The Membrane Binding and Insertion Dynamics of pHLIP Peptide Studied by All-atom Molecular Dynamics Simulations

Yonghua Deng[1], Yun Zhang[1], Yin Luo[1], Yuguang Mu[2] and Guanghong Wei*[1]

[1]*Department of Physics, Fudan University*

[2]*School of Biological Sciences, Nanyang Technological University, Singapore*

Motivation

- The pH low-insertion peptide (pHLIP) serves as a model system for peptide insertion and folding across a lipid bilayer.
- Recent experimental studies show that it can spontaneously insert into the membrane.
- The mechanism is poorly understood.
- Use all atomistic molecular simulations (MD) to explore the detailed information.
- POPC +pHLIP, different initial configurations

Methods

- MD (Molecular Dynamics simulation)
- GROMACS 3.3 package
- forcefield: Gromos87
- coulombtype: PME
- rcoulomb =1.2; rvdw =1.4
- reference temperature: 315 K
- pcoupl=Berendsen; pcoupltype=semiisotropic

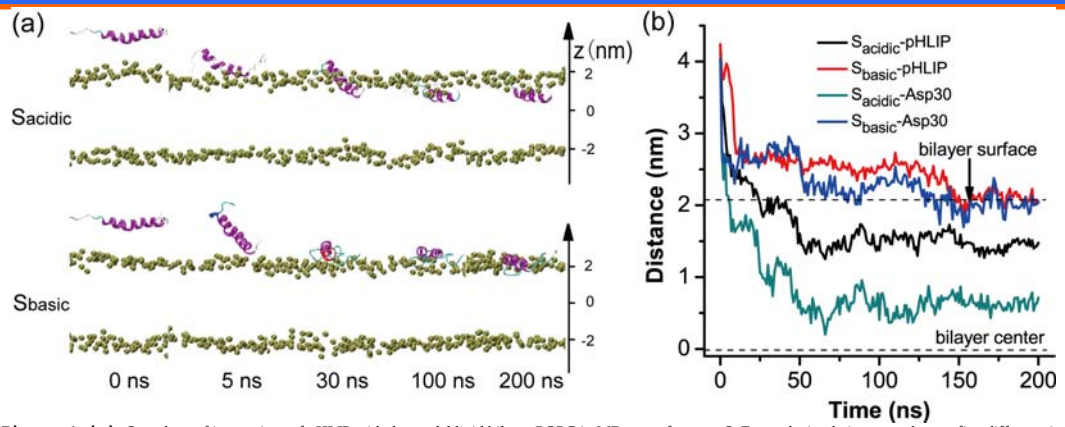

Figure 1.(a) Snapshots of interactions of pHLIP with the model lipid bilayer POPC in MD runs of system S. For each simulation, snapshots at five different time points are shown. The phosphorous atoms of the lipids are shown in tan spheres to represent the bilayer surface. The pHLIPs are shown in ribbons. The other atoms of POPC lipid molecules and water molecules are not shown for clarity. The bilayer center is at z=0. (b) The time evolution of the COM distance between the bilayer and pHLIP for system S. The COM distances between the bilayer and residue Asp30 of the pHLIP is also displayed.

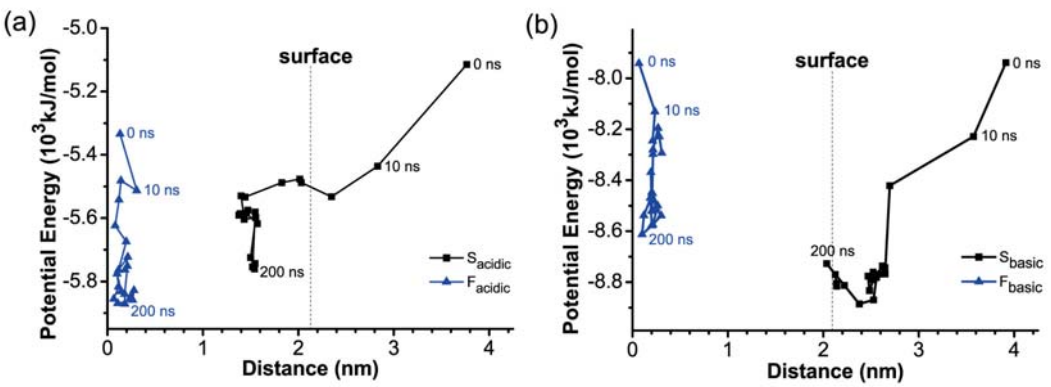

Figure 2. Time-averaged interaction energy between peptide and POPC bilayer as a function of residue number in the two MD runs of S system. The amino acids of the sequence are given above the horizontal axis. (a) For the first 5 ns. (b) For the last 50 ns.

Conclusions

1. A single pHLIP peptide is initially immersed in an aqueous medium, it moves the bilayer surface and spontaneously inserts into the bilayer at acidic pH, while it binds to the membrane surface and stays there at basic pH.
2. The preference of the pHLIP insertion into bilayer or binding on the bilayer surface at different pH is energetically favorable.

References

[1]Yana et al, Energetics of peptide (pHLIP) binding to and folding across a lipid bilayer membrane, PNAS, 105,40,2008

[2]Yana et al, Engleman, Translocation of molecules into cells by pH-dependent insertion of a transmembrane helix, PNAS, 103,17,2006

[3] Kandt, C.; Ash, W. L.; Peter Tieleman, D., Setting up and running molecular dynamics simulations of membrane proteins. Methods 2007, 41, (4), 475--488.