An MD simulation-enhanced machine learning virtual screening for permeability and accumulation of antimicrobials

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The rise of antibiotic resistance poses a critical challenge to global healthcare, demanding the discovery of novel antibiotics. However, this endeavor is hindered by several bottlenecks, particularly for Gram-negative bacteria, where assessing the permeability of small molecules through outer membranes lacks a systematic approach. An efficient screening of vast libraries of drug-like compounds is essential for antimicrobial discovery.

In this poster, we introduce a machine learning (ML) model for predicting the permeability and accumulation of small molecules in Enterobacteriaceae. Our innovative approach incorporates statistical properties of selected molecular descriptors derived from Molecular Dynamics (MD) simulations. Traditionally, models rely on average values, assuming a normal distribution, potentially overlooking vital information. Small molecules, however, exhibit diverse conformational states with varying frequencies, leading to non-normal descriptor distributions.

By integrating higher-order statistical moments derived from MD simulations, we enhance existing models. Our work quantifies the improvement achieved through this integration and proposes a virtual screening workflow. This workflow allows for the rapid identification of small molecules with optimal permeability and accumulation, thereby advancing the discovery of antimicrobial agents.

References

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