SMALL-ANGLE SCATTERING GROUP
JOINT INSTITUTE FOR NUCLEAR RESEARCH
FRANK LABORATORY OF NEUTRON PHYSICS

Investigating the competitive effects of cholesterol and melatonin in model lipid membranes

Structural studies

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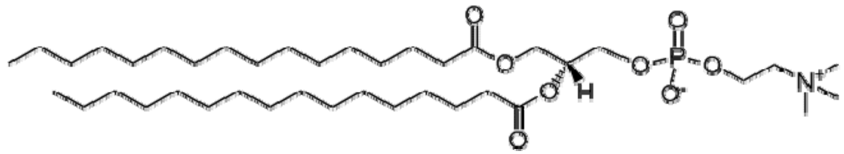
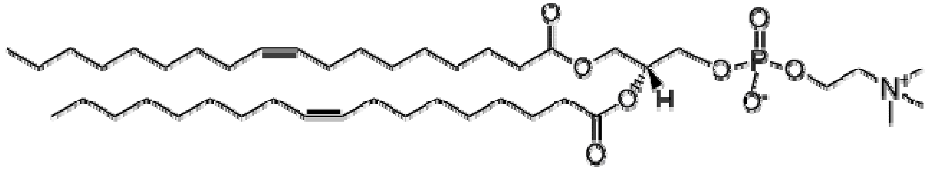
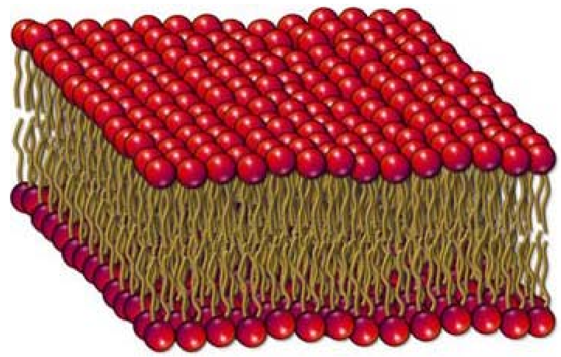
Model lipid membranes

DPPC

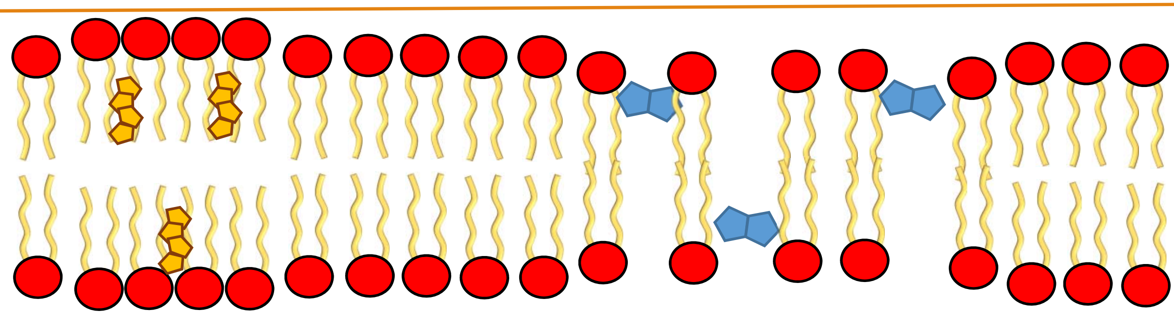


DOPC





Cholesterol and melatonin in lipid membranes



- Cholesterol is located in lipid tails region
- Lipid molecules become more ordered
- Membrane became stiffer and thicker (**condensing effect**)
- Decreasing Area per lipid molecule

- Melatonin is located between lipid heads
- M. decrease order of lipid molecules
- Membrane became more fluidic and thinner (**fluidizing effect**)
- Increasing Area per lipid molecule

Through changing the spatial structure, cholesterol and melatonin affects membrane permeability and fluidity, lateral diffusion of membrane proteins, and thermodynamics of the system in general

Both have been suggested to play a role in the onset of Alzheimer's disease

Motivation and methods

The effect of cholesterol/melatonin (separately) on lipid membrane in two-component lipid system are quite well known.

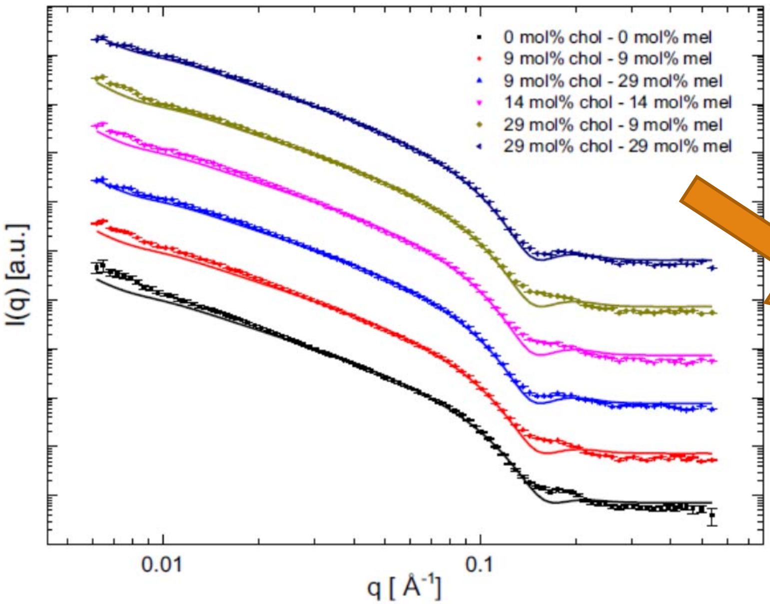
The case of the three-component system of lipid, cholesterol, and melatonin is particularly interesting as it is not clear a priori how the opposing effects of the two additives should affect the membrane properties when added simultaneously.

The main goal of our work was studying the **concurrent effect** of cholesterol and melatonin in ternary systems
Lipid/Cholesterol/Melatonin

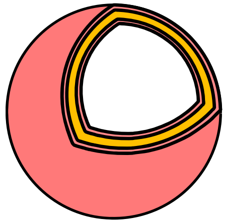
via

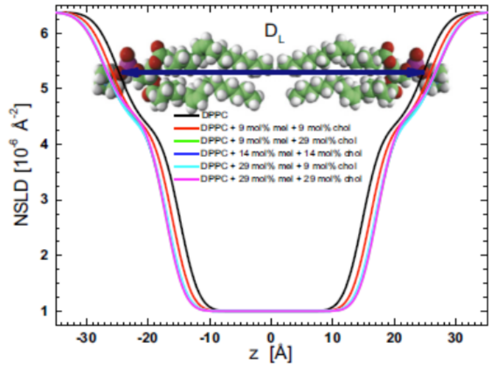
Small angle neutron scattering (SANS) and diffraction (SAND), Raman spectroscopy and molecular dynamics (MD) simulations

SANS and SAND experiments



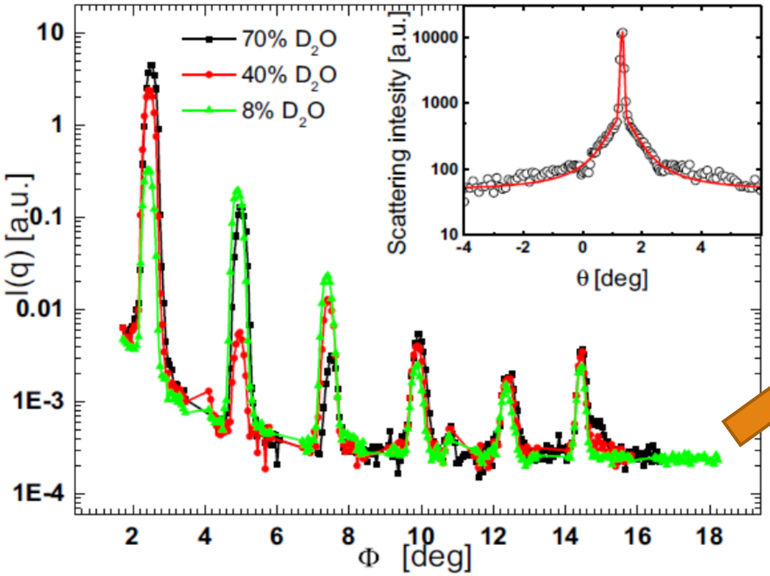
Unilamelar vesicles



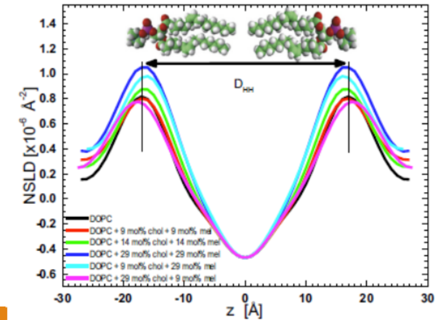


a) DPPC		Cholesterol (f_{Ch})			
		0%	9%	14%	29%
Melatonin (f_M)	0%	0	2.6*		3.2*
	9%	−1.2*	2.5		4.7
	14%			4.4	
	29%	−7.3*	4.1		4.8

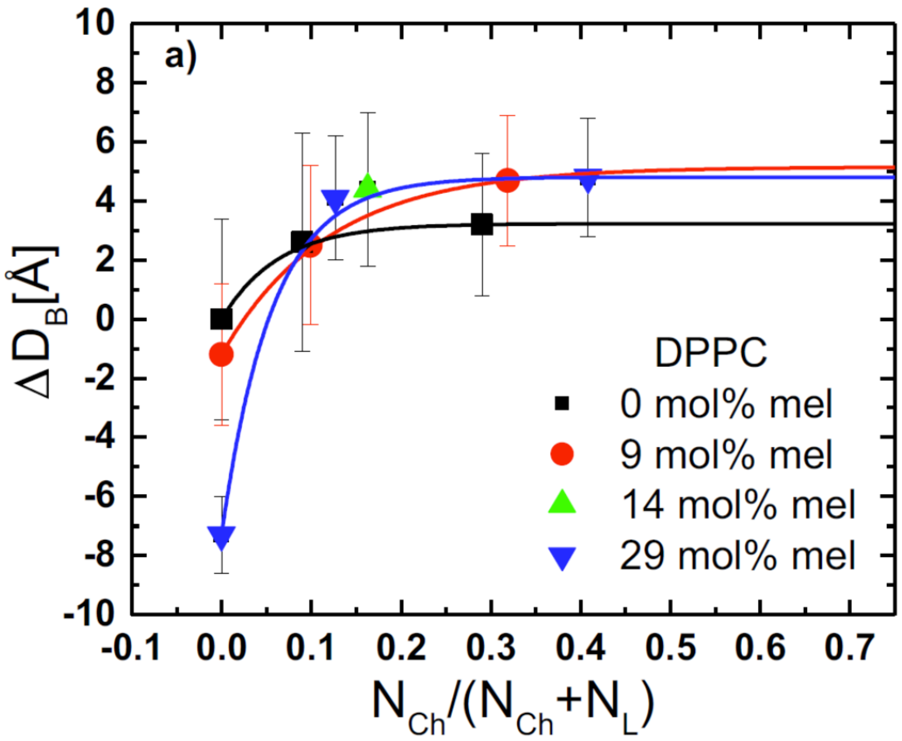
b) DOPC		Cholesterol (f_{Ch})				
		0%	9%	14%	17%	29%
Melatonin (f_M)	0%	0	0.8*		1.3*	3.3*
	9%	−1.2*	−0.2			1.6
	14%			−0.8		
	29%	−2.2*	−1.4			−0.6

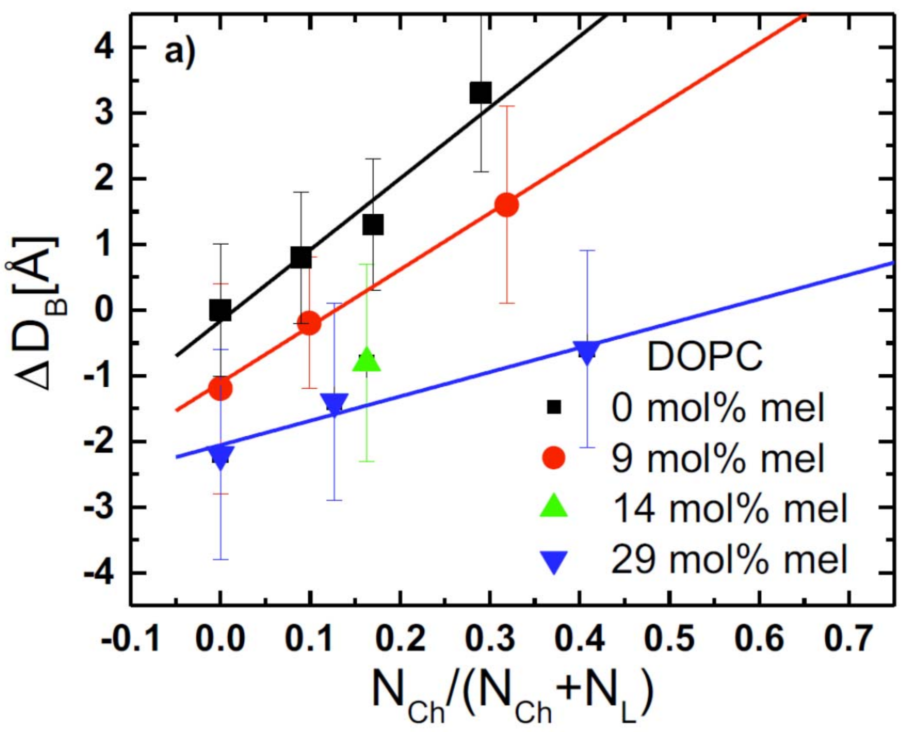


Oriented multilamelar stack



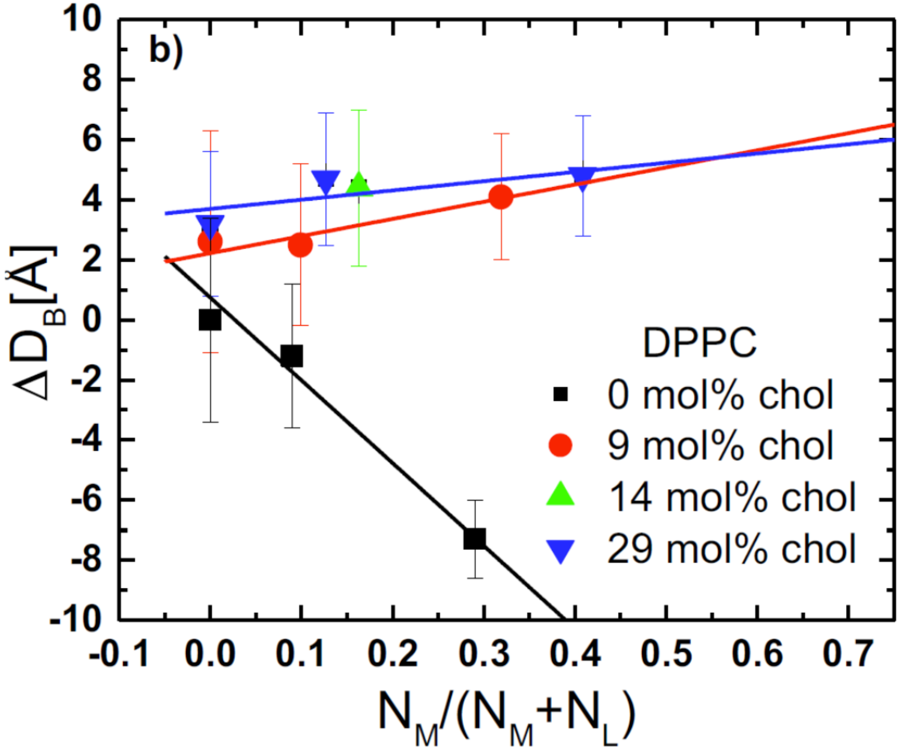
Results: Condensing effect of Cholesterol

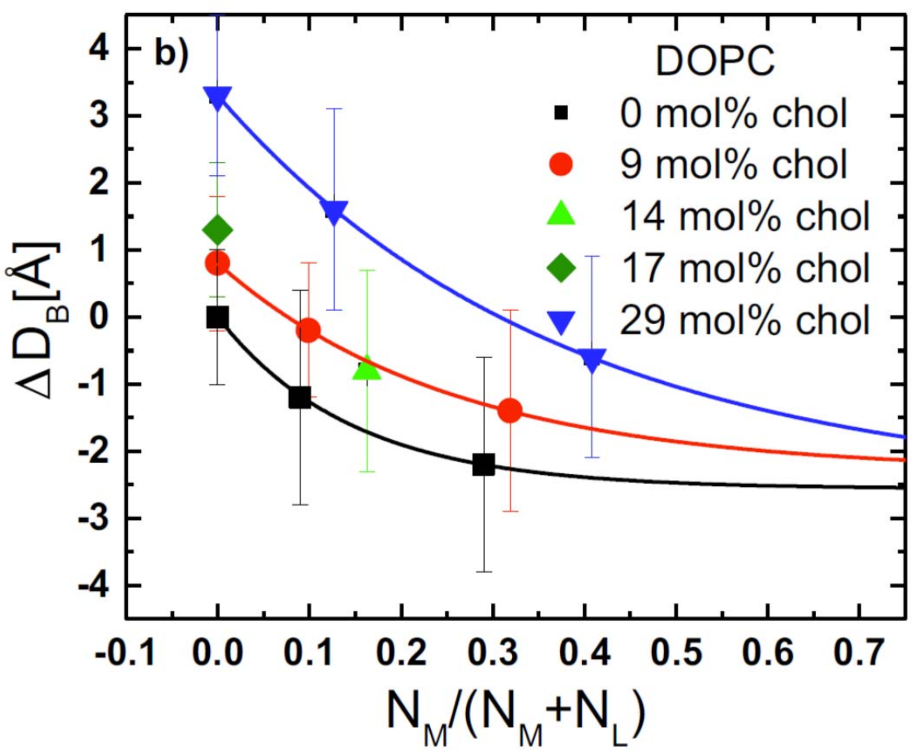




- Increasing the Cholesterol concentration up to 29 mol% is suggested to increase a mean value of bilayer thickness up to more than 3 Å for pure DPPC and pure DOPC membranes
- Addition of Melatonin to DOPC membrane leads to decrease the Cholesterol condensing effect
- In case of DPPC membranes interactions between the Cholesterol and lipid are not modulated by the presence of melatonin, and their effects on the DPPC bilayers saturate at about the level of 5 Å

Results: Fluidizing effect of Melatonin





- Melatonin leads to decrease mean values of bilayer thickness on 8Å in case of pure DPPC and up to 2Å in case of pure DOPC membranes
- DOPC based bilayers show thinning in all studied systems with increasing of Melatonin concentration.
- The increasing concentration of Melatonin in the DPPC-based systems loaded with Cholesterol practically not affect on the membrane thickness. This again reaffirms the prevailing interactions between the DPPC and cholesterol that quickly overcome the interactions between the DPPC and melatonin

Conclusions

- ✓ The impact of cholesterol and melatonin is opposite and competitive in the case of three-component systems of lipid/cholesterol/melatonin. We report that cholesterol induced an increase in bilayer thickness, while melatonin induced a decrease in the bilayer thickness.

- ✓ The effect of cholesterol appears to prevail over that of melatonin in the case of structural properties of DPPC-based bilayers, which can be explained by its interactions targeting primarily the saturated lipid chains.

- ✓ The demonstrated condensing effect of cholesterol and the fluidizing effect of melatonin appear in an additive manner upon their mutual presence.

- ✓ The latter two effects could be hypothesized the origins of structural changes to the membrane leading to the onset of Alzheimer's disease

Kondela, T., et al., *Investigating the competitive effects of cholesterol and melatonin in model lipid membranes. Biochimica et Biophysica Acta (BBA) - Biomembranes, 2021.* ***1863(9): p. 183651.***

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