Machine Learning Guided Exploration of Antimicrobial Peptide Chemical Space

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Antimicrobial peptides play a crucial role in combating antimicrobial resistance. The sequence of KKLLKLLKLLL (ln65), a short membrane disrupting but hemolytic linear undecapeptide discovered, and its over 30 diastereomers have been investigated by our group to date and many promising sequences in terms of antibacterial activity have been discovered. However, there are 2048 possible diastereomers that could be investigated. Based on this, our goal is to discover the chemical space of possible 2048 diastereomers using machine learning and our high-capacity parallel synthesizer.

Our proposed method integrates computational design with a semi-automated synthesizer. We compare three design approaches: random sequence selection, genetic evolution through single point mutations of active sequences, and machine learning-guided design using GPT-3 fine-tuned on experimental data. The iterative process involves synthesizing novel peptide sequences by our parallel synthesizer, which operates at a high temperature, resulting in significantly shorter reaction times and is capable of synthesizing 48 sequences simultaneously. Our testing protocol consists of testing the antibacterial activity on 5 bacterial strains and testing the hemolytic activity on human red blood cells (hRBCs). And finally, the activity and hemolysis data obtained are used to refine computational designs for subsequent iterations.

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