Congreso Internacional de Informática y Sistemas

Neoantigen Detection Using Transformers and Transfer Learning

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Content

Content

Immunotherapy to Treat Cancer

Immunotherapy is a type of cancer treatment that helps your immune system fight cancer [1].

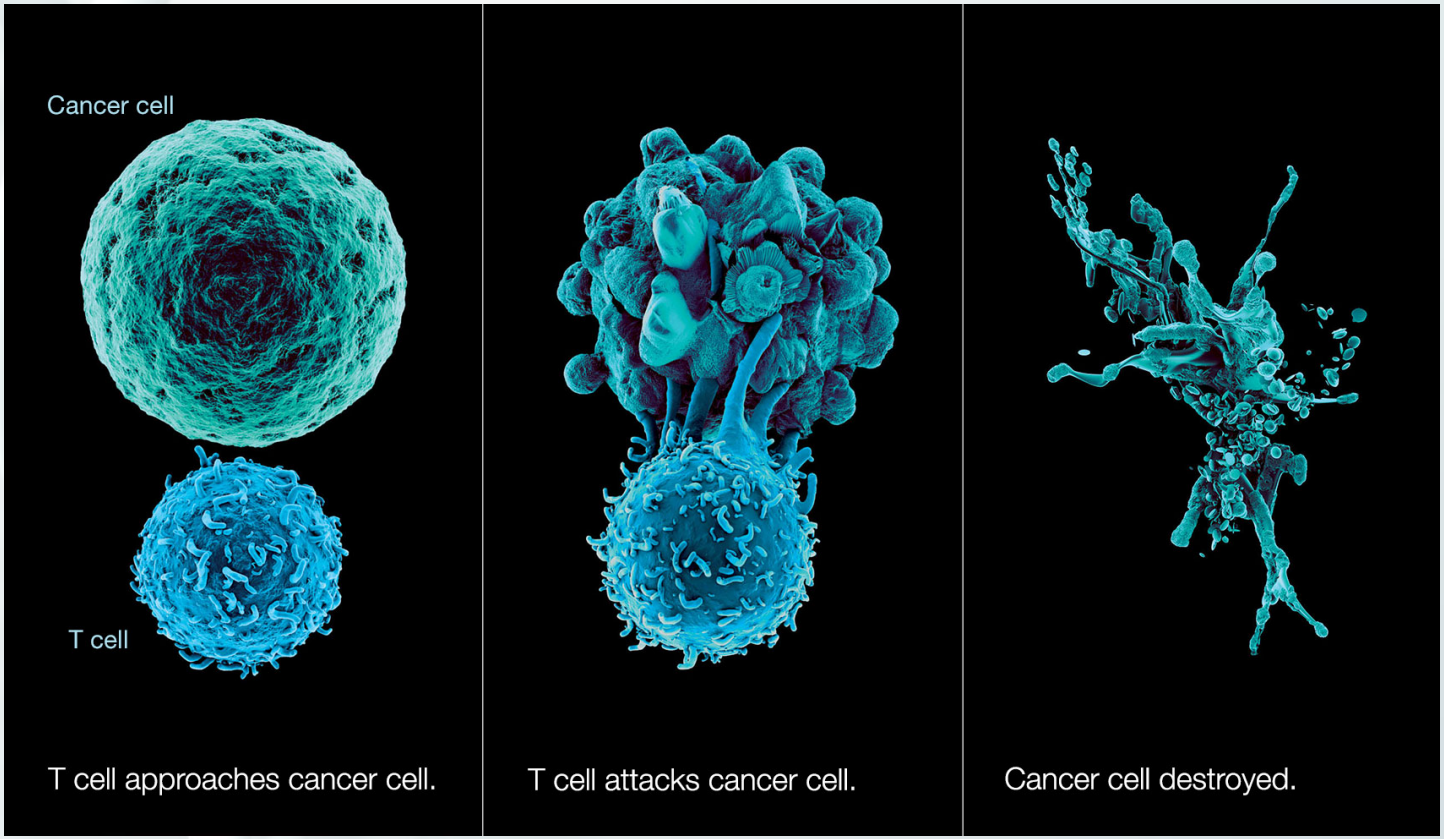

Figure: Example of how a T cell attack a cancer cell [2].

Neoantigen

A new protein that forms on cancer cells when certain mutations occur in tumor DNA. Neoantigens used in vaccines and other types of immunotherapy are being studied in the treatment of many types of cancer [3, 4].

Currently, there is a lot of methods to detect neoantigens; however, only a small number of them manage to stimulate the immune system [5, 6].

Immunotherapy for Cancer
Personalized Vaccines

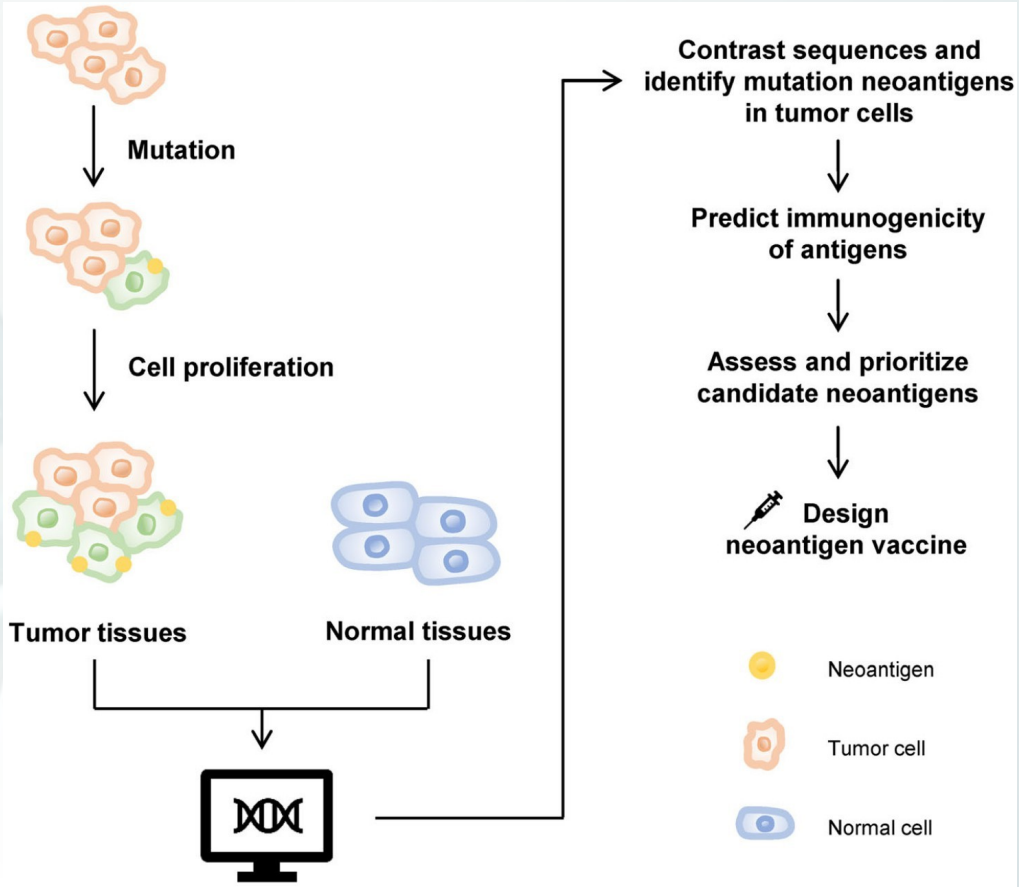

Figure: Personalized vaccines process for Cancer [7].

Immunotherapy for Cancer
Personalized Vaccines

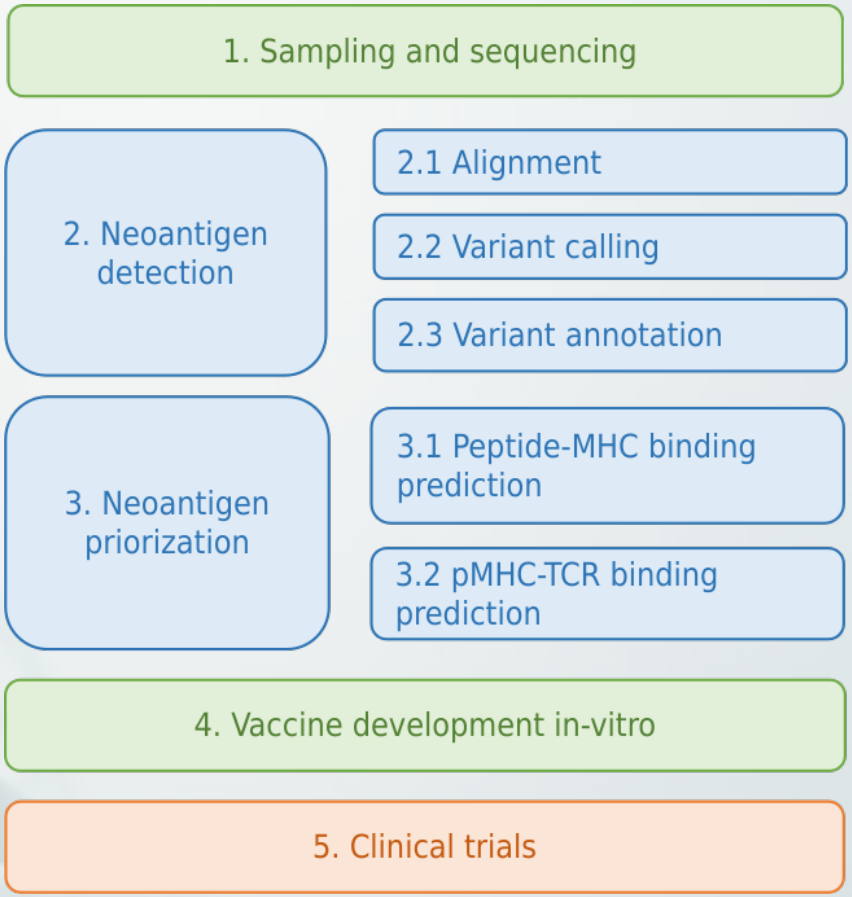

Figure: Personalized vaccines process for Cancer.

pMHC binding prediction

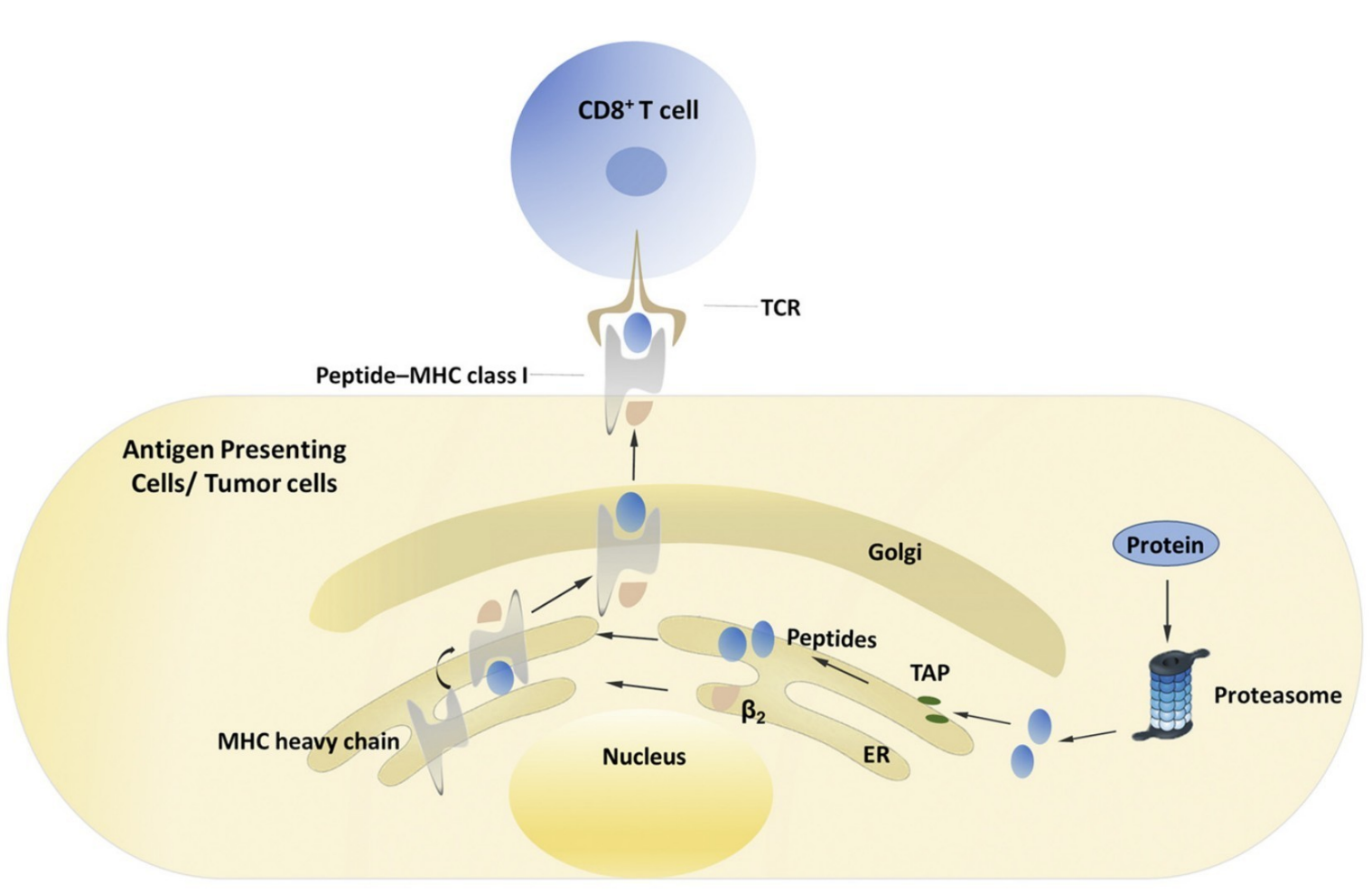

Figure: pMHC presentation process in MHC class I [8].

Content

Problem

Less than 5% of detected neoantigens (peptides binded to MHC) succeed in activating the immune system [9].

This is a **binary classification problem**. A peptide could be represented like: $p = \{A, ..., Q\}$ and a MHC like: $q = \{A, N, ..., Q, E\}$. Finally, we need to know the probability of affinity between p and q (pMHC)

Problem

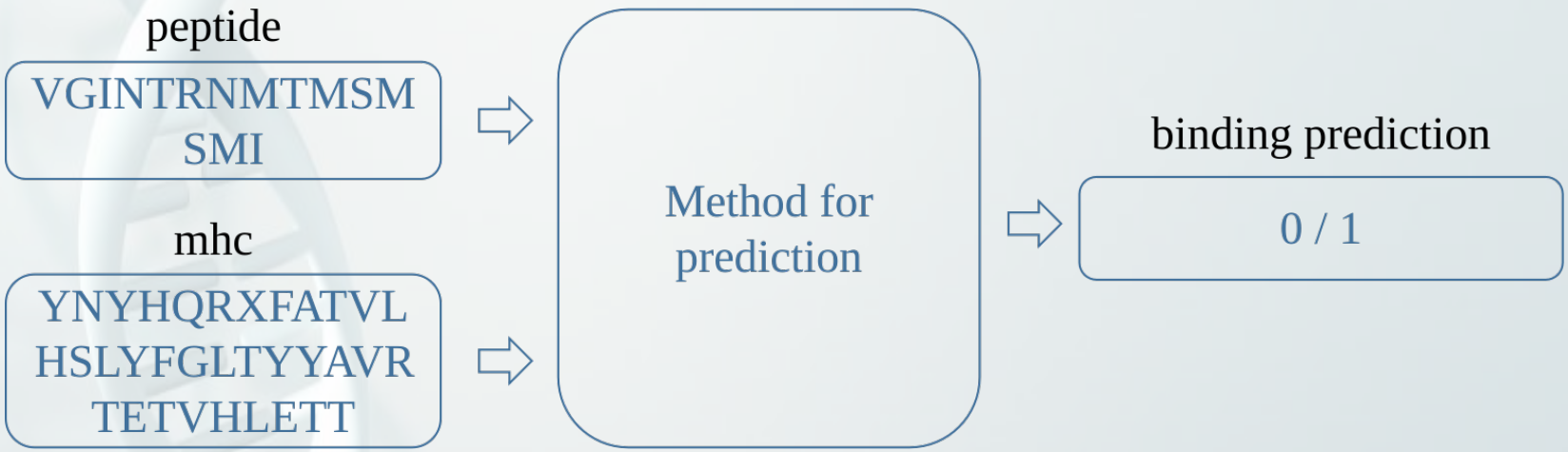

Figure: pMHC binding prediction problem.

Content

Proposal

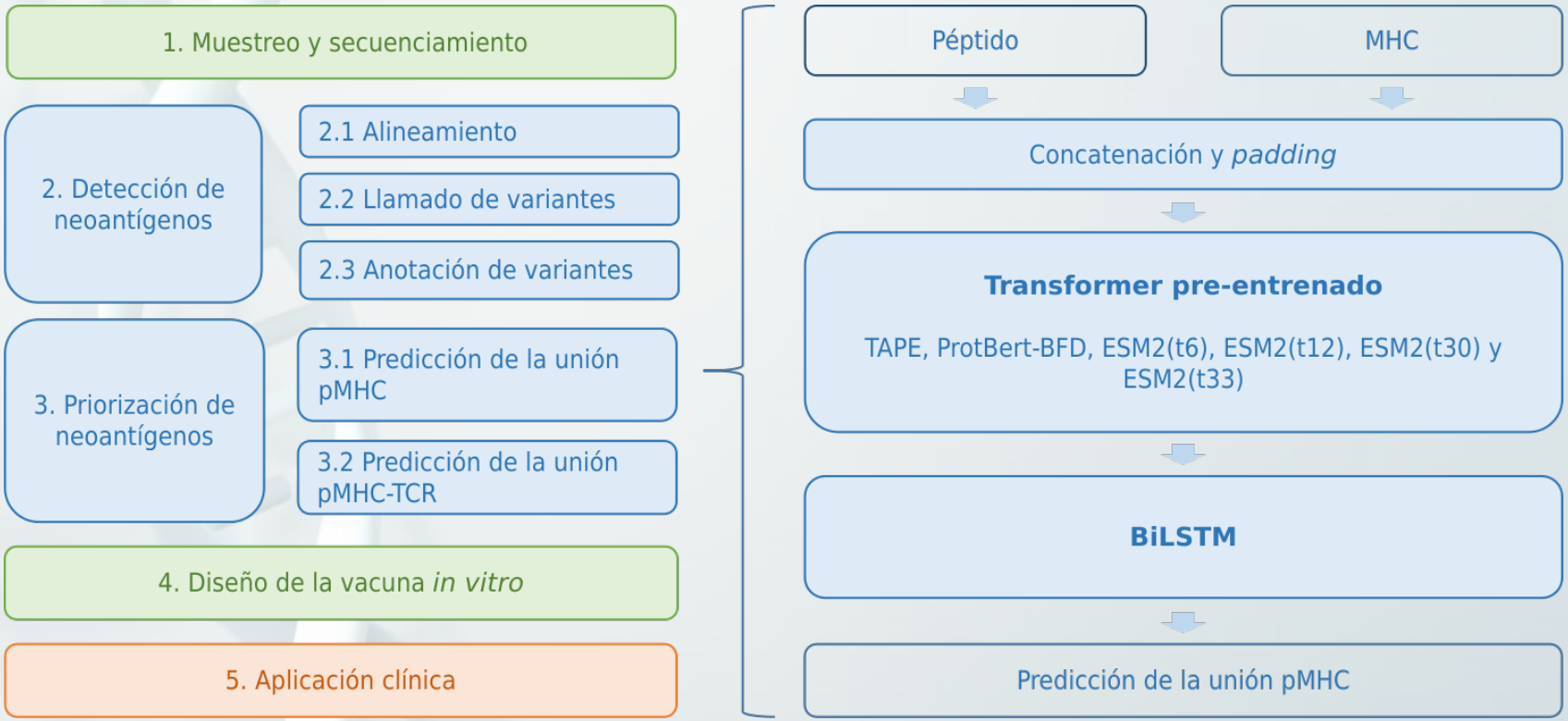

Figure: Proposal for pMHC binding prediction.

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Databases

Training: 539,019; Validation: 179,673; and Testing: 172,580.

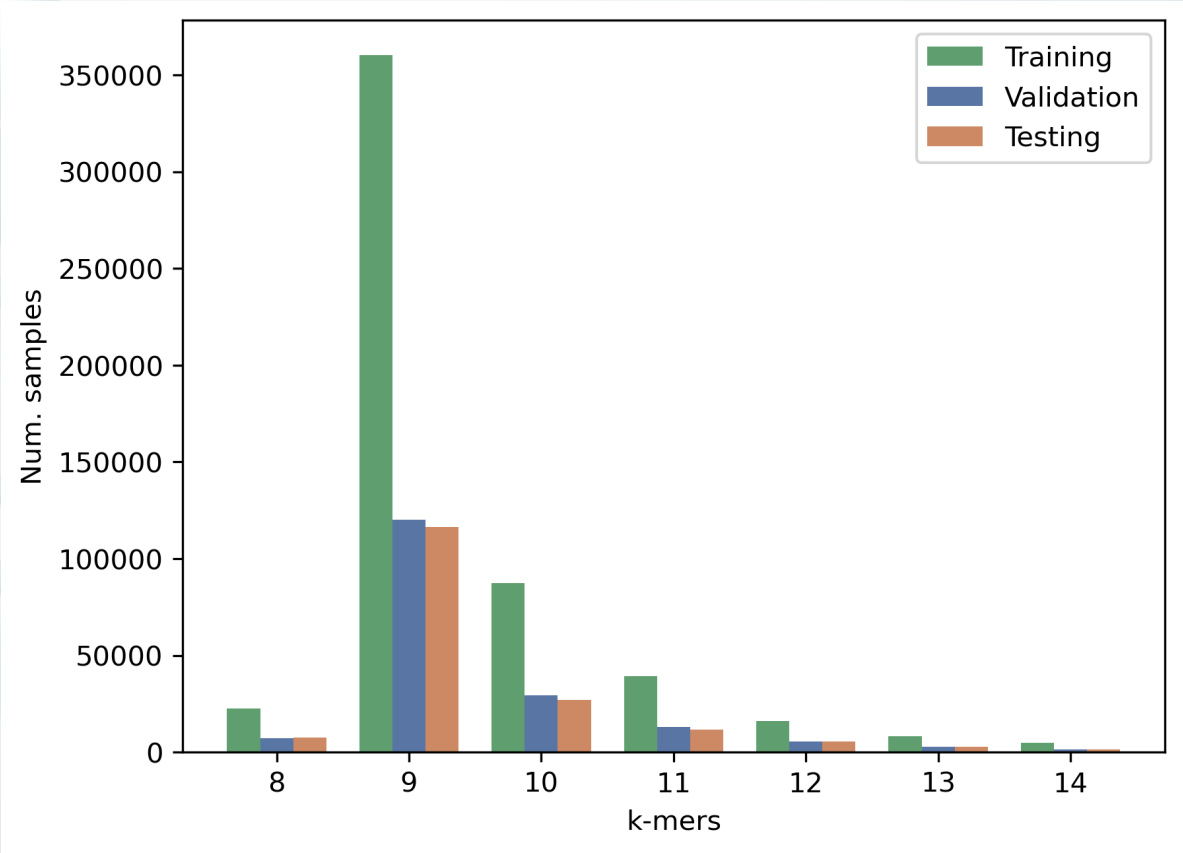

Figure: Number of samples per k-mer.

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Pre-trained models

Table: Differences between TAPE, ProtBert-DFB, and ESM2. HS: *Hidden size*; AH: *Attention heads*.

Model	BD	Samples	Layers	HS	AH	Params.
TAPE	Pfam	30M	12	768	12	92M
ProtBert-BFD	BFD	2122M	30	1024	16	420M
ESM2(t6)	Uniref50	60M	6	320	20	8M
ESM2(t12)	Uniref50	60M	12	480	20	35M
ESM2(t30)	Uniref50	60M	30	640	20	150M
ESM2(t33)	Uniref50	60M	33	1280	20	650M

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Results
(Training for 3 epochs)

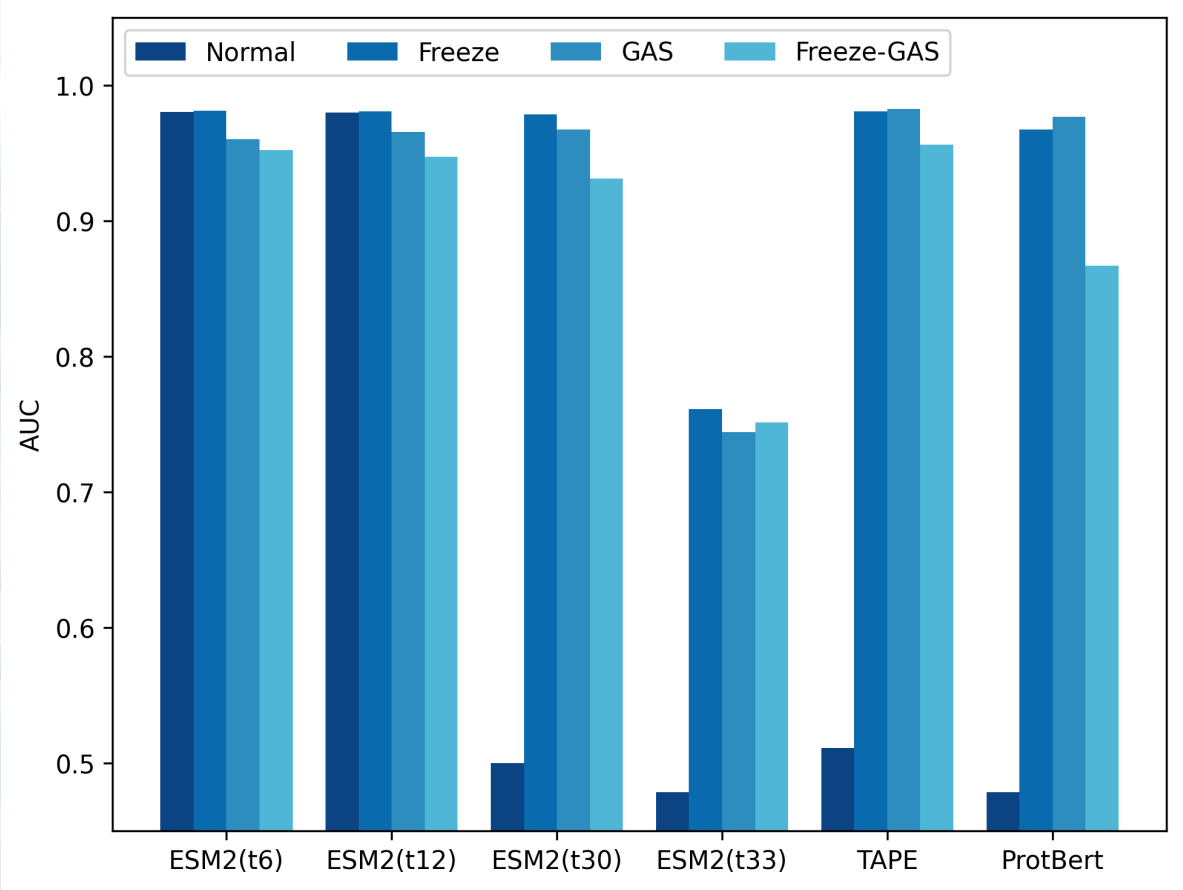
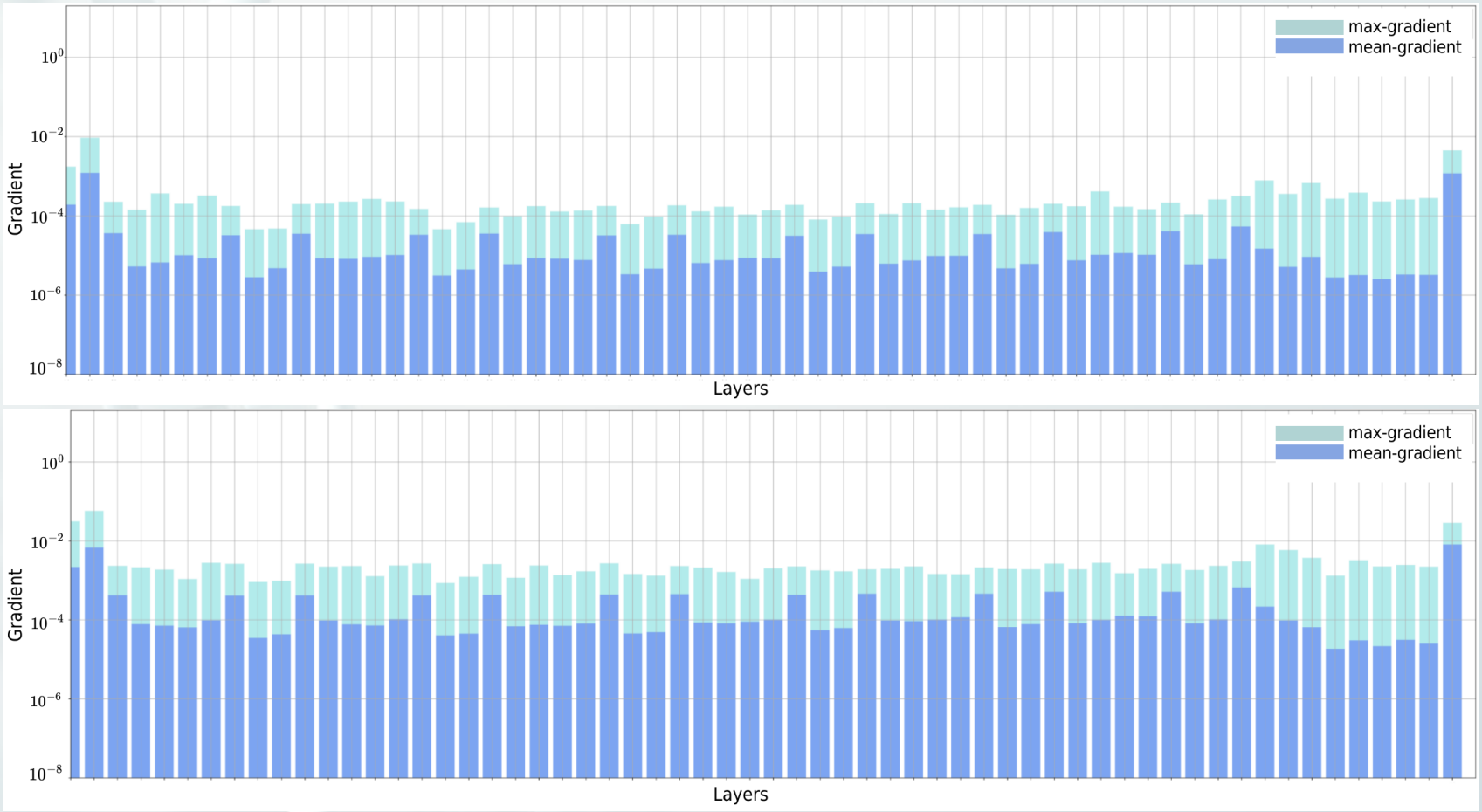


Figure: Comparative analysis of Area Under the Curve (AUC) in Transformer model architectures using various training methodologies.

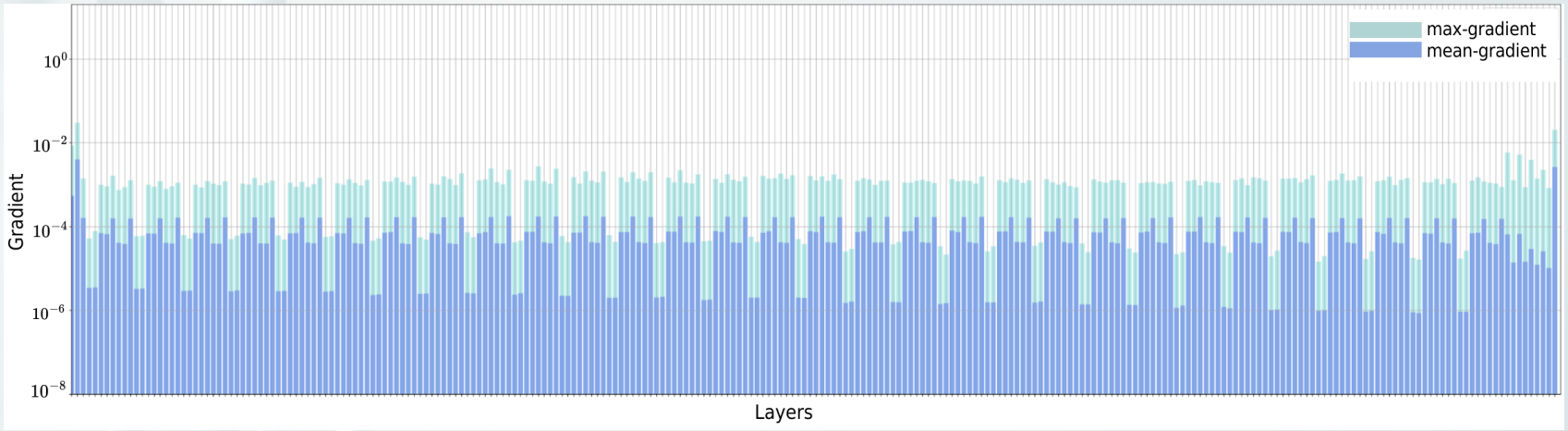
Results
Vanish gradient problem

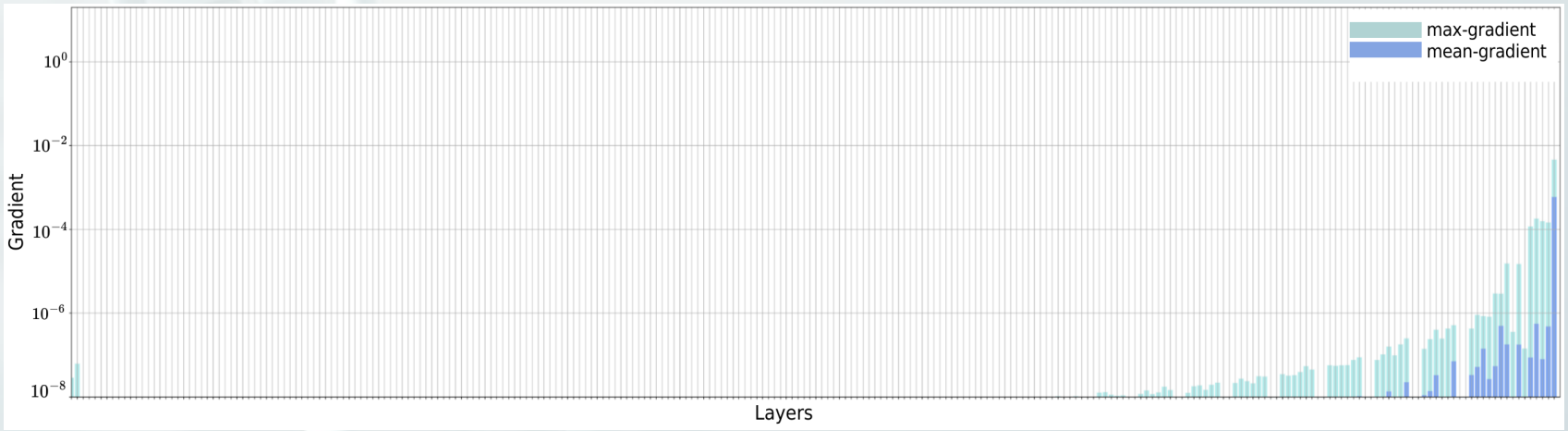
Gradients for ESM2(t6)



Results
Vanish gradient problem

Gradients for ESM2(t30)





Results

Comparison (Training for 30 epochs)

	Accuracy	Precision	Recall	F1-score	AUC	MCC
ESM2(t6)-Normal	0.9390	0.9333	**0.9453**	0.9392	0.9797	0.8780
ESM2(t6)-Freeze	**0.9401**	**0.9398**	0.9402	**0.9400**	**0.9830**	**0.8802**
ESM2(t6)-GAS	0.9366	0.9322	0.9413	0.9368	0.9818	0.8732
ESM2(t6)-Freeze-GAS	0.9354	0.9326	0.9383	0.9355	0.9813	0.8708
ESM2(t30)-Normal	-	-	-	-	-	-
ESM2(t30)-Freeze	**0.9393**	0.9304	**0.9493**	**0.9397**	0.9787	**0.8787**
ESM2(t30)-GAS	0.9346	**0.9337**	0.9352	0.9345	0.9808	0.8691
ESM2(t30)-Freeze-GAS	0.9363	0.9319	0.9411	0.9365	**0.9818**	0.8726
TAPE-Normal	-	-	-	-	-	-
TAPE-Freeze	0.9395	**0.9404**	0.9382	0.9393	0.9815	0.8790
TAPE-GAS	**0.9415**	0.9352	**0.9484**	**0.9418**	**0.9841**	**0.8831**
TAPE-Freeze-GAS	0.9359	0.9297	0.9428	0.9362	0.9820	0.8719

Results
Comparison with state-of-art tools

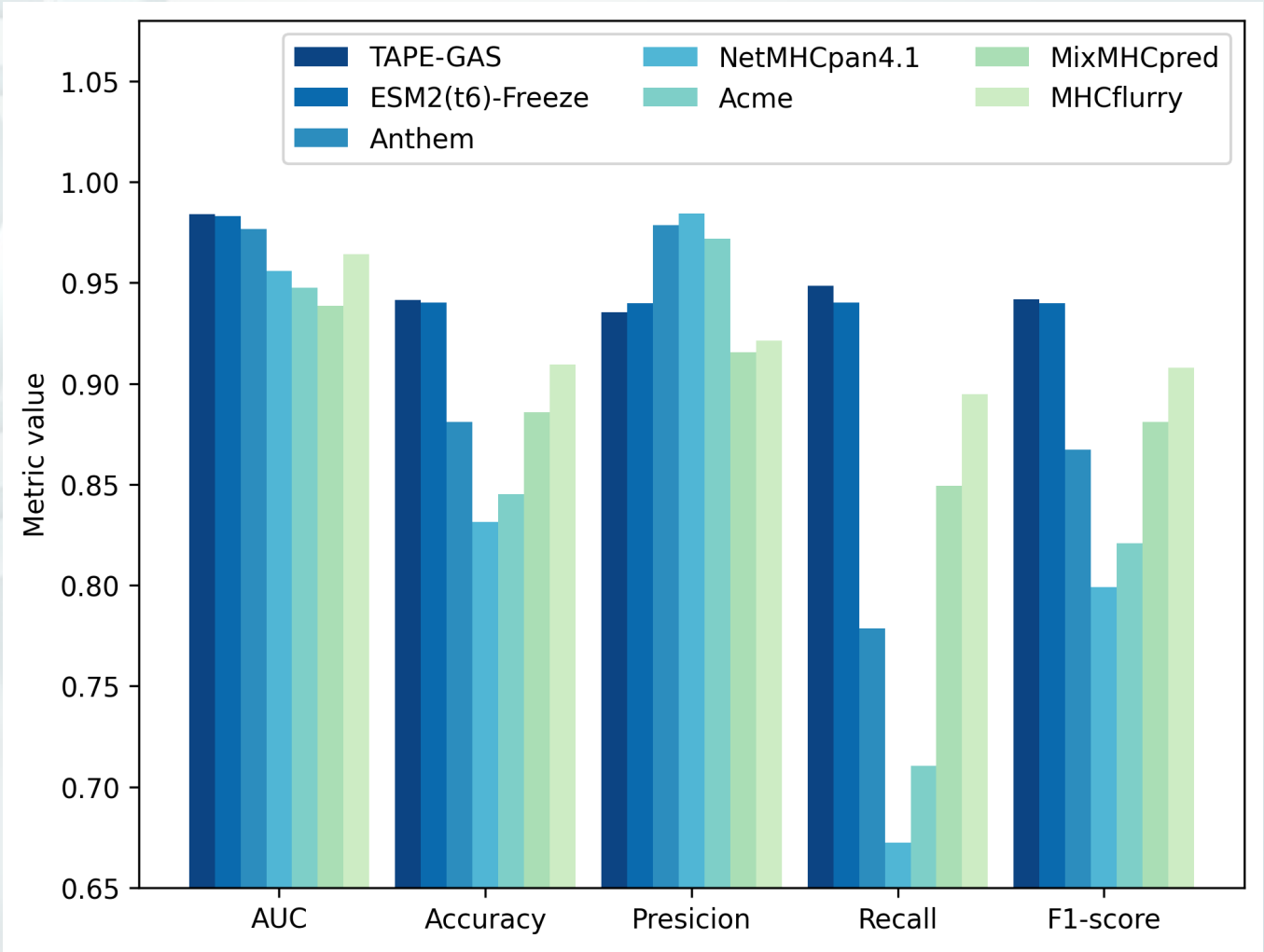


Figure: The AUC values for TAPE-GAS and ESM2(t6) trained for 30 epochs, in comparison to state-of-the-art methods.

Results
Comparison with state-of-art tools

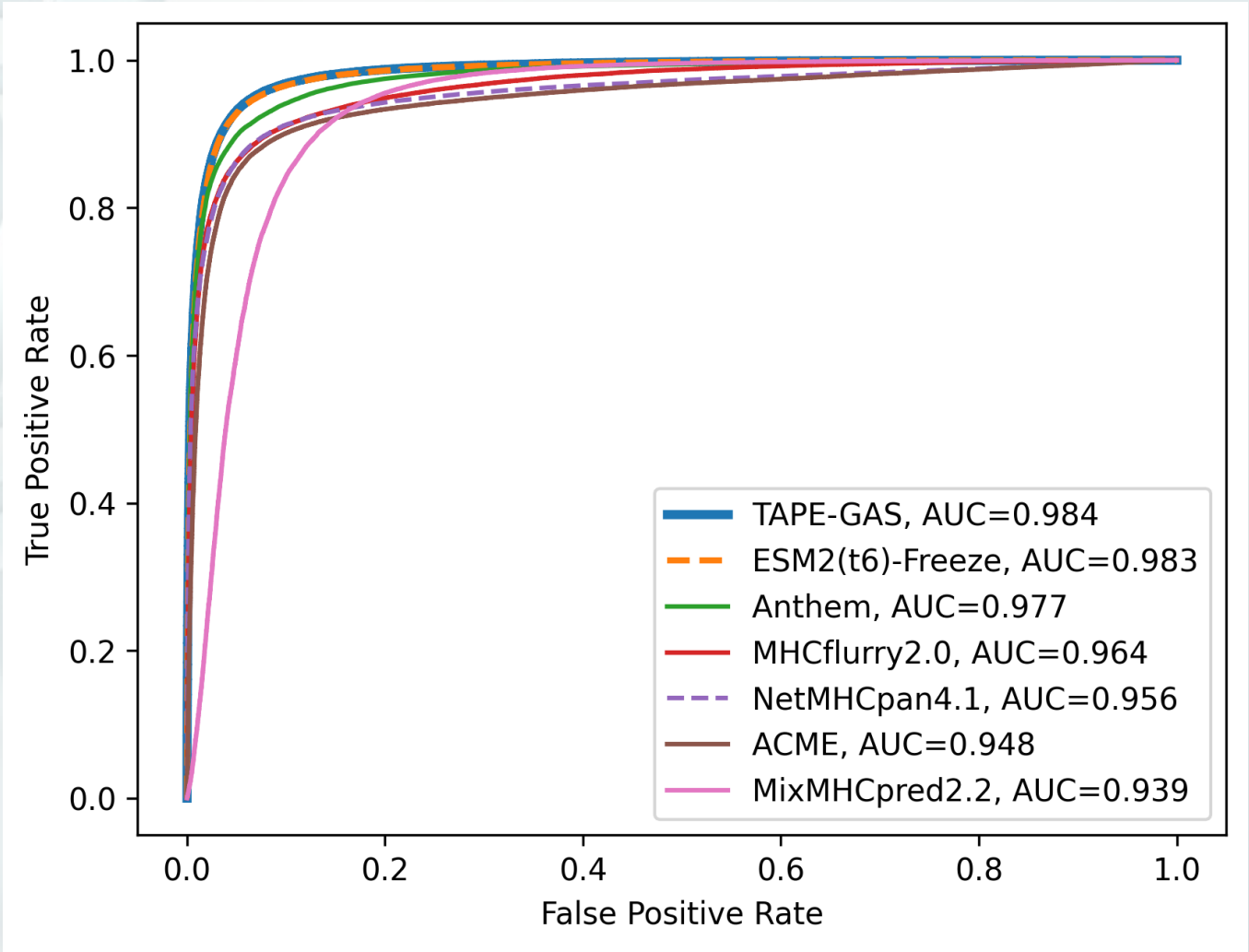


Figure: ROC curves for TAPE-GAS and ESM2(t6) trained for 30 epochs, in comparison to state-of-the-art methods.

Results

Comparison with state-of-art tools

Table: Performance evaluation of Transformer models TAPE-GAS and ESM2(t6)-Freeze, trained for 30 epochs, against Anthem, NetMHCpan4.1, ACME, MixMHCpred2.2, and MhcFlurry2.0.

	Accuracy	Precision	Recall	F1-score	AUC	MCC
TAPE-GAS	**0.9415**	0.9352	**0.9484**	**0.9418**	**0.9841**	**0.8831**
ESM2(t6)-Freeze	**0.9401**	0.9398	**0.9402**	**0.9400**	**0.9830**	**0.8802**
Anthem	0.8811	**0.9786**	0.7787	0.8673	0.9768	0.7785
NetMHCpan4.1	0.8312	**0.9844**	0.6724	0.7991	0.9557	0.6982
ACME	0.8452	0.9717	0.7105	0.8208	0.9476	0.7165
MixMHCpred2.2	0.8857	0.9155	0.8493	0.8811	0.9386	0.7733
MhcFlurry2.0	0.9093	0.9211	0.8948	0.9078	0.9642	0.8189

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Discussion

Fine-tuning ESM2 models

The most favorable results were obtained with the smallest model, **ESM2(t6)**. we believe is not sufficiently large for ESM2(t33), a model boasting 650 million parameters.

Another potential reason could be attributed to the use of **Rotary Position Embedding (RoPE)** used instead of absolute positional encoding.

Discussion

Layer Freezing and GAS

This approach involves locking the Transformer model while updating only the BiLSTM parameters. This method is generally well-suited to accelerate the training process, even though it may lead to a slight sacrifice in performance.

Surprisingly, **for ESM2 models, this methodology yielded the best results, while for TAPE and ProtBert-BFD, it yielded the expected outcomes**.

Discussion

TAPE, ProtBert-BFD and ESM2

ProtBert-BFD got the worst result despite this model were pre-trained with the largest dataset BFD with 2122M samples. We believe, this result is caused by the noisy information and sequence mistakes in BFD dataset.

TAPE achieved the best results. TAPE models were pre-trained using the Pfam dataset, it is derived from UniProtKB and **selectively includes sequences belonging to Reference Proteomes rather than the entire UniProtKB**

ESM2(t6) achieved results that closely rival TAPE. ESM2(t6) comprises only 8 million parameters, compared to 92 million parameters of TAPE.

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