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Proton transfer and water exchange in the green fluorescent protein[1]

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The green fluorescent protein (GFP) is the only naturally occurring protein in which excited-state proton-transfer has been identified. Upon excitation, a proton is ejected from its chromophore, travelling through the "privileged water molecule" (PWM) and Ser205 to Glu222, on a 10 ps timescale or faster. However, time-resolved fluorescence from the chromophore exhibits a $t^{-\alpha}$ power-law decay extending into the ns regime. With increasing temperature, α switches from 1/2 (below 230 K) to 3/2 (above it). This has been interpreted as pseudo one-dimensional proton hopping along an internal "proton wire," with an activated process that opens a "doorway" for proton escape to solution at the higher temperatures [1]. To identify such putative pathways, we have developed a computer code mapping all "proton wires" within a protein structure. Applying it to a X-ray GFP structure of 0.9 Angstrom resolution [2], a proton wire indeed continues from Glu222 along the axis of the GFP "barrel," connecting to a negatively charged surface patch (a "proton collecting antenna"?). This might explain the $t^{-1/2}$ behavior. However, a direct escape pathway opening from the chromophore to solution is not readily identified in the X-ray structure. Here we report molecular dynamics results showing that the PWM escapes to solution on the 100 ps timescale. This occurs by fluctuations of the beta-sheet, creating an opening through which water molecules can leave and enter the protein. The exact pathway of the PWM on its way in and out has been identified, as well as the water-exchange kinetics that follows a stretched-exponential time behavior.

[1] Agmon, N. *J. Phys. Chem. B* 2007, **111**, 7870.
[2] Shinobu, A.; Palm, G. J.; Schierbeek, A. J.; Agmon, N. *J. Am. Chem. Soc.* 2010, **132**, 11093.

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