Title: A project-based course in computational and virtual medicinal chemistry

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Learning Outcomes: The students will recognize the availability and the ease of retrieval of a substantial amount of annotated chemical and structural biology data and how these are leveraged in inquiry-based research projects. Web-accessible databases and cheminformatics tools facilitate linking of multi-layered and cross-referenced data into an effective framework for early-stage drug design, discovery, and optimization. The students will also gain a practical knowledge of how the structure of drug molecules and biological protein receptors are represented to model and understand their similarities, physiochemical properties, and their interactions that lead to biological/therapeutic responses. Subsequently, they will use the data to create hypotheses that can be tested and validated both virtually and experimentally.

Prerequisite: One year of freshman chemistry and freshman biology courses; scripting skill is not required

Maximum number of students: 24

Assessment methods: Hands-on exercises, case studies, and a final report in a poster format. Students will be encouraged to present their posters in the 2021 annual LBRN meeting (in person or virtual!)

Description:

Computational-Aided Drug Discovery (CADD) of Anti-Viral Therapeutics for COVID-19

The novel coronavirus, SARS-CoV-2 is the causative agent for COVID-19, and it has created an unprecedented global viral pandemic with a significant negatively disruptive impact on human health and the economy. Due to the lack of approved drugs for COVID-19, there is an urgent unmet medical need for new and effective therapeutics against this deadly virus. This course provides a practical overview of how modern computational and cheminformatics tools are now used as virtual shortcuts in making drug discovery pipeline more efficient in time and cost and less risky. Concepts and technical skills related to CADD, including virtual **high-throughput drug** screening, ligand- and structure-based drug library design, and molecular docking will be discussed. This course will enable students to integrate various public domain and proprietary computational tools in the context of an anti-viral drug library design and optimization process (a virtual drug to a first-in-human drug) for COVID-19. This includes:

I. **Molecular Fingerprints and Similarity Searching.** We will use a three-pronged metric framework to expand the drug library for chemotype diversity based on a promising antiviral drug, arbidol, these include: **Chemical** (2D/3D structure, electrophores, spectrophores); **Biological** (binding affinity, bioactivity), and **Pharmacophore** descriptors.
Tools and Databases: *Swiss Bioinformatics Institute* (SIB), SEA, UniProt, Novartis *HTP-FP*, and *Open Babel*

II. **Chemical Structure Optimization.** We will use standard protocols to prepare the energy-minimized conformational ensembles for the drugs and the respective protein targets (SPIKE and SPIKE-ACE2 complex).
Tools: *Spartan* and *YASARA*

III. **Virtual Molecular Docking**. We will include practical predictive application of ligand binding sites in targets, binding modes in drug-protein complexes, and scoring functions for drug binding affinity to their respective targets.
Tools and Databases: *MOE-CCG*, *AutoDock Vina*, *BIND*, *Binding Interface Database*

IV. **Selection of Drug Candidates for Experimental Validation**. We will use a two-pronged metric framework to select four final drug candidates for phenotypic viral cell-based assays. The first approach is ligand-based, which includes the application of the lead- triage concept to filter out drugs with undesirable physiochemical properties and those that are over-promiscuous using ADMET, PAINS, Lipinski's ROF filters. The second approach is structure-based, the application of dynamic molecular modeling and simulations to rank drugs for their affinities towards the protein targets of interest (SPIKE & SPIKE-ACE-2) and the corresponding stability of those complexes.