pH-dependent gating of the human voltage-gated proton channel

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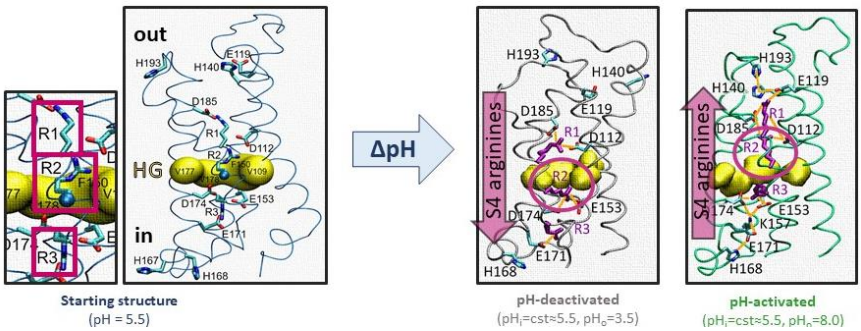
Gating of the voltage-gated proton channel H_V1 is strongly controlled by pH which evidently involves the sidechains of titratable amino acids. Despite experimental investigations to identify the amino acids involved in pH sensing only few progress has been made, including one histidine that is involved in sensing intracellular pH. We have used constant pH molecular dynamics simulations in symmetrical and asymmetrical pH conditions across the membrane to investigate the pH- and ΔpH-dependent gating of the human H_V1 channel. Our simulations captured initial conformational changes between a deactivated and an activated state of the channel induced solely by changes of the pH. The pH-dependent gating is accompanied by an outward displacement of the three S4 voltage sensing arginines (R1-R3 in figure below) that moves the second arginine past the hydrophobic gasket (HG) which separates the inner and outer pores of the channel. H_V1 activation, when outer pH increases, involves amino acids at the extracellular entrance of the channel that extend the network of interactions from the external solution down to the HG. Whereas, amino acids at the cytoplasmic entrance of the channel are involved in activation, when inner pH decreases, and in a network of interactions that extend from the cytoplasm up to the HG.



[1] Jardin C, Ohlwein N, Chaves G and Musset B. The pH-dependent gating of the human voltage-gated proton channel from computational simulations. *Phys Chem Chem Phys*. **2022**, *24*: 9964-9977. doi: 10.1039/d1cp05609c