Master Bio-Informatique

In Silico

Drug Design

University of Paris
(2021-2025)

DETAILED LIST OF ECU's of the MASTER 2

BIOINFORMATIQUE - ISDD: In silico Drug design

Two tracks are offered in the BI-ISDD master's degree, a track "ISDD-Macromolecule Modeling" in research (initial training, FI) or in alternating training (alternating training FA) and a track "ISDD-Bioactive Molecules" in research. Each of these two courses offers the possibility of obtaining a double degree (French-Russian or French-Italian).

The main blocks of teaching units "*Unité d'enseignements*" (UE) include one module (ECUE) of project or application. The aim of these different projects is to analyze (in structure and flexibility) a protein target and to select candidate molecules for the binding of this target, and in fine, to model and simulate their interaction and molecular docking. These projects correspond to the ECUE: "BQ2CY060 Application in Drug Design & QSAR + BQ2CY080 Structural and dynamic modeling + BQ2CY190 Application of high-throughput screening", in connection with the other ECUE (BQ2CY090 Structural exploration of proteins, BQ2CY130 Ligand-based, ...).
In the ECUE "BQ2CY170 3-projects in Drug Design", students will then have to analyze in a combined way the results of these different complementary projects in an integrated (individual) project of Drug Design in Silico.

The summary then the detailed content of the UEs is presented.

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SUMMARY OF THE MASTER BIOINFORMATICS-ISDD (2021-2025)
University of Paris - Research course
ISDD-Macromolecule Modeling (Initial training)

MASTER 1 - SEMESTER 1 (30 ECTS)

Block UE0 - **Refresher course** (G. Moroy)

UE0-BQAAY000 Unix and R basics (Refresher course) (G. Moroy & L. Regad)

Block UE1 - **Fundamentals of biochemistry and biostatistics (7 ECTS)** (C. Etchebest)

BQAAY210 Enzymology (J. Dairou) (2ECTS)
BQAAY240 Structure of Biomolecules (N. Caulet) (2 ECTS)
BQAAY020 Biostatistics and R programming (L. Regad) **OR BQAAY030** Tutored project in biostatistics and R (A-C Camproux & A.Badel) (3 ECTS)

Block UE2 - **Programming and mathematical tools (9 ECTS, 3 ECUE according to level)**(J.C Gelly & A.Badel)

BQ2AY040 Mathematics I (A-C Camproux) **OR BQAAY060** Optimization and Learning in Biology (D. Flatters, F. Guyon) (3 ECTS)
BQAAY070 Python programming 1 **OR BQAAY080** Python programming 2 (P. Fuchs & P. Poulain) (3 ECTS)
BQAAY090 Algorithmics 1 (C. Delporte) OR **UE BQ2AC060 List of UE** (to be chosen in M1 IPFB-BIB course) (3ECTS)

Block UE3 - **Practice and deepening (8 ECTS)** (O. Taboureau) *recommended*

BQ2AY120 Systems biology & ligands, database (O. Taboureau & K. Audouze) (3 ECTS)
TX1CY090 Basics of Toxicology (A. Baeza) (3 ECTS)
BQ2AE140 ADME/chemometry (in English, O. Taboureau) (2 ECTS) * + **UE BQ2AU150** English (2 ECTS)

Block UE4 - **Thematic Orientation I in Chemistry and Chemoinformatics (6 ECTS, 2 ECUE to be chosen)**
(O. Taboureau)

BQ2AE160 Chemoinformatics (K. Audouze) (3 ECTS)
BQ2AE170 Chemistry: chirality - non-covalent bonds (F. Maurel, O. Taboureau) (3 ECTS)
BQ2AY180 Option for Drug Design (O. Taboureau) (3 ECTS)

MASTER 1- SEMESTER 2 (30 ECTS)

Block UE5 - **Advanced fundamentals (6 ECTS)** (A-C. Camproux)

BQABY010 : Massive data analysis (A-C. Camproux, A. Badel) (3 ECTS)
BQABY020: Biophysics of interactions (V. Gruber & W. Majeran) (3 ECTS)

Block UE6 - **Thematic orientation II (18 ECTS)** (O. Taboureau)

BQ2BY030 Protein-Protein Docking (course in English) (A-C. Camproux, O. Taboureau) (3 ECTS)
BQ2BY040 Introduction to Drug Design In Silico (G. Moroy) (3 ECTS)
BQABY050 Dynamics of macromolecules (D. Flatters, P. Fuchs) (3 ECTS)
BQ2BY060 Structural bioinformatics in Toxicology (D. Flatters, G. Moroy, O. Taboureau) (3 ECTS)
BM0BY250 Reactivity and organic synthesis (F. Chau) (3 ECTS)
Options to choose from *(* recommended)*
BQ2BY080 *In silico* practices in 3D protein complexes* (K. Moncoq, O. Taboureau) (3 ECTS)
BQ2BY090 Advanced simulation methods* (S. Murail) (3 ECTS)
BQ2BY100 Research in drug design (O. Taboureau) (3 ECTS)
UE BQ2BC110 among UE course M1BIB-IPFB (Web programming, ...) (3 ECTS)

Block UE7 - **Internship 4 BQ2BT130 (6 ECTS)** (G. Moroy, V. Gruber, O. Taboureau)

OR International Study Semester 2
- **SEMESTER 2 ERASMUS** University of Milan of the ISDD course Bioactive Molecules
- **STUDY SEMESTER at** the University of Sechenov (MOSCOW) within the framework of the French-Russian double degree

Research course
ISDD-Macromolecule Modeling (Initial training)

MASTER 2 - SEMESTER 3 (30 ECTS)

Block UE0 - Refresher course (A-C. Camproux)

BQAAY010 Unix and R Basics (Upgrade) (L. Regad)

BQ2CY021 Toxicology -Methodology upgrade (A-C Camproux)

Block UE1 - **Data analysis in drug design (8 ECTS)** (A-C. Camproux)

BQAAY070 (Python1 programming (Fuchs & P. Poulain) (3 ECTS)

Or **BQAAY080** Python programming 2 or **BQAAY030** Python project (S. Murail) (3 ECTS)

BQ2CY050 Data analysis in Drug Design (A-C Camproux & L. Regad) (3 ECTS)

BQ2CY060 Application in Drug Design & QSAR (O. Taboureau & L. Regad) (1 ECTS)

BQ2CY070 Seminars and R&D (A-C Camproux) (1 ECTS)

Block UE2 - **Molecular analysis and dynamics & drug design (7 ECTS)** (D. Flatters)

BQ2CY090 Structural exploration of proteins (L. Regad) (3 ECTS)

BQ2CY100 Dynamic Target Analysis I (D. Flatters) (2 ECTS) Or according to level

BQ2CY110 Dynamic analysis of targets II (G. Moroy) (2 ECTS)

BQ2CY080 Structural and dynamic modeling (G. Moroy & D. Flatters) (2 ECTS)

Block UE3 - **High-throughput screening: structure & ligand-based (5 ECTS)** (G. Moroy)

BQ2CY120 Structure-based (G. Moroy) (3 ECTS)

BQ2CY130 Ligand-based (O. Taboureau) (1 ECTS)

BQ2CY140 Hits to lead (O. Taboureau) (1 ECTS)

Block UE4 - **Molecular Space Analysis (4 ECTS)** (O. Taboureau)

BQ2CY150 Toxicology and biotransformation (A. Baeza, F. Rodrigues-Lima) (3 ECTS)

BQ2CY160 Medicinal chemistry, pharmaceutical molecules (C. Mayer & F. Barbault) (1 ECTS)

Block UE5 - **Preparation for research in Drug Design (6 ECTS)** (L. Regad)

BQ2CY170 3-projects in Drug Design (L. Regad & O. Taboureau) (2 ECTS)

BQ2CY180 Tutored research project design (A-C Camproux) (2 ECTS)

BQ2CY190 Application of high throughput screening (G. Moroy) (2 ECTS)

MASTER 2 - SEMESTER 4 (30 ECTS)

INTERNSHIP (30 ECTS) (A-C. Camproux)

UE6- **BQ2DY010** Preparation of a tutored research project (A-C Camproux & S. Murail) (3 ECTS)

UE7- **BQ2DT020** International research internship (A-C Camproux) (27 ECTS)

OR SEMESTER 4 of a compulsory research internship (30 ECTS) at the SECHENOV UNIVERSITY (MOSCOW) for the French-Russian double degree

Research course
ISDD-Macromolecule Modeling (Initial training)

MASTER 2 - SEMESTER 3 (30 ECTS)

Block UE0 - Refresher course *(A-C. Camproux)*

BQAAY010 Unix and R Basics (Upgrade) (L. Regad)

BQ2CY021 Toxicology -Methodology upgrade (A-C Camproux)

Block UE1 - Data analysis in drug design (8 ECTS) (A-C. Camproux)

BQAAY070 (Python1 programming (Fuchs & P. Poulain) (3 ECTS)

Or **BQAAY080** Python programming 2 or **BQAAY030** Python project (S. Murail) (3 ECTS)

BQ2CY050 Data analysis in Drug Design (A-C Camproux & L. Regad) (3 ECTS)

BQ2CY060 Application in Drug Design & QSAR (O. Taboureau & L. Regad) (1 ECTS)

BQ2CY070 Seminars and R&D (A-C Camproux) (1 ECTS)

Block UE2 - Molecular analysis and dynamics & drug design (7 ECTS) (D. Flatters)

BQ2CY090 Structural exploration of proteins (L. Regad) (3 ECTS)

BQ2CY100 Dynamic Target Analysis I (D. Flatters) (2 ECTS) Or according to level

BQ2CY110 Dynamic analysis of targets II (G. Moroy) (2 ECTS)

BQ2CY080 Structural and dynamic modeling (G. Moroy & D. Flatters) (2 ECTS)

Block UE3 - High-throughput screening: structure & ligand-based (5 ECTS) (G. Moroy)

BQ2CY120 Structure-based (G. Moroy) (3 ECTS)

BQ2CY130 Ligand-based (O. Taboureau) (1 ECTS)

BQ2CY140 Hits to lead (O. Taboureau) (1 ECTS)

Block UE4 - Molecular Space Analysis (4 ECTS) (O. Taboureau)

BQ2CY150 Toxicology and biotransformation (A. Baeza, F. Rodrigues-Lima) (3 ECTS)

BQ2CY160 Medicinal chemistry, pharmaceutical molecules (C. Mayer & F. Barbault) (1 ECTS)

Block UE5 - Preparation for research in Drug Design (6 ECTS) (L. Regad)

BQ2CY170 3-projects in Drug Design (L. Regad & O. Taboureau) (2 ECTS)

BQ2CY180 Tutored research project design (A-C Camproux) (2 ECTS)

BQ2CY190 Application of high throughput screening (G. Moroy) (2 ECTS)

MASTER 2 - SEMESTER 4 (30 ECTS)

INTERNSHIP (30 ECTS) (A-C. Camproux)

UE6- **BQ2DY010** Preparation of a tutored research project (A-C Camproux & S. Murail) (3 ECTS)

UE7- **BQ2DT020** International research internship (A-C Camproux) (27 ECTS)

OR SEMESTER 4 of a compulsory research internship (30 ECTS) at the SECHENOV UNIVERSITY (MOSCOW) for the French-Russian double degree

Block UE 0 : REFRESHER COURSE
Persons in charge: A-C Camproux

ECUE 001- BQAAY000- Basics of Unix and R
Persons in charge: L. Regad & G. Moroy

Title : Unix and R base (Upgrade)
Teachers: L. Regad, O. Taboureau, K. Audouze, S. Murail

Program
Fundamental concepts of the Unix operating system and R software.
Acquire the basics of using the Unix operating system and the R software.

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

ECUE 002- BQ2CY020 - Upgrading in Toxicology (Biochemistry) -Methodology
Person in charge : A-C CAMPROUX

Title : Toxicology (Biochemistry)-Methodology upgrade
Teachers: J. Dairou, V Arluison, F. Rodrigues, N. Triballeau, A. Badel, A-C Camproux

Program :
The aim of the course is to introduce students to different experimental methods to detect and characterize molecular interactions, to introduce them to biochemical tools necessary to understand drug design: The drug designer is generally at the interface between the biologist, the clinician and the chemist. He must therefore have an initiation to the biophysical methods used in drug design projects. For in silico modeling in drug design, basic biostatistics is a crucial prerequisite.

Necessary in Toxicology and Biochemistry (J. Dairou, V Arluison, F. Rodrigues)
The drug designer must have an initiation to certain biophysical methods frequently used in drug design projects. There is a wide range of biophysical methods that allow the study of protein/protein or protein/ligand interactions by defining the contact zone or characterizing the thermodynamic and/or kinetic constants that govern the interaction.
Methods to understand the basic principles of thermodynamics, scattering, and optical methods will be covered. In particular, some 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 characterization of biomolecule interactions in vitro: Nuclear Magnetic Resonance, Isothermal Titration Calorimetry (ITC), FRET, acronym of "Fluorescence Resonance Energy Transfer", and BRET, acronym of "Bioluminescence Resonance Energy Transfer
Papers using other fundamental approaches for drug design such as Surface Plasmon Resonance (SPR) and immunological methods (ELISA, GST pulldown assays) will be analyzed and presented by the students. The course will include enzymology lessons focusing on the study of interactions between enzymes and ligands (substrates, inhibitors, allosteric effectors...).

* Reminder of Biostatistics, R and basic biostatistics (A. Badel, A-C Camproux)
Training in R and Biostatistics for students to manipulate and analyze data. At the end of the training, the goal is that students are able to determine the statistical analysis that can answer the biological question posed and implement that analysis. Interpret and conclude on the statistical and biological results of their study
Reminder of probability, introduction to biostatistics
- Estimation and statistical inference
- Classical tests, Student's t test, Chi2 test,
- Pearson correlation coefficient test and simple linear regression
Fundamentals+of+Biostatistics (Chapters [1,13]) in English (available on the internet) is a suitable medium: https://collegelearners.com/ebooks/fundamentals-of-biostatistics-8th-edition-pdf-free/

⋆ Chemistry kit for drug design: (N. Triballeau)
The aim of the course is to introduce students to different tools in chemistry, necessary for the understanding of drug design methods and the characterization of molecular interactions
The drug designer is generally at the interface between the biologist, the clinician and the chemist. He/she must therefore have an introduction to biophysical methods and chemical chemistry concepts used in drug design projects.
Pharmacophore, Chemical chemistry toolbox,
"Atoms useful for drugs, hybridization, chemical functions, heteroaromatics, families of drugs IUPAC names & nomenclatures Isomers, Tautomers Stereochemistry, pseudo stereochemistry pKa of common groups, Most reactive groupsPreferred
conformations of important groups (3, 4, 5 and 6 saturated rings, amide, sulphonamide, biphenyls)-Introduction to matched molecular pair analysis - Elements of IP (Intellectual Property), SciFinder (CAS database query software) "

Block UE1 - DATA ANALYSIS IN DRUG DESIGN (8 ECTS)
Person in charge : A-C. CAMPROUX

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3 Python modules to choose from depending on level: EC101 or EC102 or EC 103

EC 101 - BQAAY070- Python I programming (3 ECTS)
Persons in charge: P. FUCHS & P. POULAIN

Title : Python I programming
Teachers : P. Fuchs, P. Poulain, S. Murail

Program :
- Main data types (integers, floats, lists, strings, dictionaries, tuples)
- Loops, comparisons, tests
- Modules
- Input/output management with files
- Functions
- Regular expressions
- Notion of classes in Python

Targeted Skills:
Training bioinformaticians in Python programming
Know the main concepts related to Python programming.
Be able to write programs (i) analyzing large amounts of data, (ii) producing data (e.g. simulation of a system).
Be able to develop/debug a program in Python.

Or EC 102 - BQAAY080-Python 2 programming (3 ECTS)
Persons in charge: P. FUCHS & P. POULAIN

<u>**Title :**</u> **Programming python 2**
<u>**Teachers :**</u> **P. Fuchs, P. Poulain, S. Murail**

<u>**Objectives in terms of knowledge:**</u> Train bioinformaticians in Python programming. Acquire autonomy in the development of a Python program. Python is the most widely used programming language in bioinformatics today, especially for data analysis. It is very much in demand in laboratories, but also in private companies.

<u>**Targeted skills:**</u> Know the main concepts related to Python programming.
Be able to write programs (i) analyzing large amounts of data, (ii) producing data (e.g. simulation of a system).
Be able to develop/debug a program in Python.

<u>**Program :**</u>
Main data types (integers, floats, lists, strings, dictionaries, tuples)
- Loops, comparisons, tests
- Modules
- Input/output management with files
- Functions
- Regular expressions
Notion of classes in Python

Or EC 103 - BQ2CY030-Python project (3 ECTS)
Person in charge: S. Murail

Title : Python project
<u>**Teachers :**</u> **S. Murail**

Objectives in terms of knowledge: a) Training in Python programming or/and b) Carrying out projects in Python (advanced level in the context of drug design or structural bioinformatics projects).
Program :
    a. Know the main concepts related to Python programming.
Be able to write programs (i) analyzing large amounts of data, (ii) producing data (e.g. simulation of a system). Be able to develop/debug a program in Python.
    b. Be able to develop a project in Python in the context of drug design or structural bioinformatics projects.

<u>**Title :**</u> **Data analysis and Drug Design**
<u>**Teachers:**</u> **A-C Camproux & L. Regad, O. Taboureau, F. Guyon**

<u>**Program:**</u> Optimize and combine different learning methods on drug design datasets Example on molecule space

- Unsupervised methods: descriptive or exploratory methods that propose groupings into object classes following algorithmic calculations

Factorial methods (Principal Component Analysis) and Classification methods (hierarchical or partitioning)

- Supervised methods: explanatory and/or predictive:

Cross-validation protocol, optimization criteria.
Linear and PLS model, knn, CART, Logistic regression
Presentation of SVMs and opening towards deep learning

<u>**Knowledge objectives:**</u> **To** teach students to combine and optimize different unsupervised and supervised learning methods to analyze drug design data. Both in the target space (structure-based application) and in the molecule space (ligand-based application) with the particular problems associated, descriptor selection and selection criteria, optimization, comparison and robustness of models in cross-validation.
Applications and projects will be done with different packages of the statistical software R.
Evaluation : Comparative reports on unsupervised methods on the one hand and supervised methods on the other hand + a presentation of articles or book chapters

<u>**Title:**</u> **Application in Drug Design & QSAR**
<u>**Teachers: O. Taboureau & L. Regad**</u>

<u>**Program :**</u>
The goal of this course is to apply the various unsupervised and supervised techniques seen in class to develop a QSAR model to predict the activity of small molecules for a given target. These models will then be used to develop chemical library filters from the supervised methods. Application of these filters to the search for new inhibitors of a given target This project will be carried out with the statistical software R.

<u>**Targeted competences :**</u> Implementation 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 supervised model development and optimization

EC 105 - BQ2CY070 - Seminars and R&D (1 ECTS)
Person in charge : A-C CAMPROUX

Title : Seminars and R&D
Teacher: A-C Camproux, ISDD Master alumni, future colleagues ...

Program: This module aims to enable students to understand the functioning and networks of research in ISDD, whether at the academic level or in companies (start-ups and large pharmaceutical companies). Meetings will allow students to exchange and discuss with people from the private and academic sectors, who are confronted with current research problems in drug design. These seminars will include presentations from recognized laboratories in drug design, structural bioinformatics and chemoinformatics, both national and international, and depending on the year, presentations from platforms (RPBS, Orphanet), PhD students and former students of the Master's program, participation in a conference in the field, and company visits.

Part 1: How to network: presentation of linkedIn, ISDD Master Group, create a linkedIn CV, learned societies of chemoinformatics and bioinformatics...
Preparation for the post-Master's period: information on the functioning of research in France and abroad. Operation of doctoral schools. National (doctoral schools), European and international (DIM, ANR) thesis funding.
Part 2: Seminars and communication: ISDD alumni will come to present their profession and career (Examples of obtaining a ministerial grant by ISDD Masters students), students will meet professional speakers (Sanofi or Servier start-up or DassaultSystems) who will present their company and its operations, and/or participation in a scientific conference (2021: SFCI and GGM conference)

Evaluation methods: Attendance and summary of seminars, registration, and CV on linkedIn,

Block UE2 - MOLECULAR ANALYSIS AND DYNAMICS & DRUG (7 ECTS)
Person in charge : D. FLATTERS

EC 203 - BQ2CY090- Structural exploration of proteins (3 ECTS)
Person in charge: L. REGAD

Title : Structural exploration of proteins
Teachers: L. Regad, Delphine Flatters, AC Camproux, F. Pierruccini, M.Bonomi

Program :
Structural analysis of the target 3D- STRUCTURE-BASED PREPARATION
Optimize a therapeutic target, model the loops of a target. Analysis of protein structure and variability at the global, local and pocket levels. Search for druggable pockets and the effect of mutations.
Targeted Skills: To provide students with the basis for advanced exploration of protein structure in preparation for the search for active compounds

3D Macromolecule Analysis
1) Construction of 3D protein models by homology modeling and advanced sequence alignment (modeller, pymol), loop optimization
2) Study of mutations and structural variability, (SA-Conf)
3) Identification-estimation of pockets and their druggability (Pockdrug)
4) Metadynamics and accelerated dynamics
5) MMPBSA

CHOICE OF EC 202 or EC 203 depending on the level

EC 201 - BQ2CY100- Dynamic analysis of targets I (2 ECTS)
Person in charge : D. FLATTERS

Title : Dynamic analysis of targets I
Teachers: D. Flatters, C. Etchesbest

Program: Understand the theoretical concepts governing molecular modeling techniques (force field, minimization, molecular dynamics)
- Semi-empirical force field and molecular mechanics: description of the basic forces
(Harmonic and torsional potentials, electrostatic interactions, van der Waals interactions)
- Optimization of molecular geometry (energy minimization)
- Molecular Dynamics (MD) Simulation and Trajectory Analysis (algorithm & conformational property calculations)
Each theme will be approached in a theoretical way in CM and in a practical way in TP (modeling of a biomolecule in water with the GROMACS software)

Targeted competences: Model a basic molecular system (a biomolecule in water). Know how to apply these notions to biomolecules (peptides, proteins, etc.)
Critical reading of a publication using molecular modeling. Be able to do an internship in a laboratory using molecular dynamics.

Title: **Dynamic analysis of targets II**
Teachers: **G. Moroy**

Program: Know how to select the appropriate bioinformatics tools to study the flexibility of a protein.
Study of the flexibility of proteins.
Analysis of molecular dynamics simulation results.

Objectives in terms of knowledge: **To** know how to apply the knowledge acquired for the study of protein dynamics to the modeling of a therapeutic target.

Title : **Structural and dynamic modeling**
Teachers: **G. Moroy & D. Flatters**

Program: Generation and analysis of structures from molecular dynamics simulation trajectories of a protein of interest. To be able to propose and apply a protocol combining structural and dynamic studies of proteins + MMPBSA
Targeted competences: Understand and master the bioinformatics tools that help in the structural and dynamic study of proteins.

Block UE3 – HIGH-THROUGHPUT SCREENING : STRUCTURE & LIGAND-BASED (5 ECTS)
Person in charge : G. MOROY

EC 302 - BQ2CY130- Ligand-based (1 ECTS)
Person in charge: O. TABOUREAU

<u>Title</u> : Ligand-based
Speakers: O. Spérandio, G. Moroy, S. Murail, O. Taboureau

<u>Program:</u> This course is designed to provide hands-on learning of in silico preparation of chemical libraries for virtual screening based on the structure of reference ligands and to perform ligand-based virtual screening. The program includes parts
- Mastery of the different molecule file formats and handling of PDB, **smile**, SMARTS, mol2, MDL-sdf, 3D molecules with Pymol, Advantages, limitations and frameworks of use of different file types.
- Generation of three-dimensional molecular models for small molecules (1D/2D to 3D) and calculations of ligand descriptors and transformation from 2D to 3D format and dimensions using software (knime rdkit, frog and openbabel) (different behaviors: Smart change, isomer, tautomer).
- Descriptors visualization, molecules visualization
- Pharmacophores & main ADME/tox rules : Lipinski, Weber, Egan,...
   Notion of Frequent, Hitter, Aggregants, Toxic Fragments using FAFdrug,
- Ligand-based screening, (notion of decoys)

<u>**Objectives in terms of knowledge:**</u> Practical learning of 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), how to go from 1D-2D-3D ii) calculation of ligand descriptors, iii) pharmacokinetic aspects (ADME/tox) based on specific physicochemical criteria, iv) application of a ligand-based screening

M1 chemoinformatics information/materials (MOE descriptors) are made available to MB students.
<u>Targeted skills</u>: Generation of compound libraries and ligand-based screening

EC 301- BQ2CY120- Structure-based screening (3 ECTS)
Person in charge : G. MOROY

<u>Title</u> : Structure-based
<u>Person in charge of training</u> : G. Moroy

<u>Program:</u> The objective of this course is to present advanced theoretical concepts, algorithms and associated programs for the design of therapeutic molecules by approaches based on the structure of the target protein. Taking into account the flexibility of the protein and the ligand. How to dock with covalent bonds?
Molecular dynamics stability study of the protein-ligand interaction.
Presentation and use of several docking and virtual screening programs.
Autodock & Rdock, seed (fragment-based), a therapeutic target screening
using @TOME-3

<u>**Targeted skills:**</u> Understand and master some bioinformatics tools that help in the design of therapeutic molecules based on the structure of the target protein.

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Title : Hits to lead
Speakers: O. Taboureau & H. Xhaard

Program: Several experimental approaches and rational in silico design methods can be used to transform a "hit" into a "lead" (X-ray diffraction, NMR, medicinal chemistry, SAR, QSAR, rescoring, molecular simulation, ligand-based, fragment-based methods...).
Several examples of optimization will be discussed with applications in infectious diseases, cancer, cardiovascular diseases and the reproductive system.
The aim of screening is to identify molecules with biological activity of therapeutic interest with respect to a therapeutic target. High throughput, in silico or in vitro, allows the testing of several thousand molecules per week. Pharmacological screening is the first step in the drug discovery process. The molecules identified during the initial screening phase (hits) are far from being drugs yet. Their binding to their target is still too weak, so they will have to be optimized (leads). Thanks to subtle and progressive transformations of the structure of the hit, the medicinal chemist and the drug designer will allow it to bind more efficiently to its target. However, this increase in affinity alone will not be enough to make the key a drug candidate. Before being evaluated in animal efficacy models and then in humans, the product will have to satisfy several other constraints: a) specificity, b) adequate bioavailability, c) appropriate pharmacokinetic properties, d) absence of toxicity.

Targeted skills: Students will discover, through specific examples, the main strategies to optimize an initial touch to the drug candidate and the marketed therapeutic molecule

Block UE4- RESEARCH COURSE – MODELING OF MOLÉCULES
ANALYSIS OF MOLECULE SPACE (4 ECTS)
Person in charge: O. TABOUREAU

EC 401 - BQ2CY150- Toxicology and Biotransformation (3 ECTS)
Persons in charge: F. BUSI, A. BAEZA

Title : **Toxicology and biotransformation**
Teachers: A. Baeza, F. Rodrigues-Lima, J. Dairou, F. Buzi

Program :
- Enzymes of drug metabolism
- Xenobiotic transporters
- Pharmacokinetics
- the different types of toxic response
- mechanisms of action of toxic substances

Targeted Skills: To give the basics of the fate of xenobiotics (drugs) and toxicology

EC 402 - BQ2CY160 - Medicinal chemistry, pharmaceutical molecules (1 ECTS)
Persons in charge: C. MAYER & F. BARBAULT

Heading : Medicinal chemistry, pharmaceutical molecules
Teachers: C. Mayer & F. Barbault

Program :
After acquiring drug design skills, students will be working at the interface between several disciplines, so they will need to have some background in molecular medicine, knowledge of some of the drugs in use today, as well as information on some of the molecules in development. A basic understanding of computational drug design methods, such as structure-based and ligand-based approaches, is required.
The teaching will present in an integrated way concepts of chemistry, molecular medicine, drug discovery and biology. After a brief review of medicinal chemistry, stereochemistry and nomenclature, the course will introduce the principles of molecular medicine and present several examples of therapeutic molecules currently on the market or in clinical trials. A detailed description will be given of the modeling methods used to improve the biological activity of a first ligand (hit to lead), with particular emphasis on QSAR methods and bioisosterism. Major biological systems and associated pathologies will be addressed, including infectious diseases such as malaria and tuberculosis, and cancer. Examples of therapeutic molecules targeting different protein systems will be discussed. Several three-dimensional structures of therapeutic target-drug complexes will be examined to illustrate the main concepts of therapeutic molecule research combining in silico and experimental approaches in the context of molecular medicine.
- Chemistry kit for drug design: (N. Triballeau), see Biochemistry reminder

Targeted skills: The students will be able to acquire knowledge on the major human pathologies and have relevant examples of therapeutic molecules currently used or under development

Block UE5. PREPARATION FOR RESEARCH IN DRUG DESIGN (6 ECTS)
Person in charge: L. REGAD

EC 503- BQ2CY190 - High throughput screening application (2 ETCS)
Person in charge : G. MOROY

Heading : **High speed screening application**
Person in charge of training : **G. Moroy**

Program :
Application of the knowledge acquired to propose inhibiting molecules of a target protein.
Analysis and preparation of the structure of a target protein.
Preparation of an adequate chemical library.
Selection and adaptation of a virtual screening protocol.
Targeted Skills:
Use and selection of appropriate tools for virtual screening to propose inhibitor molecules for a given target protein.

EC 501-BQ2CY170 - 3-projects in Drug Design tutorial (2 ECTS)
Persons in charge: L. Regad & O. Taboureau

Title : **3-projects in Drug Design tutored**
Teachers : **L**. Regad, O. Taboureau, G. Moroy, S. Murail, O. Taboureau, AC Camproux, S. Pasquali, D. Flatters,

The main UE blocks of the first semester include training modules and a project module. These different projects aim at proposing the analysis (and dynamics) of a protein target and the selection, analysis and screening of candidate molecules for the binding of this target. The molecular docking of partners on the same system is dealt with throughout the semester and in the different projects corresponding to the ECUE: "BQ2CY060 Application in Drug Design & QSAR + BQ2CY080 Structural and dynamic modeling + BQ2CY190 High-throughput screening application", in connection with other modules (BQ2CY090 Structural exploration of proteins, BQ2CY130 Ligand-based, Hits to lead EU ...).
In this ECUE3-projects in Drug Design", students (individually) will have to analyze in a combined way and synthesize the results of these different projects) in an integrated and complete project of drug design in silico.

Program :
An integrated analysis of the results of the different projects [combining molecular modeling on a target to assess its flexibility, selection of candidate molecules by statistical filtering approaches to create an optimized chemical library and virtual screening (ligand-based and structure-based) of the target by its molecules to predict inhibitor molecules from the optimized chemical library], will be performed by the students in order for them to gain hands-on experience on an in silico drug design project. This target and molecules are treated and analyzed in a concrete way in the form of projects or reports during different modules of the semester. The objective of this project is for the students to link the different approaches studied and projects obtained on the same system in order to understand the complementarity and the finality of these approaches for a complete in silico drug design project.

Targeted Skills:
- Know how to apply, analyze and combine the different steps of a drug design protocol

Know a drug design protocol to identify new inhibitors of a target of interest

At the end of the semester, students combine and analyze the results of different projects obtained on the same target system in order to understand the complementarity and the purpose of the approaches studied in the M2 core curriculum. Know how to develop an optimized pipeline to identify new inhibitors of a given target, optimize and combine the different tools needed in a drug design protocol.

As part of this module, depending on the year, if the D3R Grand Challenge is offered, students have the opportunity to participate in the D3R Grand Challenge, which is the international Drug Design Challenge hosted by the University of California, San Diego. Its goal is to predict the position of small molecules in the binding site of a given protein and to predict the affinity of small molecules for that same protein. https://drugdesigndata.org/about/grand-challenge

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EC 502 - BQ2CY180 - Tutored research project design I (2 ECTS)
Persons in charge: A-C. Camproux

Title : Design of a tutored research project
Person in charge of training: A-C Camproux

Program: Preparation of the course *:
- Build your research networks: presentation of linkedIn, ISDD Master Group, create a linkedIn CV, contact alumni (linkedIn, facebook), chemoinformatics and bioinformatics companies.
How to make an oral presentation, an internship report, structure a publication?
- Preparation of the research internship topic, involving bibliographic work and reflection on possible collaborations. Writing of the internship topic in a 3 to 4 page format

Targeted Skills:
Understanding by the students of what a research project involves. Reflection, preparation of their internship research topic, requiring bibliographic work.
You can consult the Pôle de l'Orientation et de la Professionnalisation https://u-paris.fr/orientation-et-insertion/

MASTER 2 - SEMESTRE 4 (30 ECTS)

UE6 INTERNSHIP (30 ECTS)
Person in charge : A-C. Camproux

EC 601 - BQ1DY010- Preparation of a tutored research project II (3 ECTS)
Persons in charge: A-C. Camproux, S. Murail

Title : **Preparation of a tutored research project**
Pedagogical coordinators: **A-C. Camproux, S. Murail**

Program: In preparation of the research internship topic, a reflection on possible collaborations and the integration of the different in silico modules followed in Master for a three-year extended research project. In preparation of the research internship topic, involving bibliographic work, reflection on possible collaborations and integration of the main in silico modules followed in Master for the research project. Budgeting of the project. Pairs of tutors guide them in this work.

Evaluations
Students prepare a worksheet for the interviews, a long report (maximum 10 pages) before the internship in order to prepare it as well as possible. Two tutorial meetings to discuss and advise on the preparation of this project are proposed with the tutors during semesters 1 and 2.

In addition, a report (2 to 3 pages) is requested midway through the course in March.

UE7 - BQ1DT020- International research internship or internship in a company
(27 ECTS)
Person in charge : A-C. Camproux

Title: **International research internship or in a company**
Person in charge of training : **A-C. Camproux**

Program: Laboratory internship or equivalent bibliographic work
The aim of the course is to introduce students to research in academic or private laboratories, depending on the student's international project, which is strongly recommended for the Macromolecules course

OR SEMESTER 4 of compulsory research internship (30 ECTS) at the SECHENOV UNIVERSITY (MOSCOW) for the French-Russian double degree