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PARAINFLUENZA FUSION PEPTIDE FORMS PORE-LIKE STRUCTURES WHEN AT HIGH CONCENTRATIONS INSIDE A MEMBRANE

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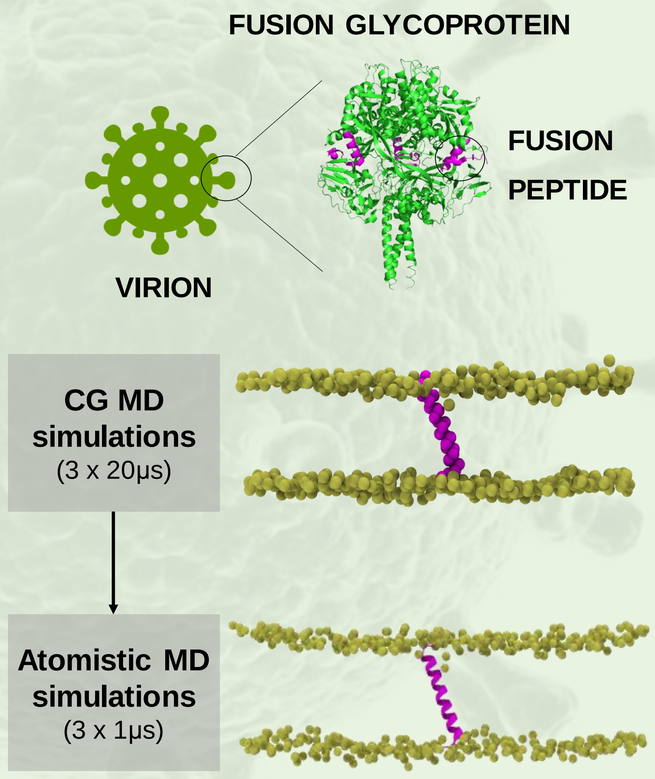
Background

Paramyxoviruses are enveloped viruses that must enter the host's cell to infect it. In the case of the parainfluenza virus, the cell entry process starts with the attachment to target receptors, followed by proteolytic cleavage of the fusion glycoprotein (F) protein, exposing the fusion peptide (FP) region.

The FP is responsible for binding and disrupting the target membrane. It is believed to play a crucial role in the fusion process, however, the mechanism by which the parainfluenza FP (PIFP) promotes membrane fusion is still unclear.



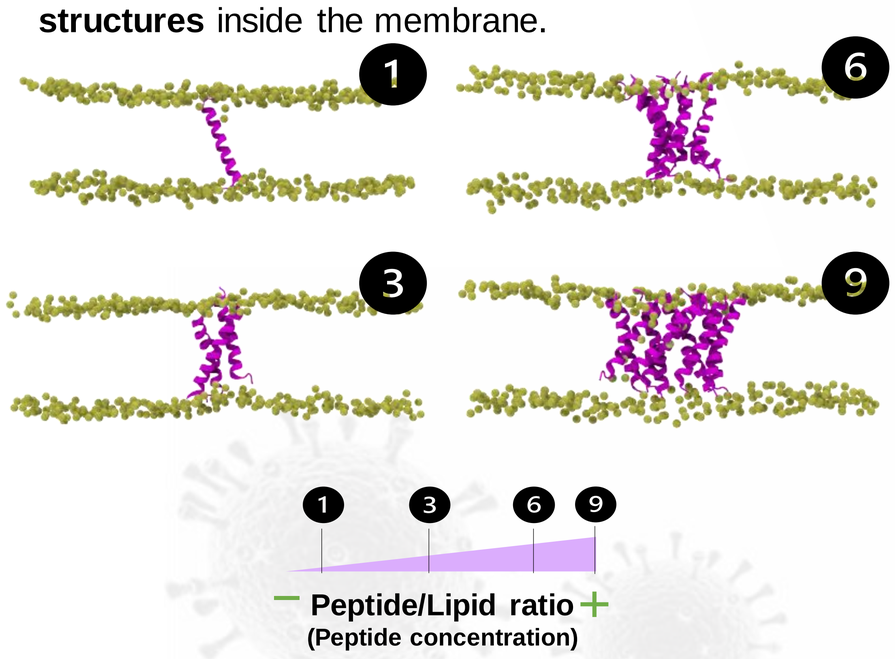
Workflow

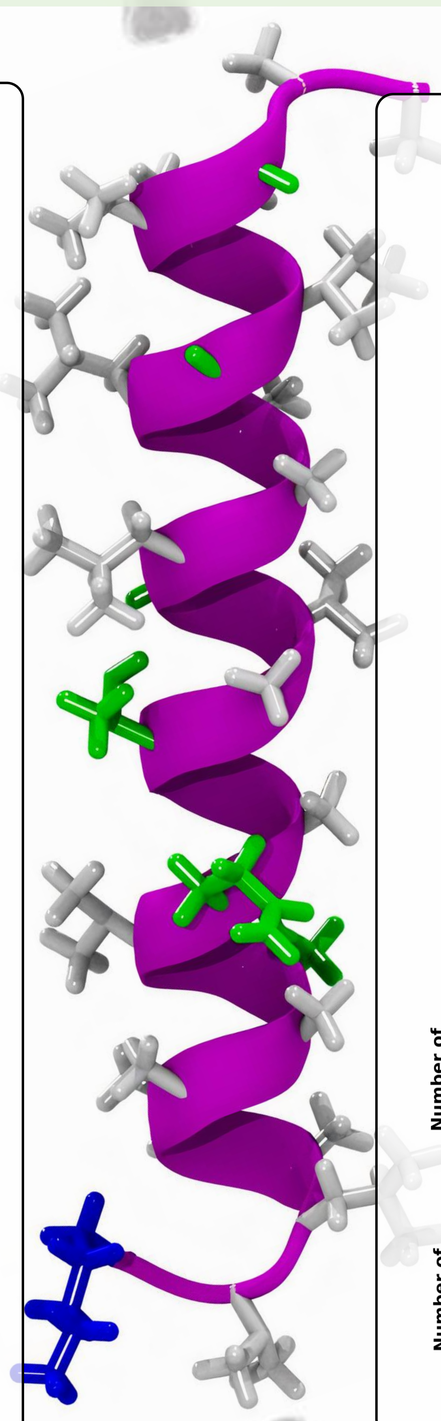
To elucidate the mechanism by which the parainfluenza PIFP promotes membrane fusion, we performed molecular dynamics (MD) simulations at different PIFP concentrations and spectroscopic experiments of the parainfluenza fusion peptide in membranes.

Coarse grain (CG) and atomistic (AA) simulations were performed with the GROMACS 2020.3 package, in triplicate, using the MARTINI 3.0 and CHARMM force field, respectively.

PIFP peptide-peptide interactions stabilize pore-like structures

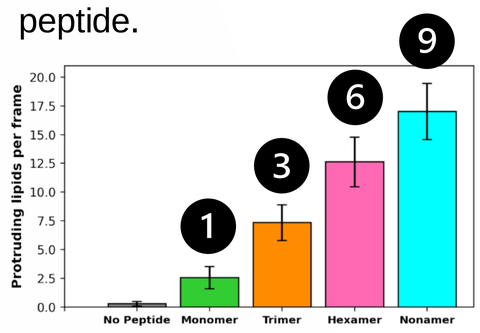
- CG simulations showed that the **PIFPs tend to aggregate** when inside a membrane.
- Increasing PIFP concentrations facilitate the formation of **peptide-peptide interactions** between the PIFP's hydrophobic and polar residues.
- The stable interactions between the peptides are of upmost importance for the assembly of **pore-like structures** inside the membrane.

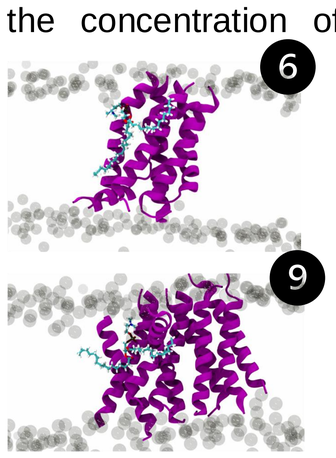




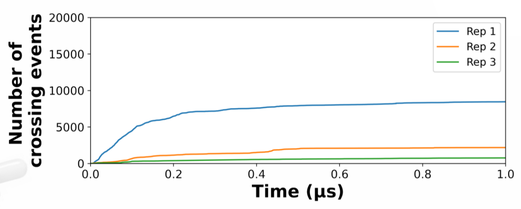
PIFP induced membrane perturbations

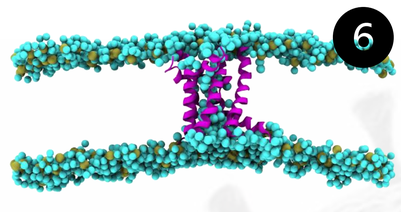
- In order to promote membrane fusion, the FPs must perturb the equilibrium of the membrane bilayer.
- PIFP induces **lipid-tail protrusion** that is linearly increased with the increase in the concentration of peptide.

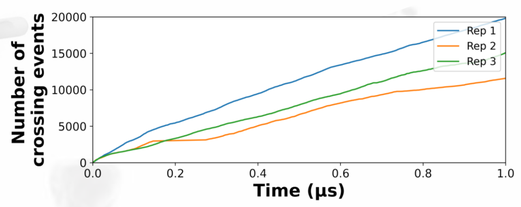


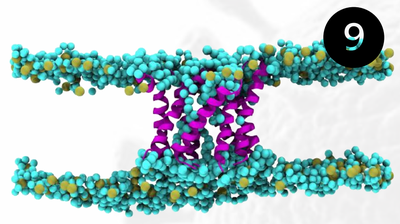


- At higher PIFP concentrations there is a continuous **flux of water** through PIFP pore-like structures.









PARAINFLUENZA FUSION PEPTIDE

^{103}FAGVVIGLAALGVATAAQVTAAVALVK^{128}

This work was supported by:
- PTDC/CCI-BIO/28200/2017
- SFRH/BD/148542/2019

At high PIFP concentrations peptide-peptide interactions stabilize the formation of a pore-like structure.

Our findings contribute to the understanding of the membrane fusion process induced by the PIFP and can be very useful in the future for the development of antiviral therapies.