The importance of water in biology - an example of receptor function and implications for optogenetics

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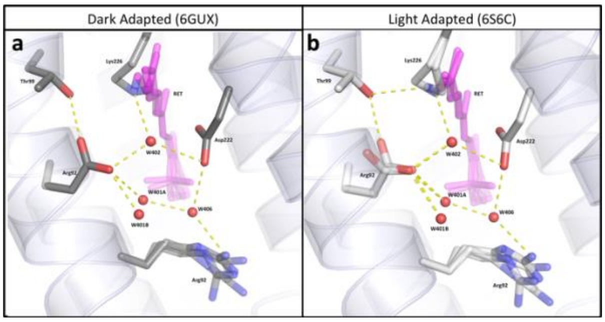
Water, in its many states, has a pivotal role in biology. But resolving it at the molecular level has been a challenge. Here, we resolve and describe how water determines the way in which an external stimulus, light in this example, intimately controls how the stimulus is conformational changes in membrane receptors in response to a stimulus, and capturing their functionally relevant dynamics, is very challenging. Over the years we have addressed this challenge using a range of spectroscopic approaches[1,2,3] on functionally competent photoreceptors, often in their natural membranes[4] or Lipodisqs™ [5,6]. More recently, we have complemented this work with functional studies, mass spec characterization[7] and very high resolution (1.07Å) crystallography[8,9,10] , as well as photo-induced x-ray, free electron laser studies (XFELS), without the use of detergents and including natural lipids. This high-resolution information reveals waters and their importance in both receptor activation-desensitization and QM(SCC-DFTB)/MM MD trajectories give information about the activation process. The system studied is achearhodopsin-3 (AR3), a photoreceptor utilized widely in optogenetics despite the lack of structures until now. We suggest that the different arrangement of internal water networks in AR3 is responsible for the faster photocycle kinetics compared to homologs – AR3 is ~10x more efficient than bacteriorhodopsin at current generation. These insights may well have generic implications for other receptors.



(1). Higman *et al*., (2011) *Angew. Chemie* 50(36):8432
(2). Dijkman *et al*., (2018) *Nature Comms*. 9:1710
(3). Dijkman *et al*., (2020) *Science Advances*, 6:33
(4). Lavington & Watts (2020) *Biophys. Rev*. 12:1287
(5). Juarez *et al*., (2019) *Chem. Phys. Lipids* 221:167
(6). Sawczyc *et al* (2023) Eur. Biophys J. 52:39
(7). Hoi *et al*., (2021) *Nano Letters*, 21(7):2824
(8). Axford *et al*., (2022) *Acta Cryst* D78:52
(9). Juarez *et al* (2021) *Nature Comms*. 12:629
(10). Birsh et al., (2023) J. Appl. Cryst. 56:1361