

## AMPHOTERICIN-DRIVEN STEROL EXTRACTION: PROBING THE MECHANISM

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### EXECUTIVE SUMMARY

The need for effective and nontoxic antifungal drugs is ever-present. By utilizing the petascale computing capabilities of Blue Waters, the research team aims to corroborate the experimental observation of the extraction of sterols from a membrane by an extramembranous amphotericin (AmB) sponge. The detail provided by all-atom molecular dynamics simulations will shed light on the nature of the AmB–sterol interactions and characterize the mechanism of extraction. Current simulations demonstrate AmB sponge–membrane surface interactions. Full characterization of the sterol extraction mechanism will open new directions for antifungal and antimicrobial drug design.

### RESEARCH CHALLENGE

Life-threatening systemic fungal infections are on the rise, and their effect is particularly severe for immunocompromised patients [1]. AmB is a potent antifungal drug with a remarkably low incidence of resistance development [2]. Unfortunately, AmB is toxic not only to fungal cells but also to human cells through cholesterol extraction [3], which limits the drug's use. Understanding the method of sterol extraction is the first step in the modification of AmB such that it becomes less toxic to humans.

### METHODS & CODES

Molecular dynamics (MD) is a versatile and powerful technique that allows for the study of large membrane systems at atomistic detail. The research team's simulations employed NAMD [3], a publicly available and highly scalable MD program that has demonstrated scalability on Blue Waters [4,5].

In preparation for simulations on Blue Waters, molecular systems were constructed using the highly mobile membrane mimetic model (HMMM), which reduces lipid tail lengths and fills the resulting inner leaflet space with a hydrophobic solvent [6,7]. The benefit of using this type of system in the preparation stage is that it accelerates the dynamics of the lipid headgroups by eliminating the steric bulk and hindrance caused by long lipid tails while simultaneously maintaining the atomistic detail of the headgroups. Accelerating lipid dynamics decreases the amount of simulation time necessary for sampling while maintaining the atomistic detail of the headgroups, which allows for the capture and characterization of lipid membrane interactions [8–10]. After the preparation phase, full lipid tails were grown on the lipids using the HMMM Builder [10]. The full-tail systems were then submit-

ted to replica exchange MD (REMD), which allows for the system to be simulated at different temperatures in parallel. REMD simulations are available in the NAMD software on Blue Waters.

### RESULTS & IMPACT

The researchers assembled two systems incorporating the extramembranous AmB sponge: one with a phosphatidylcholine (POPC) and cholesterol membrane and a second with a POPC and ergosterol membrane. (POPC is a lipid that is prevalent in human cells.) The team's MD simulations of the full-tail membrane systems revealed spontaneous movement of the sponge toward the membrane and the formation of an encounter complex. The stable orientations of the sponge and membrane demonstrate the existence of favorable AmB–membrane surface interactions. The researchers expect to observe AmB–sterol-specific interactions and eventually sterol extraction from the membrane into the sponge with longer simulation timescales conducted as part of the team's ongoing study.

The mechanism by which AmB kills fungal and human cells has not been determined. Recent studies have shed some light on that mechanism by demonstrating that the extramembranous sponge efficiently extracts ergosterol from yeast cells [11]. Using the petascale computing power of Blue Waters with MD to simulate the extraction of sterols by the AmB sponge will allow the team to more completely characterize the mechanism of sterol removal. Understanding this mechanism will enable new directions in the constant and time-demanding battle of pharmaceutical chemistry in the development of new antifungal drugs.

### WHY BLUE WATERS

To complete the proper sampling for the large membrane and extramembranous AmB sponge systems, the petascale computing power of Blue Waters is essential. These systems contain hundreds of thousands of atoms and require long simulation timescales of hundreds of connected replicas, each using hundreds of compute cores to observe AmB sponge–membrane interactions and, ultimately, sterol extraction. The goal of this project highlights the need for Blue Waters and future petascale resources for researchers to advance the development not only of less toxic antifungal medications but also the entire process of drug design.