

## Using molecular simulations to gain insight into the behavior and interactions of biomolecules

Over the last 60 years, molecular simulations have developed into a standard biophysical tool to study the behavior of (bio)molecules at a resolution that is difficult to achieve experimentally. Studying the interactions between proteins and small molecules is of high relevance in drug design, where the binding free energy of drug candidates is central to activity of compounds. The challenge in calculating free energies lies in the appropriate description of all actors and effects, both in terms of energy and entropy. At the same time, computer simulations offer pathways to compute molecular properties that are impossible experimentally. For instance, physically relevant free-energy differences can be calculated via simulations of unphysical reference states, an approach we exploit in the accelerated enveloping distribution sampling (A-EDS) method that we developed in recent year to screen for optimal protein-ligand interactions [1-3].

[1] J.W. Perthold, D. Petrov, C. Oostenbrink. *J. Chem. Inf. Model.*, **2020**, *60*, 5395 – 5406. doi: 10.1021/acs.jcim.0c00456/

[2] O. Gracia Carmona and C. Oostenbrink. *J. Chem. Inf. Model.*, **2023**, *63*, 197 – 207. doi: 10.1021/acs.jcim.2c01272

[3] O. Gracia Carmona, M. Gillhofer, L. Tomasiak, A. de Ruiter, C. Oostenbrink. *J. Chem. Theory Comput.*, **2023**, *19*, 3379 – 3390. doi: 10.1021/acs.jctc.3c00109