What drives the membrane permeability of drugs? A study on untackled effects

Place of work/: BioISI, Chemistry for Biological Systems Group, Computational Laboratory, 8.5.50D

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As most drug discovery campaigns aim to target cytosolic or nuclear proteins, prior knowledge of cell membrane permeability is crucial to identify and discard the less permeable, hence, poor drug candidates. Several factors can affect the membrane permeability of small molecules, including the size, charge, pH, and the presence of specific chemical groups that allow the formation of noncovalent interactions such as hydrogen or halogen bonds [1]. The understanding, at the molecular level, of the interplay between these factors is paramount for drug design, and in this scope, computational methods are the tool of excellence.

Our laboratories have been at the forefront of this research area. Indeed, Machuqueiro's Lab has been studying and developing methods to tackle pH effects on membrane permeability [2], whereas Costa's Lab provided, for the first time, evidence for the existence of halogen-membrane recognition phenomena with a possible effect on the permeation of halogenated drug-like molecules [3]. Building on the previous knowledge of both Labs, which collaborated before on related issues [4], this project aims to study the interaction of several small drug-like molecules with a membrane model at the molecular level. We will calculate the membrane crossing energy profiles for these molecules, which can be used to estimate their membrane permeability coefficients. By performing systematic in silico chemical substitutions, our data will allow for the rationalization of the effect of hydrogen or halogen bonds (the latter is unknown), but also their possible interplay with protonation/deprotonation events of titrable groups at the water-lipid interface. We will start with small prototype systems in order to decouple the different degrees of freedom that impact membrane permeability, thus decreasing the complexity of the process. However, we ultimately aim to understand how the presence of both halogens and Lewis base groups affect and contribute to the permeability (or lack thereof) of drugs such as Cobimetinib, an anti-cancer medication to treat patients with unresectable or metastatic BRAF V600 mutation-positive melanoma. In the end, we will compile the results in a master thesis and prepare a manuscript submission to an international scientific journal.

Students selected for this project, after thesis registration, are eligible to apply to the BioISI Junior Programme which supports 8 students with a 6-month Scholarship(BII), being the selection criteria, the academic merit of the candidates.

References

[1] Costa, P. J. The halogen bond: Nature and applications. Physical Sciences Reviews, 2017, 2, 20170136

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[3] Nunes, R. S.; Vila-Viçosa, D.; Costa, P. J. Halogen Bonding: An Underestimated Player in Membrane−Ligand Interactions, J. Am. Chem. Soc. 2021, 143, 4253−4267

[4] Nunes, R.; Vila-Viçosa, D.; Machuqueiro, M.; Costa, P. J. Biomolecular Simulations of Halogen Bonds with a GROMOS Force Field. J. Chem. Theory Comput. 2018, 14, 5383–5392