Stabilization of the GluCl Ligand-Gated Ion Channel in the Presence and Absence of Ivermectin

Özge Yoluk,[†‡] Torben Brömstrup,[†‡‖] Edward J. Bertaccini,[§] James R. Trudell,[¶] Erik Lindahl[†‡‖*]

[†]Science for Life Laboratory, KTH Royal Institute of Technology and Stockholm University, Solna, Sweden; [‡]Theoretical and Computational Biophysics and Swedish e-Science Research Center, KTH Royal Institute of Technology, Stockholm, Sweden; [§]Department of Anesthesia, Palo Alto Veterans Affairs Health Care System, Palo Alto, California; ; [¶]Department of Anesthesia and Beckman Program for Molecular and Genetic Medicine, Stanford University School of Medicine, Stanford, California; and [‖]Center for Biomembrane Research, Department of Biochemistry and Biophysics, Stockholm University, Stockholm, Sweden

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*Correspondence: erik.lindahl@scilifelab.se

Supporting Information

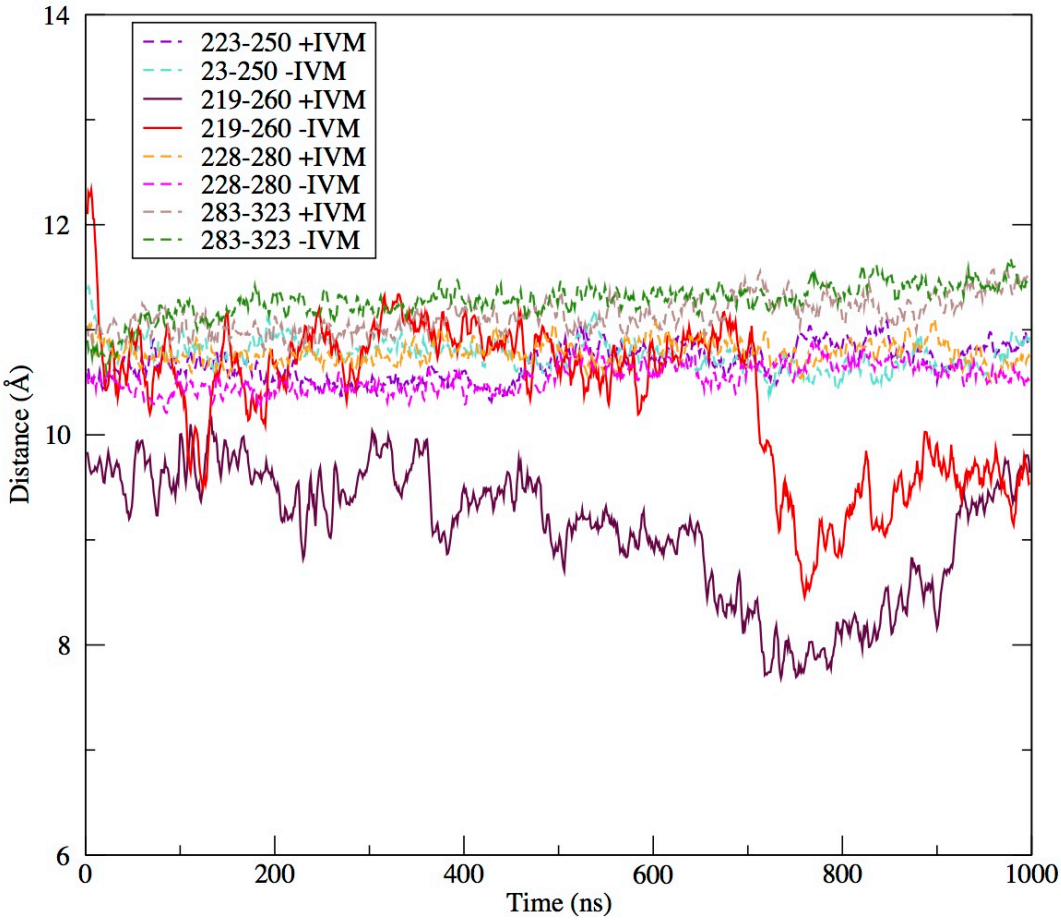

Fig. S1: Intrasubunit distances are not affected by ivermectin. The M1-M3 and M3-M4 intrasubunit distances (dashed lines) remained constant through simulations both with and without ivermectin, and were not affected by ligand binding. The distance M1-M2 was influenced by secondary structure fluctuations in the upper part of M2, but this too was shorter without ivermectin (dark brown) than with the ligand present (red).

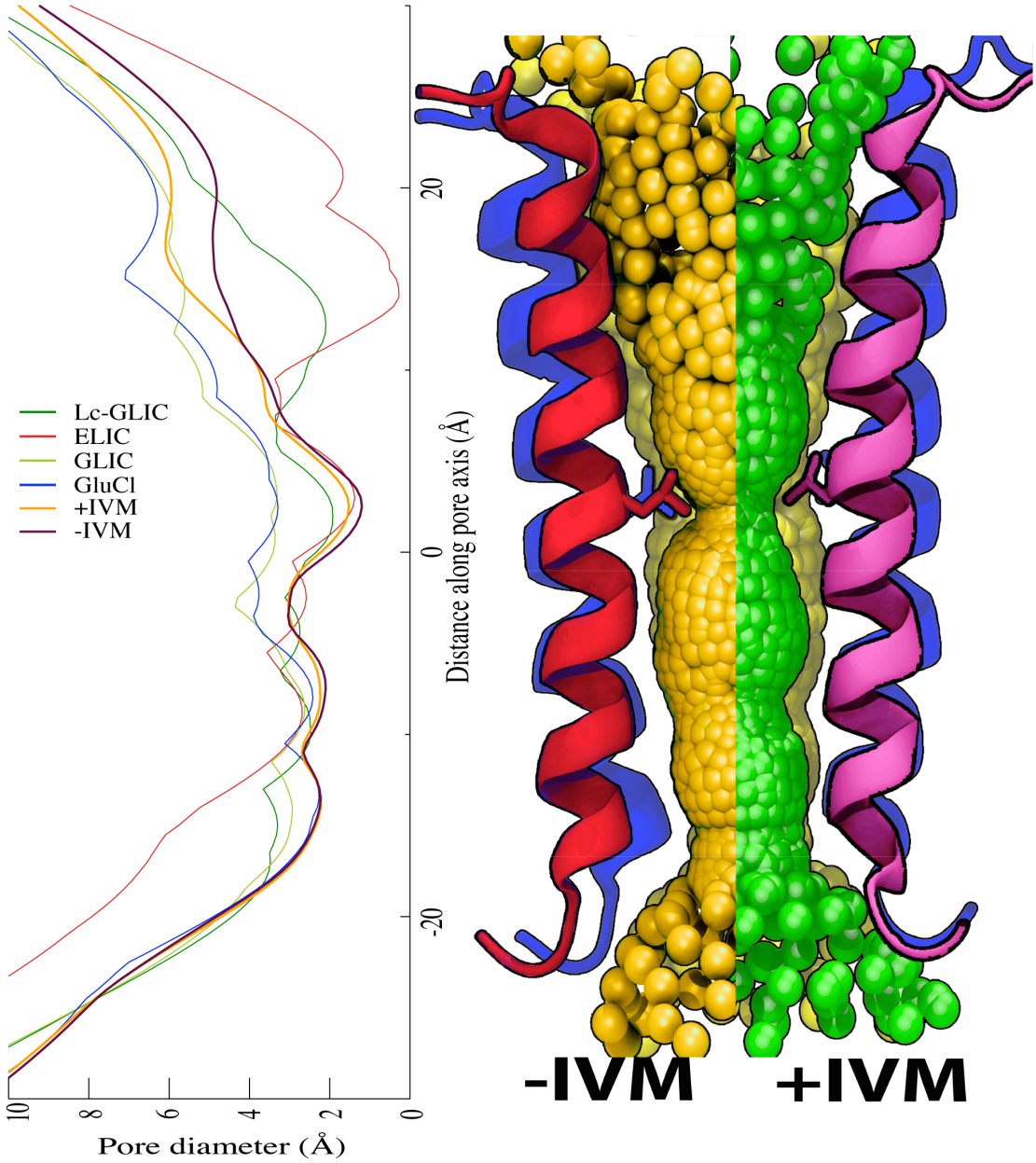

Fig. S2: Effect of ivermectin on the pore diameter. Left: Channel diameter as a function of the z-position (membrane normal direction) inside the pore, with the z-scale in units of Å. The zero position corresponds to the center-of-mass, which is almost exactly the 6' position. Lc-GLIC is the locally closed conformation of GLIC. Both present trajectories with (+)/without(-) ivermectin had the narrowest region at the 9' position region, with the ivermectin simulation being slightly more open. At the 16' position, the simulation with ivermectin explored conformations as open as GluCl and GLIC crystal structures, even after 1μs. In contrast, the simulation without ivermectin adopted a more closed state, though not as closed as the locally closed GLIC structure or ELIC. Right: Corresponding space-filling models of the pore computed from simulations with/without ivermectin, respectively.

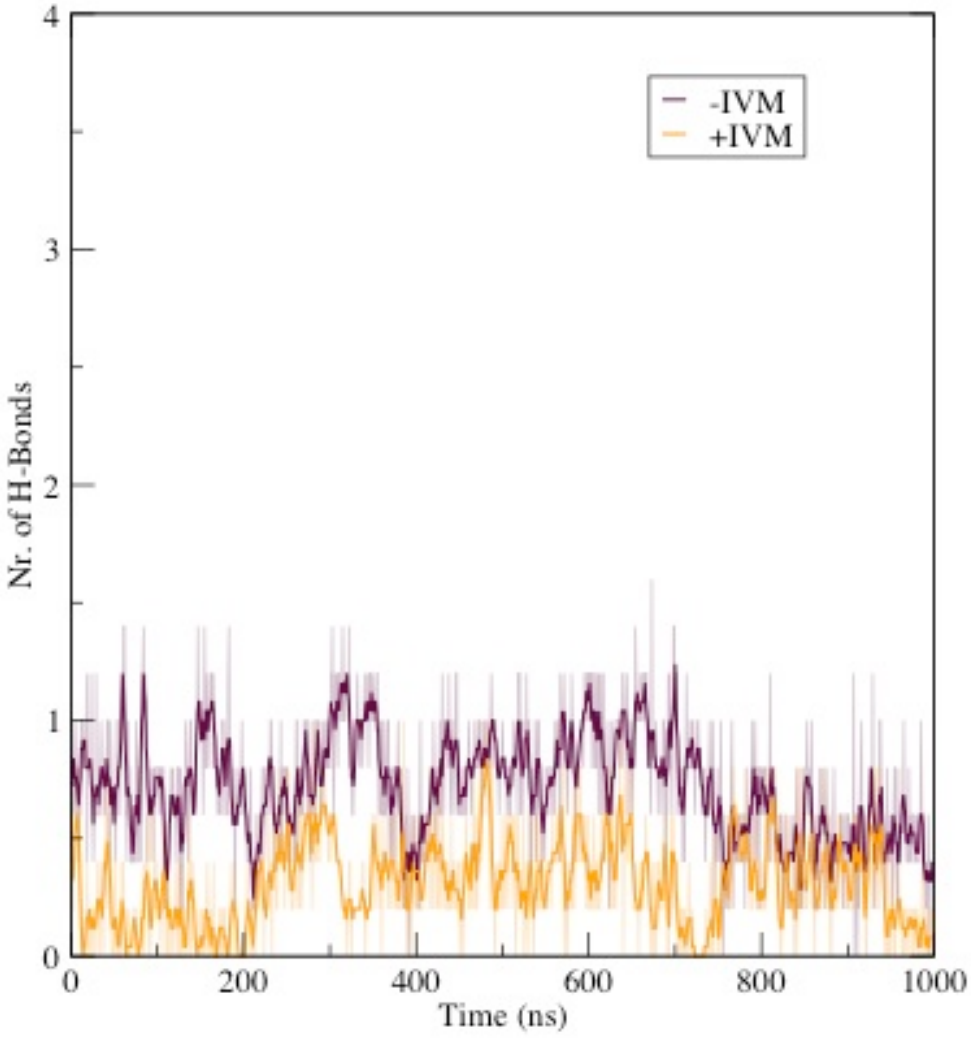

Fig. S3: Variation of hydrogen bonds between adjacent subunits. The total number of hydrogen bonds between residues 218-221 in helix M1 with residues in the adjacent subunit was clearly reduced by ivermectin binding (blue, +IVM) compared to simulations without ivermectin (yellow, -IVM).

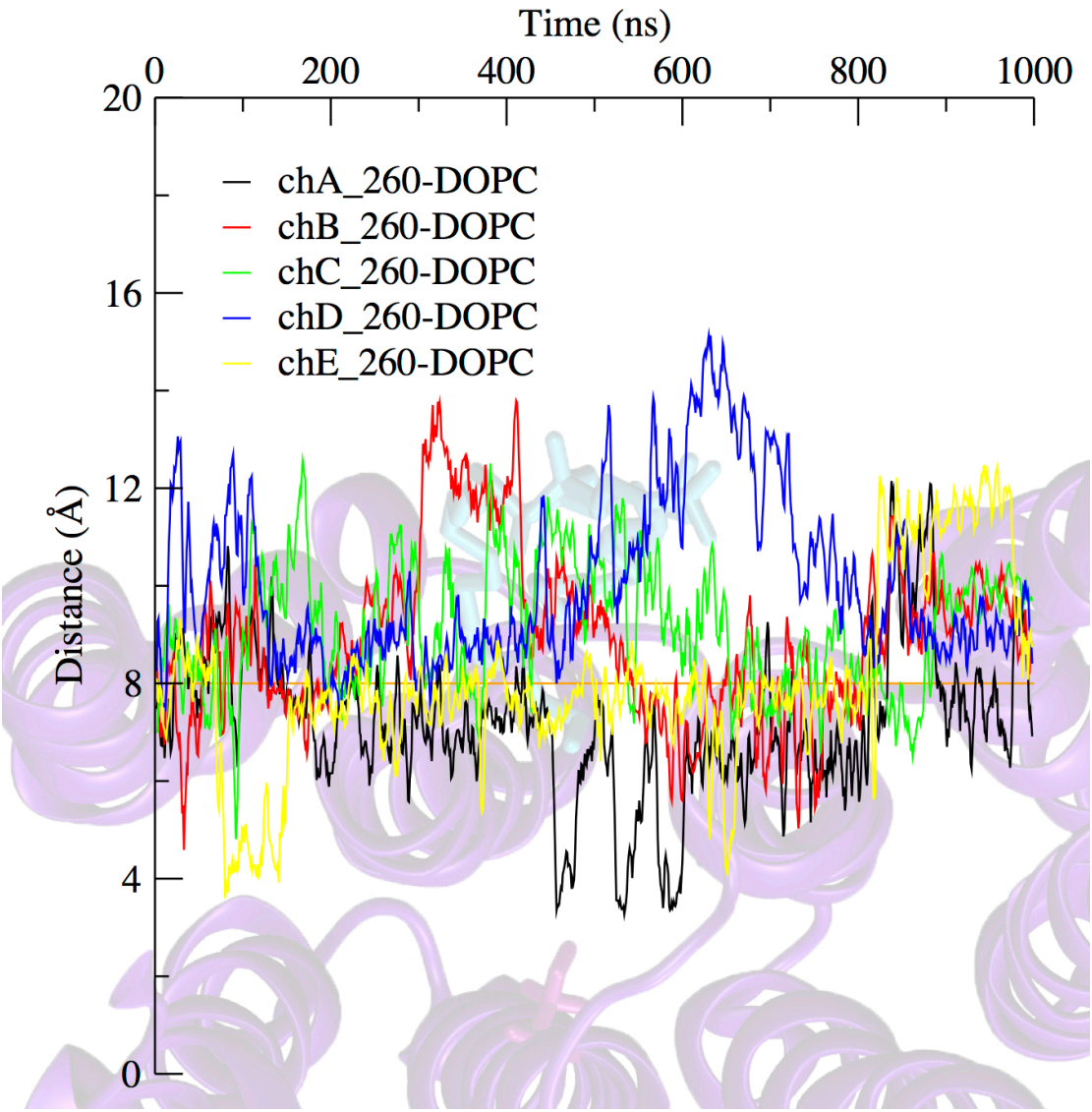

Fig S4. Lipid occupancy in the intersubunit binding pocket. The occupancy of the binding pocket measured as a distance to residue 260 (15'). When the distance between DOPC and 15' exceeded 8Å (marked with orange line), lipids were considered to be out of the binding pocket. Although towards the end of the simulation most of the binding pockets were not occupied, the process was rather dynamic with lipids unbinding and re-binding.

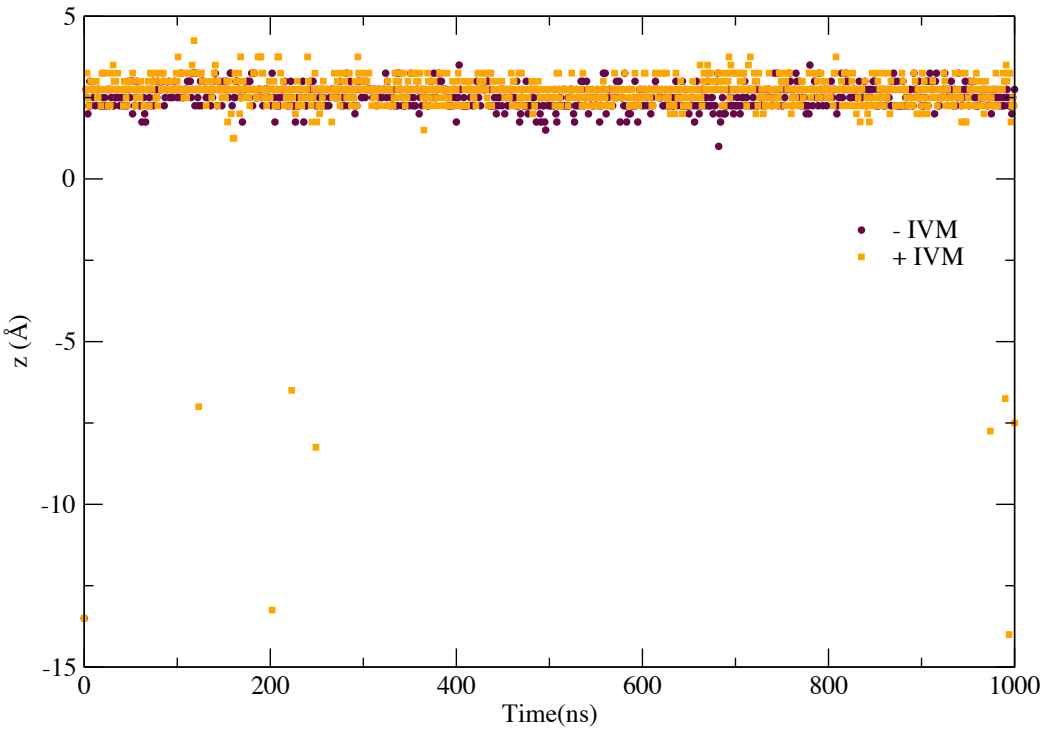

Fig S5. Position of the minimum radius in the channel. The zero coordinate refers the center-of-mass of the channel, roughly at the 6' position. When IVM was present, the position of the minimum radius shifted towards the intracellular part of the pore for a small fraction of the time (0.8%). This shift indicates a pattern similar to the crystal structure, where the minimum radius is also at the intracellular part of the pore.