Review of: "Effects of Cholesterol on the mechanism of fengycin, a biofungicide"

Łukasz Nierzwicki

Potential competing interests: The author(s) declared that no potential competing interests exist.

In the article titled “Effects of Cholesterol on the mechanism of fengycin, a biofungicide”, the Authors explores the mechanism by which cholesterol reduces the membrane leakage induced by fengycin. With this purpose, the Authors use corse-grained molecular dynamics simulations and enhanced sampling method, namely the weighted ensemble method. In their research, the Authors find that, contrarily to the previous hypothesis, the presence of cholesterol does not reduce the affinity of fengycin to self-aggregate; instead, it increases the self affinity of fengycin in some extent. They also find that fengycin does not show any specific affinity to the examined lipids, consistently with the previous all-atom MD findings. Instead, the Authors show that fengycin disorders the neighbouring lipids and bends the membrane, which can facilitate the membrane leakage. On the other hand, cholesterol was shown to reduce the membrane perturbation, which is expected as cholesterol increases the lipid ordering and increases the bending modulus of the membrane.

I think that the manuscript is very well written - it is clear, not overstated and provides a reasonable explanation of how cholesterol might reduce the fengycin-induced membrane leakage. It is also notable that the Authors discuss in detail the drawbacks of the coarse-grain models, stressing the limitations of their predictions to the reader.

The only suggestion I would have to the Authors is that it would be beneficial for the article to discuss at least in some extent the current state of knowledge on the cholesterol impact on the membrane properties. As I mentioned before, cholesterol is known to increase both the lipid ordering and the bending modulus of biological membranes. There are also articles that discuss how cholesterol suppresses the membrane leakage in other cases, e.g. here: https://doi.org/10.1039/C8SM00644J. Other than that, I am happy to recommend the article to be published.