Contribution ID: **46** Type: **Poster Communication**

A computational study of the mode of action of the DAD photoswitch in the NaV1.5 channel

Wednesday 6 September 2023 19:15 (20 minutes)

Azobenzene derivatives are becoming increasingly popular in pharmacology due to their improved selectivity based on trans-cis isomerization upon light irradiation. In the context of ion channels, one of the conformations may block ion conduction, while the other allows it. We studied an azobenzene derivative, DAD, designed with the aim of avoiding excitation wavelengths in the UV region of the electromagnetic spectrum. Two binding pockets of DAD in the cardiac sodium channel were obtained by means of Gaussian Accelerated Molecular Dynamics combined with free-energy calculations, showing that the most relevant ligand-protein interactions were of electrostatic nature. Comparison of the absorption spectra reveals similar results in water and in the binding pockets. The photoisomerization mechanism is analogous to azobenzene: it begins with the population of the second excited state (S2), fast crossing to S1 and relaxation along the rotation of the azo dihedral to a S1/S0 conical intersection that connects the trans and cis geometries on the ground state. However, it seems more favourable in the case of DAD.

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Session Classification: Poster Session