Insights into Mechanism of Proton Translocation Assisted by Membrane Proteins

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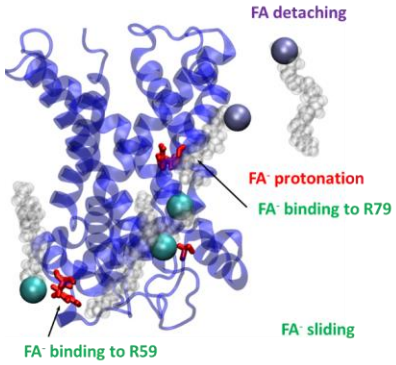
Molecular dynamics simulations are a powerful tool for the investigation of complex systems in atomistic detail. In the last 20 years, these methods have been extensively used to study biological systems, such as DNA, proteins and model biological membranes. In this study we focus on the latter subject, particularly on the phenomenon of membrane permeation, which governs biological processes and underlying cell mechanisms. In this respect, while the neutral species can quite readily permeate across the cell bilayer, the unmediated transport of charged species is usually slow and does not occur on biologically relevant timescales. [1] The transport of such species is thus generally occurring via various supporting mechanisms which commonly involve membrane proteins, used to arbitrate and assist their passage through lipid bilayers. [2]



One of the most prominent membrane proteins located in the inner mitochondrial membrane is adenine nucleotide transporter 1 (ANT1). While its main function is transport of ADP and ATP nucleotides, ANT1 is also found to catalyze translocation of other charged species through inner mitochondrial membranes in the ATP independent manner. [3] In this work, we use classical MD simulations to obtain a detailed insight into the translocation of protons assisted by fatty acids across model bilayers with embedded ANT1 protein. In particular, we use both unbiased MD simulations and "state-of-the-art umbrella sampling along the pathway" technique to investigate this phenomenon. Our results led us to suggest a novel mechanism of proton transport assisted by fatty acid and catalyzed via ANT1 protein.

[1] S. Škulj, M. Vazdar, *Phys. Chem. Chem. Phys.*, **2019**, *21*, 10052-10060.
[2] N. P. Bethel, M. Grabe, *Proc. Natl. Acad. Sci. U. S. A.*, **2016**, *113*, 14049-14054.
[3] Y. Wang, E. Tajkhorshid, *Proc. Natl. Acad. Sci. U. S. A.*, **2008**, *105*, 9598-9603.