Predicting Small-molecule Accumulation in Gram-negative Bacteria to Design Better Antibiotics

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The rise of antibiotic resistance has turned up the pressure for the discovery of novel therapies against Gram-negative pathogens. Unfortunately, a lack of understanding how and why only certain molecules can penetrate bacteria has greatly hindered the development of new drugs. The first large-scale prospective study of small-molecule accumulation in *Escherichia coli* was conducted using a highly diverse compound library. Results from this study were used to train a predicting model of accumulation. By measuring variable importance in this model, we identified four factors as significantly contributing to small-molecule accumulation: presence of a primary amine, amphiphilicity, flexibility, and three-dimensionality. The molecular mechanism by which these factors contribute to accumulation was evaluated via a series of molecular dynamics simulations of OmpF, the principle mode of entry for small-molecules into *E. coli*. Further, several antibiotics with activity against only Gram-positive bacteria were modified in accord with the newly learned design principles. The bioactivity and mechanism of action of active compounds were evaluated so as to assess translation potential.