TWIN2PIPSA

https://twin2pipsa.campus.ciencias.ulisboa.pt/

Ciências ULisboa
Faculdade de Ciências da Universidade de Lisboa

FCiências.ID
ASSOCIAÇÃO PARA A INVESTIGAÇÃO E DESENVOLVIMENTO DE CIÊNCIAS

In silico methods to capture the pH effects in drug binding to proteins and membranes

Miguel Machuqueiro

Many biomolecules have their structure, stability, and reactivity properties significantly modulated by pH. The pKa values of common titratable sites in proteins, peptides, lipids, or other simple organic molecules are usually coupled with their conformation and the observed electrostatic environment. In inhomogeneous media, this coupling becomes harder to capture and sample correctly using our state-of-the-art computational methodologies, like constant-pH MD (CpHMD) [1]. This is particularly important to study protein-protein and protein-drug binding or membrane permeability values. I will show our most recent methodological developments where CpHMD, often coupled to an Umbrella Sampling scheme [2], was used to calculate the donepezil binding affinity to acetylcholinesterase and the membrane permeability coefficients of several chemotherapeutic drugs (tyrosine kinase inhibitors), including sunitinib and nintedanib. The results will showcase the effectiveness of our methodologies in predicting key attributes related to drug design, trafficking, and affinity toward the target.

We acknowledge financial support from FCT through grant CEECIND/02300/2017 and projects UIDB/04046/2020 and UIDP/04046/2020. We also acknowledge the funding by the European Union (TWIN2PIPSA, GA 101079147). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or the European Research Executive Agency (REA). Neither the European Union nor the granting authority can be held responsible for them.

[1] Gomes, A. M. M., Costa, P. J., Machuqueiro, M. (2023) "Recent Advances on Molecular Dynamics-Based Techniques to Address Drug Membrane Permeability with Atomistic Detail", BBA Advances, 4, 100099.

[2] Oliveira, N. F. B., Machuqueiro, M. (2022) "A novel US-CpHMD protocol to study the protonation-dependent mechanism of the ATP/ADP carrier", J. Chem. Inf. Model., 62, 2550.

Funded by the European Union (TWIN2PIPSA, GA 101079147). Views and opinions expressed are however those of the author(s) only and do not necessarily reflect those of the European Union or European Research Executive Agency (REA). Neither the European Union nor the granting authority can be held responsible for them.