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TUNING THE ASSEMBLY OF PROTEINS AND PEPTIDES IN LIPID BILAYERS

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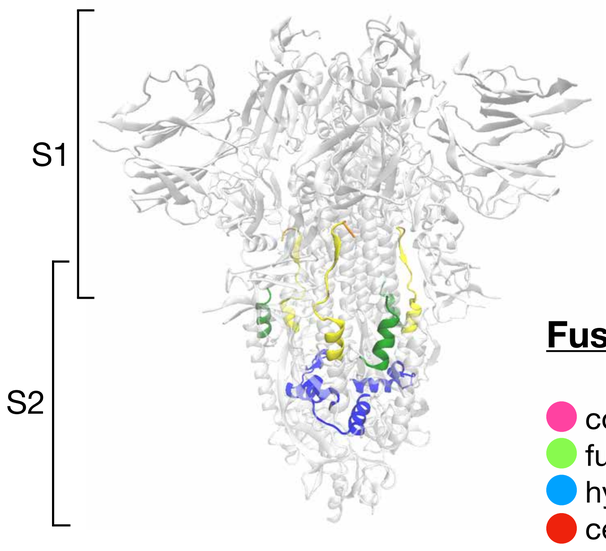
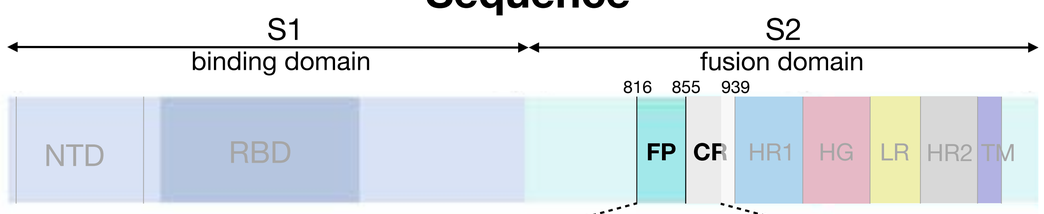
Viral fusion proteins facilitate membrane binding of the viral envelope to the host cell, enabling the release of the viral genetic material into the cell. Within the fusion domain of the SARS-CoV-2 Spike protein, several peptides have been identified to interact with the cell membrane. We aim to understand the viral infection role of these fusion peptides by studying their interaction with biomimetic model membranes.

SARS-CoV-2 Spike protein



PDB: 6VXX[1]

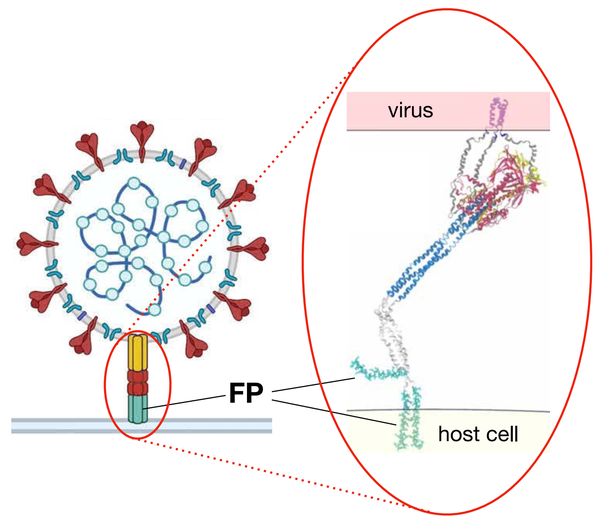
Sequence



Fusion Peptides

- conserved motifs
- fusion tripeptide
- hydrophobic
- central proline

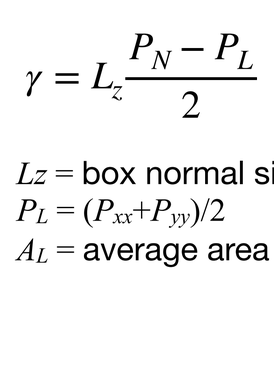
FP1 816 - SFIEDLLFNKVTLADAGFIKQY - 837
FP2 835 - KQYGDCLGDIAARDLICAQKFN - 856
FP3 854 - KFNGLTVLPPLLTDEMIAQYT - 874
FP4 885 - GWTFGAGAALQIPFAMQMAYRFNGI - 909



The fusion peptides bind to the host cell membrane driving the cell and virus together to initiate membrane fusion[2,3]

COARSE-GRAINED (CG) MOLECULAR DYNAMICS (MD)

Fusion peptides in bulk

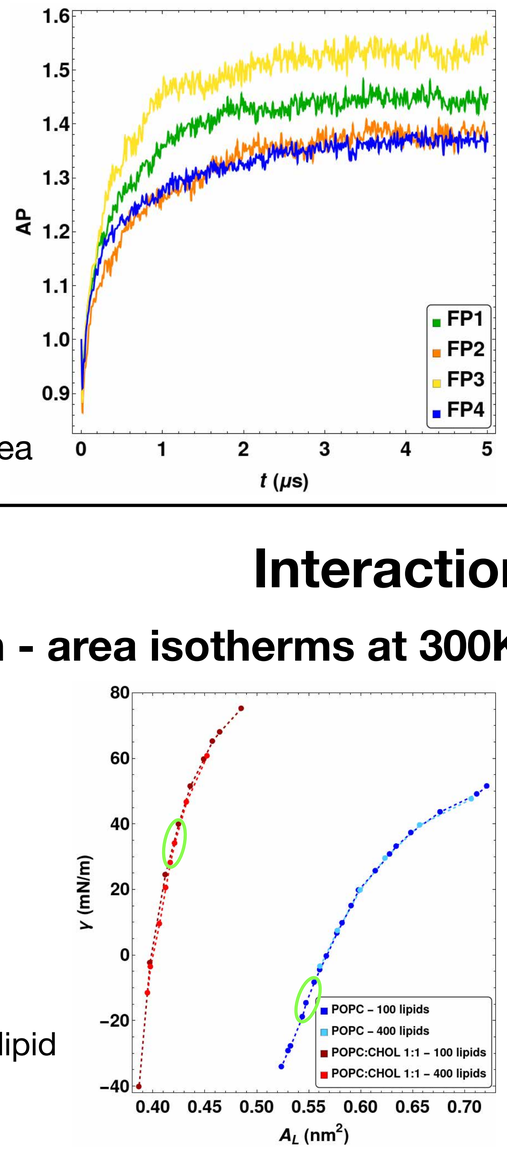


- Martini 2 force field[4,5]
- 4-1 mapping

$$AP = \frac{SASA_0}{SASA_f}$$

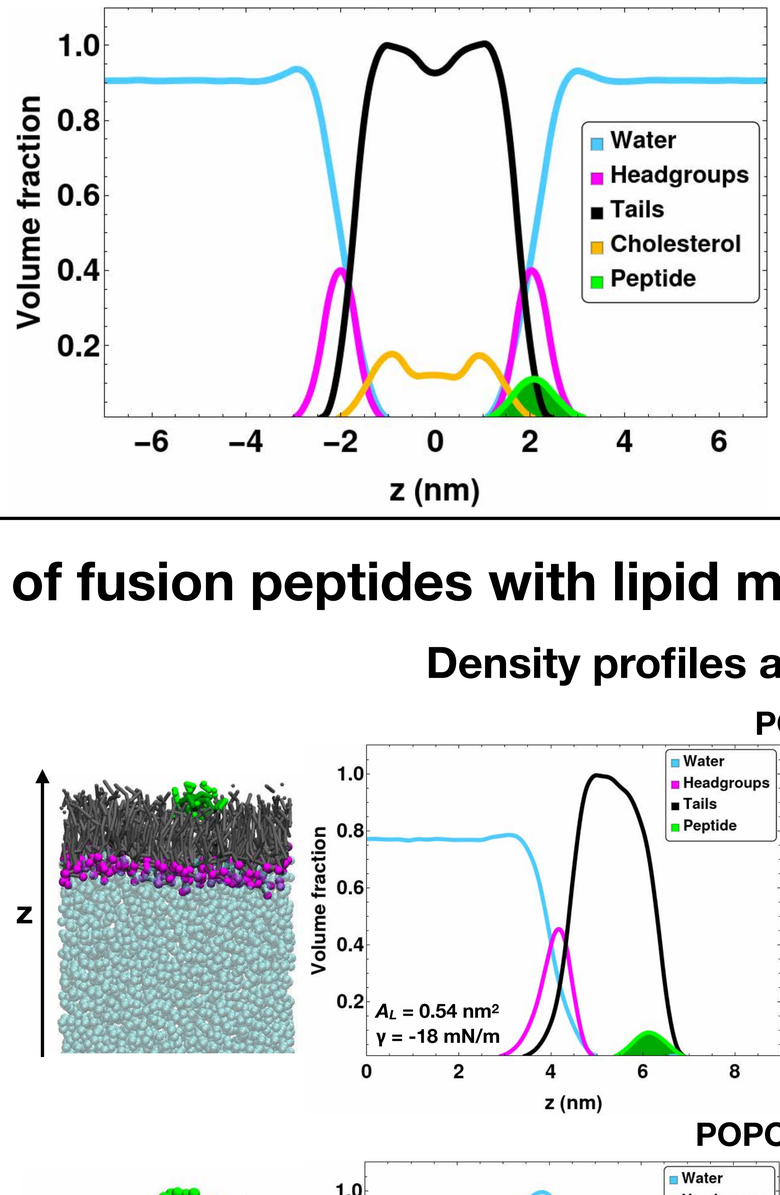
$SASA$ = solvent accessible surface area

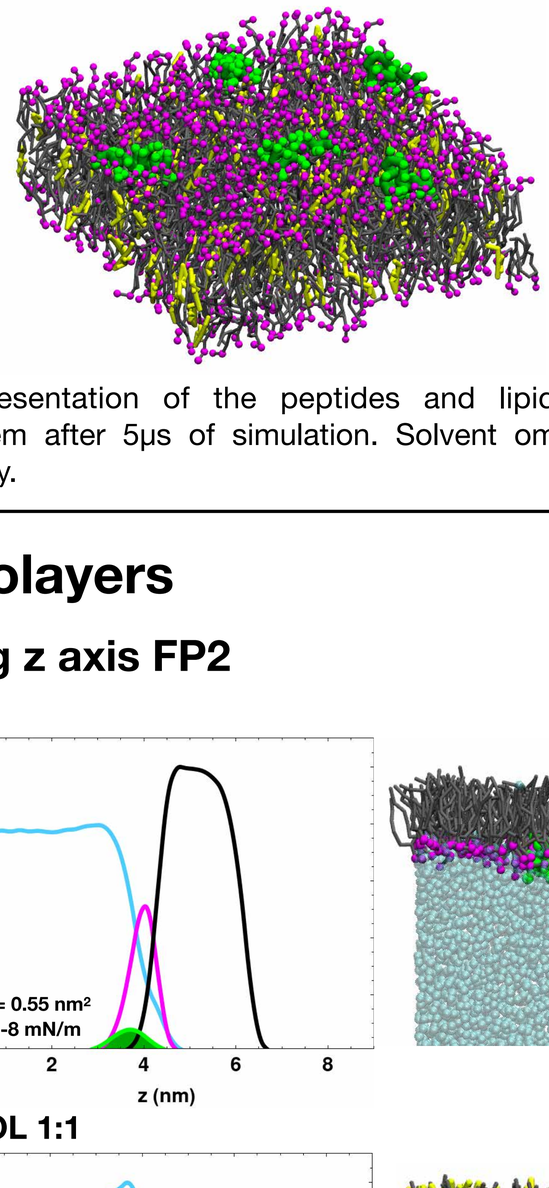
Aggregation Propensity



Interaction of fusion peptides with lipid bilayers

Density profile along z axis FP1





Representation of the peptides and lipid bilayer system after 5μs of simulation. Solvent omitted for clarity.

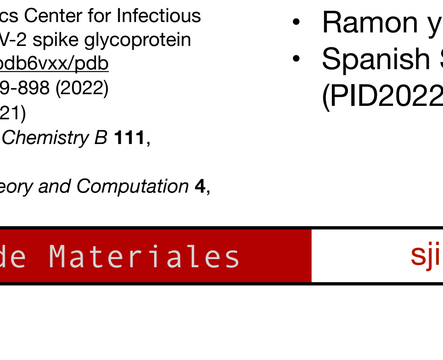
Interaction of fusion peptides with lipid monolayers

Surface tension - area isotherms at 300K

lipid monolayer surface tension

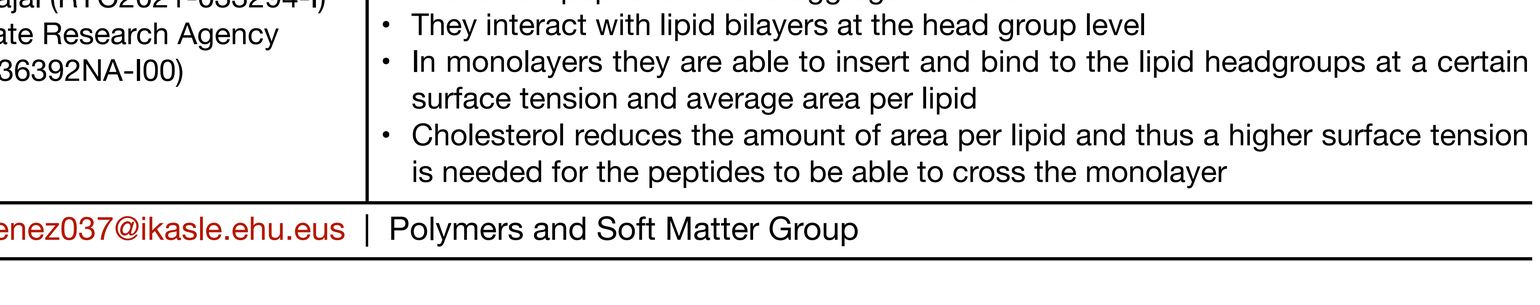
$$\gamma = L_z \frac{P_N - P_L}{2}$$

Lz = box normal size
$P_L = (P_{xx}+P_{yy})/2$
A_L = average area per lipid



Density profiles along z axis FP2

POPC



POPC:CHOL 1:1

RDF POPC

RDF cholesterol

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Conclusions

- The fusion peptides tend to aggregate in solution
- They interact with lipid bilayers at the head group level
- In monolayers they are able to insert and bind to the lipid headgroups at a certain surface tension and average area per lipid
- Cholesterol reduces the amount of area per lipid and thus a higher surface tension is needed for the peptides to be able to cross the monolayer

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