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X-ray diffraction of a gram-negative bacterial membrane mimetic

This thesis applies x-ray diffraction to measure the membrane structure of lipopolysaccharides and to develop a better model of a LPS bacterial membrane that can be used for biophysical research on antibiotics that attack cell membranes. We have modified the Physics department x-ray machine for use as a thin film diffractometer, and have designed a new temperature and relative humidity controlled sample cell. We tested the sample cell by measuring the one-dimensional electron density profiles of bilayers of POPC with 0%, 1%, 10%, and 100% by weight lipo-polysaccharide from Pseudomona aeruginosa.

Traditional antibiotics are losing their effectiveness against ever-evolving bacteria. This is because traditional antibiotics work against specific targets within the bacterial cell, and with genetic mutations over time, the antibiotic no longer works.

One possible solution are antimicrobial peptides. These are short proteins that are part of the immune systems of many animals, and some of them attack bacteria directly at the membrane of the cell, causing the bacterium to rupture and die. Since the membranes of most bacteria share common structural features, and these features are unlikely to evolve very much, these peptides should effectively kill many types of bacteria without much evolved resistance.

But why do these peptides kill bacterial cells, but not the cells of the host animal? For gram-negative bacteria, the most likely reason is that their outer membrane is made of lipopolysaccharides (LPS), which is very different from an animal cell membrane. Up to now, what we know about how these peptides work was likely done with phospholipid models of animal cell membranes, and not with the more complex lipopolysaccharides. If we want to make better peptides, ones that we can use to fight all types of infection, we need a more accurate molecular picture of how they work. This will hopefully be one step forward to the design of better treatments for bacterial infections.