Computational study of the pH-dependent interaction between the GALA peptide and a lipid membrane

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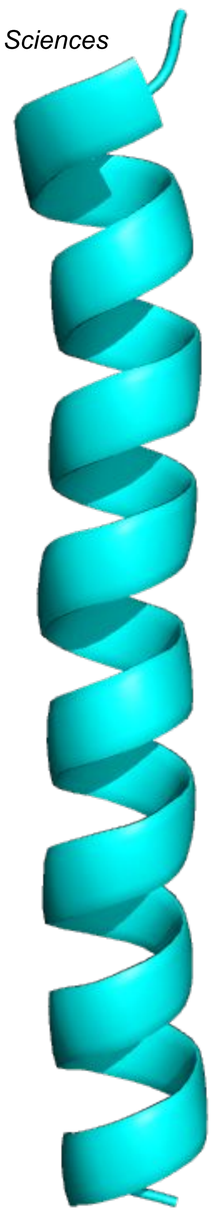
Introduction

The cell membrane consists of a lipid bilayer that selectively allows passage of chemical compounds. Membrane proteins can be inserted across the lipid bilayer and perform several functions, including acting as membrane transporters. Due to the membrane's unique biophysical properties, it can induce peptide/protein conformational, configurational and protonation changes that are very important to their functions.

GALA (**WEAALAEALAEALAEHLAEALAEALEALAA**) is a human designed peptide that, at slightly acidic pH values, tends to protonate/neutralize, which leads to membrane insertion as an α-helix [1]. In this structured conformation, GALA exhibits amphiphilic behaviour and is prone to a concentration-dependent aggregation in multimeric, barrel-like structures, with inward-facing polar residues.

In cells, these structures can form pores in the lipid bilayer, which can can lead to membrane potential decoupling and disruption.



Methods

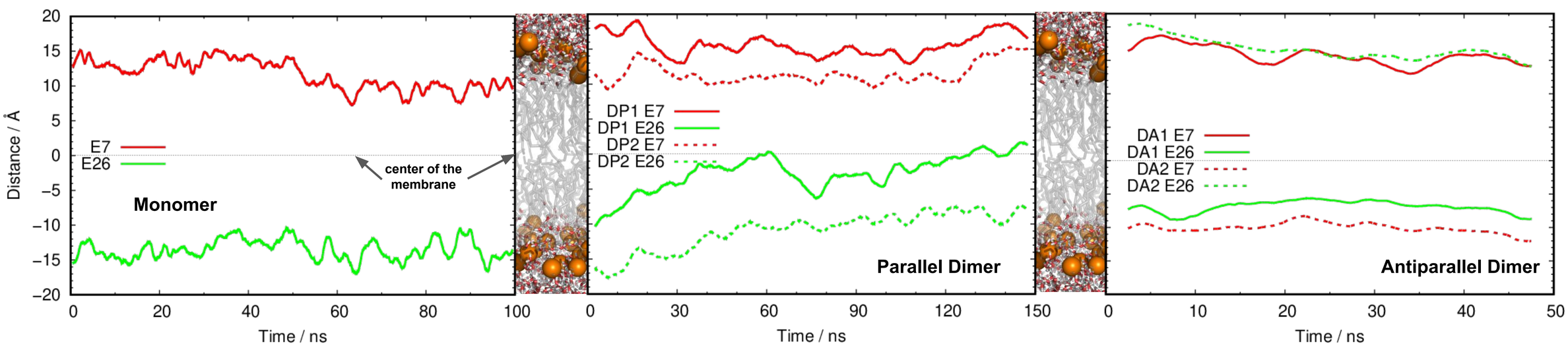
The constant-pH molecular dynamics (CpHMD) simulations were performed with GROMACS and the GROMOS 54A7 force field [2].

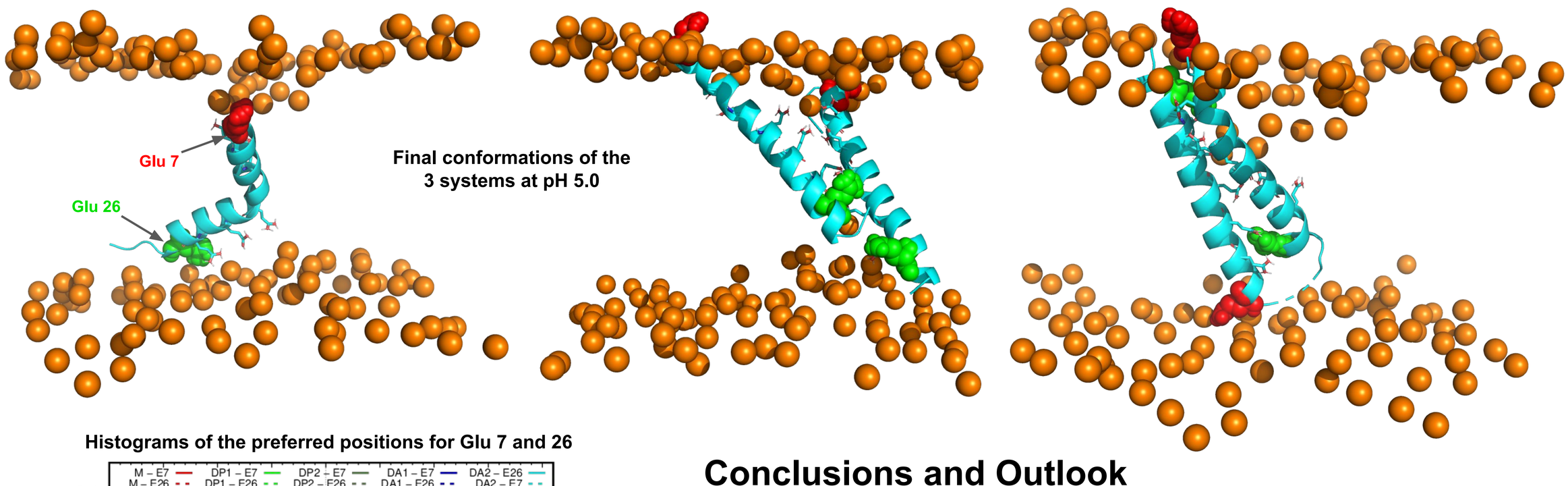
The preliminary systems built consisted of a single monomer (Mono), and two dimer setups, with parallel (Dimer P) and antiparallel (Dimer A) orientations. The peptides were inserted in a 160-lipid POPC membrane and the whole setup was minimized/initialized and equilibrated using CpHMD simulations at pH 5.0. The protonation bias is eliminated by running CpHMD simulations, while the conformation/configuration bias needs long equilibration steps to be circumvented.

Several properties were calculated to assert the system equilibration: DSSP helicity to assure that the helices do not unfold; the system area to test the lateral equilibration of GALA in POPC; and membrane insertion of key residues in the peptides to check their equilibration along the membrane normal.

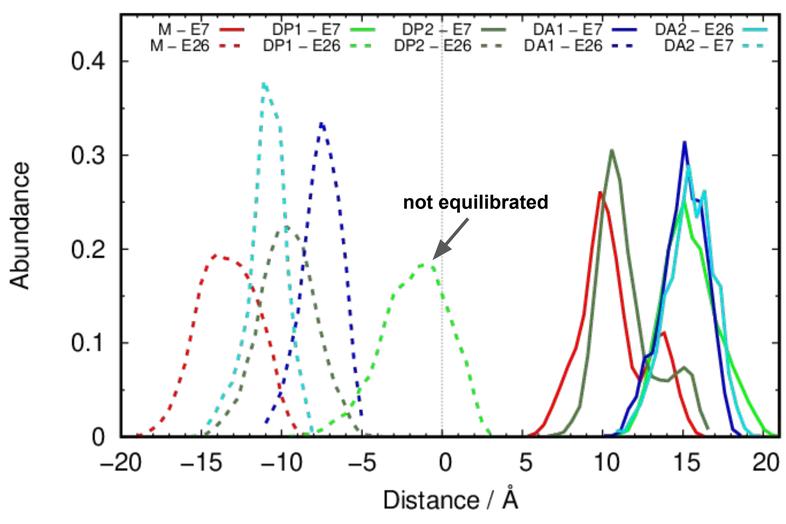
GALA equilibration in the lipid bilayer

Position of Glu7 and Glu26 relative to bilayer center





Histograms of the preferred positions for Glu 7 and 26



Conclusions and Outlook

- Most membrane and GALA properties (helicity or area per lipid) equilibrate relatively fast (data not shown). However, the peptide insertion along the membrane normal is a relatively slow process.
- In this preliminary work, we are running several long equilibration steps at pH 5.0 to mitigate any bias introduced in the system construction.
- The monomer and the antiparallel dimer seem to be equilibrated in the membrane, while, on the contrary, the parallel dimer is still changing.
- From these equilibrations, we will start CpHMD simulations at different pH values, including systems with larger number of monomers (3, 5 and 10).

Acknowledgements

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References

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[2] Hess, B., Kutzner, C., Van Der Spoel, D., & Lindahl, E., J. Chem. Theory Comput, 2008, 4(3), 435-447.