

## **Description of Additional Supplementary Files**

**Supplementary Data 1:** Summary of HDX-MS analyses and full list of the peptides obtained for different TRPV4 protein constructs.

**Supplementary Data 2:** Peptides analyzed by HDX-MS mapped on TRPV4-NTD sequence.

**Supplementary Data 3:** Summary of XL-MS analyses

**Supplementary Movie 1:** Atomistic MD simulation of core *G. gallus* TRPV4 ion channel in a lipid membrane

**Supplementary Movie 2:** Ensemble of TRPV4 IDR structures from MARTINI Simulations on the membrane, side view.

**Supplementary Movie 3:** Ensemble of TRPV4 IDR structures from MARTINI Simulations on the membrane, view from the cytosol.