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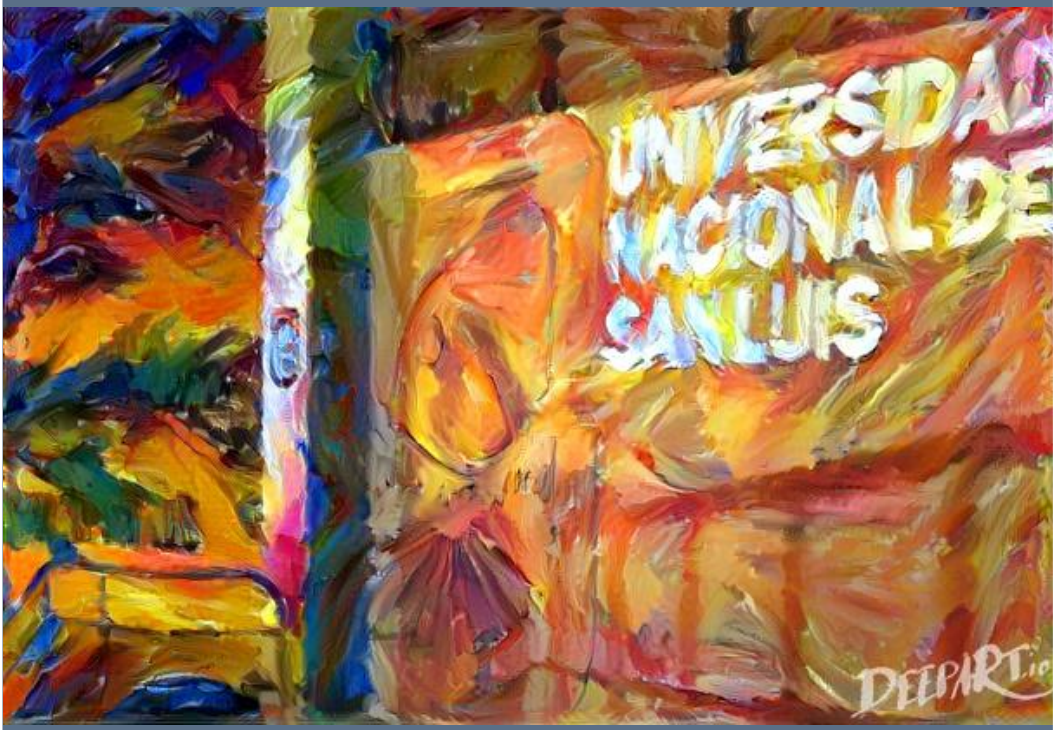

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Simulations of the optical activity of voltage sensitive probes in polarized model membranes

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Voltage sensitive dyes (VSD) are widely used to determine membrane potential both in imaging diagnosis field and in scientific research. However, their application is limited by their sensibility and rate of response [1].

We are developing a thorough computational study of optically active molecules sensitive to membrane potential. As sample cases, we chose di-3-ANEPPDHQ, widely used for *in vitro* determinations [2]; and indocyanine green (ICG), an infrared fluorescent dye with FDA approval for medical use [3]. The mechanism of response of these chromophores is basically electrochromic, i.e. the stationary electronic states responsible for the optical activity (light absorbance and fluorescence emission) are sensitive to the external electric field. Thus, the challenge in this kind of study is to combine the electronic description of the dye, prohibitive over a couple of hundreds atoms, with the complex condensed phase of biological systems, which is in turn determinant of the external field magnitude and fluctuations.

We built atomistic models for the probes embedded in polarized membrane bilayers, and performed enhanced sampling calculations to determine the potential of mean force for membrane insertion, in order to establish the energetics of the partition process and to deconvolute the configurational contribution to the optical response.

We appealed to the time-dependent resolution of Kohn-Sham equations (TD-DFT) and hybrid potentials from quantum mechanics and molecular mechanics (QM/MM) to calculate the absorption spectra of the VSDs. We obtained the spectral shifts corresponding to different configurations of the dye in the bilayer: adsorbed and inserted, and differential response to the transmembrane potential. The long-term objective is to develop a methodology that allows the study and molecular optimization of CSVs.

References

[1] L Loew, Membrane Potential Imaging in the Nervous System: Methods and Applications (Springer-Verlag New York, 2010).

[2] JA Fisher, et al. , J. of Neurophysiology 99 , 1545 (2008).

[3] JS Treger, MF Priest, R Lezzi, F Bezanilla, Biophys. J. 107, L09 (2014).

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