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MafAFP: a mechanism-aware protein language model for antifungal peptide activity prediction

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Invasive fungal infections affect over one billion people annually and remain a major threat to immunocompromised patients. Current antifungal drugs are increasingly challenged by host toxicity and emerging resistance [1]. Antifungal peptides (AFPs) represent promising alternatives owing to their rapid activity, low resistance propensity, and diverse membrane-disruption mechanisms. However, experimental AFP discovery remains costly and time-consuming, motivating the development of computational prediction methods.

AFP predictors have evolved from traditional machine-learning models based on handcrafted physicochemical features to deep-learning approaches using pretrained protein language models (PLMs). Representative methods include Deep-AFPpred [2] and AFP-MFL [3]. Despite their success, most existing approaches incorporate physicochemical information as static auxiliary features, while PLM representations are not explicitly guided by the biophysical mechanisms underlying antifungal activity.

Mechanistically, AFPs act through a hierarchical membrane-interaction process involving membrane attraction, hydrophobic insertion, and subsequent disruption. These events are governed by local biophysical properties, such as interfacial hydrophobicity, amphipathicity, and helical propensity, encoded within short sequence segments. Existing predictors neither explicitly model these mechanism-relevant signals nor provide interpretable links between sequence patterns and antifungal activity, highlighting the need for mechanism-aware AFP prediction frameworks, with further details provided in Appendix A.

We introduce MafAFP, a mechanism-aware framework that addresses this gap through biophysically grounded feature modulation. MafAFP first computes local membrane-interaction descriptors at multiple sequence scales using a multi-attribute feature extractor (MafExtractor), and then injects these mechanism signals into PLM representations through feature-wise linear modulation (FiLM) [4] and gated residual fusion. This design enables adaptive emphasis on membrane-active regions within sequence embeddings, improving prediction performance while providing biologically interpretable decision evidence.

Method. The MafAFP architecture comprises three components (Figure 1): (i) a MafExtractor, (ii) a fine-tuned ESMC-600M protein language model [5], and (iii) a feature-level modulation and fusion module.

MafExtractor. This module performs local scanning using multi-scale sliding windows of sizes $w \in \{4, 6, 8\}$ residues, corresponding to one α-helical turn, membrane-insertion fragments, and two-turn amphipathic segments, respectively. At each window position i, three biophysical descriptors are computed.

(1) Local interfacial free energy (ΔG_{if}), quantifying membrane-binding propensity via convolution kernels initialized from the Wimley–White hydrophobicity scale:

$$\Delta G_{\text{if}}^{(w)}(i) = \frac{1}{w} \sum_{j=0}^{w-1} K_{\text{WW}}(j) \cdot x(i+j),$$

where K_{WW} is initialized from amino-acid-level interfacial transfer free energies and $x(i)$ denotes the one-hot encoded residue at position i.

(2) Hydrophobic moment (HM), quantifying amphipathicity under α-helical folding:

$$\text{HM}^{(w)}(i) = \frac{1}{w} \sqrt{\left(\sum_{j=0}^{w-1} H(x_{i+j}) \cos(j\delta) \right)^2 + \left(\sum_{j=0}^{w-1} H(x_{i+j}) \sin(j\delta) \right)^2},$$

where $H(x_{i+j})$ is the Eisenberg consensus hydrophobicity of the residue at position $i+j$ and $\delta = 100$ for ideal α-helices.

(3) Helix propensity, computed from Chou–Fasman parameters, reflecting structural compatibility with membrane-active conformations.

The convolution kernels remain trainable during optimization, allowing refinement of biophysical priors with task-specific data. Multi-scale outputs are aggregated via min, mean, and top-k pooling, then projected through an MLP into a 128-d global MAF vector: $\mathbf{f}_{\text{MAF}} = \text{MLP}(\text{Concat}[\text{Pool}(\mathbf{s}^{(4)}), \text{Pool}(\mathbf{s}^{(6)}), \text{Pool}(\mathbf{s}^{(8)})])$.

PLM backbone. We adopt ESMC-600M [5] as the sequence encoder, a 600M-parameter protein language model with 30 transformer encoder layers (hidden dim = 1152) pretrained on billions of

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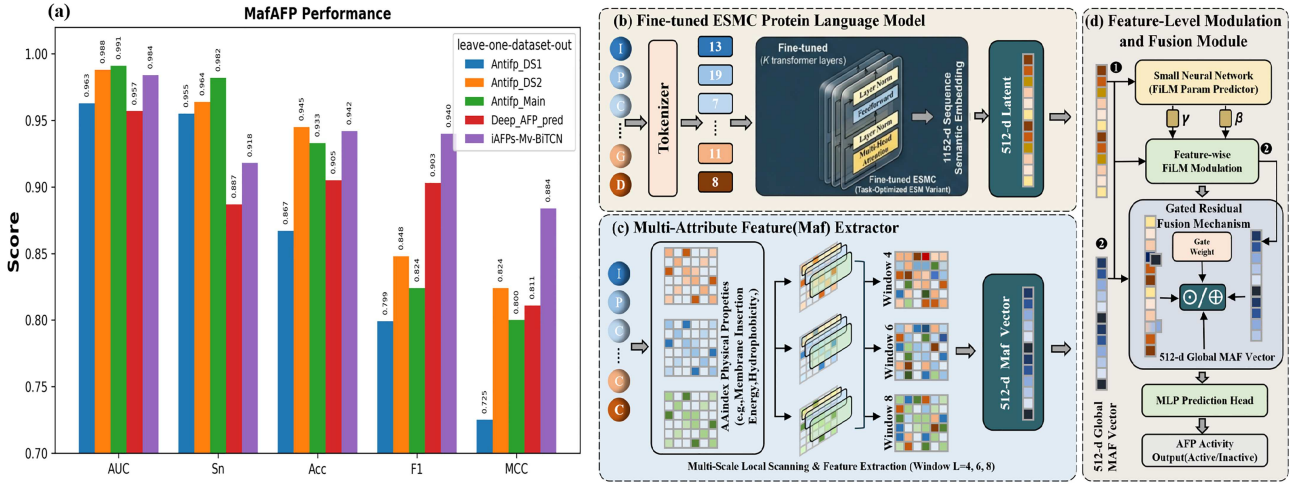

Figure 1 (Color online) (a) Leave-one-dataset-out performance of MafAFP across AFP benchmarks (AUC, Sn, Acc, F1, MCC); (b) fine-tuned ESMC protein language model with selective layer unfreezing; (c) multi-attribute feature (Maf)extractor: multi-scale sliding windows (L=4, 6, 8) compute local biophysical descriptors and produce a 512-d global MAF vector; (d) feature-level modulation and fusion module: FiLM modulation conditioned on MAF features, followed by gated residual fusion, yielding the final representation for MLP prediction of AFP activity (active/inactive).

evolutionary sequences. The model produces per-residue embeddings $\{\mathbf{h}_i\}_{i=1}^{L}$, which are passed as full token-level representations to the downstream fusion module. Only the final 2 encoder layers are fine-tuned to balance task adaptation against overfitting on small AFP datasets (∼1200 training samples).

Feature modulation and fusion. Rather than simple concatenation, we employ a two-stage modulation strategy.

(i) FiLM modulation. The global MAF vector predicts dimension-wise affine parameters γ and β via a two-layer MLP, performing feature-wise conditioning of the projected PLM embeddings:

$$\mathbf{h}' = (1 + \gamma(\mathbf{f}_{\text{MAF}})) \odot \mathbf{q} + \beta(\mathbf{f}_{\text{MAF}}),$$

where $\mathbf{q}$ is the query vector obtained by projecting the PLM token embeddings into a shared latent space, and $\gamma = \tanh(\tilde{\gamma}) \cdot s$ with s being a learnable scale parameter that constrains the modulation magnitude. The residual form $(1 + \gamma)$ ensures identity mapping when γ=0, allowing stable training while selectively amplifying PLM dimensions that encode membrane-relevant semantics.

(ii) Gated residual fusion. A learned gate dynamically regulates the contribution of mechanism-aware features as a residual correction to the PLM representations:

$$g_{\text{maf}} = \sigma(\mathbf{W}_g \mathbf{f}_{\text{MAF}} \,/\, \tau),$$

$$\mathbf{z} = \mathbf{h}' + \alpha_{\text{maf}} \cdot (g_{\text{maf}} \odot \mathbf{z}_{\text{maf}}),$$

where τ is a temperature parameter, $\mathbf{z}_{\text{maf}}$ is the projected MAF representation in the shared latent space, and $\alpha_{\text{maf}} = \sigma(\text{logit}_\alpha)$ is a learnable scalar that controls the global contribution of the mechanism-aware branch. The gate adaptively weights the MAF signal on a per-dimension basis, while the global α_{maf} prevents over-injection of physical priors. The resulting representation is passed to a two-layer MLP classifier (512→256→1) with dropout (0.2) for AFP prediction. Additional details are provided in Appendix B.

Results and discussion. MafAFP was evaluated on public AFP benchmarks with balanced positive and negative samples. It achieved the highest average AUC (0.987), consistently outperforming AFP-MFL, ESM2-AFPpred, iAFP-fLRM, and DeepAFPpred across all datasets. The largest improvement was observed on Antifp_DS1, where negative samples comprise non-AFP antimicrobial peptides with closely related activities, indicating enhanced discrimination of functionally similar peptides.

To evaluate cross-dataset robustness, leave-one-dataset-out experiments were performed with sequence redundancy controlled at 40% identity. MafAFP maintained strong performance on unseen datasets (Figure 1(a)). Furthermore, replacing FiLM-based modulation with simple feature concatenation substantially reduced performance gains, supporting the importance of mechanism-guided feature integration.

Mechanistic interpretability analyses further supported the biological relevance of the learned representations. Gate activations were enriched in Trp-rich and Arg-rich membrane-active regions, while FiLM modulation preferentially emphasized residues with favorable interfacial transfer free energy. These results suggest that MafAFP improves AFP prediction while providing biologically grounded and mechanistically interpretable decision evidence. Details on these experiments can be found in Appendix C.

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Supporting information Appendixes A–C. The supporting information is available online at info.scichina.com and link.springer.com. The supporting materials are published as submitted, without typesetting or editing. The responsibility for scientific accuracy and content remains entirely with the authors.

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