Unraveling the molecular mechanisms of cholesterol structural effects through Langmuir experiments and atomistic Molecular Dynamics simulations

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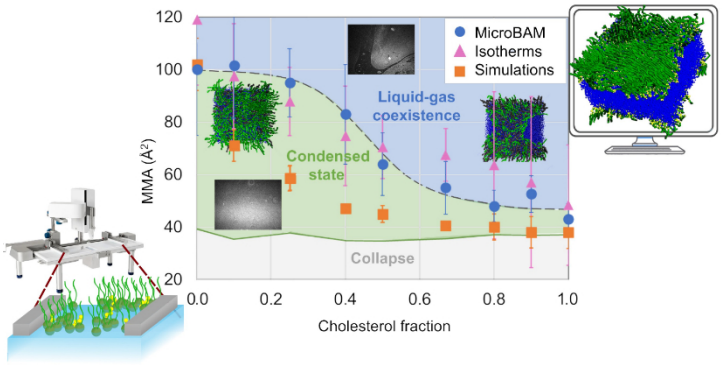
Cholesterol is the main modulating agent of the structure, rigidity, and stability of animal cell plasma membranes. This study analyzes the influence of Chol on model membrane organization and phase separation through a multi-scale analysis of DPPC-cholesterol Langmuir monolayers, to uncover the microscopic mechanisms behind cholesterol's effect. By integrating experimental surface pressure-molecular area isotherms and Micro-Brewster Angle Microscopy (MicroBAM) with atomistic Molecular Dynamics (MD) simulations, we provide an atomic-level characterization of lipid-cholesterol interactions. Our results demonstrate a strong attraction between DPPC fatty acyl chains and cholesterol, which increases the monolayer stiffness and packing density. This interaction drives lipid chains into a more perpendicular orientation relative to the water surface, thereby minimizing their projected area and restricting chain entanglement. This reduced molecular flexibility leads to a distinct phase separation at low areas per lipid, characterized by the emergence of low-density voids and high-density domains, a phenomenon captured by both MicroBAM imaging and MD trajectories. These findings clarify the biophysical mechanisms by which cholesterol reg ulates biological membra ne organization and validate the integration of atomistic simulations with microscopy as a robust framework for exploring complex lipid environments.

Keywords:
Cholesterol, DPPC, Langmuir monolayers, atomistic Molecular Dynamics simulations



Phase diagram denoting different states of a cholesterol-DPPC monolayer in terms of mean molecular area (MMA) and cholesterol mole fraction, integrating data from both experimental methods (MicroBAM images and surface pressure-area isotherms) and Molecular Dynamics simulations.

References:

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