A journey through the computational discovery of bromodomain inhibitors.

Computer simulations increasingly complement experimental efforts in drug discovery. Simulations, like experiments, do not always provide the correct answer. They clarify the problem, push investigations forward, and point out gaps and inconsistencies in existing information. At the cornerstone of this thesis, we present the application of computational methods to the discovery of drug-like small molecule inhibitors of bromodomains. Bromodomains are important epigenetic domains that read acetylated lysine marks of proteins. Under physiological conditions, bromodomains recognize acetylated lysine of histone tails and are part of multiprotein complexes that modulate the DNA accessibility. As of fall 2017, 16 bromodomain inhibitors are investigated in oncology and cardiovascular diseases clinical trials.

We applied computational techniques to identify 37 binders of human bromodomains, namely ATAD2, BAZ2B, BRD4(1), and CREBBP, and characterized a Lin28-bromodomain dual inhibitor. In particular, we developed a new version of the anchored-library tailoring approach for virtual screening (ALTA-VS), a high-throughput docking protocol first introduced by the Caflisch group in 2005. This is a four-step procedure, composed of (1) decomposition of a chemical library into its essential rigid fragments; (2) docking of the fragments and evaluation of binding energy; (3) flexible docking of the parent molecules that contain the top ranking fragments that are used as anchor; and (4) energy minimization with final evaluation of binding energy. The final axis of work of my Ph.D., which will be presented as an outlook, focused on the development of a novel implicit solvation model for the evaluation of the binding free energy of drug-like molecules to target proteins.

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Location: Lecture Hall Y13-M-12, UZH Irchel
Contact: Prof. Amedeo Caflisch, Email: caflisch@bioc.uzh.ch