

Multiscale-Modeling of Sterols in Membrane Environment

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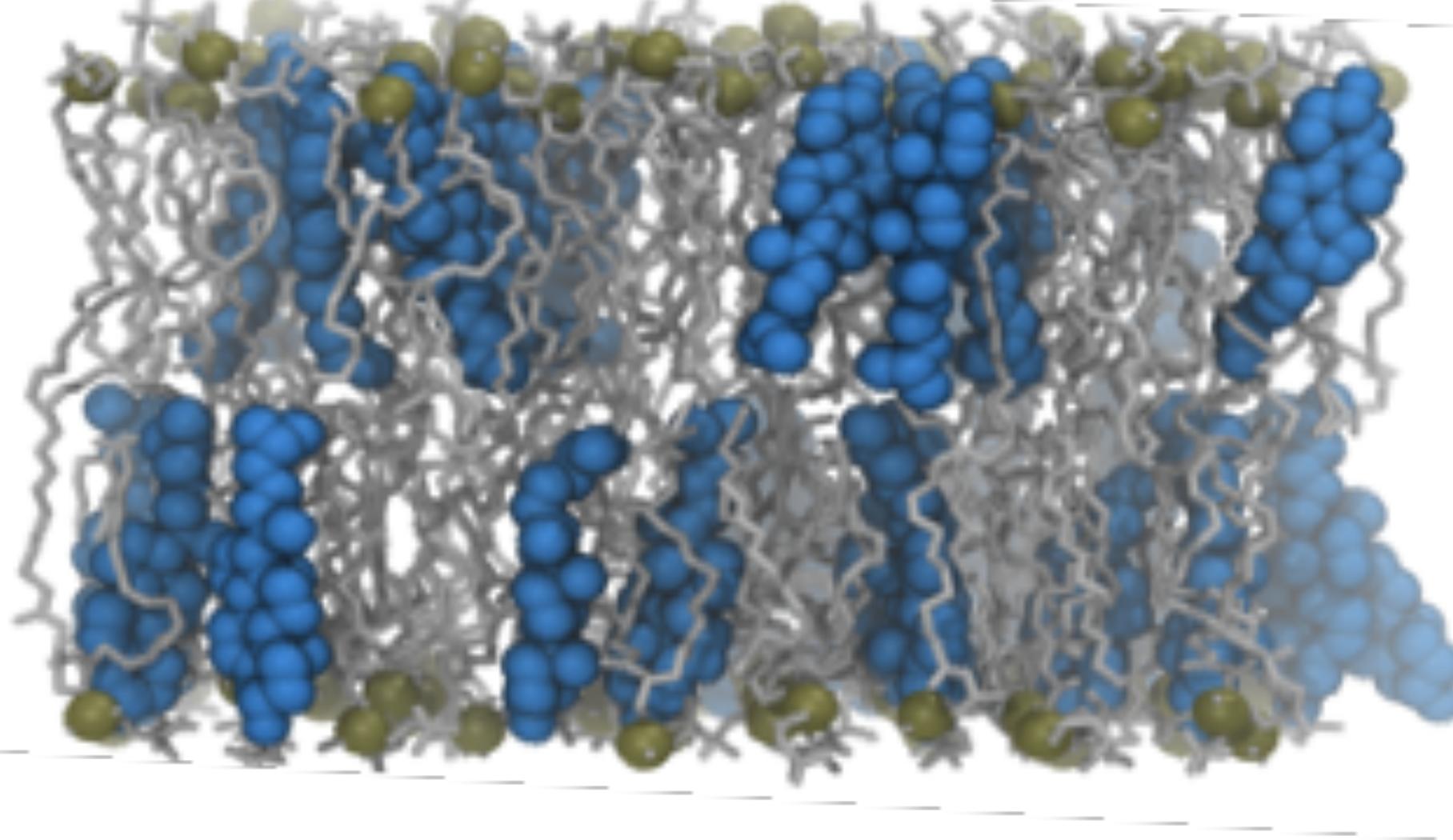
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Abstract

Sterols are a group of active-organic molecules that share a common property: the ability to regulate the dynamics of the cell membrane. Sterols come in a wide array of classes that plays roles in the anatomy of organisms. The prevailing challenge to differentiate the dynamics of ergosterol and cholesterol are not definitive, but progressive usage of MD simulations and new XSEDE Supercomputer resources has revealed structural differences in the lipids. The correlation of my computations with experimental data lead to the verification of varying dynamics and structure.

Overview

Study the comparative dynamics of ergosterol and cholesterol alongside the comparison of the computational and experimental data to provide an improved understanding of the mechanism of action of the antifungal drugs, particularly AmB.



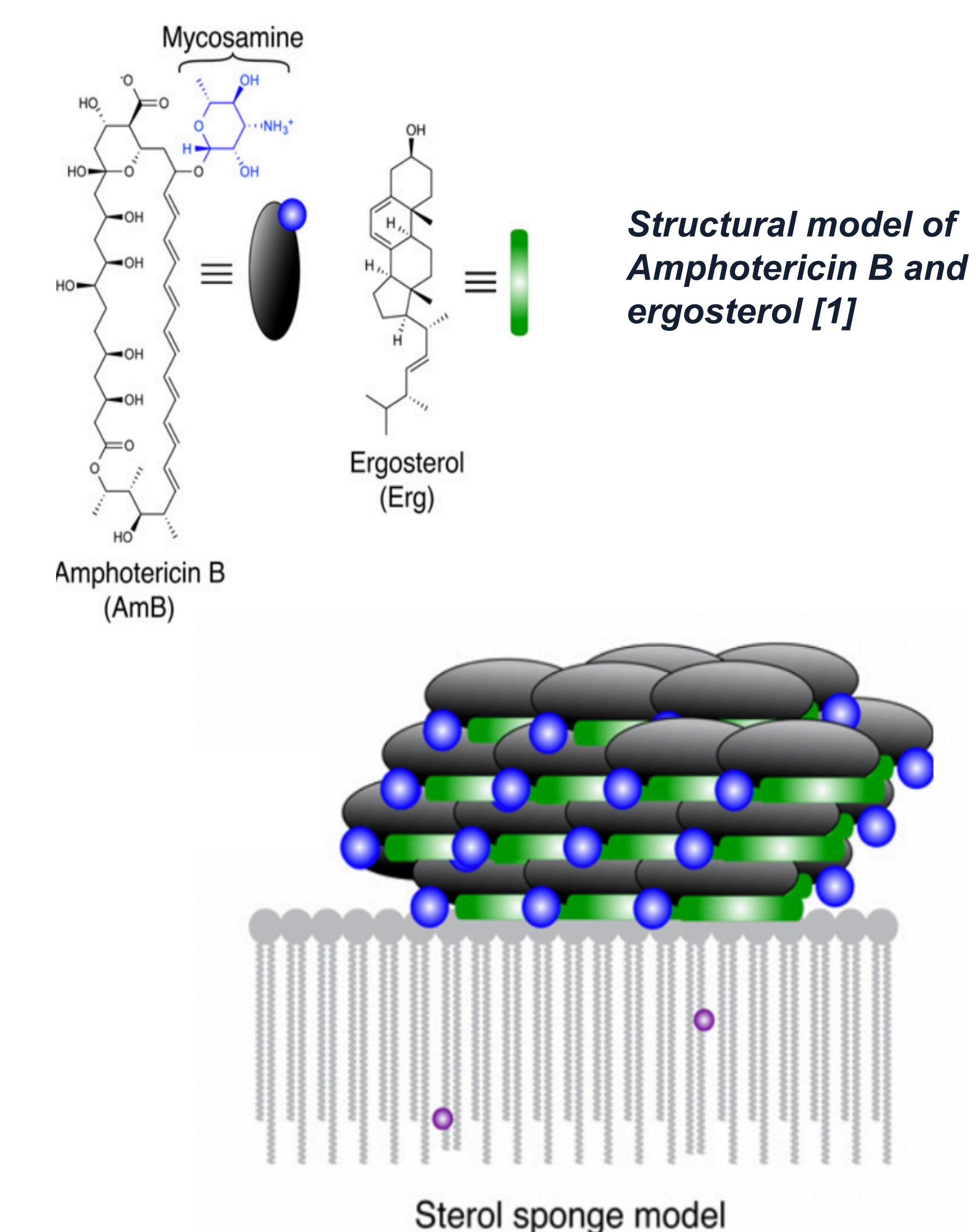
Goals

Study ergosterol dynamics in the membrane by utilizing various approaches classical molecular dynamics, quantum chemistry methods, and comparing ergosterol to the solid-state NMR data

Compare computational and experimental data with the comparative dynamics of ergosterol and cholesterol to instigate an improved understanding of the mechanism of action of antifungal drugs.

Background

AmB Sterol Sponge Model



Sponge formation on Amphotericin B that extracts ergosterol

Method

Ergosterol Parameters:

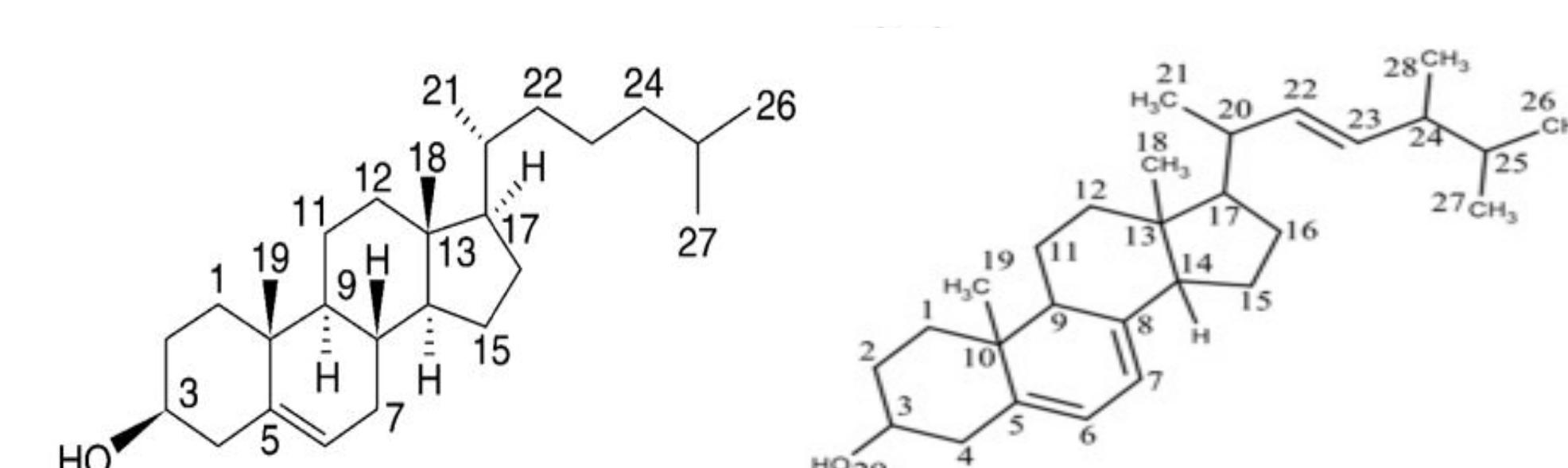
Number of Calculated Lipids (ratio of ERG:PC): 3:10

Force Field: CHARMM 36

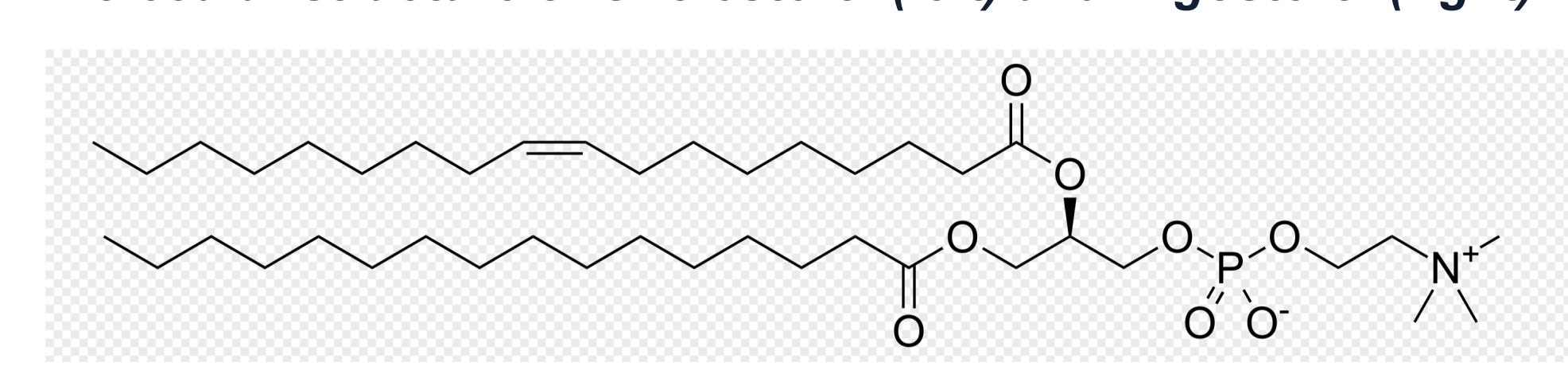
Temperature: 293 K

Run Time: 100 ns

Number of Replicates: 10



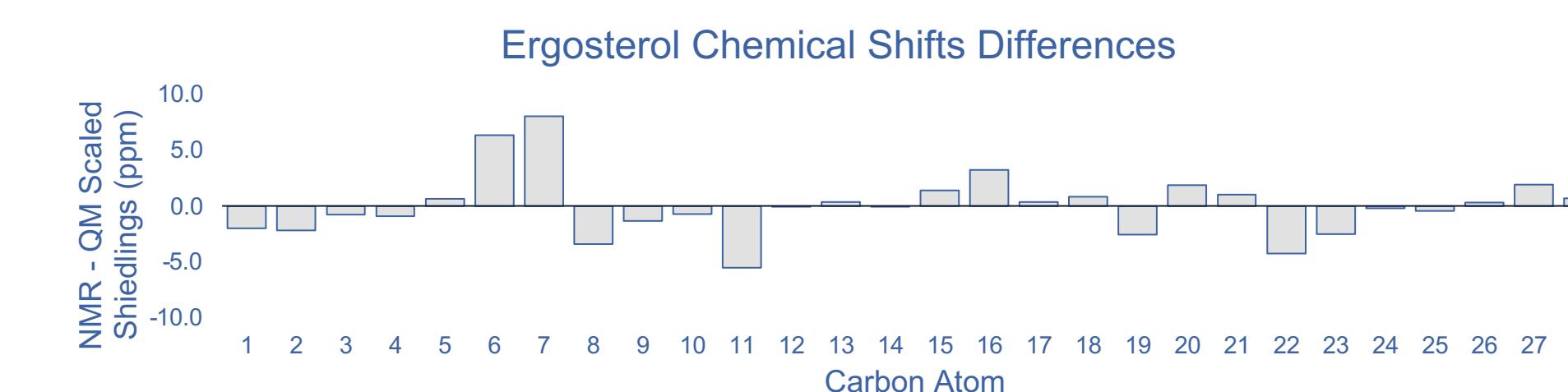
Molecular structure of Cholesterol (left) and Ergosterol (right)



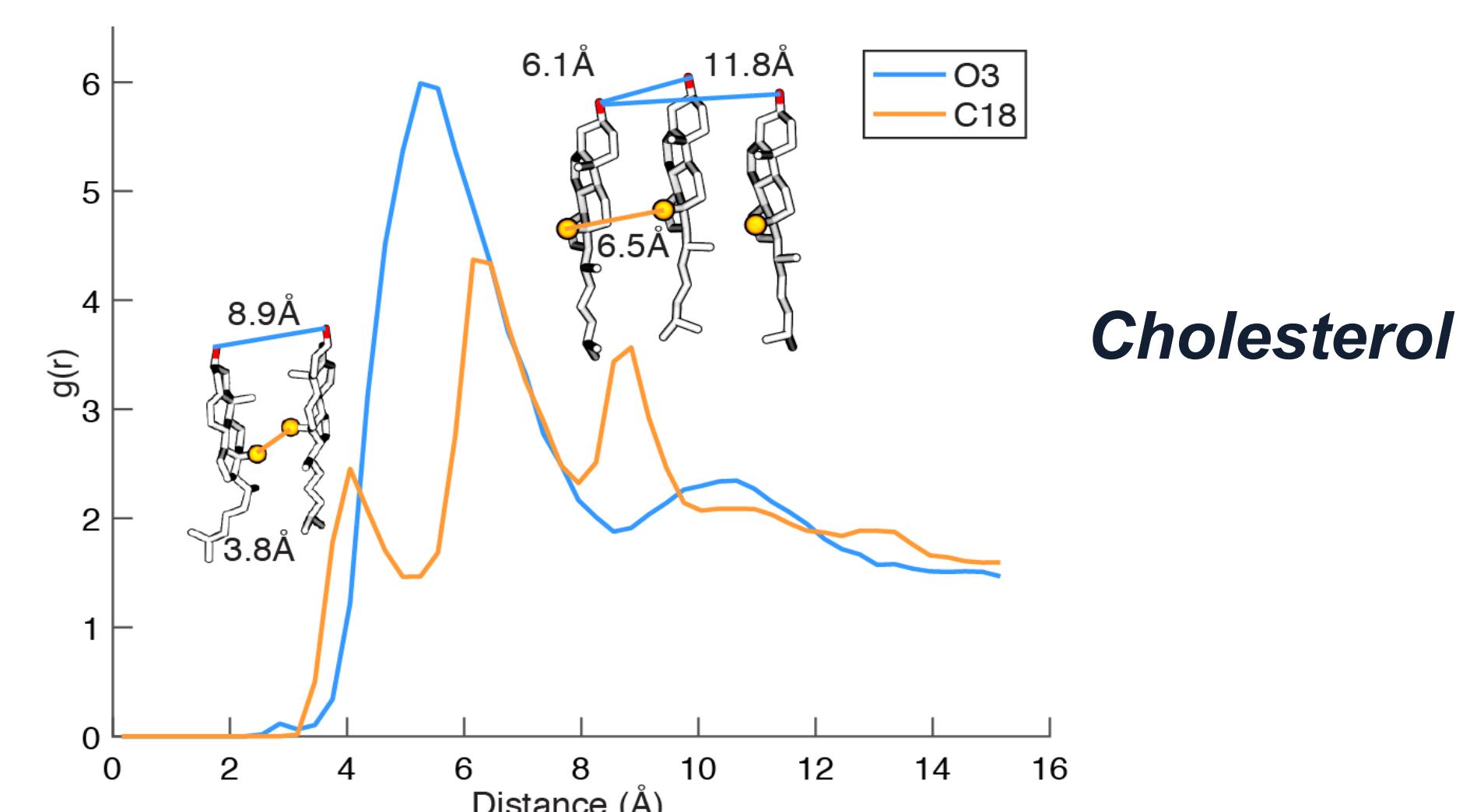
Molecular structure of phosphatidylcholine (POPC)

Results

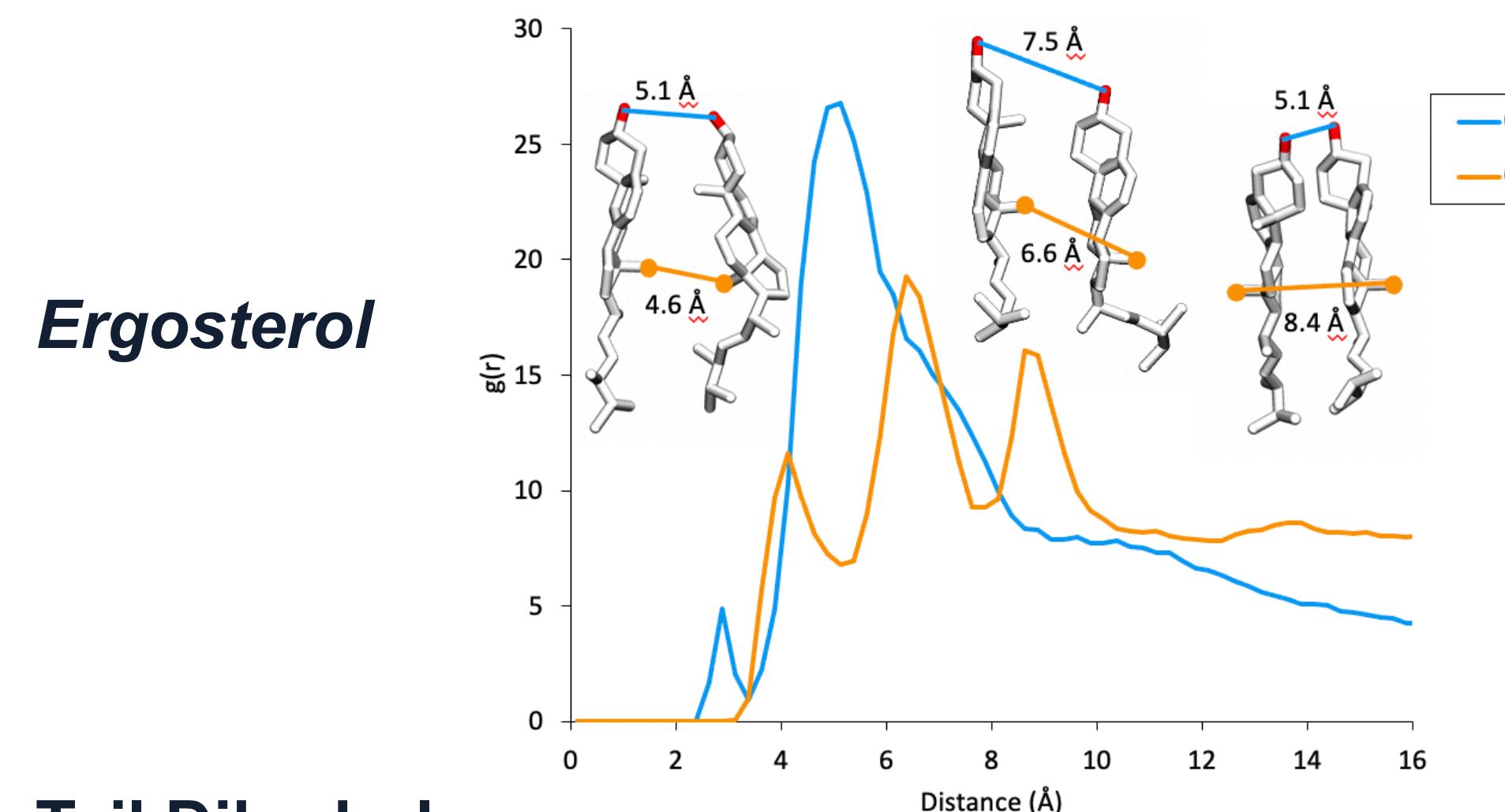
Chemical Shift



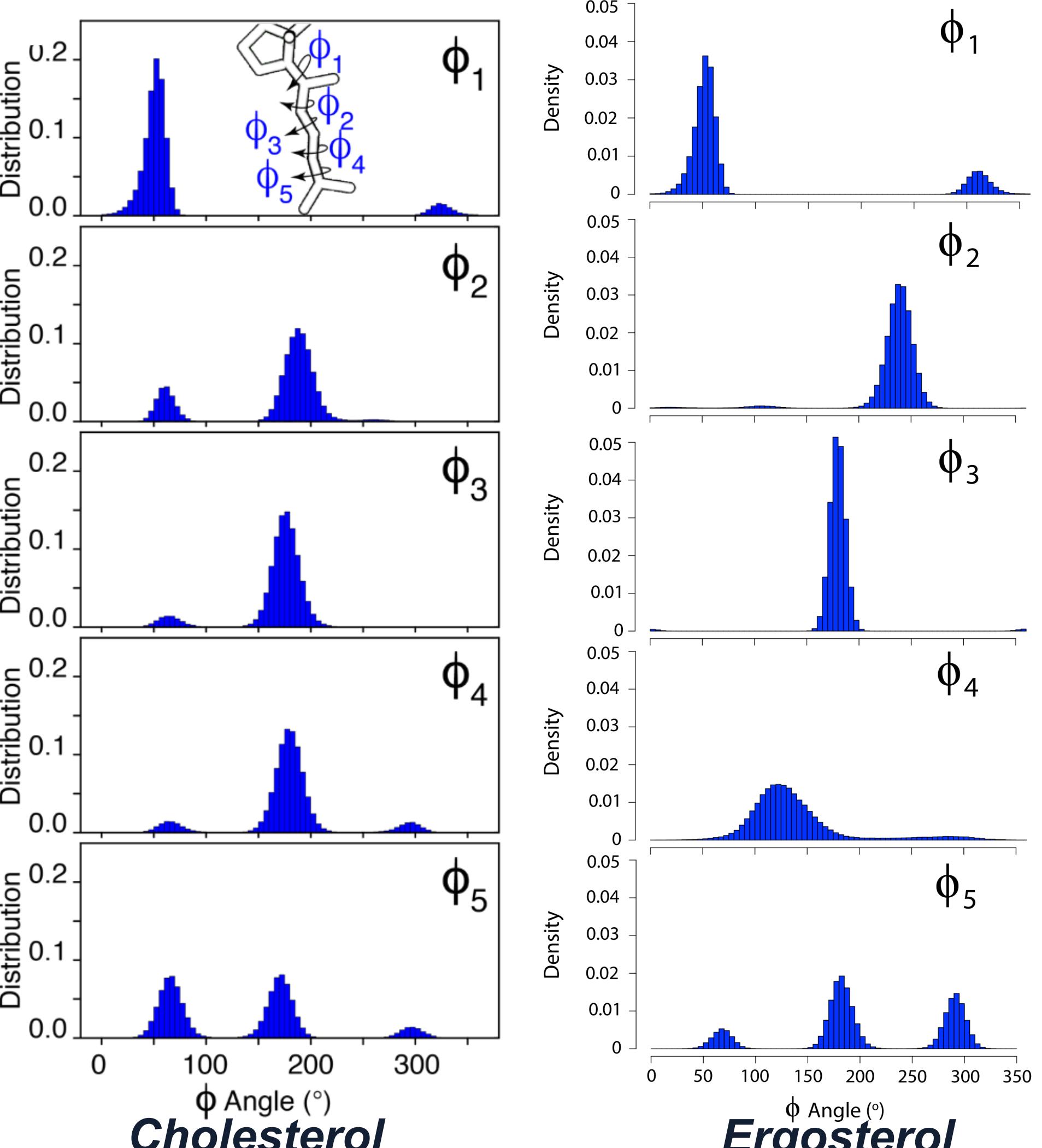
Inter-Sterol Pair Distances



Ergosterol



Tail Dihedrals



Conclusion

Through the combination of chemical shifts data on ergosterol and QM vs NMR simulations, it will be possible to ascertain the dynamic differences in the two sterols, cholesterol and ergosterol. Recognizing these differences is important in the advancement of amphotericin B. The process of developing and analyzing 10 replicate ergosterol models allowed for a more detailed and consistent collection of order parameters for deeper analysis.

Having the unique opportunity to compare 10 replicate ergosterol models to previously performed cholesterol simulations is what allowed for these findings. In addition, the analysis described here is capable of paving new ways to better understand the mechanism of amphotericin B action and design new safer versions of the drug.

References

- [1] Anderson, T. M.; ... Rienstra, C. M.; Burke, M. D. "Amphotericin Forms an Extramembranous and Fungicidal Sterol Sponge" *Nature Chemical Biology* 2014, 10, 400-406. doi: 10.1038/nchembio.1496

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