Interpeptide Interaction of Antimicrobial Peptides on Membranes Characterized with Atomistic Simulations

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Antimicrobial peptides (AMPs) are widely occurring host defence agents of interest as one route for addressing the growing problem of multidrug-resistant pathogens. Understanding the mechanisms behind their antipathogen activity is instrumental in designing new AMPs. Previously, our atomistic molecular dynamics simulations of cecropin B on a model anionic membrane revealed a cooperative mode of action (MOA) involving an interpeptide salt bridge between Glu and Lys. Similar modes of action have also been observed for other AMPs.

It was further demonstrated that such cooperative MOA does not solely rely on charged side chains. Namely, polar side chains forming hydrogen bonds may also contribute to a similar MOA. Assuming that mutated cecropin B can insert the membrane, it is of interest to investigate the probability of the aforementioned MOA among mutants by comparing their potential of mean forces (PMFs) along the degree of freedom between the two side chains in question.

On the other hand, PMF is a useful property in indicating the activities of AMPs. It is often calculated along the path where peptides permeate the membrane as the reaction coordinate, based on the observation that AMPs insert the cell membrane and cause cell death. However, it is not uncommon that the resulting PMFs do not cross the transition state ensemble and thus the comparison of AMPs activities using PMFs becomes ambiguous. We are therefore also interested in whether the PMFs along the aforementioned alternative reaction coordinate are indicative regarding the antimicrobial activity.