Design of highly potent anti-biofilm, antimicrobial peptides using explainable artificial intelligence

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Antimicrobial peptides (AMPs) are being recognized as viable alternatives to conventional small molecule antibiotics, offering broad-spectrum efficacy and progressively addressing the challenges of bacterial resistance, particularly the adaptive resistance of biofilms.[1] To enhance the efficacy of AMPs, advanced methods for rational peptide design are essential to optimize their properties while reducing the costs of synthesis and screening. In this work, we introduce a computational approach for the rational *de novo* design of antimicrobial and anti-biofilm peptides (ABPs) using an explainable artificial intelligence (XAI) framework. This framework integrates a Wasserstein Autoencoder (WAE)[2,3] with a non-linear dimensionality reduction method - generative topographic mapping (GTM)[4]. The WAE was used to learn the latent representations of peptide sequences, while the GTM facilitated the generation of new AMPs and ABPs through an illustrative visualisation of the latent space in the form of 2D maps. The high potency of the peptides designed with this pipeline was confirmed experimentally by their synthesis and subsequent activity testing against methicillin-resistant *Staphylococcus aureus* (MRSA), achieving a 100% hit rate in targeting biofilms. The most effective anti-biofilm peptide identified in this study demonstrated almost one order of magnitude improvement in IC_{50} value compared to the potent anti-biofilm peptide termed "1018", which served as a positive control. The developed pipeline is readily extendable for the optimization of other peptide properties, such as cytotoxicity, aggregation potential, and proteolytic stability, highlighting its prospective use in the rational design of peptide-based therapeutics.

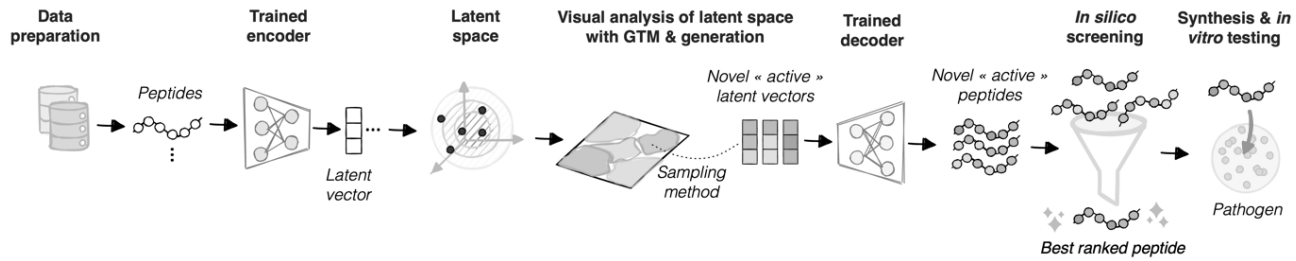

Figure 1. Summary of the pipeline created in this study, which was effectively utilized to generate ABPs and AMPs.

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