. CAMPROUX**

**EC 001 Unix and R:Base (Upgrade)**

**Coordinator: G. MOROY**

**Title: Unix and R:Base (Upgrade)**

**Teaching coordinator: Gautier Moroy**

**Knowledge objectives:** Acquire the basics of using the Unix operating system and R software.

 **Targeted skills:** To be familiar with Unix and R to be autonomous during the practical sessions of computer science, bioinformatics, and statistics.

**Programme**

Fundamentals of the Unix operating system and R software.

**EC 002 Upgrade Toxicology-Biochemistry-Chemistry**

**Coordinators: AC CAMPROUX**

**Title: Upgrade Toxicology-Biochemistry-Chemistry**

**Teaching coordinators: AC Camproux**

**Knowledge objectives:** The drug designer is usually at the interface between the biologist, the clinician and the chemist. He/she must therefore have an introduction to certain biophysical methods frequently used in drug design projects. There is a wide range of biophysical methods that can be used to study protein/protein or protein/ligand interactions by defining the area of ​​contact, or characterising the thermodynamic and/or kinetic constants that govern the interaction.

Chemistry toolbox: Chemistry Pharmacophore \* Chemical chemistry toolbox

**Targeted skills:** The aim of the course is to introduce students to different experimental methods for detecting and characterising molecular interactions

**Programme:**

Methods to understand the basic principles of thermodynamics, diffusion, and optical methods will be addressed. In particular, certain physico-chemical techniques such as light scattering, optical methods, linear and circular dichroism, fluorescence and UV-visible spectroscopies. In addition, the course will introduce three other experimental methods for the identification and characterisation of biomolecule interactions in vitro: Nuclear Magnetic Resonance, Isothermal Titration Calorimetry (ITC), FRET, acronym for "Fluorescence Resonance Energy Transfer" , and BRET, acronym for "Bioluminescence Resonance Energy Transfer".

 Articles using other fundamental approaches to "drug design" such as Surface Plasmon Resonance (SPR) and immunological methods (ELISA tests, GST pulldown), will be analysed and presented by the students. The course will include teaching of enzymology centres, especially on the study of interactions between enzymes and ligands (substrates, inhibitors, allosteric effectors, etc.).

**UE1 DATA ANALYSIS IN DRUG DESIGN (8 ECTS)**

**Coordinator: AC. CAMPROUX**

**CHOICE OF EC 101 or EC 102 depending on the level**

**EC 101 Python Project 1 (3 ECTS)**

**Coordinators: P. FUCHS & P. POULAIN**

**Title: Data analysis in drug design**

**Teaching coordinators: P. Fuchs & P. Poulain**

**Knowledge objectives:** Train bioinformaticians in Python programming. Python is the most used programming language today in bioinformatics, especially for data analysis.

**Targeted skills:** Know the main concepts related to Python programming.

Be able to write simple analysis scripts.

Evaluate the relevance of a result returned by a program.

**Programme:**

* Programming concept
* Introduction to the Python language
* Main data types (integers, real numbers, lists, character strings, dictionaries, tuples)
* Loops, comparisons, tests
* Modules
* Input/output management with files

Functions

**EC 102 Python Programming 2 (3 ECTS)**

**Coordinator: P. FUCHS**

**Title: Python Programming 2**

**Teaching coordinator: P Fuchs**

**Knowledge objectives:**

Train bioinformaticians in Python programming. Acquire autonomy in the development of a Python program. Python is the most used programming language today in bioinformatics, especially for data analysis. It is in great demand in laboratories, but also in private companies.

**Targeted skills:**

Know the main concepts related to Python programming.

Be able to write programs (i) for analysing large amounts of data, (ii) producing data (e.g. a system simulation).

Be able to develop/debug a program in Python.

**Programme:**

* Main data types (integers, real numbers, lists, character strings, dictionaries, tuples)
* Loops, comparisons, tests
* Modules
* Input/output management with files
* Functions
* Regular expressions

Python classes

**EC 103 Data Analysis and Drug Design (3 ECTS)**

**Coordinators: AC CAMPROUX & REGAD L.**

**Title: Data Analysis and Drug Design**

**Teaching coordinators: AC Camproux, L. Regad, O. Taboureau, A. Badel**

**Knowledge objectives:** Teach students to combine and optimise different unsupervised and supervised learning methods to analyse drug design data, in the target space and molecules with associated special problems, descriptor selection and criteria of selection, optimisation of models, comparison and robustness of models in cross-validation. The application of the various concepts will be made using the statistical software R.

**Targeted skills:** Optimise and combine different learning methods on a drug design dataset

**Programme:** Example on protein space

* Descriptive or exploratory methods:

Factorial methods (Principal Component Analysis and Classification Methods (hierarchical or partitioning) that propose groupings into object classes following algorithmic calculations

* Explanatory and/or predictive methods:

Methods to explain or predict, Linear model, PLS, Logistic regression, CART. Discriminant analysis. Cross-validation, optimisation criterion.

Evaluation methods: record and x project or report

**EC 104 Application in Drug Design & QSAR (1 ECTS)**

**Coordinators: O. TABOUREAU & L. REGAD**

**Title : Application in Drug Design & QSAR**

**Teaching coordinators: O. Taboureau & L. Regad**

**Knowledge objectives:** Application of supervised learning methods and QSAR to predict the activity of small molecules against a target of interest.

Development of chemical library filters from supervised methods. Application of these filters to search for new inhibitors of a given target.

**Targeted skills:** Establishment of a protocol to identify the best QSAR model to predict the activity of a molecule.

Development of chemical library filtering as part of a *drug design* project.

R script development for the development and optimisation of supervised models

**Programme:** The purpose of this programme is to apply the various unsupervised and supervised techniques currently seen in order to develop a QSAR model to predict the activity of small molecules for a given target. These models will then be used to filter chemical libraries. This project will be carried out with the R statistical software.

The target of interest and the candidate molecules for the fixation of this target, will be dealt with in the other UEs of the Master in order to propose a complete in silico drug design project, see Drug design project.

**EC 105 Seminars and R & D (1 ECTS)**

**Coordinator: AC. CAMPROUX**

**Title: Seminars and R & D**

**Teaching coordinator: AC Camproux**

**Knowledge objectives:** These meetings will allow students to exchange and discuss with people confronted each day with the problems of current research in drug design. These seminars will include presentations from recognised laboratories for national and international drug design and chemoinformatics, Platforms (RPBS, Orphanet), field research teams, PhDs students, alumni of the Master. Visit to Sanofi site + presentation of research issues (peptides) in private and academic

### Targeted skills: These meetings will allow students to interact with people confronted each day with the problems of research and development of in silico drug design.

### Programme: This EC aims to make students aware of how IsDD research works, whether at the academic level or in companies (start-ups and large pharmaceutical companies).

**Part 1:** Seminars on the preparation for an internship "How to find an internship, and to find the right internship? How to prepare a CV and a cover letter (SAOIP)

* How to make an oral presentation, an internship report, structure a publication (AC Camproux)
* Complete an internship agreement (...)

**Part 2:** Seminars and the functioning of post-Master, and the functioning of research in France and abroad.

Presentation of the doctoral schools: AC Camproux. Examples of a presentation to obtain a ministerial scholarship by ISDD and BI Masters students: DIMs, ANR and similar scholarships. Theses abroad and European and international funding. Making a network (linkedIn, the ISDD Master Association Group of the master, registering, alumni, society of chemoinformatics and bioinformatics)

*Company research* Students will meet *professional speakers* (Sanofi, [Discngine](https://www.discngine.com/), Servier start-up) who will present their company and their operations, **a visit to the site of Sanofi and/or Servier will be organised.**

**UE2 MOLECULAR & DRUG ANALYSIS AND DYNAMICS (7 ECTS)**

**Coordinator: D. FLATTERS**

**EC 201 Structural exploration of proteins (3 ECTS)**

**Coordinator: L. REGAD**

**Title: Structural exploration of proteins**

**Teaching coordinators: L. Regad, AC Camproux, O.Taboureau, Gautier Moroy, D. Flatters**

**Knowledge objectives:**

Optimise a therapeutic target, Knowledge of the structure of proteins and their variability. To give students the basics of an advanced exploration of the structure of proteins for preparation to search for active compounds. Druggable pocket search and the effect of mutations

### Targeted skills: Optimise a therapeutic target, Knowledge of the structure of proteins and their variability. To give students the basics of an advanced exploration of the structure of proteins for preparation to search for active compounds.

**Programme:**

3D- STRUCTURE-BASED PREPARATION

**Analysis of 3D Macromolecules**

1) Construction of 3D models of proteins by homology modelling and sequence alignment (modeller, pymol)

1. 3D structures of biological macromolecules: visualisation under Pymol, electronic density map
2. Study of mutations and structural variability, SA-Conf, foldX
3. Identification/estimation of the pockets and their druggability (Pockdrug)
4. Free energy calculation

**CHOICE OF EC 202 or EC 203 depending on the level**

**EC 202 Dynamic Target Analysis I (2 ECTS)**

**Coordinator: D. FLATTERS**

**Title: Dynamic Target Analysis I**

**Teaching coordinators: D. Flatters, Catherine Etchebest**

**Knowledge objectives:** Understanding the theoretical concepts governing molecular modeling techniques (force field, minimisation, molecular dynamics)

Know how to apply these concepts to biomolecules (peptides, proteins, etc.)

**Targeted skills:** Be able to model a basic molecular system (a biomolecule in water)

Be able to read a publication critically using molecular modelling

Be able to complete an internship in a laboratory using molecular dynamics

**Programme:**

1. - Semi-empirical force fields and molecular mechanics: description of the basic forces
2. (Harmonic and torsional potentials, electrostatic interactions, van der Waals interactions)
3. - Optimisation of molecular geometry (energy minimisation)
4. - Simulation and Analysis of molecular dynamics (MD) trajectory (algorithm & conformational properties calculations)

Each theme will be addressed theoretically in lectures and in a practical manner in practical sessions (modelling of a biomolecule in water with the software GROMACS)

**EC 203 Dynamic Target Analysis II (2 ECTS)**

**Coordinator: G. MOROY**

**Title : Dynamic Target Analysis II**

**Teaching coordinator: G. Moroy**

**Knowledge objectives:** Know how to apply the knowledge acquired for the study of protein dynamics.

**Targeted skills:** Be able to select the appropriate bioinformatics tools to study the flexibility of a protein.

**Programme:**

Study of the flexibility of proteins.

Analysis of results of molecular dynamics simulation.

**EC 204 Structural and Dynamic Modelling (2 ECTS)**

**Coordinators: G. MOROY & D. FLATTERS**

**Title: Structural and Dynamic Modelling**

**Teaching coordinators: G. Moroy & D. Flatters**

**Knowledge objectives:** Be able to propose and apply a protocol combining structural study and protein dynamics.

**Targeted skills:** Understand and master the bioinformatics tools that aid the structural and dynamic study of proteins.

**Programme:** Generation and analysis of structures from molecular dynamics simulation trajectories of a protein of interest.

**UE3 HIGH THROUGHPUT SCREENING: STRUCTURE & LIGAND-BASED (5 ECTS)**

**Coordinator: G. MOROY**

**EC 301 Structure-based** **(3 ECTS)**

**Coordinator: G. MOROY**

**Title: Structure-based**

**Teaching coordinator: G. Moroy**

**Knowledge objectives:** The objective of this course is to present the advanced theoretical concepts, algorithms and associated programs for the design of therapeutic molecules by approaches based on the structure of the target protein.

**Targeted skills:** Understand and master the bioinformatic tools aiding the design of therapeutic molecules based on the structure of the target protein.

**Programme:** Presentation and use of several docking programs and virtual screening.

**EC 302 Ligand-based** **(1 ECTS)**

**Coordinator: O. TABOUREAU**

**Title: Ligand-based**

**Teaching coordinator : O. Taboureau**

**Knowledge objectives:** Practical learning of the in silico preparation of chemical libraries for virtual screening, based on the structure of reference ligands including a part i) generation of three-dimensional molecular models for small molecules (1D/2D to 3D), ii) calculations of ligand descriptors, and iii) pharmacokinetic aspects (ADME/tox) based on specific physicochemical criteria.

**Targeted skills:** Generation of libraries of compounds

**Programme:** The aim of this UE is to provide practical learning of the in silico preparation of chemical libraries for virtual screening, based on the structure of reference ligands. The programme includes in part the generation of three-dimensional molecular models for small molecules (1D/2D to 3D) and ligand descriptor calculations as well as a chapter on pharmacokinetic aspects (ADME/tox) based on specific physicochemical criteria.

+ Molecule files (small reminder)

+ Proficiency in different file formats molecule, PDB, smi, SMARTS, mol2, MDL-sdf. Advantages, limitations and frameworks of different types of files.

+ Manipulation of 3D molecules with Pymol ... PDB, mol2, sdf, different behaviours.

+ Understanding of ADME/tox main rules: (FAFdrug)

* Lipinski, Weber, Egan, etc.
* Frequent, Hitter, Aggregants concept
* Toxic fragments

Experience calculating descriptors on software: Knime, edragon + Pipeline Pilot (Rotation of ligands), Faf-Drug

Pharmacophore concept

**EC 303 Hits to lead** **(1 ECTS)**

**Coordinator: O. TABOUREAU**

**Title: Hits to lead**

**Teaching coordinator : O. Taboureau**

**Knowledge objectives:** The purpose of screening is to identify molecules having a biological activity of therapeutic interest vis-à-vis a therapeutic target. The high throughput, in silico or in vitro, allows the testing of several thousand molecules per week. Pharmacological screening ("screening") is the first step in the process of discovering new drugs. The molecules identified during the initial screening phase (Hits) are still far from drugs. Their link to their target remains too weak, so they must be optimised (leads).

Thanks to subtle and progressive transformations of the structure of the hit, the medicinal chemist and the drug designer will allow this to be fixed more effectively to its target. However, this single increase in affinity will not be enough to make the hit a drug candidate. Before being evaluated in animal efficiency models, then in humans, the product must satisfy several other constraints, a) specificity, b) adapted bioavailability, c) appropriate pharmacokinetic properties, d) absence of toxicity.

**Targeted skills:** Students will discover, through specific examples, the main strategies for optimising an initial hit towards a drug candidate and the therapeutic molecule placed on the market

**Programme:** Several experimental approaches and rational in silico design methods can be used to transform a "hit" into "lead" (X-ray diffraction, NMR, medicinal chemistry, SAR, QSAR, rescoring, molecular simulation, ligand-based, fragment-based methods, etc.).

Several optimisation examples will be addressed with applications in the field of infectious diseases, cancer, cardiovascular diseases and the reproductive system.

**UE4 ANALYSIS OF THE SPACE OF MOLECULES (4 ECTS)**

**Coordinator: O. TABOUREAU**

**EC 401 Toxicologie et Biotransformation (3 ECTS)**

**Responsables : A. BAEZA, F. RODRIGUES-LIMA**

**Intitulé : Toxicologie et biotransformation**

**Responsables pédagogiques** : **A. Baeza, F. Rodrigues-Lima**

**Objectifs en termes de connaissances :**

- Enzymes du métabolisme des médicaments

- Transporteurs des xénobiotiques

- Pharmacocinétique

- les différents types de réponse toxique

- mécanismes d’action des toxiques

**Compétences visées :** Donner les bases du devenir des xénobiotiques (médicaments) et de toxicologie

**Programme :**

- Enzymes du métabolisme des médicaments

- Transporteurs des xénobiotiques

- Pharmacocinétique

- les différents types de réponse toxique

- mécanismes d’action des toxiques.

**EC 402 Chimie médicinale, molécules pharmaceutiques (1 ECTS)**

**Responsables : C. MAYER & F. BARBAULT**

**Intitulé : Chimie médicinale, molécules pharmaceutiques**

**Responsables pédagogiques : C. Mayer & F. Barbault**

**Objectifs en termes de connaissances :**

Les étudiants après avoir acquis des compétences en « drug design » travailleront à l’interface entre plusieurs disciplines, ils devront donc avoir certaines bases de médecine moléculaire, des connaissances sur certains médicaments utilisés à ce jour ainsi que des informations sur certaines molécules en phase de développement.

**Compétences visées :** Les étudiants pourront acquérir des connaissances sur les grandes pathologies humaines et avoir des exemples pertinents de molécules thérapeutiques couramment utilisées ou en cours de développement

**Programme :**

L’enseignement présentera d’une manière intégrée des notions de chimie, de médecine moléculaire, de drug discovery et de biologie. Après un bref retour sur des éléments de chimie médicinale, stéréochimie et nomenclature, le cours introduira des principes de médicine moléculaire et présentera plusieurs exemples de molécules thérapeutiques actuellement sur le marché ou en phase clinique. Les grands systèmes biologiques et les pathologies associées seront abordés, notamment, les maladies infectieuses telles que la paludisme et la tuberculose, et le cancer. Des exemples de molécules thérapeutiques ciblant différents systèmes protéiques seront discutés. Plusieurs structures tridimensionnelles de complexes « cible thérapeutique-médicament » seront examinées afin d’illustrer les principaux concepts de recherche de molécules thérapeutiques couplant des approches *in silico* et expérimentales dans le contexte de la médecine moléculaire

**UE5 PREPARATION FOR RESEARCH IN DRUG DESIGN (6 ECTS)**

**Coordinator: L. REGAD**

**EC 501 3-projects in Drug Design - tutored (2 ECTS)**

**Coordinators: L. REGAD & O. TABOUREAU**

**Title : 3-projects in Drug Design - tutored**

**Teaching coordinators: L. Regad & O. Taboureau**

**Knowledge objectives:**

* Know the different stages of a drug design protocol
* Combine the different stages of a drug design protocol

Know how to propose a drug design protocol to identify new inhibitors of a given target

**Targeted skills:**

Know how to develop an optimised pipeline to identify new inhibitors of a given target

Know how to use different tools needed in a drug design protocol

**Programme:**

ISDD research project: Student defence of the research project, including one part QSAR, data analysis, MD, Docking, Screening, hits to lead

A project combining the different steps of a research protocol for new inhibitors, having a given target aiming at allowing the students to acquire practical experience on an in silico drug design project . This project will be based on:

* molecular modelling of the target of interest to assess its flexibility
* QSAR models to develop statistical filters to create an optimised library
* virtual screening (ligand-based and structure-based) to predict inhibitory molecules from the optimised library.

The various stages of the project will be specifically addressed in the form of projects during various modules of semester I (UE: Data analysis & QSAR, UE: Structural analysis of targets and their dynamics, UE: high throughput screening, UE Hits to lead for hit optimisation).

The objective of this project is that students link the different approaches studied and projects obtained to the same target system in order to understand the complementarity and finality of these approaches for a complete in silico drug design project.

**EC 502 Design of Research Project - tutored (2 ECTS)**

**Coordinator: AC. Camproux**

**Title: Design of Research Project - tutored**

**Teaching coordinator: AC Camproux**

**Knowledge objectives:**

Design of a research project, at the level of a PhD thesis or a 3 year in silico drug design project. In preparation for the research internship, involving a bibliographic work, reflection on possible collaboration, and integration of the various in silico modules followed in Master, for the research project. Budgeting of the project.

**Targeted skills:**

Students' understanding of what a research project entails. Reflection of their research topic. Tutors will guide them in this work. Presentation of this module: design of a research project for the students will be carried out in the middle of the semester so that students will have time to reflect and prepare the bibliography on their internship subject. Two tutorials to give help and advice with the preparation of this project will be arranged with the tutors during the semester.

**Programme:**

**EC 503 High Throughput Screening Application (2 ETCS)**

**Coordinator: G. MOROY**

**Title: High Throughput Screening Application**

**Teaching coordinator: G. Moroy**

**Knowledge objectives:**

Know how to apply the knowledge acquired to propose molecules that inhibit a target protein.

**Targeted skills:**

Know how to select the appropriate bioinformatic tools of virtual screening aiming at proposing inhibitory molecules for a given target protein.

**Programme:**

Analysis and preparation of the structure of a target protein.

Preparation of a suitable chemical library.

Selection and adaptation of a virtual screening protocol.

**Evaluation methods:**

* Session 1: 100% Final exam
* Session 2: 100% Final exam: report

**SEMESTER 4 (30 ECTS)**

**UE6 INTERNSHIP (30 ECTS)**

**Coordinator: AC. CAMPROUX**

**EC 601 Preparation of tutored research project (3 ECTS)**

**Coordinators: AC. CAMPROUX & S. MURAIL**

**Title: Preparation of tutored research project**

**Teaching coordinators: AC Camproux, S. Murail**

**Knowledge objectives:**

In preparation for the research internship, involving a bibliographic work, reflection on possible collaboration, and integration of the various in silico modules followed in Master, for the research project. Budgeting of the project.

**Targeted skills:**

Design the research project, identify the field laboratories and the competition, Presentation of the project in terms of feasibility and schedule

**Programme:**

In preparation for the research internship, involving a bibliographic work, reflection on possible collaboration, and integration of the various in silico modules followed in Master, for the research project. Budgeting of the project.

Two tutorials to give help and advice with the preparation of this project will be arranged with the tutors during the semester.

Presentation of a punctual report at the mid-term of the internship

**EC 602 International or company research internship (27 ECTS)**

**Coordinator: AC. CAMPROUX**

**Title: International or company research internship**

**Teaching coordinator: A-C Camproux**

**Knowledge objectives:**

Laboratory internship or equivalent bibliographic work.

**Targeted skills:**

The aim of the course is to introduce students to research in an academic or private laboratory according to the international project of the student, highly recommended internationally for the Macromolecules career

**Programme:** Laboratory internship or equivalent bibliographic work