SFB 1078 Protonation Dynamics in Protein Function

Colloquium

Mon, **Nov. 28,** 2022

15:15 & 16:30

Freie Universität Berlin
Physics Department
Hörsaal B
(Arnimallee 14, 14195 Berlin-Dahlem)

Dr. Patricia Saura – *Institute of Biochemistry and Biophysics, University of Stockholm, SE*

Molecular principles of water-gated proton transfer reactions in cytochrome c oxidase

Cytochrome c oxidase (CcO) functions as the terminal electron acceptor in the respiratory chain, catalyzing the reduction of oxygen to water that couples to proton pumping across the membrane. However, the molecular principles of how CcO sorts protons along the *pumping* and *chemical* pathways, and how the proton uptake is regulated, remain poorly understood. In this talk, I will present our recent results on the molecular gating principles in proton transfer reactions in CcO. Using a combination of large-scale quantum chemical DFT calculations, hybrid quantum/classical (QM/MM) simulations, and molecular dynamics (MD) explorations, we show that redox reactions coupled to conformational changes generate oriented electric fields around the CcO active site that direct the protons along the *chemical* and *pumping* pathways. These principles apply similarly to proton transfer along the proton-conducting D- and K-channels. By combining our multiscale computational approach with biophysical and structural experiments, we also show that proton uptake via the K-channel is modulated by lipid interactions at regulatory sites that couple to key conformational changes at the K-channel entrance. Our mechanistic principles show distinct similarities with other energy converting enzyme complexes, suggesting that electric fields modulate catalysis in enzyme reactions, and the relevance of lipid interactions in bioenergetic complexes.

Prof. Boris Musset *– Paracelsus Medizinische Privatuniversität, Nürnberg, DE*

The voltage-gated proton channel (H_V) discovers its family, and a detailed investigation of pH-dependent gating.

The voltage-gated proton channel H_V has been found in a multitude of species ranging from humans, over fish, insects, algae, to acidians and even dinoflagellates. In all these species exclusively a single gene coded for the voltage-gated proton channel. The one gene per species rule appeared to be a dogma representing voltage-gated proton channels. Recently, we discovered the genes of three paralogs of H_V (H_V1, H_V2, H_V3) in *Aplysia californica*, a common model organism of neurobiology. All three paralogs have distinct biophysical properties. Intriguingly, AcH_V3 permeates a prominent proton selective leak current. The voltage gating of H_V is strongly coupled to the pH gradient across the plasma membrane. Recently, we investigated pH-dependent gating of H_V1 using constant pH MD simulations in symmetrical and asymmetrical pH conditions across the membrane. In our study, the *pKa* of every titratable amino acid was assessed in single simulations. The simulations show initial conformational changes between a deactivated and activated state of H_V1, solely by changing the inside or outside pH.

Coffee and tea will be available during the break at 16:15. www.sfb1078.de

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