Methods	AMP			ACP		
	Similarity	Instability	Antimicrobial	Similarity	Instability	Anticancer
MMCD (w/o InterCL & IntraCL)	27.4794	42.5359	0.8013	31.2820	34.6888	0.6996
MMCD (w/o IntraCL)	26.6889	41.2631	0.8584	28.9782	33.0268	0.7513
MMCD (w/o InterCL)	24.9079	41.7646	0.8494	28.0143	33.9816	0.7352
MMCD	24.4107	39.9649	0.8810	27.4685	31.7381	0.7604

Table 3: Ablation study on the sequence-level generation task.

were operated on both AMP and ACP datasets, and the results are shown in Table 3 and Appendix Table 1. When the Inter-CL was removed (w/o Inter-CL), we observed a decline in all metrics for peptide sequence and structure generation, implying the importance of aligning two modalities via CL. The variant (w/o Intra-CL) results signified that using the CL to differentiate therapeutic and non-therapeutic peptides contributes to the generation. As expected, the performance of MMCD dropped significantly after removing both Inter-CL and Intra-CL (w/o Inter-CL & Intra-CL).

To better understand the strengths of Inter-CL and Intra-CL, we performed the t-SNE (**?**) visualization using the learned embeddings of peptides on the AMP dataset. As illustrated in Figure 3-a, Inter-CL effectively promoted the alignment of sequence and structure embeddings, facilitating the shared crucial information (dashed circle) to be captured during diffusion. The t-SNE of Intra-CL (Figure 3-b) also revealed that it better distinguished therapeutic peptides from non-therapeutic ones in the embedding distribution. And the resulting distribution bias may identify more potential generation space, thus leading to higher quality and diversity of therapeutic peptides generated by MMCD. Overall, MMCD with all the modules fulfilled superior performance, and removing any modules will diminish its generation power.

Peptide-docking analysis

To test the validity of generated peptide structures, we conducted a molecular-docking simulation. Here, a peptide was randomly selected from the AMP dataset as the reference, and the methods (Figure 4) were employed to generate corresponding structures based on the sequence of the reference peptide (see details in Appendix C). The lipopolysaccharide on the outer membrane of bacteria (**?**) was selected as the target protein for molecular docking. Then, we extracted the residues within a 5 proximity between peptides (i.e., the reference and generated structures) and the active pocket of target protein in docking complexes, to visualize their binding interactions (**?**). Of these docking results, all methods yielded a new structure capable of binding to the target protein, and our method exhibited the highest docking scores and displayed binding residues most similar to the reference structure. This prominent result underscored the reliability and therapeutic potential of our method for peptide generation.

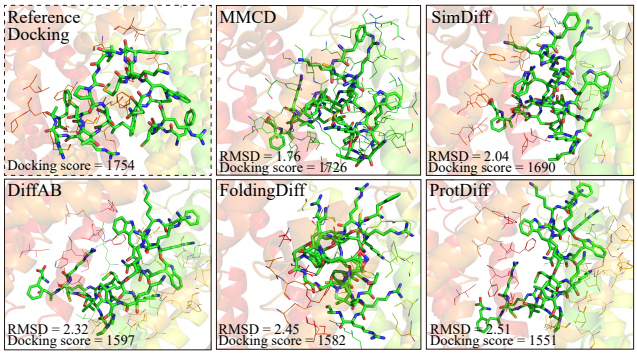

Figure 4: Docking analysis (interactive visualization between target protein and peptides) of the reference and generated structures by MMCD and baselines. Thick lines represent the residues of peptides, and the thin lines show the binding residues for protein-peptide complexes.

Conclusion

In this work, we propose a multi-modal contrastive diffusion model for the co-generation of peptide sequences and structures, named MMCD. MMCD is dedicated to leveraging a multi-modal contrastive learning strategy to capture consensus-related and difference-related information behind the sequences/structures and therapeutic/non-therapeutic peptides, enhancing the diffusion model to generate high-quality therapeutic peptides. The experimental results unequivocally demonstrate the capability of our method in co-generating peptide sequence and structure, surpassing state-of-the-art baseline methods with advantageous performance.

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