REVIEW ARTICLE

Advances in the Application of Deep Learning for Antimicrobial Peptide Screening

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Abstract

The problem of bacterial resistance to antibiotics is becoming more and more serious, and it is urgent to develop new antibacterial drugs to cope with this situation. Antimicrobial peptides (AMPs) are a group of natural peptides with advantages including broad-spectrum antibacterial activity and a low tendency to induce resistance, and have become attractive alternatives to antibiotics. However, their broad application is constrained by the inefficiency and high cost of conventional screening methods. Recently, deep learning (DL) has enabled more streamlined identification, design, and prediction of AMP activity through advanced data processing and pattern recognition. A few review articles have previously summarized the application of machine learning (ML) in the identification of antimicrobial peptides, but none of them have detailed the latest advancements in DL. In this review, the latest AMP classification and screening approaches achieved by DL techniques are surveyed. First, the biological background of AMPs is introduced, followed by current applications of antimicrobial peptides in industry and medical treatment. The most popular DL techniques are explained, and state-of-the-art research based on these techniques for classifying antimicrobial peptides and designing novel peptide sequences is highlighted. Finally, the limitations and challenges of AMP prediction are discussed.

Keywords: deep learning, antimicrobial peptides, classification, screening, prediction, drug resistance.

1 Introduction

The introduction of antibiotics significantly reduced mortality from bacterial infections. However, the extensive use of antibiotics has resulted in major challenges, particularly the growing crisis of antimicrobial resistance and the inappropriate use of antibiotics in clinical practice. As a result, the discovery of new therapeutic agents has become a critical priority. Given the shortcomings of conventional antibiotics, antimicrobial peptides (AMPs) have arisen as highly appealing alternatives [1].

Antimicrobial peptides are a class of small basic peptides called AMP formed by several to hundreds of amino acids, which are abundant in nature. They are highly water-soluble, usually cationic amphipathic molecules (possessing both hydrophobic and hydrophilic regions) with a molecular weight of approximately 4000 Da [2]. AMPs have been

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discovered in animals, microorganisms, and plants. For instance, cationic AMPs found in wheat endosperm and other cereal species show broad-spectrum efficacy against mammalian cells and various pathogenic bacteria [3]. Based on secondary structure, AMPs can be classified into four categories: α-helical peptides, β-sheet peptides, extended peptides, and loop peptides [4]. The different structures and mechanisms of action of AMPs enable unique interactions with various microbial targets, conferring a wide range of antiviral, antifungal, and antibacterial properties.

Deep learning technology is opening up a new path for efficient screening of antimicrobial peptides. By constructing deep neural network models, researchers can establish multi-level associations between the sequence characteristics, physicochemical properties, and biological activities of known AMPs. Attention models capture synergistic effects among key amino acid residues, while transfer learning leverages cross-species peptide library data. This data-driven method can not only quickly predict potential antibacterial activity in a large number of candidate peptides but also reverse design new peptide molecules with a specific antibacterial spectrum by generating an adversarial network, which is much more efficient than traditional experimental screening, and provides an artificial intelligence solution for coping with the crisis of antibiotic resistance.

1.1 Discovery of Early AMPs

Discovered by Alexander Fleming in 1922 during investigations on a patient with acute coryza, lysozyme—a bacteriolytic substance named for its ferment-like properties—was first identified in nasal mucus for its ability to rapidly dissolve Micrococcus lysodeikticus; later found widely distributed in human tissues (e.g., cartilage, epidermis) and secretions (e.g., tears, sputum, saliva), as well as in animal tissues, egg white and some vegetables, it exhibits inhibitory, bactericidal and lytic effects on various bacteria, especially Gram-positive cocci. In 1928, L. A. Rogers and E. O. Whittier identified nisin, an antimicrobial peptide produced by lactic acid bacteria, during their studies on limiting factors in lactic fermentation; this peptide was found to inhibit bacterial growth by contributing to the formation of inhibitory metabolites and diffusible inhibitory substances, and it was later recognized for its natural antimicrobial activity [5].

The discovery of antimicrobial agents is not limited to bacteria. Zeya and Spitznagel detected a class of antimicrobial peptides in the neutrophils of rabbits and guinea pigs in the 1960s, and the same class of antimicrobial peptides (HNP-1, HNP-2, HNP-3) was later identified from human neutrophils by Ganz and Lehrer in the 1980s; these antimicrobial agents were named defensins [6, 7]. In 1987, Michael Zasloff discovered magainins, from the ventral skin of the African clawed frog Xenopus laevis exhibit broad-spectrum antimicrobial activity against bacteria, fungi, and protozoa [8]. In 1998, Yan and Michael identified two antimicrobial peptides from the venom of the wolf spider Lycosa carolinensis exhibit potent broad-spectrum antimicrobial activity against bacteria and yeasts via pore-forming mechanisms, and may play dual roles in prey capture and protecting the spider from infections [9].

Antimicrobial peptides also exist in plants. Plant AMPs, a key component of plants' barrier defense system, were first isolated as purothionin from wheat (Triticum aestivum) endosperm by Balls and collaborators in 1942 [10]. Later in 1990, another class of AMPs isolated from wheat endosperm by Collila and Mendez [11].

1.2 Mechanisms of Action

Antimicrobial peptides exert their antibacterial activity through complex mechanisms of action, including targeting bacterial cell walls, cell membranes, and fungi.

1.2.1 Mechanism Against Bacteria

Antimicrobial peptides (AMPs) are predominantly positively charged and are strongly attracted to negatively charged lipopolysaccharides (LPS) through electrostatic adsorption, leading to their enrichment on the bacterial surface. Alternatively, AMPs may displace magnesium ions: they can replace the divalent cations that stabilize the LPS structure, causing outer membrane disruption and the formation of transient pores or "self-promoted uptake" pathways, thereby enabling the peptides to traverse the outer membrane. Following this disturbance, AMPs can penetrate the bacterial cell wall, target peptidoglycan and the inner membrane, ultimately causing cell death. Thanatin forms dimers on the bacterial LPS outer membrane, enhancing cationicity and amphipathicity, disrupting outer membrane permeability and neutralizing surface charges, thereby directly inducing bacterial agglutination and death. After outer membrane damage, Thanatin enters the periplasmic space as monomers, binds to the Lpt transporter complex, blocks LPS transport to the

outer membrane, further destabilizes outer membrane integrity, and accelerates bacterial death [12]. For Gram-positive bacteria, higher concentrations of AMPs are generally required, leading to cytoplasmic leakage and dissipation of membrane potential.

In addition to the aforementioned mechanisms, certain antimicrobial peptides can achieve antibacterial efficacy by inducing bacterial autolysis [13]. Both Pep 5 and nisin are cationic peptides carrying positive charges. These cationic peptides competitively bind to the negatively charged teichoic acids of bacteria, displacing the amidases originally bound there, thereby restoring amidase activity to initiate cell wall hydrolysis. This leads to cell wall damage, bacterial osmotic lysis, and death [14].

1.2.2 Mechanism Against Fungi

Fungi are eukaryotic microorganisms widely distributed in nature, including yeasts and molds. The mechanism of action of antifungal peptides, a subset of antimicrobial peptides, generally involves inhibiting fungal growth and reproduction or directly killing fungi [15].

AMP targets fungal cells by binding to specific components of the cell membrane and cell wall. The primary targets of AMPs are ergosterol (found exclusively in fungal plasma membranes) and fungal cell wall components, including chitin, mannoproteins, chitosan oligomers, and β-glucans. By interacting with these targets, AMP can cause the destruction of fungal cells. The main destruction mechanisms are as follows:

1. Disruption of Membrane Integrity: Binding to the fungal membrane via electrostatic interactions and forming pores (e.g., Polybia-CP). Upon discovering its antifungal properties, researchers utilized structure-guided peptide design techniques to find that polybia-CP also exhibits antiplasmodial and anticancer activities, thereby expanding the functional scope of antimicrobial peptides [16].

2. Interference with Cell Wall Synthesis: Inhibiting enzymes involved in β-glucan or chitin synthesis (e.g., LL-37). Candida albicans is a major pathogenic fungus in humans, typically causing infection by adhering to host mucosal cells. Tronchin et al. [17] demonstrated that LL-37 binds to Xog1p, a cell wall protein of C. albicans , thereby inhibiting the β-1,3-glucan hydrolase activity of Xog1p and subsequently disrupting the remodeling of the cell wall β-1,3-glucan network. This impairment of adhesion-related cell wall structures consequently reduces the adhesive capacity of the fungal cells [18].

3. Damaging mitochondrial function: Upon mitochondrial dysfunction, fungi undergo energy collapse, metabolic arrest, and reproductive failure, ultimately leading to cell death.

For example, Lp-Def1 investigated by Brambila Vieira et al. [19] exerts its antifungal mechanism independently of cell membrane perforation and massive reactive oxygen species (ROS) generation. Its core mechanism lies in significantly disrupting mitochondrial function in Candida albicans , thereby providing a candidate molecule for the development of novel anti-Candida peptide-based therapeutics.

1.2.3 Mechanisms of Interaction with Cell Membranes

The interaction between AMPs and cell membranes is described by four primary models (Figure 1.):

1)Toroidal Pore Model: In the toroidal model, the hydrophilic region of the antimicrobial peptide associates with the polar headgroups of the lipid membrane, whereas the hydrophobic region interacts with the nonpolar tails [20]. When the peptide-to-lipid ratio reaches a critical threshold, the peptides insert vertically into the lipid bilayer without specific peptide-peptide interactions. The interactions between the peptides and the polar headgroups of phospholipids create voids within the lipid membrane, inducing inward membrane curvature and compromising the cell's ability to maintain normal osmotic pressure [21].

Research findings indicate that AMPs inducing curvature in the bacterial phospholipid monolayer to form toroidal pores with diameters of 1-2 nm, ultimately leading to bacterial death [22].

2)Barrel-Stave Model: After adsorbing to the membrane surface, the hydrophobic regions of AMPs remain within the membrane interior, forming pore structures that cause bursting of bacterial cellular contents [23]. Yang et al. [24] investigated the distinction between the barrel-stave model and the toroidal model using melittin pores as an example, demonstrating that oriented circular dichroism (OCD) can distinguish the barrel-stave model—composed exclusively of peptide helices—from the toroidal model, which is formed by both peptides and lipid headgroups.

3)Carpet Model: AMPs initially align parallel to the

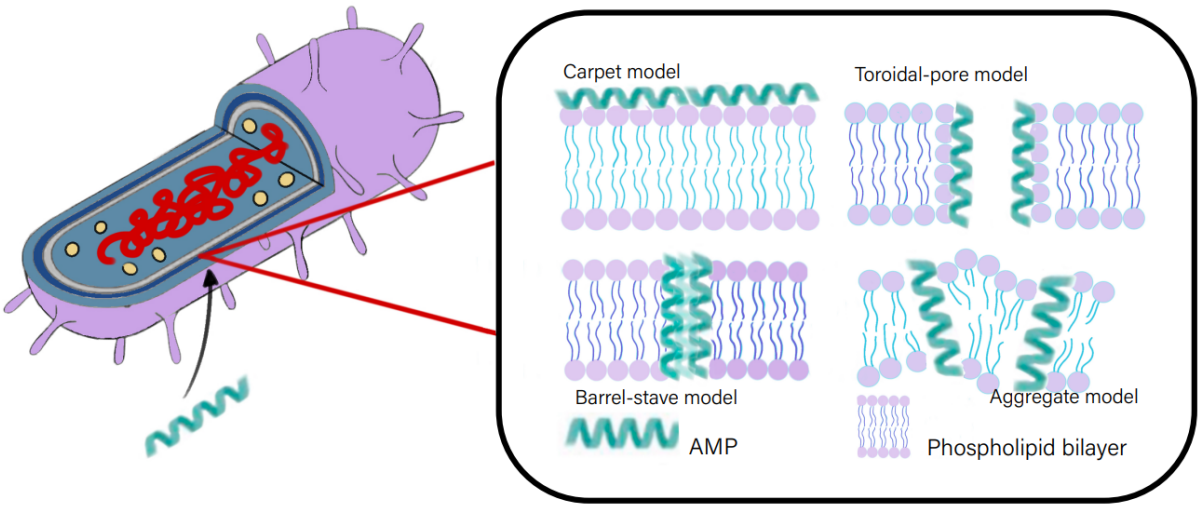

Figure 1. Interaction with Cell Membranes.

cell membrane. Upon reaching a critical concentration threshold, they alter the membrane surface tension, causing deformation and eventual disintegration of the membrane [25]. Electrostatic-driven action — Positively charged AMPs adsorb onto negatively charged bacterial cell membranes, disrupting membrane integrity and transmembrane potential, thereby leading to intracellular substance leakage and bacterial death [26].

4)Aggregate Model [25]: Antimicrobial peptides form stochastic transmembrane aggregates with lipids and water on the membrane, which not only induce membrane leakage for bacterial killing but also enable the peptides to penetrate into the cell interior to attack intracellular targets. This represents the broadest-spectrum and most authentic mode of action for the majority of antimicrobial peptides.

The specific mechanism involves two sequential steps. First, cationic peptides bind electrostatically to the negatively charged bacterial membrane surface via charge adsorption, orienting parallel to the interface between hydrophilic headgroups and hydrophobic tails. Upon reaching a threshold concentration, the peptides undergo rearrangement and aggregation, forming stochastic, amorphous transmembrane micelle-like aggregates.

Then, these transmembrane channel aggregates penetrate through the bilayer, serving as conduits for ion or cytoplasmic content leakage, thereby inducing membrane depolarization, intracellular efflux, and ultimately bacterial cell death [27].

1.3 Therapeutic and Industrial Applications

1.3.1 Biomedicines in Pharmaceutical Industry

Published and clinically applied in 1941, this AMP isolated from a soil bacillus is used in the lab to inhibit gram-positive bacteria growth and clinical treatment for gram-positive bacterial infections like ulcers and sinusitis. This marks the rise of AMPs in the medical field [28]. As a Type A (I) lantibiotic, nisin is an antimicrobial peptide produced by certain Gram-positive bacteria, commercially marketed in England in 1953 as an antimicrobial agent. It can be used alone or in combination with conventional therapeutic drugs for the treatment of drug-resistant bacterial infections, oral diseases, cancers and other disorders. Although minor nisin resistance has been observed under laboratory conditions, the risk of resistance development is extremely low, making it a promising alternative and adjunctive therapeutic agent to conventional antibiotics [29].

Another domain for AMPs lies in preventive healthcare, specifically targeting the prophylaxis of latent diseases. Implantable medical devices are prone to infection, whereas hydrogels containing antimicrobial peptides, when injected into the interfacial region between the implant and prosthesis,

exhibit high antibacterial activity and low toxicity, demonstrating their feasibility [30]. Similarly, catheter-associated infections account for 75% of nosocomial infections, with common causative pathogens including Escherichia coli , Staphylococcus aureus , Klebsiella pneumoniae , and Candida species, among others. The D-amino acid antimicrobial peptide Chain201D was selected and covalently immobilized onto the device surface via a covalent grafting strategy, achieving contact-killing efficacy while circumventing the systemic toxicity associated with systemic drug administration [31].

1.3.2 Food Preservatives and Packaging in the Food Industry

Extending the shelf life of food products is one usage for peptides [32] having antibacterial/antifungal action. The proliferation of microorganisms, particularly fungus, inhibits the long-term preservation of fresh goods like bread or necessitates the application of preservatives to improve the product's quality. Antimicrobial peptides might thus be employed to enhance the functioning of these products by limiting their proliferation [33].

Packaging plays a crucial role in the food industry as it provides food safety, improves shelf-life, facilitates handling, and provides protection against physical harm [34]. In food packaging, antimicrobial peptides (e.g., ε-polylysine, nisin) are applied by encapsulation in liposomes or direct incorporation into edible films/biopolymer matrices; they enhance food preservation by inhibiting pathogenic bacteria (Listeria monocytogenes, Escherichia coli, etc.), while liposome encapsulation protects peptides from environmental factors, and the resulting packaging (with desirable low water solubility and versatility) enables functional food design with sustainable value addition [35].

Tanhaeian et al. [36] employing a food-grade Lactococcus lactis expression system, camel lactoferrin chimeric peptide (cLFchimera) was successfully recombinantly expressed. This peptide exhibits broad-spectrum antimicrobial activity against various foodborne pathogenic bacteria, concurrently possessing antibiofilm and antioxidant capabilities alongside excellent thermal stability. Molecular dynamics simulations confirmed that it can strongly bind to bacterial LPS and DNA via positively charged residues, establishing it as a highly promising bio-preservative for food applications. Therefore, although antimicrobial peptides are primarily employed in medicine and agriculture, their potential applications in food packaging and preservation should not be overlooked.

1.3.3 Substitutes for Antibiotics and Pesticides in Agriculture and Animal Husbandry

In recent years, the emergence of antibiotic-resistant bacteria and the increasing health and environmental risks have raised serious concerns. In animal husbandry, antimicrobial peptides(AMPs) serve as promising alternatives to antibiotics [37], applied via oral intake, in ovo administration, or as feed additives to prevent/treat bacterial infections (e.g., Salmonella, Escherichia coli) in poultry, modulate immune responses, promote growth performance by improving intestinal health and microbiota balance, and reduce antibiotic resistance risks [38]. In aquaculture, antimicrobial peptides such as penaeidins, crustins, and anti-lipopolysaccharide factors (ALFs) serve as viable alternatives to antibiotics, applied via recombinant production, dietary supplementation, or nanoformulation to combat pathogens like Vibrio parahaemolyticus and white spot syndrome virus (WSSV) in shrimp, modulate innate immunity [39].

In agriculture, to increase crop yields [40], various chemical pesticides are frequently applied during the plant growth period to combat plant diseases and insect pests. However, the long-term use of chemical pesticides has made the hazards of residues to humans and animals increasingly evident. Schaefer et al. [41] employed Agrobacterium tumefaciens -mediated transformation to introduce three disease resistance-related genes into tomato cotyledons: the iris ribosome-inactivating protein gene (I-RIP), the maize β-glucanase gene (M-GLU), and the four o'clock antimicrobial peptide gene (Mj-AMP1). They found that tomato plants transformed with the antimicrobial peptide gene exhibited significantly enhanced resistance to early blight. And hevein Pn-AMP from Pharbitis nil protected tobacco against Phytophthora parasitica [42]. This demonstrates that antimicrobial peptides can play a significant role in agricultural disease management and, to a certain extent, serve as substitutes for chemical pesticides.

1.4 Limitation of AMPs and Bacterial Resistance

Although antimicrobial peptides have been proposed as promising alternatives for bacterial therapy, AMPs possess certain limitations that hinder their success in the development process. The main limitations include: time-consuming and costly validation

processes such as cell experiment and toxicity testing, inconsistent protein stability, and the specificity of host physiological conditions.

Although the likelihood is low, some studies have indicated that bacteria may have evolved survival strategies to resist the bactericidal modes of antimicrobial peptides. With an array of antimicrobial peptides being produced by different human cells, bacteria have developed a number of strategies to prevent AMP binding, to avoid their lytic effects or to degrade the peptides, in order to thrive in the human host [43].

2 Deep Learning Model

Deep learning is a subfield of machine learning that focuses on automatically learning and extracting complex features of data through multi-layer neural networks. It can gradually abstract higher-level features from basic data, so as to solve complex tasks that legacy algorithms are difficult to deal with. Several fundamental deep learning models, each having particular strengths and application domains (Figure 2).

2.1 Deep Learning with CNN Layers

Convolutional Neural Network (CNN) is a well-known deep learning architecture inspired by the natural visual perception mechanism of the living creatures. There are numerous variants of CNN architectures in the literature. However, their basic components are very similar. Taking the famous LeNet-5 as an example, it consists of three types of layers, namely convolutional, pooling, and fully-connected layers. The convolutional layer aims to learn feature representations of the inputs. The pooling layer aims to achieve shift-invariance by reducing the resolution of the feature maps. It is usually placed between two convolutional layers. Each feature map of a pooling layer is connected to its corresponding feature map of the preceding convolutional layer. The last layer of CNNs is an output layer. Deep CNNs have made breakthroughs in processing image, video, speech and text (Figure 2). Current CNN model works very well for various applications [44]. Xu et al. [45] constructed a comprehensive AMP dataset and proposed the iAMPCN two-stage CNN framework using four amino acid encodings, exhibiting excellent performance, especially for short AMPs. Ding et al. [47] proposed the AMP-EBiLSTM strategy using BPF and PSEAAC for feature extraction, with the EBiLSTM model achieving 92.39% accuracy and an AUC of 0.9771 on the test set.

CNNs can be employed in antimicrobial peptide (AMP) screening to filter AMPs from massive sequence datasets and evaluate peptide potential, as well as to combine with other models to enhance the performance of ensemble models. Xiao et al. [46] developed the iAMP-CA2L classifier based on Cellular Automata Images (CAI) and a CNN-BiLSTM-SVM architecture, attaining high accuracy (0.9413) and MCC (0.88296) using dataset S1.

2.2 Deep Learning with RNN Layers

Recurrent Neural Networks (RNNs) represent a class of deep learning architectures particularly suited for temporal data analysis. The defining characteristic of these networks is their recurrent neuronal connections, which facilitate information transfer between successive time steps and enable the model to learn sequential dependencies. Structurally, RNNs comprise three fundamental components: an input layer that receives sequential vectors at each time step, a hidden layer for internal state representation, and an output layer for generating predictions [48]. However, standard RNNs often encounter the problem of vanishing or exploding gradients when processing long sequences. To address the vanishing gradient issue in long-sequence modeling, Long Short-Term Memory (LSTMs) networks were developed. Liu et al. [49] constructed an ALSTM model, based on a long short-term memory (LSTM) neural network and an attention mechanism, along with a combined screening deep network. They analyzed the characteristics of peptide segments derived from simulated enzymatic hydrolysis of proteins expressed by the sludge microbial genome to screen for potential antimicrobial peptides. The screening results were supported through molecular docking and dynamic simulations. The trained fusion model reached an accuracy, precision, recall, and F1-score of 1. The screening results were verified by molecular docking and dynamic simulation. The accuracy, precision, recall, and F1 score of the fusion model reached 1. From the screening, 17 high-scoring short peptide sequences were identified. Through molecular docking and dynamic simulations, three peptide segments—LLPRLLARRY, GVREIHGLNPGGCLHTVRLVCR, and FRTTLAPHVLTRLLAPCW—were confirmed to possess high antimicrobial activity and good stability. This study overcomes the limitations

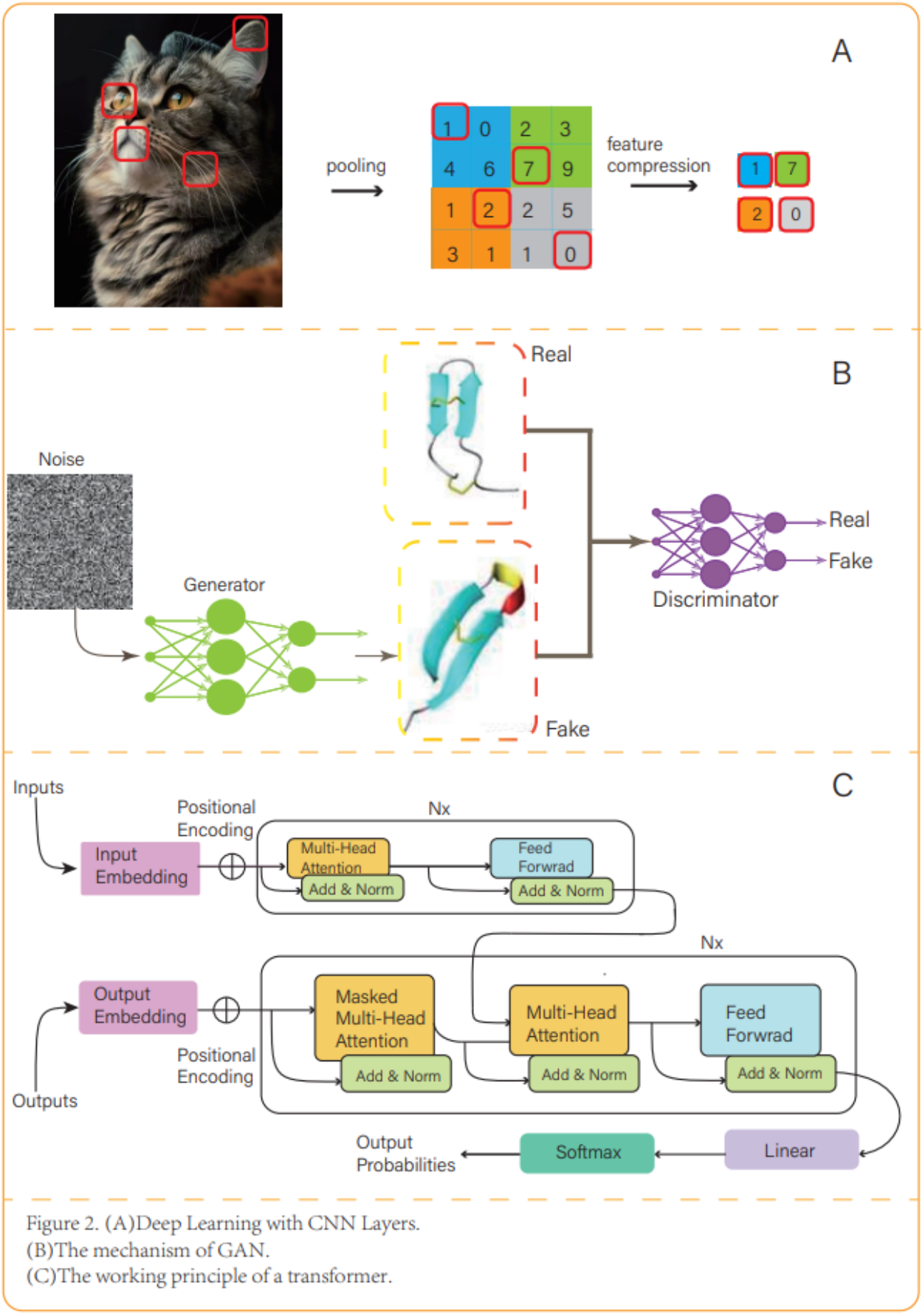

Figure 2. (A)Deep Learning with CNN Layers.
(B)The mechanism of GAN.
(C)The working principle of a transformer.

Figure 2. Deep Learning Model.

of classic screening methods, improves screening efficiency and accuracy, offers a new perspective for combating multidrug-resistant bacterial infections, and provides firm support for the future development of antimicrobial drugs. Another RNN variant, the Gated Recurrent Unit (GRU), simplifies the gating structure, further reducing the computational complexity of the model.

2.3 Applications of GANs

Since their inception in 2014, Generative Adversarial Networks (GANs) have rapidly emerged as a powerful tool for generating realistic and diverse data across multiple domains, including computer vision and other application areas [50]. GANs have emerged as a transformative deep learning approach for generating high-quality and diverse data. In GAN, a generator network produces data, while a discriminator network evaluates the authenticity of the generated data (Figure 2). Through an adversarial mechanism, the discriminator learns to distinguish between real and fake data, while the generator aims to produce data that is indistinguishable from real data [51]. Zhao et al. [52] developed dsAMP (for classification/function prediction using CNN-Attention-BiLSTM and transfer learning) and dsAMPGAN (a GAN for generating candidate sequences). dsAMP achieved over 95% accuracy on small datasets with transfer learning. The success of GANs has spurred their widespread adoption across numerous applications, including image and video synthesis, data augmentation, super-resolution, inpainting, anomaly detection, and image editing. GANs have also been employed to address data scarcity issues in machine learning by generating synthetic data to enhance the effectiveness of models trained on limited datasets [51].

GAN can undertake core tasks in antimicrobial peptide screening, including de novo design of AMP sequences and simultaneous optimization of multiple critical AMP properties (high antimicrobial activity, low cytotoxicity), as well as auxiliary tasks such as providing high-quality training data and integrating with screening tools to ensure safety.

2.4 The Use of VAEs

Variational autoencoders (VAEs) that have been widely used for data imputation, augmentation, and batch effect correction. Autoencoders are unsupervised deep learning models widely employed for dimensionality reduction and feature extraction tasks—specifically, embedding. The model architecture utilizes neural networks to compress input data into a low-dimensional latent space through an encoder, and attempts to reconstruct it back into the original space via a decoder [53]. Using a variational autoencoder (VAE), Dean et al. [54] trained on the known antimicrobial peptide database APD3, generated new peptide sequences by linear interpolation, and performed antibacterial activity experiments on the generated peptides. The new peptide sequence with antibacterial activity was successfully generated, and the peptide generated near the active peptide region in the potential space had stronger antibacterial activity. This approach proficiently produced new peptides with antimicrobial properties; peptides generated from regions closer to known active peptides in the latent space exhibited stronger activity. Experimental results confirmed that the generated peptides inhibited the growth of Escherichia coli, Acinetobacter baumannii, and Staphylococcus aureus. This study describes a novel method for automated antimicrobial peptide generation, points out the potential of VAEs in antimicrobial peptide design, and contributes to progress in the wider field of peptide and protein engineering.

Based on the VAE model, a series of analogs with similar properties can be generated from known high-activity antimicrobial peptides, and it can also serve as a foundational architecture to integrate with other advanced technologies to enhance the quality of generated outputs.

2.5 Transformers For Deep Learning Tasks

Deep Neural Networks (DNNs) have emerged as the primary infrastructure and state-of-the-art solution for most learning-based machine learning tasks in the field of artificial intelligence. Transformers are a type of DNNs that offer a solution to the limitations of sequence-to-sequence (seq-2-seq) architectures (Figure 2). Unlike traditional recurrence methods, Transformers utilize attention to learn from an entire segment of a sequence, using encoding and decoding blocks [55]. Furthermore, transformers are faster because they can operate in parallel, unlike recurrent networks, and can be computed via Graphics Processing Units (GPUs), thereby enabling more rapid computation for tasks with large input volumes [56]. Fang et al. [57] proposed the CELA-MFP deep learning framework, using the protein language model (pLM) to extract peptide sequence features, combined with comparative learning and a Transformer decoder to

predict multifunctional therapeutic peptides. On the MFBP and MFTP datasets, CELA-MFP outperforms the existing methods in most evaluation indicators. The interpretability of the model was demonstrated through the visualization of attention patterns. This model delivers a more accurate and effective method for the prediction of multifunctional peptides, which is helpful to understand the function of peptides and promote peptide-based drug development.

During screening, Transformers can accurately distinguish antimicrobial peptides from non-antimicrobial peptides, comprehensively parse multiple bioactivities of peptides, or design and optimize peptides on demand. Moreover, Transformers can also serve as feature extractors to enhance the performance of other models.

These models and technologies continuously evolve and integrate, advancing innovation and development throughout varied fields, including AMP research.

3 AMP Screening by Deep Learning

3.1 AMP Identification and Classification

AMP identification is the starting point of screening workflows. It entails determining whether a peptide is an AMP, followed by classifying different AMPs to reduce computing load and stop overfitting. Deep learning has achieved substantial progress in this area. Numerous studies use deep learning systems tomatically extract features from sequences for AMP identification and classification, obtaining high accuracy on several datasets and exceeding traditional machine learning methods. Various online tools have been developed for subsequent research and reference.

Accurate AMP identification is important. Research efforts remain to concentrate on improving model effectiveness to better discriminate between AMPs and non-AMPs. Researchers examine algorithm optimization and integrate multi-source effective features, refining processes from data treatment and model design selection to parameter fine-tuning. Sharma et al. [58] developed the Deep-ABPpred model using a BiLSTM combined with amino acid-level features derived from word2vec for antibacterial peptide (ABP) prediction. It outperformed other models on test and independent datasets, identifying 10 novel ABPs from phage tail proteins with potent activity against various bacteria. Zhang et al. [59] pre-trained a BERT-based model on UniProt protein data, fine-tuned it with three tokenization methods on six AMP datasets, and built a new dataset to train a general AMP recognition model. Their model is superior to the present methods in multiple general quantitative indicators, confirming the importance of pre-training and data set balance. Singh et al. [60] proposed a binary classification method based on Time Convolutional Networks (TCNs), using transfer learning (pre-training on AMP datasets, fine-tuning on Antifungal Peptide (AFP) datasets). Their model attained 94% accuracy as well as precision on the primary test set. Dee [61] employed pre-trained language models (BERT, T5, XLNet) to generate contextual embeddings of amino acid sequences, combined with CNN classifiers. The T5-based classifier achieved 93.33% accuracy on the Veltri dataset. Li et al. [62] built the attention-based deep learning model AMPlify. Trained on public AMP sequences with carefully selected non-AMP negatives, it outperformed other tools across metrics, including accuracy, F1-score, and AUROC. It identified 4 novel AMPs in the bullfrog genome, two of which showed potent activity against multidrug-resistant E. coli. Yao et al. [63] proposed ABPCaps, integrating CNNs, LSTMs, and Capsule Networks, achieving 93.33% accuracy and 91.34% F1-score on an independent test set. Yao et al. [64] built the DeepAFP framework, integrating binary profile, BLOSUM62, and Z-Scale encodings with a pre-trained BERT module and a multi-branch CNN-BiLSTM network, achieving 93.29% accuracy on their main dataset for AFP prediction. Shaon et al. [65] used an RNN-based AMP-RNNpro model with a meta-model approach, reporting 97.15% accuracy for identifying novel AMPs. Chen et al. [66] developed the peptide prediction graph neural network TP-LMMSG, which uses multiple pre-trained language models for embeddings and graph attention networks, and exceeds available models on several datasets. Hao et al. [67] proposed the PGAT-ABPp model, utilizing AlphaFold2-predicted structures and ProtT5-XL-U50 embeddings to build graphs for Graph Attention Network (GAT) learning, outperforming 14 other models. Otero et al. [68] developed PepMNet, a hierarchical graph method that integrates atom- and amino acid-level information to predict peptide chromatographic retention time and AMP activity, achieving an AUC-ROC of 0.978.

Lee et al. [69] developed AMP-BERT by fine-tuning the pre-trained ProtBERT-BFD model on the benchmark dataset compiled by Veltri and colleagues. The amino acid sequences were tokenized and analyzed using an attention mechanism. In 10-fold cross-validation evaluations, AMP-BERT outperformed other

models across most metrics. This work delivers a more accurate model for AMP prediction, offers comprehensibility in the classification process, assists the identification of candidate AMPs, and advances the development of novel antimicrobial agents. Fang et al. [70] proposed a multi-view feature learning model based on deep learning (AFP-MFL), which integrates features from a pre-trained protein language model (ProtT5), evolutionary information (BLOSUM62 matrix), and physicochemical properties (CPP). A co-attention mechanism fuses these multi-source features, followed by classification using a multilayer perceptron (MLP). Evaluated on four independent test sets, AFP-MFL achieved an accuracy (ACC) of 95.84%, substantially beating existing methods. This study represents the first integration of multi-view feature learning with a co-attention mechanism, significantly increasing both the accuracy and explainability of antifungal peptide prediction, hence offering an efficient tool for novel antifungal drug development. Sun et al. [71] proposed the SenseXAMP cross-modal framework, which combines protein pre-training models and traditional protein descriptors to construct new data sets and set classification and regression tasks. Various experiments were carried out to evaluate the performance of the model. SenseXAMP has excellent performance on multiple antimicrobial peptide-related datasets, which is superior to the available models. It is capable of effectively integrating the advantages of two input features, perform well on imbalanced datasets, and has small prediction error for positive samples in regression tasks. Xing et al. [72] treated each amino acid in preprocessed antimicrobial peptide (AMP) and non-AMP sequences as an individual token. These tokens were input into a pre-trained BERT model for feature extraction. The extracted features were then fed into a composite model consisting of a one-dimensional CNN, BiLSTM, and an attention mechanism, followed by a flatten layer and fully connected layers for final classification. The proposed predictor, iAMP-Attenpred, achieved higher performance than existing predictors on two test datasets in terms of accuracy, Matthews correlation coefficient, and other metrics. This research assists researchers in more precisely identifying AMPs. Wang et al. [73] proposed the UniproLcad model, which integrates multiple pre-trained protein language models for antimicrobial peptide prediction. Classification prediction is performed using a deep neural network combined with an attention mechanism. UniproLcad demonstrates excellent performance in antimicrobial peptide identification, surpassing various existing methods. This research provides a new approach for the accurate identification of antimicrobial peptides and contributes to advancing their practical applications. Nguyen et al. [74] proposed iAMP-DL, which combines long short-term memory (LSTM) and convolutional neural networks (CNN). Four feature schemes were used to extract amino acid features, and the model was trained using ensemble learning with 10-fold cross-validation. iAMP-DL outperformed other methods in predicting short antimicrobial peptides, achieving an AUC-ROC value of 0.8811 on reference datasets. This provides an effective, robust, and stable framework for screening promising short antimicrobial peptides, facilitating antimicrobial drug research and development.

Antimicrobial peptide sequences and functions are diverse, and research focused on the identification of specialized types, or those derived from specific genomes or structural classes, holds significant importance. Different categories of antimicrobial peptides, such as short peptides, multifunctional peptides, and antifungal peptides, possess unique structural and functional characteristics. Identifying antimicrobial peptides from specific genomes can improve screening efficiency and facilitate the discovery of peptides with particular antimicrobial advantages. Yan et al. [75] developed Deep-AmPEP30, which focuses on short peptides ($\leq$ 30 amino acids) prediction based on PseKRAAC features (pseudo-K-reduced amino acid composition) and a convolutional neural network (CNN). Feature selection is optimized by clustering, such as evolution, physical, and chemical properties, and an attention mechanism is combined to improve the robustness of the model. On the balance test set of 188 samples, the accuracy rate was 77 %, and the AUC-ROC was 85 %.A potent antimicrobial peptide, P3, was identified from the genome of Candida glabrata, exhibiting antimicrobial activity comparable to ampicillin. Deep-AmPEP30 represents the first efficient prediction tool specifically for short antimicrobial peptides, addressing the performance limitations of conventional methods in this area. An online server (AxPEP) is available, supporting genome-scale screening, reducing drug development costs, and advancing the practical application of peptide-based therapeutics. Sharma et al. [76] constructed the AniAMPpred model using all available animal AMP sequences with lengths ranging from 10 to 200 amino acids. The model employs

Table 1. summarizes deep learning in AMP identification and classification.

Model Name	Architecture Type	Key Features	Year
Deep-AmPEP30	CNN	Short AMP prediction, genome-scale screening	2020
ACEP	CNN, LSTM	Visualization of key amino acid motifs, enhanced interpretability	2020
Deep - ABPpred	BiLSTM	Amino acid-level feature extraction identifies new ABPs from proteins.	2021
UniProt BERT-based model	BERT	Transfer learning, universal AMP recognition	2021
iAMP-CA2L	CNN, BiLSTM, SVM	Prediction of antimicrobial peptides and their functional types	2021
AniAMPpred	ALF	Accurately classify AMP and non-AMP sequences of different lengths ; Identify antibacterial proteins in animal genomes	2021
StaBle-ABPpred	biLSTM	Classification and identification of antimicrobial peptides using amino acid-level and peptide-level features	2021
TCN-AFPpred	TCN	Identification of potential AFPs in plant and animal representative proteins	2022
Dong et al.'s method based on sequence multidimensional representation	The model consists of coding layer, an embedding layer and a convolution layer	High-precision classification of AMPs and non-AMPs with lengths of 10-200	2022
LABAMPsGCN	GCN	Prediction of antimicrobial peptides of lactic acid bacteria based on amino acids, tripeptides, and their relationships	2022
AMP-BERT	BERT	The amino acid sequence was labeled, and the attention mechanism was used to analyze the features and predict AMP	2022
Hanpaibool et al.	RoseTTAFold	The full-length protein structure of MCR-1 to MCR-10 was predicted to understand the function of the MCR protein	2022
Lee fine-tuned BERT architecture	BERT	The self-attention mechanism is used to analyze the structural and functional associations of key residues for AMP classification	2022
AFP-MFL	MLP	Multi-view feature learning combined with a co-attention mechanism to predict antifungal peptides	2022
AMPlify	NLP	Capture the specific features of new data and the common features between AMP sequences, and mine new antimicrobial peptides	2022
LSTM_Pep	LSTM	Screening candidate peptides for SARS-CoV-2 main protease	2023
ABPCaps	CNN, LSTM	Identifying ABP with high precision	2023
iAMPCN	CNN	Four amino acid information was used to encode peptide sequences to identify short AMP and most functional activity predictions	2023
AMP-EBiLSTM	EBiLSTM	AMPs were predicted by local sequence capture and amino acid information extraction	2023
DeepAFP	CNN, BiLSTM	Fast and accurate identification of AFPs	2023
SenseXAMP	VAE, CNN, RNN	Screening candidate AMPs in the theoretical sequence and identifying functional AMPs	2023
iAMP-Attenpred	CNN, BiLSTM	Amino acid sequences were extracted for AMPs prediction	2023
DeepGlap	CNN, BiLSTM	The protein language features of antimicrobial peptides were extracted to predict antimicrobial peptides	2024
ALSTM	LSTM	To analyze the characteristics of peptide fragments of simulated enzymatic hydrolysates of proteins expressed by the sludge microbial genome, and to screen for potential antimicrobial peptides	2024
UniproLcad	1D-CNN, BiLSTM	Comprehensive extraction of protein features, rapid and efficient identification of antimicrobial peptides	2024
COMDEL	NNAs	Screening of broad-spectrum AMP in edible crops and screening of probiotics with high AMP production	2024
AMP-RNNpro	RNN	AMP is detected according to eight features of different standards	2024
iAMP - DL	CNN , LSTM	Four feature schemes were used to extract amino acid features and predict short antimicrobial peptides	2024
TP-LMMSG	GAT	Accurately predict the properties of antimicrobial peptides	2024
CELA-MFP	Transformer	Predict multifunctional therapeutic peptides	2024
PGAT-ABPp	GAT	Efficient and accurate identification of active ABP	2024
APEX 1.1	APEX	Dig the archaeal proteome, synthesize and test related peptides	2024
dsAMP	CNN, BiLSTM	Classification and function prediction of antimicrobial peptides	2024
PepMNet	HGNN	The chromatographic retention time and antibacterial peptide activity of the predicted peptides were predicted.	2024
AMPidentifier	DenseNet	Exploring antimicrobial peptide candidates from the gut microbiome of Blattella germanica	2024
ADLAMP	CNN, LSTM	Screening potential antimicrobial peptides from soil metagenomic data	2024
Shen et al.'s model is based on deep learning	CNN , LSTM , BERT	Identification of antimicrobial peptides from microbiome	2025

support vector machines and deep learning-based automatic feature learning (ALF). Compared with seven existing models and applied to screen the genome of Helobdella robusta, AniAMPpred demonstrated superior performance on test sets and independent datasets, accurately classifying AMP and non-AMP sequences of varying lengths. The analysis identified 436 potential antimicrobial proteins (PAPs) in the H. robusta genome, with BLAST analysis confirming the function of several candidates. This work provides a new model for identifying antimicrobial proteins within animal genomes, aids in determining protein antimicrobial functions, can be utilized to mine host defense proteins across different animal species, and offers an online prediction server for subsequent research. Sun et al. [71] developed the LABAMPsGCN framework, based on graph convolutional networks (GCN), for predicting antimicrobial peptides from lactic acid bacteria (LABAMPs). The study constructed a heterogeneous graph based on amino acids, tripeptides, and their relationships, learning weights through the GCN, and employed 10-fold cross-validation. Results showed higher accuracy on datasets compared to other machine learning and graph neural network algorithms. This framework provides a new effective tool for predicting LABAMPs, facilitates the screening of lactic acid bacteria strains with antimicrobial activity, and promotes their application in fields such as food production and agriculture. Hanpaibool et al. [77] utilized deep learning with RoseTTAFold to predict the protein structures of MCR-1 to MCR-10. Subsequent analyses included multiple sequence alignment using ClustalW, tunnel analysis with CAVER 3.03, and molecular docking via SwissDock. The study identified six conserved residues in the active site of MCR proteins and determined that the substrate PE most likely enters the active site through tunnel 1. This research provides a structural basis for understanding MCR protein function and developing inhibitors. Zhang et al. [78] constructed an LSTM model (LSTM_Pep), trained on a general peptide dataset and fine-tuned with known active peptides, to generate novel potentially active peptides. A deep learning model for protein-peptide prediction (DeepPep) was developed, integrating docking and molecular dynamics simulations to screen novel peptides. The model successfully identified six candidate peptides targeting the SARS-CoV-2 main protease and effectively recognized protein-peptide complexes. This study offers a method for efficiently generating and obtaining novel peptides with specific activities, aids in discovering new active peptides for particular targets, and supports peptide-based drug development. Zhang et al. [79] developed the COMDEL model, integrating neural network algorithms with high-throughput screening technologies, combined with phage-assisted evolution and cell-free AMP synthesis systems, for screening AMPs and probiotics. The COMDEL model achieved 94.8% accuracy on test sets and 88% accuracy in experimental validation, outperforming other models. Screening with COMDEL identified a Lactobacillus plantarum mutant with high AMP production, increasing yield. The development of COMDEL provides an efficient and accurate method for AMP and probiotic screening, supports related industries, and offers potential solutions to antibiotic resistance. Shen et al. [80] employed a deep learning-based model to identify antimicrobial peptides from the gastrointestinal microbiome of ruminants. Integrating data from multiple databases, multi-step screening, and experimental validation, the study discovered peptide 4, which exhibited high antimicrobial activity against methicillin-resistant Staphylococcus aureus (MRSA) and proved effective in a mouse wound infection model. This research provides an effective approach for discovering novel antimicrobial peptides from the ruminant microbiome, and peptide 4 shows promise for treating MRSA wound infections. Xu et al. [81] combined deep learning, bioinformatics, and laboratory assays to screen for potential antimicrobial peptides from soil metagenomic data. A prediction model incorporating attention mechanisms, LSTM, and CNN was constructed. Through data collection, feature extraction, and encoding, nine candidate antimicrobial peptides were identified. Among these, peptide P4 demonstrated significant antimicrobial activity against Klebsiella pneumoniae, Escherichia coli, and Staphylococcus aureus. This study provides an effective method for discovering novel antimicrobial peptides from metagenomic data, and peptide P4 shows potential as an alternative to conventional food antimicrobial agents.

Table 1 summarizes key research from the past five years, presenting the advantages of deep learning in AMP identification and classification. Through integrating pre-trained language models, composite architectures (e.g., CNN-BiLSTM), and attention components, researchers achieve high-performance feature extraction along with sequence analysis. These models can not only improve classification effectiveness but also augment interpretability, e.g.,

by visualizing key amino acid motifs. The creation of specialized tools for short or specific AMP types resolves shortcomings in generating and capability, providing more intelligent solutions for large-scale screening and functional analysis.

3.2 AMP Design and Synthesis

Rational design and efficient generation of antimicrobial peptides are the key to breaking through the bottleneck of traditional experimental screening. Leveraging powerful data processing and modeling capabilities, deep learning employs generative models such as Variational Encoders(VAEs) and Generative Adversarial Networks (GANs) to learn underlying distributional patterns from known AMP sequences. Combined with activity prediction and computational dynamics simulations, it enables the intelligent design of novel AMPs, ultimately generating new sequences with desired properties based on existing data.

Wang et al. [82] constructed a long short-term memory (LSTM)-based generative model alongside a bidirectional LSTM-based classification model. Both models were trained and optimized using Bayesian hyperparameter adjustment. The classification model secured validation accuracies ranging from 81.6% to 88.9%, while newly generated antimicrobial peptides were classified with accuracies between 70.6% and 91.7%. Structural analysis showed that several generated short peptides adopted α-helical conformations with amphipathic surfaces. This work shows that LSTM models can effectively generate novel antimicrobial peptides targeting specific bacteria, possibly accelerating the discovery of new antibiotics. Mao et al. [83] proposed AMPtran-lstm, a deep generative network-based method. By combining data from 12 AMP databases and combining LSTM with Transformer architectures, the model was constructed and employed for AMP design through pre-training, transfer learning, and module recognition. The experimental results showed that the peptide sequence generated by AMPtran-lstm had higher diversity and novelty than the known AMP, while retaining the key AMP features, and the generated sequence was predicted to have a higher probability of antibacterial properties. This research provides a new computational approach for designing antimicrobial peptides, contributes to addressing antimicrobial resistance, and forms a basis for developing novel antimicrobial agents. Cao et al. [84] employed a sequence generative adversarial network (SeqGAN) for peptide generation, coupled with a classification model based on bidirectional encoder representations from transformers (BERT) and a multilayer perceptron (MLP) for screening. Candidate peptides were further evaluated using AlphaFold2 and molecular dynamics (MD) simulations, followed by chemical synthesis and experimental testing. The analysis successfully designed six candidate AMPs, among which A-222 demonstrated potent antimicrobial activity against a broad spectrum of Gram-positive and Gram-negative bacteria. Subsequent modification enhanced its activity by 4- to 8-fold. This work confirms the capacity of integrating deep learning with MD simulations to accelerate AMP discovery and provides a new means for developing novel AMPs. Fan et al. [85] constructed a library comprising 713 culturable marine biofilm bacterial strains and their associated genomes. By combining ribosome profiling (Ribo-seq) with deep learning-based predictions, candidate AMPs were identified, followed by chemical synthesis and functional validation. From 80,430 expressed small open reading frames (sORFs), 341 high-probability candidate AMPs were identified, the majority sharing less than 40% amino acid sequence similarity with known AMPs. Subsequent testing revealed that 54 of the synthesized potential AMPs exhibited antimicrobial activity, with several showing potent inhibition against drug-resistant bacteria and low cytotoxicity. This study expands the repertoire of AMP compounds, provides a new approach for discovering novel AMPs from marine biofilm microorganisms, and accelerates the AMP development pipeline. Torres et al. [16] employed the APEX 1.1 platform to mine archaeal proteomes, followed by synthesis and testing of selected peptides. The analysis predicted 12,623 molecules with potential antimicrobial activity, termed “archaeasins.” Of 80 synthesized archaeasins, 93% displayed antimicrobial activity in vitro, and in vivo validation demonstrated that archaeasin-73 significantly reduced bacterial load in a mouse infection model. This research reveals the great potential of archaea as a source of novel antibiotics, opens new directions for antibiotic development, and offers feasible strategies for combating antimicrobial resistance. Szymczak et al. [86] proposed the HydrAMP model based on a conditional variational neural network (cVAE), and introduced a pre-selection program based on an external AMP classifier and molecular dynamics (MD) simulation. HydrAMP outperformed other models in both analog generation and unconstrained generation problems, allowing

the design of peptides with desired physicochemical properties. Experimental testing confirmed the antimicrobial activity of the generated peptides, accompanied by low toxicity. HydrAMP delivers a bright tool for designing new antibiotics, contributes to addressing the antimicrobial resistance crisis, and advances the development of novel antimicrobial peptides. Dong et al. [87] constructed a deep learning pipeline containing a generator and a classifier, used transfer learning and pre-trained protein embedding, constructed a data set based on the DBAASP database, and enhanced the data through a phylogenetic tree. Of 42 chemically synthesized peptides, five demonstrated potent and selective activity against Cutibacterium acnes, with minimum inhibitory concentrations (MICs) ranging from 2 to 4 μg/mL. The designed peptides exhibited broad-spectrum antimicrobial activity, along with low hemolysis and cytotoxicity. Al-Omari et al. [88] employed short-time Fourier transform (STFT) and residual deep learning networks, combined with machine learning and deep learning approaches, to design antimicrobial peptides using Escherichia coli as a model organism. The constructed deep learning model attained 92.9% accuracy in predicting antimicrobial activity against E. coli, outperforming various traditional and deep learning methods. This model accelerates the design and discovery of antimicrobial peptides, provides an effective approach for developing novel antimicrobial peptide-based therapeutics, and holds significant effects on drug development.

Table 2. Summarizes recent models in AMP design and synthesis.

Model Name	Architecture Type	Key Features	Year
[54]	VAE	New peptide sequences are generated by linear interpolation.	2020
[82]	LSTM	Effectively generate new antimicrobial peptides against target bacteria	2021
AMPtran-lstm [83]	LSTM, Transformer	Peptide sequences with higher diversity and novelty were generated compared to known AMPs	2023
SeqGAN [84]	BERT, MLP	Design and identification of antimicrobial peptides	2023
HydrAMP [86]	cVAE	Generate peptides with the required physical and chemical properties	2023
[87]	VAE	The synthesized peptides showed high potency and selectivity against Propionibacterium acnes	2022
[88]	ResNet	Design of antimicrobial peptides based on the E. coli model	2024

Table 2 summarizes recent models in AMP design and synthesis. Deep learning, through generative models (VAEs, GANs), intelligently generates novel AMP sequences by learning patterns from existing databases. These models, integrated with activity prediction and structural simulation, efficiently design candidate peptides with specific properties (e.g., broad-spectrum activity, low toxicity), validated experimentally. For example, combining generative models with MD simulations accelerates the screening and optimization of highly active peptides, significantly shortening development cycles.

3.3 Prediction of AMP Toxicity and Activity Indicators

The clinical application of antimicrobial peptides needs to be rigorous, and a balance between efficiency and safety should be achieved. Deep learning provides an innovative solution to this problem through a multi-task prediction framework. Research in this area implements techniques such as transfer learning, attention models, and Graph Neural Networks to develop models (e.g., AMPDeep, tAMPer) that accurately predict critical indicators, such as hemolytic toxicity and Minimum Inhibitory Concentration (MIC), while boosting interpretability using feature analysis. Breakthroughs in toxicity and activity prediction significantly accelerate the screening of safe and effective AMPs, providing an intelligent assessment pathway for drug development.

Tenorio-Borroto et al. [89] combined experiments (flow cytometry) and computational models (QSAR) to study the effects of antibacterial agent G1 on Th1 / Th2 and pro-inflammatory cytokines in mice, and predicted its immunotoxicity in the CHEMBL data set.The AUC of the calculation model on the CHEMBL dataset is 0.904, and the accuracy is 83.2 %. This research provides an efficient computer-based tool for immunotoxicity assessment in drug development, confirms the safety profile of G1, and supports its possible application in anti-infective therapy. Lin et al. [90] curated an updated AMP dataset alongside unbiased negative data, proposed the PC6 encoding method, evaluated its performance on both internal and external test sets, and subsequently developed the AI4AMP web server. The PC6 deep learning model has an accuracy of 90 % on the external test set, which is better than the current method. The AI4AMP server supports accurate prediction of antimicrobial potential for protein sequences and facilitates proteome-wide screening.

This work introduces a new protein encoding method and deep learning architecture, helping to accelerate AMP discovery and providing drug developers with an effective tool for distinguishing AMPs from non-AMPs. Lee et al. [69] adopted a transfer learning strategy, initially fine-tuning a pre-trained protein language model (Prot-BERT-BFD) on a secretory peptide classification task before transferring it to hemolytic activity prediction. Selective fine-tuning (freezing specific parameters) was used to address limited data availability. On three datasets (XGBC-Hem, HLPpred-Fuse, RNN-Hem), the MCC (0.5972-0.9731) and AUC (0.8723-0.9995) of AMPDeep exceed traditional feature methods (such as XGBC) and deep learning models (such as RNN). A redundancy-reduced hybrid dataset was also constructed to lessen sequence similarity bias. This study provides the first demonstration that transfer learning can greatly improve deep learning performance in small-data scenarios, offering an efficient and solid solution for predicting AMP hemolytic toxicity and advancing drug safety assessment. Yan et al. [91] proposed the MBC-Attention model, which is based on a Multi-Branch-CNN architecture, combined with global and local attention components, performs feature coding and learning on AMP sequences, and adjusts hyperparameters through grid search. Experimental results showed that this model excelled in predicting minimum inhibitory concentrations (MIC) of AMPs against Escherichia coli, achieving an average Pearson correlation coefficient (PCC) of 0.775 and a root mean square error (RMSE) of 0.533 (log μM), outperforming 17 traditional machine learning models as well as optimized random forest and support vector machine models. This study presents a more accurate model for quantitative prediction of AMP activity, which is helpful to accelerate the discovery and development of AMP. Ebrahimikondori et al. [92] introduced the tAMPer model, which integrates peptide sequence and three-dimensional structural information using bidirectional gated recurrent units (Bi-GRUs), graph neural networks (GNNs), and self-attention layers. Evaluated on an internal peptide hemolysis dataset and protein toxicity benchmarks, tAMPer delivered superior performance, achieving leading F1-scores and other metrics. This research facilitates accelerated AMP discovery and development, reduces the call for extensive wet-lab screening, and promotes the development of safer-to-use and more effective AMPs. Almotairi et al. [93] proposed a hybrid model combining convolutional neural networks (CNNs) and transformers to predict the hemolysis potential of peptides. The model was trained on three datasets—RNN-Hem, Hlppredfuse, and Combined—and showed strong predictive performance among all datasets, achieving Matthews correlation coefficients of 0.5962, 0.9111, and 0.7788, respectively, surpassing many standard methods. This work provides guidance for experimental efforts in peptide design and drug development. Chung et al. [94] constructed an integrated deep learning model that combines antimicrobial peptide sequences and genomic features, and used eight artificial intelligence architectures for training and evaluation. Results indicated that the model performed exceptionally well in predicting minimum inhibitory concentrations (MICs) of AMPs against key pathogens, with Pearson correlation coefficients ranging from 0.756 to 0.802. This work affords a novel approach for accurate prediction of AMP activity, contributes to boosting antimicrobial treatment strategies, and supports the application of AMPs in combating antibiotic resistance. Agüero-Chapin et al. [95] performed in silico enzymatic digestion of a composite protein database derived from the salivary glands of 14 cephalopod species. The resulting peptide library was screened using eight prediction and sequence comparison programs, followed by advanced network analysis to identify unique and representative antimicrobial peptides. A non-redundant composite protein database was constructed, yielding multiple AMP datasets through digestion and screening, including 542,485 AMPs, 104,242 non-hemolytic AMPs, and 68,694 non-hemolytic and non-toxic AMPs. From these, 5,466 unique non-hemolytic and non-toxic cephalopod salivary peptides (CSPs) were identified, from which 2,114 and subsequently 808 representative non-hemolytic and non-toxic AMPs were extracted. Studies have revealed that the salivary glands of cephalopods are an important potential source of antimicrobial peptides, supplying valuable resources for peptide drug developers, helping to combat antimicrobial drug resistance and promote peptide drug development. Chen et al. [96] proposed the UniAMP prediction framework, which utilizes feature vectors derived from the UniRep and ProtT5 deep learning models, combined with a deep neural network incorporating fully connected modules and self-attention layers, for antimicrobial peptide prediction. Several datasets were constructed for experimental evaluation, and results showed that the model outperformed the present methods across

Table 3. Summarizes deep learning models for AMP activity and toxicity prediction.

Model Name	Architecture Type	Key Features	Year
[89]	FC-DNN	To investigate the effects of G1 on Th1 / Th2 and pro-inflammatory cytokines in mice, and to predict its immunotoxicity in the CHEMBL dataset	2019
AI4AMP [90]	LSTM	The antibacterial potential of protein sequences was predicted, and proteomic screening was performed	2021
AMPDeep [69]	Transformer	Predicting the hemolytic activity of antimicrobial peptides	2023
MBC - Attention [91]	CNN	It is excellent to predict the minimum inhibitory concentration of AMP on E.coli	2023
tAMPer [92]	GNN	Prediction of peptide hemolysis and protein toxicity	2024
[93]	CNN, transformer	Predict the hemolysis potential of peptides	2024
[94]	CNN, BiLSTM, MBM	The ability to predict the minimum inhibitory concentration of antimicrobial peptides against key pathogens is excellent	2024
UniAMP [96]	transformer	Predicting the antimicrobial activity of peptides against specific pathogens	2025

several assessment metrics. This work increases the accuracy of antimicrobial peptide prediction and provides a new tool for related research.

Table 3 summarizes recent deep learning models for AMP activity and toxicity prediction, presenting the field's significant and considerable potential, such as transfer learning and focus mechanisms, which allow effective prediction of key indicators while improving interpretability. However, insufficient data, high experimental testing costs, and limited model applicability remain major bottlenecks. Future efforts need to focus on data standardization and model optimization to accelerate the development and application of safe and effective AMPs.

3.4 Comprehensive Models with Multiple Capabilities

In-depth AMP research has led to the emergence of comprehensive models capable of functioning across multiple key stages of investigation. As illustrated in Figure 3, these integrated frameworks combine identification, generation, activity prediction, and optimization within a single architecture, significantly reducing costs associated with laboratory validation. Such models represent a highly promising approach, potentially becoming mainstream in future AMP research.

Pang et al. [97] proposed TransImbAMP, a model that utilizes the Transformer architecture to transfer knowledge from large collections of amino acid sequences for peptide encoding, and incorporates an asymmetric loss (ASL) strategy to address dataset imbalance. The study addressed two tasks: (i) distinguishing antimicrobial peptides (AMPs) from other peptides, and (ii) identifying AMP functional activities against seven different targets (a multi-label classification problem). TransImbAMP achieved a balanced accuracy of 96.85% for AMP identification, and an average balanced accuracy of 79.83% for predicting AMP functional activities. This research provides an effective computational procedure for computer-aided discovery of novel AMPs; the combination of transfer learning and imbalance learning strategies may be broadly applicable to other biological sequence analysis problems. Ruiz et al. [98] proposed AMPs-Net, conducting virtual screening of the Escherichia coli genome followed by molecular dynamics simulations to assess the cell-penetrating capabilities of selected peptides. This approach reliably identified two previously unreported antimicrobial motifs and two novel antimicrobial peptides, and also uncovered a multifunctional peptide designated RD10. This study provides an effective pipeline for the rational discovery of antimicrobial peptides, contributes to accelerating the development of novel AMPs, and supports their advancement toward clinical applications. Yang et al. [99] proposed AMPFinder for the identification of antimicrobial peptides and prediction of their functional types. The researchers constructed two reference datasets and employed multiple feature encoding methods and learning models. For AMP identification, CTD, DPC, AAindex1, and BLOSUM80 encodings were used in combination with a random forest model. For function prediction, pre-trained models and deep learning models embracing attention methods were utilized. Results proved that AMPFinder achieved excellent performance in both AMP identification and function prediction, with dramatic improvements in F1-score, Matthews correlation coefficient (MCC), area under the curve (AUC), and mean precision score (AP) on independent test datasets. AMPFinder provides an effective tool for rapid and accurate identification of antimicrobial peptides and their functions, and promotes the development of new antibacterial drugs. Wang et al. [100] developed the

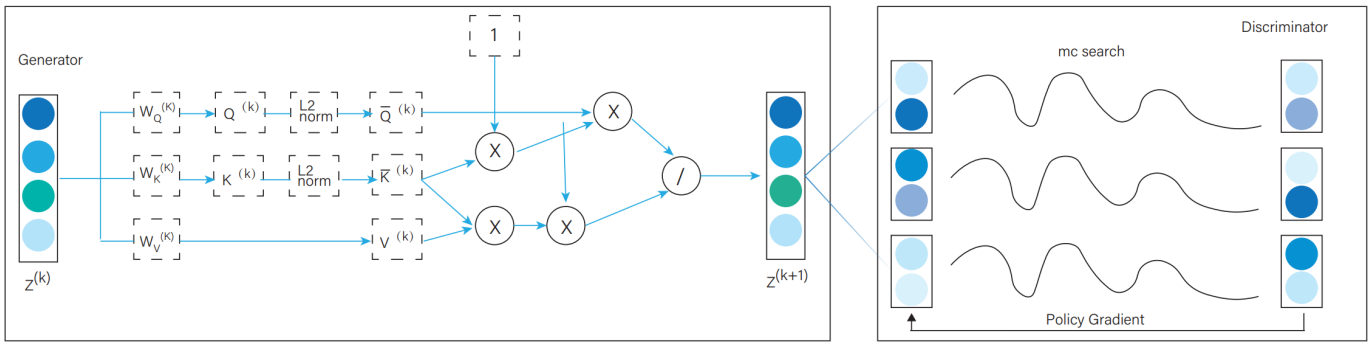

Figure 3. Comprehensive Models with Multiple Capabilities.

Diff-AMP integrated framework, which incorporates kinetic diffusion and attention systems into a reinforcement learning framework for antimicrobial peptide generation. Pre-training and transfer learning strategies were employed for AMP identification and screening, while convolutional neural networks were used for multi-attribute prediction and progressive optimization via reinforcement learning. The framework demonstrated strong performance in AMP identification, generation, and property prediction tasks, and was capable of generating AMPs with specific desired attributes. This work furthers antimicrobial peptide research, provides efficient tools for AMP development and investigation, and contributes to the progress of novel antimicrobial therapies. Pandey et al. [101] constructed the sAMP-VGG16 model through encoding features based on Drude polarizable force field atom types and employing a convolutional neural network with the VGG16 architecture. In 10-fold cross-validation evaluations, the model outperformed present approaches across multiple performance measures and demonstrated strong results on recognized datasets. This study provides a new method for the prediction of short antimicrobial peptides, improves the prediction accuracy, and promotes the development of the field of antimicrobial peptide prediction. Meng et al. [102] proposed a deep learning model, DMAMP, which uses convolutional neural networks and residual blocks to extract shared features and learns different task information through two fully connected layers. On independent test datasets, the model obtained a Matthews correlation coefficient 4.28% higher than single-task models for AMP detection. For identifying multiple activities of AMPs, the model attained an average Matthews correlation coefficient of 0.2627, surpassing both single-task models and the two available methods. In addition, the model can recognize peptides that are active against SARS-CoV-2. This result presents a new method for the discovery of new antifungal peptide drugs. Zhao et al. [103] proposed a two-stage prediction framework, deep-AMPpred, which combines feature encoding from the ESM-2 model with an integrated architecture comprising CNN, BiLSTM, and CBAM modules. The model demonstrated strong ability in identifying AMPs and predicting their functional activities, achieving 97.93% accuracy, an F1-score of 91.37%, and an AUC of 0.99157. This research provides more specific identification of antimicrobial peptides and their functional activities, supporting progress in antimicrobial drug development and related fields.

Table 4. Models use varied techniques to screen AMPs.

Model Name	Architecture Type	Key Features	Year
TransImbAMP	Transformer	Distinguish antimicrobial peptides from other peptides and recognize the functional activity of AMPs against seven different targets	2022
AMPs-Net	Deep learning technology	Two unreported antimicrobial motifs and two novel antimicrobial peptides were identified.	2022
AMPFinder	LSTM	Identify and measure the function of antimicrobial peptides	2023
Diff - AMP	CNN	Identify and generate antimicrobial peptides with specific attributes, attribute prediction	2024
sAMP-VGG16	CNN	Prediction of short antimicrobial peptides	2024
DMAMP	CNN	Detection and recognition of various activities of antimicrobial peptides	2024
Deep-AMPpred	CNN, BiLSTM	Identification of antimicrobial peptides and their functional activity	2025

In the process of deep learning-assisted antimicrobial peptide screening, extensive models with multiple capabilities serve a critical function. Researchers

continue to explore, innovate, and develop a series of powerful integrated models. As summarized in Table 4, these models use varied techniques to reliably identify AMPs, accurately predict functional activities, and excel across key screening stages, greatly accelerating the pace of novel antimicrobial drug discovery.

4 Limitations and Challenges

4.1 Data Insufficiency

The use of DL in the discovery and design of AMPs has led to labor and time savings. Despite major breakthroughs, deep learning in AMP screening faces multiple bottlenecks. The most basic challenge rests at the data level: current research relies on experimental data from fragmented sources such as individual lab results, academic literature, and public databases. This fragmented collection leads to variable sample quality. Systemic variations in testing environments and methodologies among different research teams lead to considerable fluctuations in activity metrics for similar AMPs, posing a serious challenge to the reliability of model pre-training.

Some studies have reported certain improvements through methods such as feature perturbation [104], random substitutions, and insertions [105]. However, we need to note that a large amount of data does not necessarily significantly enhance performance — issues such as noise in the dataset and data inconsistency can affect the final results. Taking the DBAASP database [106] as an example, for the same antimicrobial peptide, experimental conditions across different laboratories may not be identical. Under such circumstances, data requires preprocessing to ensure the accuracy and consistency of the dataset.

4.2 The Stability of DL when Processing Complex Datasets

The performance of some deep learning models on complicated datasets is still unstable, and they are prone to over-fitting or under-fitting problems. This is particularly true when handling AMP data with complicated structures and functions, which model correctness and reliability for further improvement. Additionally, the "black box" nature of many models is an urgent problem. Internal decision-making procedures are often difficult to interpret and lack biological explainability. This hinders researchers' ability to understand predictions and validate them from a biological perspective, limiting the application and promotion of these models within AMP screening.

To address the problem of unstable datasets (e.g., limited size, class imbalance, and distribution bias) that cause deep learning models to overfit, the paper proposes data augmentation solutions including basic image manipulations (geometric/color space transformations, random erasing, etc.) and deep learning-driven methods (GAN-based synthesis, adversarial training, meta-learning), along with design considerations like test-time augmentation and curriculum learning to enhance dataset stability and model generalization [106]. But an interesting question for practical Data Augmentation is how to determine the post-augmented dataset size. Furthermore, no consensus has been reached regarding the optimal strategy for combining data warping and oversampling techniques. A crucial consideration is the inherent bias present in the initial limited dataset. Currently, no augmentation technique can rectify datasets with extremely poor diversity relative to the test data. All these augmentation algorithms perform best under the assumption that both training and test data are drawn from the same distribution. If this is not true, it is very unlikely that these methods will be useful.

4.3 Limited Attempt in Drug-Likeness Prediction of AMPs

AMPs selected by deep learning require empirical confirmation to confirm their actual antimicrobial activity and safety. However, the validation process is often costly, time-consuming, and has a low success rate. Many peptides that perform well in silico predictions, given current realistic applications, are not yet widely used in real-life situations and may fail to achieve expected results in actual experiments. Furthermore, the translation from laboratory discovery to clinical application and industrial production encounters numerous technical and safety hurdles, including those related to large-scale production, stability, and toxicity. Those obstacles limit the effective use and dissemination of deep learning-screened AMPs.

There are still some gaps between the technical verification and actual transformation. Even after algorithmic screening yields candidate AMPs, subsequent validation of activity involves time-consuming and expensive stages such as cell assays, animal models, and toxicity testing. These major challenges in the translation pipeline mean that current deep learning screening techniques largely remain at the academic research stage, with a

significant period of technical progress needed before achieving large-scale practical application.

The existing evaluation systems fail to distinguish AMPs drugs from other pharmaceuticals, and potential toxicity issues may also exist. Despite vancomycin has received FDA approval, multiple clinical studies have demonstrated that it may cause renal damage in certain patients or at high doses. Indeed, oritavancin and dalbavancin were developed to enhance the antibacterial activity of vancomycin, thereby reducing the dosage and decreasing or preventing toxicity. Although the side effects of these compounds are mild, their effectiveness against drug-resistant Gram-positive organisms and for long-term treatment remains ambiguous [107–109].

4.4 DL Model Optimization and Reproducibility

In addition to appropriate training data, the model also needs to take into account issues such as parameter settings and reproducibility. Deep learning models face repeatability issues due to uncontrolled randomization (e.g., atomic addition operations, GPU-related variations) and inconsistent weight initialization implementations across libraries like Keras/TensorFlow, but the problem can be addressed by setting manual seeds for random number generators, enabling deterministic flags (e.g., TF_CUDNN_DETERMINISTIC), and using libraries like PyTorch that support full determinism for both classification and segmentation tasks [110, 111].

5 Conclusion

This work provides an overview of state-of-the-art DL methods for AMP discovery and screening. To this end, AMPs are first introduced, including their history of discovery, mechanisms of action, and therapeutic and industrial applications. Then the research progress and workflow of DL at different stages of AMPs screening are described, the DL methods employed are summarized, and the integrated DL models for AMPs screening are organized along with the latest research achievements. Finally, the discovery and early applications of AMPs are elaborated, and the limitations and challenges of DL technology in the field of antimicrobial peptide screening, such as interpretability issues and data processing instability, are discussed.

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Conflicts of Interest

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