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Steered MD simulations of the inactive-active transition

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We use this protocol and it's working

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Abstract

This protocol details steered molecular dynamics simulations of the transition from the inactive to the active PI3KC3-C1 complex bound to RAB1A on a lipid membrane.

Preparation of membrane-engaged inactive complex

1 Superimpose the cryo-EM structure of the inactive conformation onto a membrane-engaged active complex after relaxation.

2 Apply harmonic restraints (force constant: 100 kJ mol^{-1}) to increase the center-of-mass z-distance between residues S249 to K887 of VPS34 and the membrane lipids underneath.

3 Apply a pulling rate of 0.1 nm ns^{-1} until the regions of interest are not clashing with the membrane.

Relaxation

4 Run simulation without any steering force for 117 ns to relax the membrane.

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5 Apply a lateral force to increase the distance between the C-terminal region of VPS34 (residues S249 to K887) and the N-terminal region of VPS15 (residues G2 to K300) for 30 ns, with a force constant of 100 kJ $mol^{-1.}$

6 Apply a pulling velocity of 0.1 nm ns^{-1} until the interface between VPS34 and VPS15 breaks.

Steered MD to obtain active, membrane-engaged complex

7 Pull the center of mass of the myristate at the N-terminus of VPS15 along the z coordinate towards the membrane for 220 ns with a force constant of 100 kJ mol^{-1}.

8 Apply a negative rate of -0.1 nm ns^{-1} until the myristate is inserted in the membrane and the catalytic domain of VPS34 reaches the membrane surface.

Relaxation

9 Allow the complex to relax for 160 ns upon removal of any steering force.