Relating Outer Membrane Permeability with Activity in *E. coli* by Employing Statistics-Based Machine Learning

#!Stefan Milenkovic, &Sara Boi, @Silvia Puxedu, @Fabrizio Angius, #Matteo Ceccarelli, &Mariano Andrea Scorciapino

! Presenter # University of Cagliari, Physics Department & University of Cagliari, Chemistry Department @ University of Cagliari, Biomedical Department

Predicting antimicrobial activity is a cornerstone of successful virtual screening for novel antibiotic compounds. While advanced generative AI methods are capable of designing unknown compounds with desired activity, they often fail to accurately predict other crucial properties, such as permeability, efflux, and accumulation, which are fundamental for achieving optimal antibiotic efficiency.

In this poster, we present our efforts to develop statistically based machine learning (ML) methods for predicting permeability in *E. coli* for molecules with known minimum inhibitory concentration (MIC) values. By expanding our previous work where we have used the similar approach to create an interpretable ML model for predicting accumulation in *E. coli* we create a systematic overview where we test various models across various datasets in order to find the best permeability model.

Once, the best performing model is found, we predict permeability values for molecules with known MIC. Finally, we provide an estimate of how much of the variance in activity can be explained by permeability values.

By doing so, we aim to establish a foundational understanding of the functional dependence of antimicrobial activity on small-molecule microbiological properties, paving the way for improved predictive modeling in antibiotic research.

References:

1. Milenkovic, Stefan, et al. "Machine Learning Prediction of Small Molecule Accumulation in Escherichia Coli Enhanced with Descriptor Statistics." *Journal of Chemical Theory and Computation* 20.15 (2024): 6695-6705.
2. Milenkovic, Stefan, et al. "How the physical properties of bacterial porins match environmental conditions." *Physical Chemistry Chemical Physics* 25.18 (2023): 12712-12722.
3. Bodrenko, Igor V., Stefan Milenkovic, and Matteo Ceccarelli. "Diffusion of molecules through nanopores under confinement: Time-scale bridging and crowding effects via Markov state model." *Biomolecular Concepts* 13.1 (2022): 207-219.
4. Bodrenko, Igor V., et al. "Diffusion of large particles through small pores: From entropic to enthalpic transport." *The Journal of Chemical Physics* 150.21 (2019).