Insights into Membrane Fusion from Molecular Dynamics Simulations of SNARE Proteins

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Background

Exocytosis involves the transport of molecules stored within lipid vesicles across the vesicle and cell boundaries. The final step of this process requires fusion of the vesicles with the cell membrane mediated by SNARE proteins. SNARE function requires specific protein properties possibly in order to actively pull and subsequently hold together two membranes.

Previous work have demonstrated the stability of the SNARE soluble complex with the help of atomistic molecular dynamics simulations [1].

We now want to investigate the molecular mechanisms that could drive fusion. We focus especially on the interaction of the SNARE complex with the membrane.

The Model

The SNARE complex is composed of Synaptobrevin (red), Syntaxin (blue) and SNAP (grey / yellow) proteins forming a bundle of four α-helices.

SB and SX each have a transmembrane domain attached to the bundle by a flexible linker.

The complex is embedded between two phospholipids bilayers composed of POPC and POPS (11%).

This atomistic model is composed of nearly 400,000 atoms. Its construction is detailed in [1].
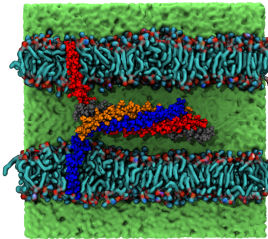
Simulations

During equilibration, the membranes move away from each other to compensate for expansion and pressure buildup, while the transmembrane domains (TMDs) remain firmly inserted within the bilayers.
The core complex holds the TMDs which maintain some lipids in place leading to a deformation of the leaflets (S)
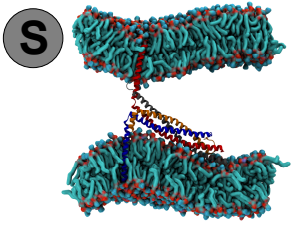
From this starting structure (S) three simulations were performed for 100ns with the CHARMM 36 forcefield :

(1) **The whole complex**. The trends observed during equilibration go on. The curvature of the membranes increases and the bundle keep lying on the vesicular membrane.

(2) **Severed linkers**. The membranes quickly retrieve a flat conformation. The tips of the bundle still interact with the membrane.

(3) **Proteins have been removed**. The membranes quickly retrieve a flat conformation (requires less than 15ns).
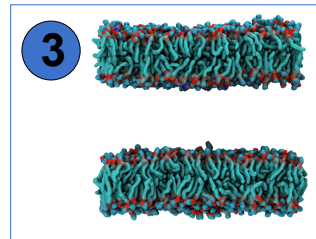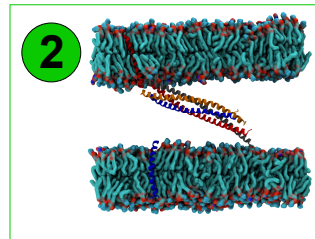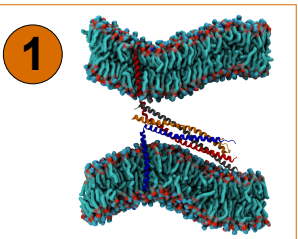
The Transmembrane Domains
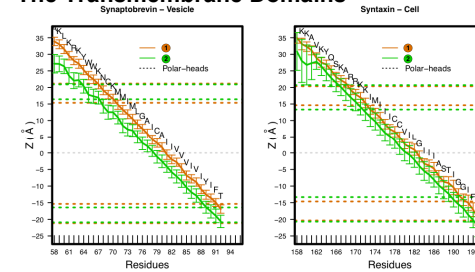
Average insertion depths of SB and SX transmembraine domains with respect to the bilayer center for each residue.

In simulation (1), TMDs are slightly pulled out of the bilayers (1 to 3 residues) compare to (2), where the TMDs are not attached to the bundle.

TMDs still span across the entire width of the membrane and stay firmly anchored between the polar heads.
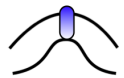
Membrane Disruption

Vesicle membrane thickness (Å) - center is the position of the TMD
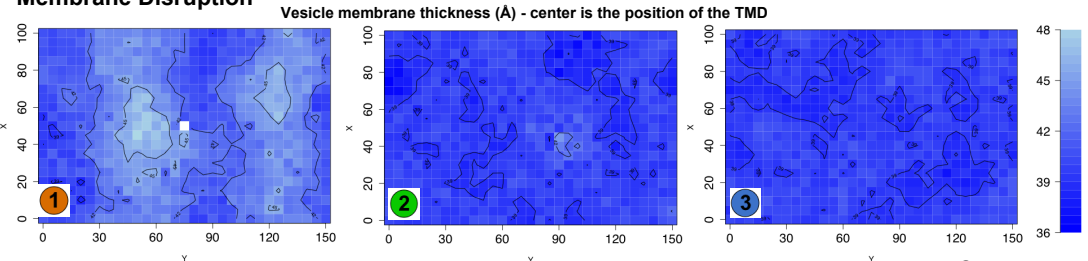
In (3), we observe an equally thick membrane. This is the case also in (2) despite the presence of the TMD.
In (1), the membrane is much more disrupted. The two thicks areas are due to the shape of the leaflets.
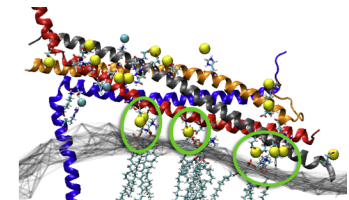The cell membrane follows the same trend.

Electrostatic contacts : Ions, Lipids, Protein Bundle
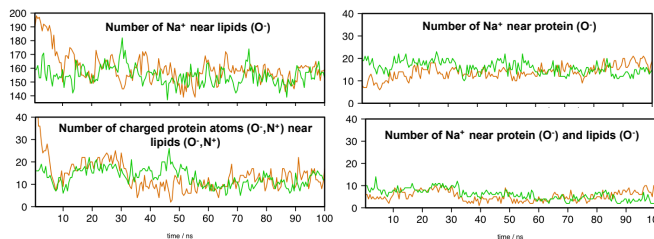
Electrostatics contacts are quite stable over time.
Half of the sodium ions are interacting with lipids. Those interacting with the protein could stabilize the core complex.
Some interaction between the bundle and the membrane could be mediated by ions.

References:
[1] M.P. Durrieu, R. Lavery and M. Baaden; Interactions between neuronal fusion proteins explored by molecular dynamics ; BIOPHYSICAL JOURNAL 2008; 94 ; 9 ; 3436-3446
[2] E. Krieger, L. Leger, M.P. Durrieu, N. Taib, P. Bond, M. Laguerre, R. Lavery, M.S.P. Sansom and M. Baaden; ParCo 2007, Parallel Computing: Architectures, Algorithms and ApplicationsVol. 38, pp. 729-736.