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CONFORMATIONAL SPACE OF THE TRANSLOCATION DOMAIN

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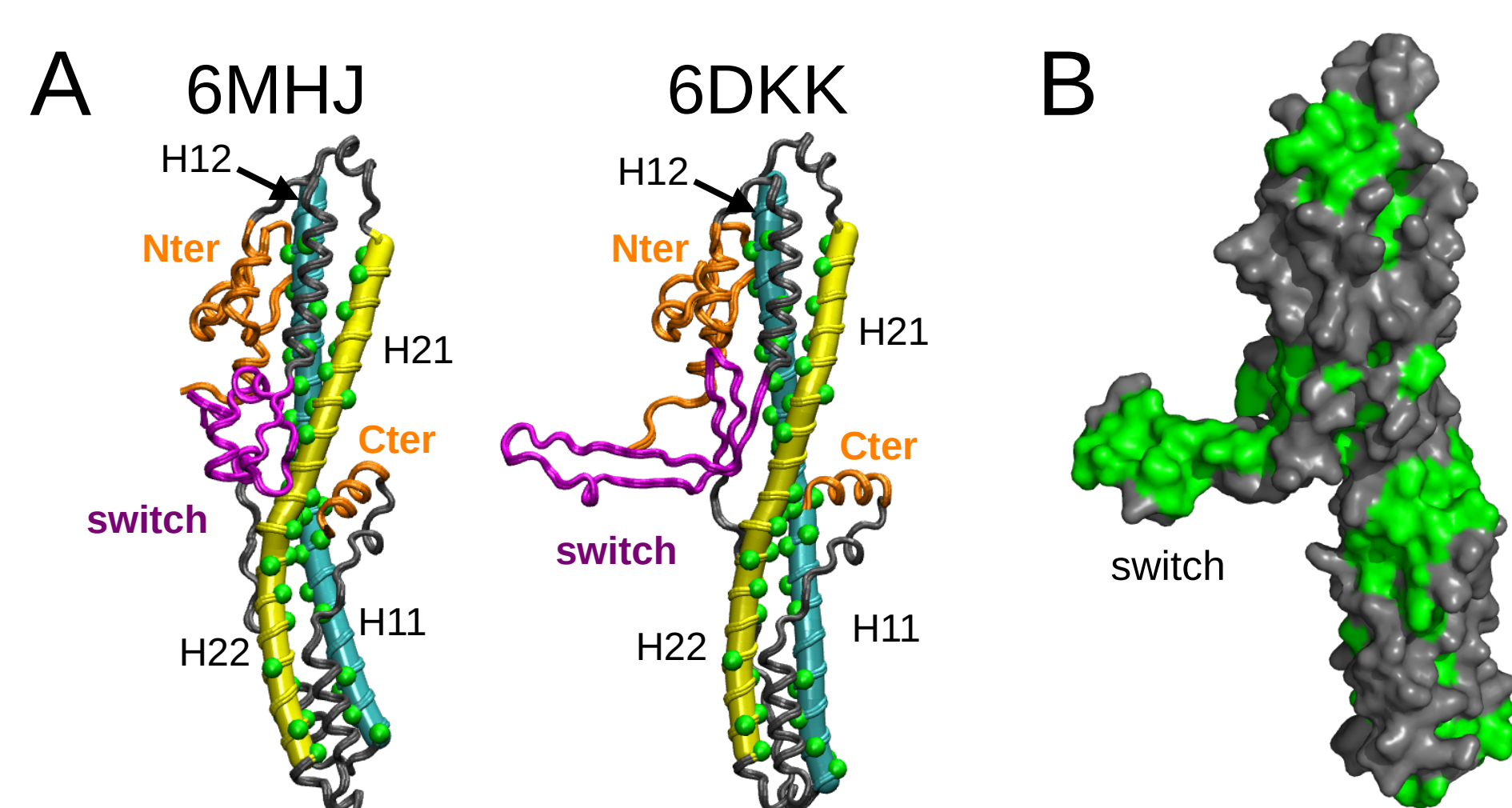
SolvATE2023 6th Meeting of the SolvATE Network. November 6-7, 2023. Nancy, France.



Abstract

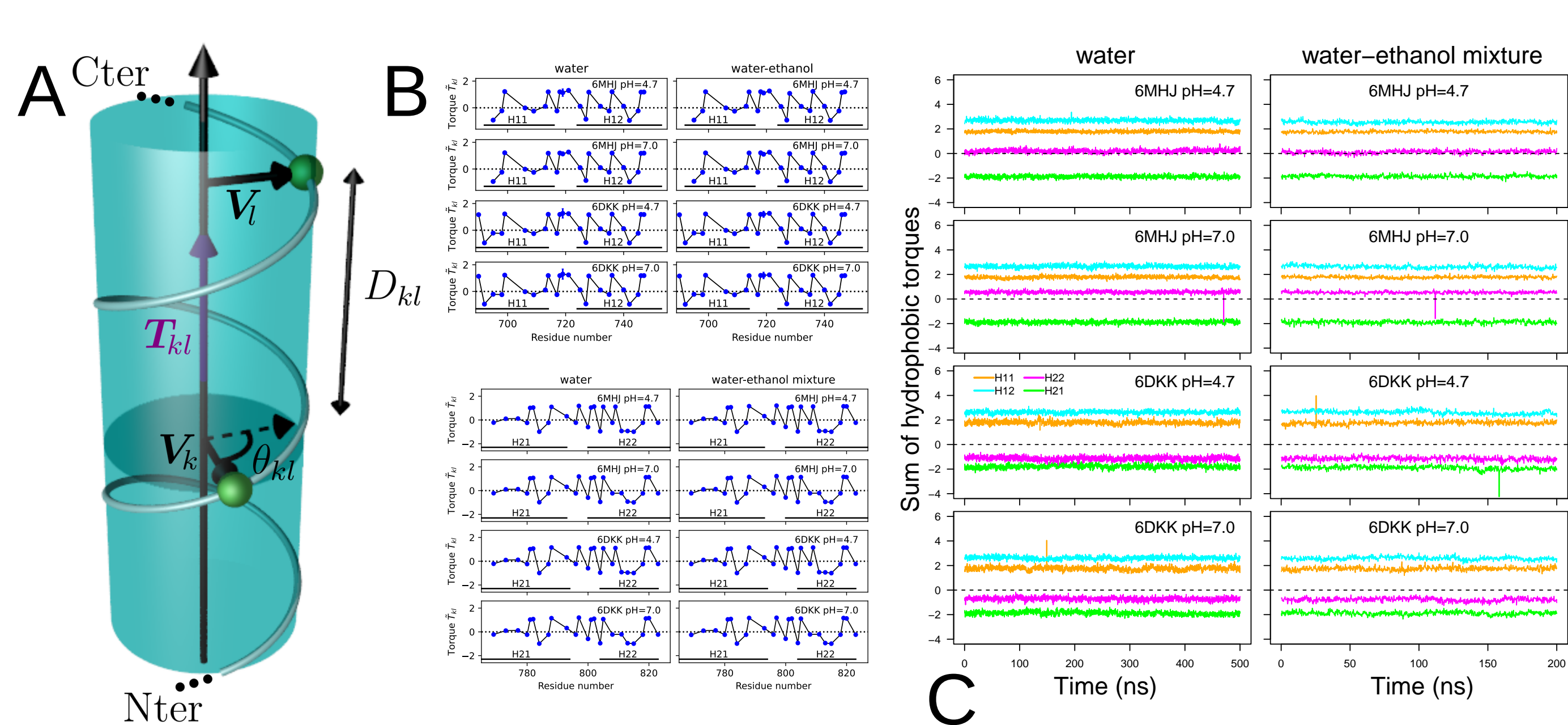
The botulinum neurotoxins (BoNTs), among the most powerful toxic compounds found in nature, are formed of various domains [1]. The underlying toxicity mechanism is based on a sequence of molecular events, in particular the translocation of the catalytic domain through the membrane of a neurotransmitter vesicle into the cytosol of the neuron. A recent structural study [2] of the isolated translocation domain of BoNT suggests a model for the interaction of this domain with the membrane, based on the transition of the α helical switch towards a β hairpin. The present work investigates this proposition and the consequences for the interaction between toxin and membrane using atomistic simulations in conjunction with the mesoscopic *Twister* model [3]. The various conformational mobilities of the translocation domain observed according to the starting conformation, protonation and solvent type, as well as the effect of the membrane examined in an implicit way by comparing water and water-ethanol solvents leads to the conclusion that the protruding switch hairpin is essential for the interaction between the protein and the membrane and that its appearance modifies the internal dynamics and the effect of hydrophobicity on the whole protein. In addition, the central two α helices, helix1 and helix2, forming two coiled-coil motifs, are analyzed in the framework of the *Twister* model, in which the deformation of the membrane by the protein is caused by the presence of local torques due to the asymmetry of the hydrophobic residues on helices. Different torque distributions are observed depending on the α or β conformation of the switch and permit to propose an origin for the mechanism opening the membrane.

The translocation domain



A. X-ray crystallographic structures determined for the translocation domain (PDB entries: 6MHJ, 6DKK) (Lam et al., 2018). The tubes generated by Bendix (Dahl et al., 2012) on the α helices 1 (cyan) and 2 (yellow) are shown for the two PDB structures. The hydrophobic residues in these helices are represented by ball colored in green. The switch is colored in magenta, and the N terminal domain and the C terminal α helix in orange. The helix halves H11, H12, H21 and H22 are indicated with labels. B. Structure 6DKK represented as surface. The hydrophobic residues GLY, ALA, VAL, LEU, ILE, PRO, PHE, MET and TRP are colored in green.

The *Twister* model

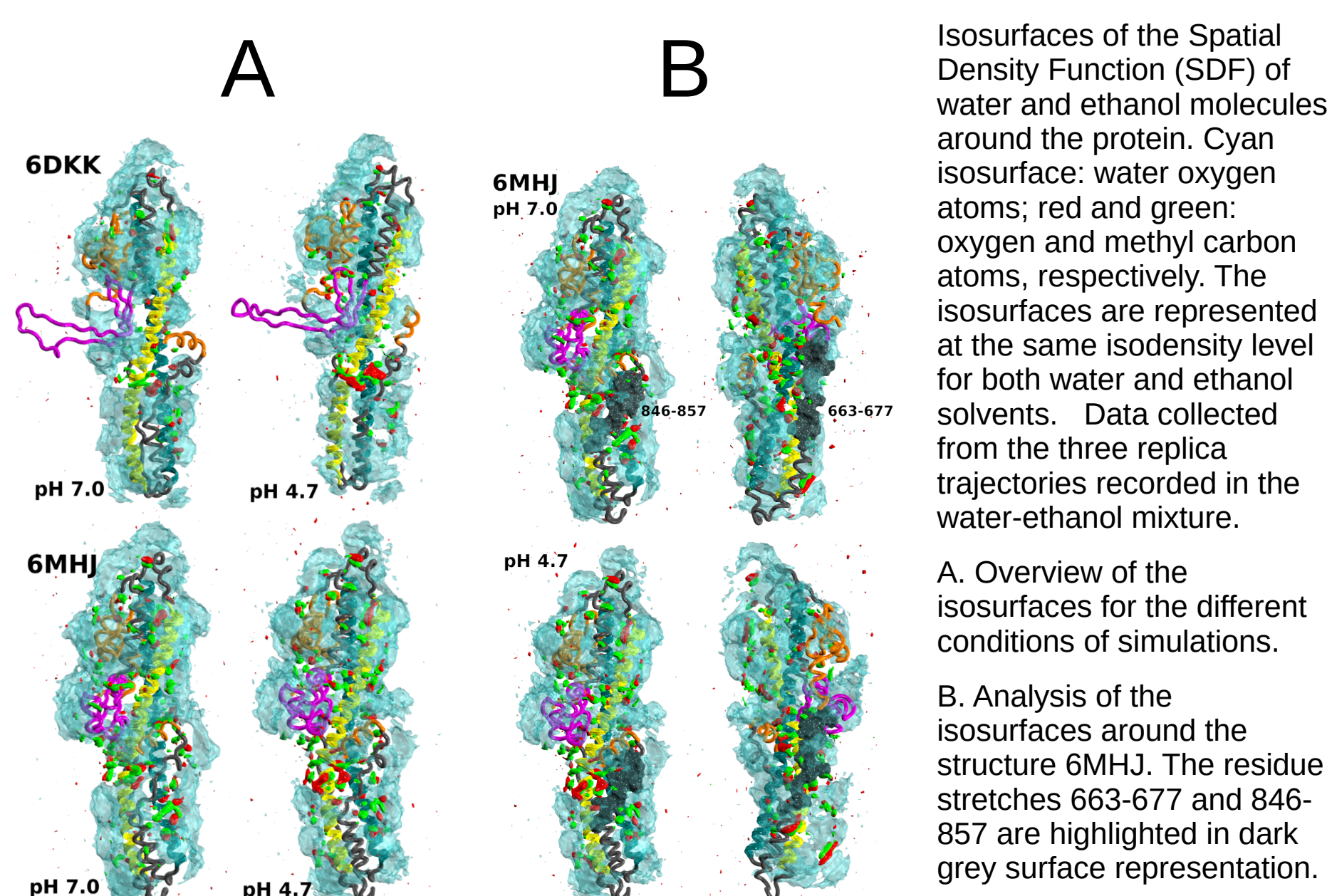


A. Geometry of the coarse-grained α helix describing the calculation of the torque T_{kl} (in purple). The α helix is represented by a transparent cylinder, the helix axis is parallel to the torque. The two vectors V_i and V_k are perpendicular to the helix axis and connect the axis to the C α atom of each residue (in green). The projection of V_i next to V_k (dashed vector) is drawn in order to illustrate the definition of θ_{kl} .

B. Local torque values T_{kl} along the α helix 1 (upper set of panels) and 2 (lower set of panels). Values averaged along the first trajectory replica and their standard deviations are plotted as a function of the residue number. Standard deviations are smaller than the size of the data points except for residue ALA-719 in helix 2.

C. Torque values averaged along the residues 695-713 (H11: orange), 730-748 (H12: cyan), 766-784 (H21: green) and 801-819 (H22: magenta) and plotted along the time. H12 and H21 are interacting through a coiled coil motif, as well as H11 and H22.

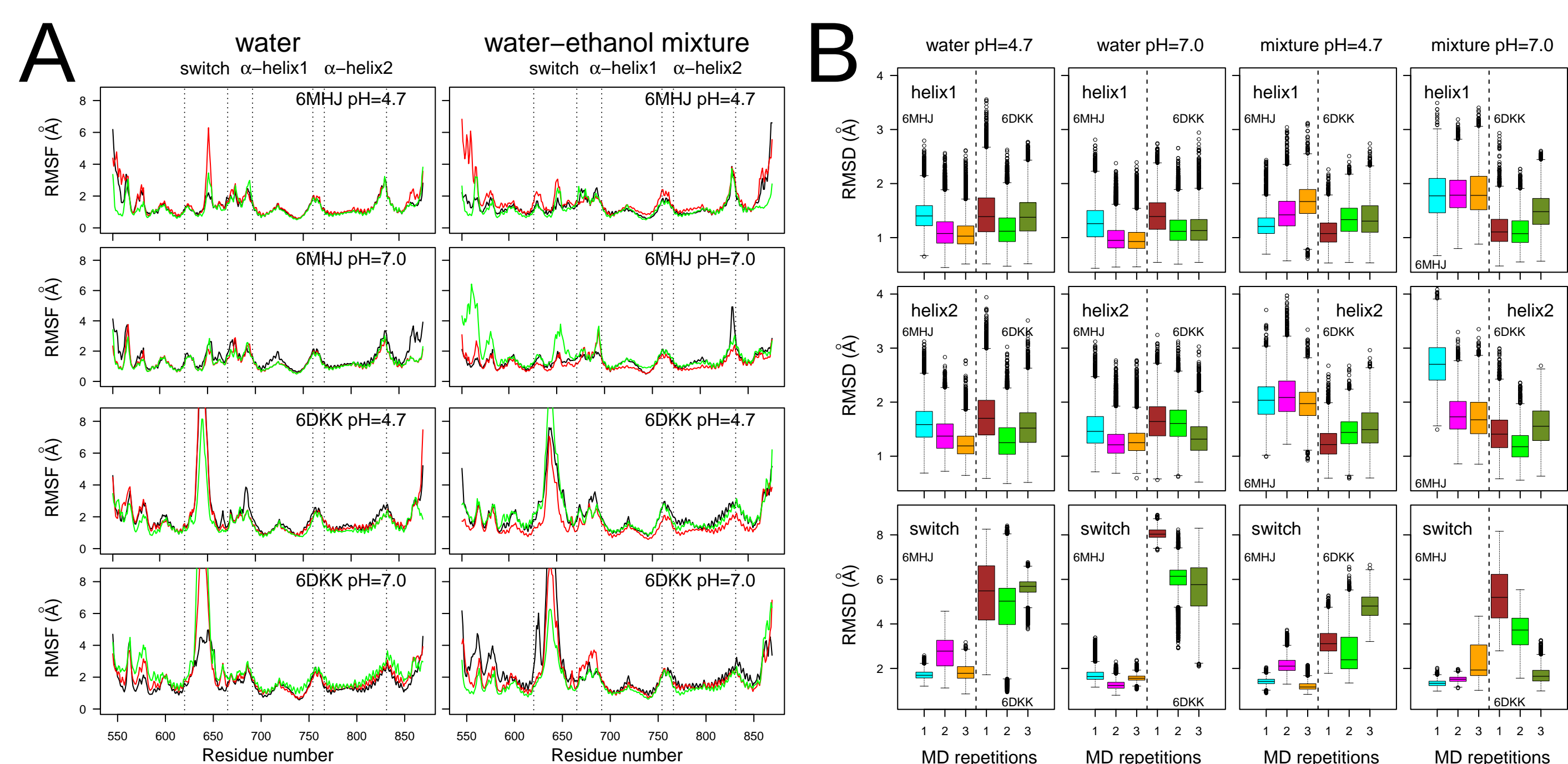
Distribution of ethanol molecules



Isosurfaces of the Spatial Density Function (SDF) of water and ethanol molecules around the protein. Cyan isosurface: water oxygen atoms; red and green: oxygen and methyl carbon atoms, respectively. The isosurfaces are represented at the same isodensity level for both water and ethanol solvents. Data collected from the three replica trajectories recorded in the water-ethanol mixture.

A. Overview of the isosurfaces for the different conditions of simulations.
B. Analysis of the isosurfaces around the structure 6MHJ. The residue stretches 663-677 and 846-857 are highlighted in dark grey surface representation.

Internal mobility



A. Coordinate root-mean-square fluctuations (RMSF, Å) calculated on the MD trajectories recorded on the two protein systems. Different colors correspond to different replicas. B. Distributions of coordinate RMSD (Å) for specific domains of the protein.

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