Fundamentals of Molecular Pharmacology and Computational Biology: Workshop Syllabus

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Workshop Description

Application of biological and computational chemistry, molecular pharmacology, mathematical abstraction and computational techniques in biology; computer-aided drug design and discovery; and conceptualization of *in silico* methodologies.

Specialization

The workshop specializes on computational discovery and design of drug for diseases with well-defined underlying molecular mechanism such as neuropsychiatric diseases and different types of cancer.

Recommended Prerequisite for Advanced Study

Various prerequisites are required for advanced and formal study of computational biology including computational chemistry, biochemistry, quantum physics, molecular and cellular pharmacology, statistics, computer science and molecular biology. Presented here are the needed prerequisites for advanced and formal study of computational biology:

1. Calculus I (Functions and Continuity), II (Single Variable Calculus), III (Multivariable Calculus, Vectors and Matrices)
2. Linear Algebra (*required for Bayesian Statistics*)
3. Bayesian Statistics
4. Programming I, II, III
5. Discrete Mathematics (*required for computer science and algorithms*)
6. Computer Science
7. Data Structures

8. Algorithms
9. Linux and System Administration
10. Advanced Molecular Biology
11. Molecular and Cellular Pharmacology
12. Biochemistry and Organic Chemistry
13. Quantum Physics/Physical Chemistry

Workshop Requirements

It is highly recommended to bring a computer (either a laptop or anything that can interpret a basic Python code.):

1. Computer (Linux, Windows, MacOS)
2. Python 3.12 Interpreter/Anaconda Python Distribution*
3. Text Editor/Integrated Development Environment (IDE)†:
   (a) VSCode
   (b) Sublime Text
   (c) Notepad++
   (d) Notepad
   (e) JetBrains PyCharm
4. Schrödinger's Python Molecular Graphics or UCSF Chimera X or Amber24 or `Vina`‡
5. Computational Biology packages:
   (a) `vina==1.2.5=py312hfd9f6ad_3`
   (b) `pillow==10.4.0=py312h287a98d_0`
   (c) `matplotlib==3.9.2=py312h7900ff3_0`
   (d) `numpy==1.26.4=py312heda63a1_0`
   (e) `pandas==2.2.2=py312h1d6d2e6_1`
   (f) `chembl_webresource_client==0.10.9=pyhd8ed1ab_0`
   (g) `rdkit==2023.09.6=py312hd93e07f_0`
   (h) `dockstring==latest`

Workshop Contents

The workshop will be heavily centered on computational drug discovery and design/computer-aided drug design/discovery (CADD) for human diseases with underlying molecular mechanism. Hence, its contents will be mainly biological and organic

*Either one will suffice, just note that the version of Python must be ≥ 3.10.
†Although any text editor should be fine for this purpose.
‡Autodock 4/Vina is also acceptable.

chemistry with review on physical or quantum chemistry/quantum physics as well as computational and analytical chemistry, cellular and molecular pharmacology, advanced molecular biology and computer science.

Case studies relevant to the chapter will be presented every lecture. Practical outputs and hands-on training will also be included in the workshop. All of the cases/training will utilize real world data derived/obtained from clinical trials of drugs, published analyses or literature.

Case Study and Applications of Computational Biology

Define computational biology and how it is a product of interrelation of different fields: biological and organic chemistry, physical and quantum chemistry/quantum physics, computational chemistry, molecular and cellular pharmacology, mathematical abstraction and computational techniques.

Demonstrate real world application of computational biology and molecular pharmacology via presentation of computer-aided drug design and its potentials and implications. Lastly, an exhibition of different methods and uses of computational biology and its importance in study of molecular and cellular biology will be presented.

1. Case Study of Cancer:
   (a) Brief Introduction to Cancer.
   (b) p53 Signaling Pathway.
   (c) Presentation of Ligand With Affinity Data.
2. Case Study of Neuropsychiatric Diseases: Psychosis, Anxiety and Depression:
   (a) Three mechanism of actions.
   (b) Role of 5-HT_{2A} and D_2DR on neuropsychiatric diseases.
   (c) Insight on Risperidone.
3. Definition of computational biology.
4. Computational Biology vs Bioinformatics vs "*In Silico*" studies.

Brief Review on Biochemistry and Quantum Chemistry

Review the basic and fundamental concepts of the macromolecules/biomolecules of life emphasizing the relationship of conformation/structure and function. Redefine the concepts of bonds, formation of molecules and theoretical basis of properties of intermolecular forces: the role of quantum mechanical principles in bond formation; and description of intermolecular forces governing its interactions. Highlight the implication and role of K_D and K_i and its importance in drug mechanism of actions.

1. Quantum mechanical basis of molecules: Molecular Orbital Theory.
2. VSEPR Theory, Valence Bond Theory: Formation of bonds
3. Description of intermolecular forces.

4. Physicochemical properties of macromolecules in physical perspective.
5. K_D and K_i and its implications.

Fundamental Molecular Pharmacology

Elucidate the molecular mechanisms of drugs and the different theories underlying the drugs mechanism of actions: agonism, inverse agonism and antagonism. Comprehensively describe the receptors associated in development and pathology of diseases and disorders such as G-protein Coupled Receptors (GPCR), Receptor Tyrosine Kinases (RTK) and Ligand-Gated Ion Channels (LGIC). Highlight the molecular pathology of some diseases including neuropsychiatric diseases and disorders, cancers, bacterial and viral infections.

Properties and interactions of protein-protein, protein-ligand and ligand-ligand complexes will also be highlighted. Formation of transcriptional activators and repressors will also be reviewed in detail. Additionally, the role of dissociation constant K_D and inhibition constant K_i, as well as association constant K_A in absorption, distribution, metabolism, excretion and toxicity (ADMET) profile of drugs will also be emphasized. Finally, Lipinski's Criteria (The RO5 of drug development) and the relationship of molecular structure and drug activity will be explored briefly and how it can be used to filter candidates of drugs.

1. Molecular mechanisms of drugs: Agonism, Antagonism and Inverse Agonism.
2. Comprehensive description of receptors.
3. Molecular pathology of some diseases.
4. Properties and interactions of different complexes.
5. Formation of transcriptional activators and repressors.
6. Role of dissociation constant K_D, inhibition constant K_i and association constant K_A in ADMET profile of drugs.
7. Lipinski's Criteria (The RO5 of drug development).
8. Relationship of molecular structure and drug activity.

Basic Molecular Docking

Explore the fundamental concept of molecular docking using the knowledge and theoretical background discussed previously. A simple demonstration utilizing UCSF Chimera X and Schrödinger's Python Molecular Graphics with real-world data using commercial drugs used in any interesting disease/disorder. Interpretation and potential implications of the obtained data will also be discussed.

1. Hands on demonstration of UCSF Chimera X.
2. Exploration of Schrödinger's Python Molecular Graphics.
3. Practical application using real world data from clinical trials.

4. Interpretation and potential implications.

Programming I: Basic Concept of Python Programming

Basic Python programming starting from `print("hello, world!")`, variable initiation and manipulation, fundamental data structures and classes, conditional statements, loops, functions, propositional calculus, logical operators on compound propositions and introduction to modules.

1. Introduction to language: `print("hello, world!")`.
2. Variables.
3. Arithmetic operators.
4. Fundamental data structures and classes.
5. Conditional statements.
6. Loops.
7. Functions.
8. Introductory Discrete Mathematics:
   (a) Introduction to propositional calculus.
   (b) Logical operators.
   (c) Compound propositions.

Programming II: Advanced Python Programming

Advanced Python programming includes the introduction of generators, decorators, transition to object-oriented programming, advanced data manipulation, advanced and external data types and structures, framework and model construction, data visualization, advanced matrix calculations and computational techniques.

1. Introduction of generators.
2. Decorators.
3. Transition to object-oriented programming (OOP).
4. Advanced data manipulation.
5. External data types and structures.
6. Data visualization.
7. Matrix calculations.
8. Computational techniques.