One of the most challenging topics in structural biology is the determination of 3D structures of membrane proteins. Cases where cholesterol has been observed to be part of the protein complex are quite common. These proteins are thereby known as cholesterol-binding, and it is assumed that cholesterol has an important effect on protein function, such as an ability to promote thermal stability or to induce conformational changes in protein structure. However, the tricky aspect of these studies is that quite often it is not cholesterol that is used in protein 3D structure determination. Instead, one commonly uses cholesterol derivatives, such as cholesteryl hemisuccinate, due to their higher solubility in water (compared to that of cholesterol).

Here we employ atomistic molecular dynamics simulations to characterize how well the properties of cholesteryl hemisuccinate actually match those of cholesterol in saturated protein-free lipid membranes. We show that the protonated form of cholesteryl hemisuccinate mimics many of the membrane properties of cholesterol quite well, while the deprotonated form of cholesteryl hemisuccinate is less convincing in this respect. Based on the results, we suggest that cholesteryl hemisuccinate in its protonated form is a quite faithful mimic of cholesterol for membrane protein crystallization, if specific cholesterol-protein interactions (not investigated here) are not playing a crucial role.