Behaviour of cholesterol in un-saturated lipid membranes

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In biological membranes, the lateral sequestration of lipids that contain polyunsaturated fatty acid (PUFA) chains into membrane domains depleted of cholesterol has been hypothesized to have a role in neurological function and in alleviating a number of health problems (1). There appears to be a strong aversion of the kinked and disordered polyunsaturated chains to the planar, rigid surface of the cholesterol's steroid moiety which is thought to be the major driving force for this kind of domain formation. Past neutron scattering experiments showed a striking manifestation of this phenomenon. Selectively deuterium labeled cholesterol incorporated into di20:4PC (1,2-diarachidonyl-phosphatidylcholine, DAPC) with its 4 double bonds on each chain, revealed that the hydroxyl of the cholesterol sterol resides at the center of the bilayer (2). This result was interpreted in terms of cholesterol preferentially sequestering inside the membrane and in contrast to its usual position where the hydroxyl group locates near the aqueous interface. Further scattering experiments have shown that cholesterol will re-orient its hydroxyl group when the bilayer is doped with highly saturated lipids. For example, 50 mol % 16:0–18:1 PC (1-palmitoyl-2-oleoyl-phosphatidylcholine, POPC) in PUFA bilayers caused cholesterol to revert to its upright orientation, and only 5 mol % di14:0 PC (1,2-dimyristoyl-phosphatidylcholine, DMPC) was needed to achieve the same effect (3). These results demonstrate cholesterol's affinity for saturated hydrocarbon chains, and its aversion for PUFAs.

The lipid 16:0-20:4PC (1-palmitoyl-2-arachidonoyl-sn-glycero-3-phosphocholine, PAPC) is abundant in retinal and neuron cells, and is the most abundant PUFA *in vivo*. In this mixed chain lipid a saturated fatty acid chain is tethered to a PUFA. This tether prevents the entropic separation of saturated and un-saturated lipids as has been observed in the case of mixing un-saturated DAPC with saturated DMPC lipids (3), while still allowing cholesterol to choose a preferential interaction. Our neutron diffraction experiment confirms without a doubt that cholesterol interacts preferentially with saturated chains by adapting orientation parallel to these chains (see Figure 1). In addition, our results suggest that saturated domain formation is not required for this interaction to happen, supporting thus a notion that such a domain formation is most likely a result of lipid-lipid interactions rather than that involving cholesterol.

References

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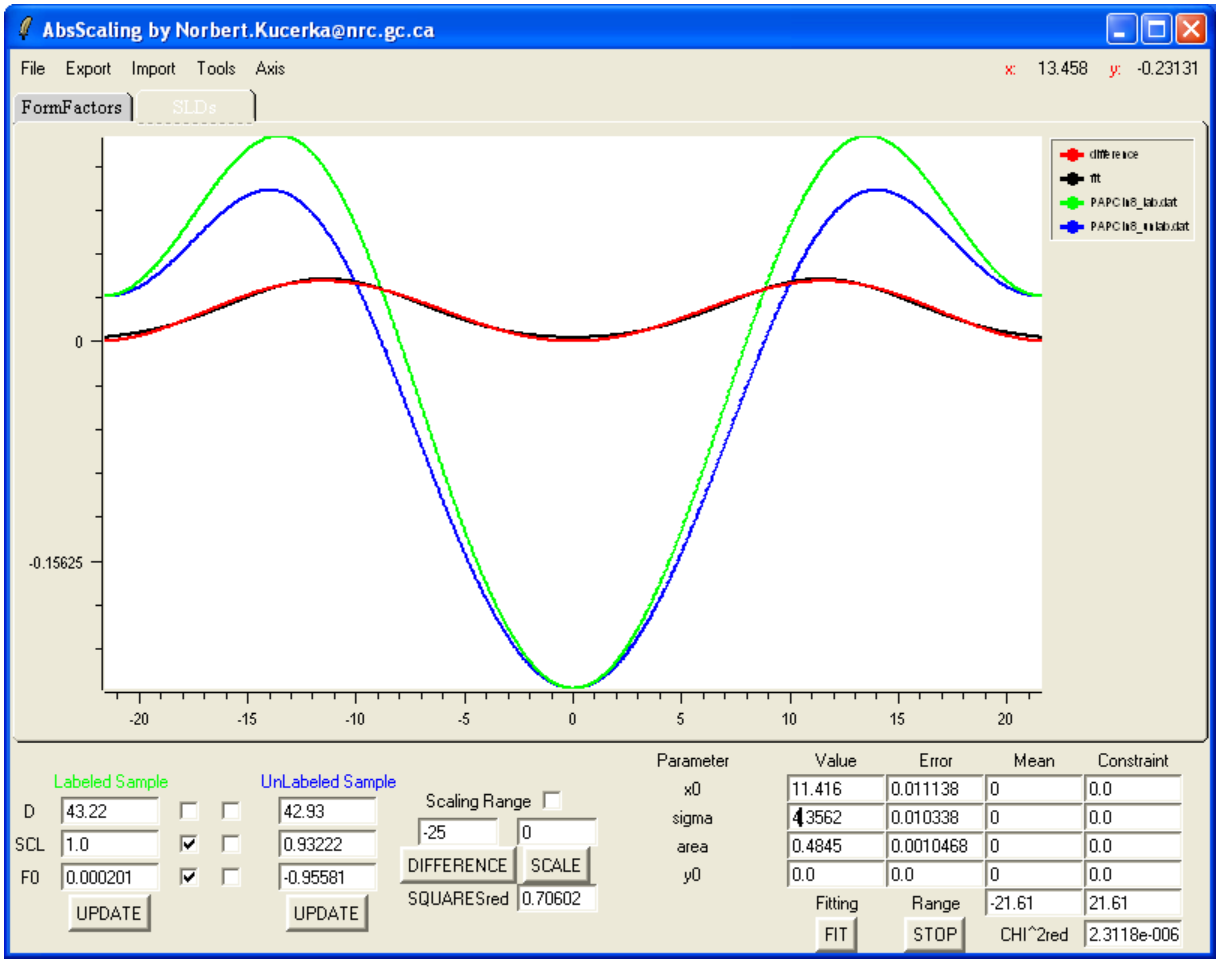

Fig. 1 Neutron scattering length density distribution of bilayers prepared of PAPC+10% cholesterol (deuterium-labelled shown by green colour, while un-labelled cholesterol is shown by blue colour) hydrated with 8% D_2O. Red curve is a difference profile showing the distribution of the cholesterol's deuterium label (effectively the mass distribution of cholesterol headgroup), and is fitted well with the Gaussian function shown in black.