Dancing with enzymes: designing the drugs of the future

Syllabus

Zoom information:
https://zoom.us/j/3843711220
Meeting ID: 384 371 1220 | Passcode: 31416 (number pi)

Instructors:
Gabriel Fuente (The Scripps Research Institute) - gabrielfuentegomez@gmail.com
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Club objective: To understand & practice how drugs are designed using molecular computational tools.

Course description: In this club, we will learn how enzymes are related to drug design, development, and their efficacy and safety for disease treatment. Throughout interactive lectures on the structure and function of enzymes, we will understand how drug action is a unique phenomenon, relying on both biology and chemistry. With hands-on activities (molecular visualization of enzymes, common drugs' docking, and molecular dynamics simulation), we will visualize how the molecular movement is essential for the binding efficiency of drugs in their biological targets. Are you ready to become the drug designer of the future?

Communication: Questions and comments can be posted on Slack at any time or on the zoom chat during the synchronous activities. We also have a WhatsApp group: https://chat.whatsapp.com/JG4gd4JevbA4UGfiBZDyB0

Diversity and Inclusivity Statement: We consider this club to be a place where you will be treated with respect, and we welcome individuals of all backgrounds, beliefs, ethnicities, genders, gender identities, gender expressions, national origins, religious aliations, sexual orientations, ability, and other visible and non-visible differences.

SCI events (all events are at 12 PM EST):

- SCI 2021 opening ceremony (1.5 hr) - **Friday, February 26th.**
- Webinar (1hr): "Art in scientific research and education" - **Wednesday, March 3rd.**
- Webinar (1 hr): "Entre a ciência e a sociedade" - **Friday, March 5th.**
- Webinar (1 hr): "La mujer en la ciencia" - **Saturday, March 13th.**
- SCI 2021 closing ceremony (2 hr) - **Sunday, March 14th.**
- SCI 2021 Symposium (2 hr) - **Saturday, March 20th.**

Resources (the list will be extended throughout the club):
Google Drive (you can find articles, slides, and other materials discussed during the club): https://drive.google.com/drive/folders/1Lr4PeXgAxrgb2OzihaStD0hDWRDIB-xu?usp=sharing
Google Drive for uploading multimedia for the closing ceremony: https://drive.google.com/drive/folders/12-NjO1HejJ90CTxP6CRK0C0bAeC2JbHs?usp=sharing
Software:

- PyMol (visualization). https://pymol.org
- MGL tools (visualization for docking). http://mgltools.scripps.edu/downloads
- Autodock (docking). http://autodock.scripps.edu/downloads/autodock-registration/autodock-4-2-download-page/
- Chimera (molecular dynamics). https://www.cgl.ucsf.edu/chimera/download.html

Literature (book chapters, journal articles, etc):

- Zhang, Linlin, et al. "Crystal structure of SARS-CoV-2 main protease provides a basis for the design of improved α-ketoamide inhibitors." Science 368.6489 (2020): 409-412.
- Bafna, Khushboo, Robert M. Krug, and Gaetano T. Montelione. "Structural Similarity of SARS-CoV2 Mpro and HCV NS3/4A Proteases Suggests New Approaches for Identifying Existing Drugs Useful as COVID-19 Therapeutics." ChemRxiv (2020).
- Braun, Efrem, et al. "Best practices for foundations in molecular simulations [Article v1. 0]." *Living journal of computational molecular science* 1.1 (2019).

Multimedia (videos, websites, graphics, etc.):

- https://www.youtube.com/watch?v=wvTv8TqWC48
- https://pdb101.rcsb.org/learn/paper-models

Program
Day 1 (Saturday, February 27 - 9 to 11 am CST)
Leading Instructor: Jesus, Gabriel, Carlos
Objective: To introduce students to proteins and online resources for protein structures. Students will learn how to create movies of proteins to help to visualize key residues on the structure important for the process of drug discovery.
Concepts:

- Protein biochemistry.
    - Peptide bonds
    - Aminoacids
    - Hydrogen bonds and disulfide bridges
    - Crystal structures.
- Protein structure representation (sheets & ribbons).

Synchronous activities - Schedule (2 hr):

- Welcome - 5 min
- Instructors' presentation - 15 min
- Icebreaker - 15 min
- Introduction to protein structure and interactions with substrates (online lecture) - 25 min - Jesus

- Protein Data Bank and online resources for the acquisition of coordinates of protein structures - 25 min - Gabriel
- Introduction to PyMOL an open-source software for the visualization of protein - 25 min - Carlos
- Q&A - Closing - 10 min

Asynchronous activities (before the session):

- Exploration of PDB databank website: Download proteins of interest.
- Installation of computational packages (PyMOL, Autodock, Chimera)
- Watch video from amoeba sisters (https://www.youtube.com/watch?v=hok2hyED9go)
- Build a paper model of a protein (https://pdb101.rcsb.org/learn/paper-models) (challenge)
- Complete initial survey (survey includes some concepts to cover and students' introductions)

Day 2 (Sunday, February 28 - 11 am to 1 pm CST)

Leading Instructor: Gabriel

Objective: To learn and implement docking techniques.

Concepts:

- Early-stage drug discovery
- Medicinal chemistry
- Protein/ligand docking
- Molecular modeling
- Binding affinity prediction and docking score

Synchronous activities (1.5 hr):

- Welcome & intro to the session - 5 min
- Advantages of in silico drug discovery -10 min
    - Selection of protein and substrate(s) for docking
- A brief introduction to cyclin-dependent kinase type-2 (CDK2) inhibitors -5 min
- Ligand and receptor preparation -15 min
- Generation of grid maps -10 min
- Docking ligands with AutoDock -15 min
- Analyzing docking runs -10 min
- Exporting docking poses -10 min
- Interpretation of docking results and comparison to literature
- Q&A - Closing - 10 min

Asynchronous activities (before the session):

- Installation of PyMOL and AutoDock
- Read the article "Demonstration of AutoDock as an Educational Tool for Drug Discovery" from the Journal of chemical education
- Watch Autodock tutorials: http://vina.scripps.edu/tutorial.html

Day 3 (Saturday, March 6 - 11 am to 1 pm CST)

Leading Instructor: Jesus

Objective: To learn and implement molecular dynamics (MD) techniques.

Concepts:

- Molecular Dynamics basics.
    - Force Fields (Newton's equations of motion)
    - Periodic boundary conditions
- MD simulation preparation
    - Force field selection
    - Hydrogen bonding capping
    - Solvation box
    - Ionization
- Molecular dynamics simulation protocol
    - Energy minimization (potential energy surfaces)
    - Equilibration (thermostats)
    - Production (trajectory analysis)

Synchronous Activities - Schedule (2 hr):

- Welcome & intro to the session - 5 min
- Why do we need MD simulations? - 10 min
- MD in a nutshell - 20 min
    - Summary of force fields concepts
    - A brief explanation of the MD protocol
- Introduction to MD tools (Chimera) - 30 min
    - Preparing PDB file for simulation
    - Build solvation box and add ions
- Trajectory analysis and comparison with recent literature. - 55 min
- Q&A - Closing - 10 min

Asynchronous activities (before the session):

- Explore the article "Best practices for foundations in molecular simulations".
- Check software installation (Chimera).
- Find an animation (GIF, video, etc) of a molecular dynamics simulation (challenge).

Day 4 (Sunday, March 7 - 10 am to 12 pm CST)

Leading Instructor: Carlos

Objective: To integrate the concepts of **drug design and discovery** with a complete **pharmaceutical development project**.

Concepts:

- Analytical tools for drug development
- Preclinical & Clinical trials (I to IV)
- Regulatory agencies

Synchronous activities - Schedule (2 hr):

- Welcome & intro to the session - 5 min
- What happens after the *in silico* drug development? - 10 min
    - QSAR
    - Predictive databases
- Drug discovery pipelines: An analytical *in vitro* view - 15 min
    - Applied enzymology for the pharmaceutical industry (HT & novel techniques)

    - State-of-the-art techniques for drug discovery
- Pharmaceutical development & translational medicine - 35 min
    - Preclinical (*in vitro* & *in vivo*)
    - Clinical trials (I to IV)
    - Bioequivalence and biosimilarity
- Drug regulation around the world - 15 min
- Q&A - 5 min
- General club wrap-up - 30 min - Carlos, Gabriel, Jesus
    - Instructions & dates for the final delivery
    - Comments
    - Final message

Asynchronous activities:

- Objective: To review QSAR concepts & their relationship with drug properties prediction
- Check any small molecule that you are interested in and explore the toxicological & pharmacokinetic properties (challenge)
- Access to DrugBank (https://go.drugbank.com/) and explore the properties of some common molecules - During the session