A Web Platform for Protein-Protein Interaction Prediction Using Transformers and Transfer Learning Applied to Peptide-MHC Bindings

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Abstract

In this work, we evaluated the use of transfer learning from TAPE, ProtBert-BFD, and ESM2, for PPI prediction of peptides and MHC-I. We will evaluate six pre-trained BERT architectures (four models from ESM-2) followed by BiLSTM layers. Furthermore, we will evaluate our results using Anthem dataset [1]. Finally, we will deploy a Web platform for the prediction of bindings between peptides and MHC-I.

Keywords: AI and machine learning, Bioinformatics, Software development, and Proteomics

1 Background, proposed project and its implementation

1.1 Introduction

Protein–protein interactions (PPI) are relevant mediator in biological processes; understanding them is beneficial as it enables us to comprehend the functions of proteins, the origins and progression of various illnesses, and can assist in the development of new drugs [2, 3]. Additionally, the human genome codes approximately 500000 proteins and 130000 to 650000 PPIs occurs in human body [2]. *In vivo* and *in vitro*, methods like biomolecular fluorescent complementary (BiFC), chromatography, and nuclear magnetic resonance (NMR) have been developed; however, they are time-consuming and labor-intensive [2, 4]. Consequently, *in silico* methods emerged as an alternative.

Moreover, in immunology, bindings between peptides and Major Histocompatibility Complex (MHC) represent a key factor for activating an immune respond. MHC class I (MHC-I) and MHC class II (MHC-II) present peptides at the cell surface to CD8+ and CD4+ T Cells, respectively [5, 6]. Lamentably, MHC proteins are encoded by highly polymorphic genes, called Human Leukocytes Antigens or (HLAs); the considerable polymorphic nature of MHC genes affords substantial variation in peptide binding, thereby influencing the set of peptides presented to T cells. [6]. In consequence, proposals methods are categorized as allele-specific or pan-specific. Allele-specific methods [7–13], train a model for each MHC allele; meanwhile, pan-specific methods [1, 14–24] train a global model taking peptides and MHC as inputs. Therefore, due to the highly polymorphic nature of MHC, pan-specific methods arise with high possibility of future applications. Additionally, immunotherapy is considered a promising approach to cancer treatment, especially since traditional methods based on surgeries, radiotherapies, and chemotherapies have low effectiveness [25, 26]. This strategy capitalizes on the observation that cancer cells generate distinctive neoepitopes recognized by the MHC [27]. Furthermore, these neoepitopes or neoantigens are considered the leading causes of an immune response [28–30].

Recently, the advent of Transformers has ushered in a new era in artificial intelligence, demonstrating significant success across various Natural Language Processing (NLP) tasks [31]. These models have also found application in neoantigen detection, particularly in predicting pMHC binding and presentation. For example, BERTMHC [32] is a pan-specific pMHC-II binding and presentation prediction

method that employs a BERT architecture and leverages transfer learning from the Tasks Assessing Protein Embeddings (TAPE) [33]. The methodology involves stacking an average pooling layer followed by a Fully Connected (FC) layer after the TAPE model. Empirical assessments have shown that BERTMHC outperforms both NetMHCIIpan3.2 and PUFFIN. Additionally, ImmunoBERT [34] utilizes transfer learning from TAPE but focuses on pMHC-I prediction. This approach involves stacking a classification token's vector after the TAPE model. Furthermore, MHCRoBERTa [35] and HLAB [24] also leverage transfer learning. MHCRoBERTa employs self-supervised training with data from UniProtKB and Swiss-Prot databases, followed by fine-tuning with data from the Immune Epitope Database (IEDB) [36]. MHCRoBERTa performs better than NetMHCpan4.0 and MHCflurry2.0 in terms of Spearman Rank Correlation Coefficient (SRCC). In contrast, HLAB leverages transfer learning from ProtBert-BFD [37] and incorporates a BiLSTM model in cascade. Notably, on the HLA-A*01:01 allele, HLAB demonstrates a slight performance advantage over state-of-the-art methods, including NetMHCpan4.1, with at least a 0.0230 improvement in Area Under the Curve (AUC) and a 0.0560 increase in accuracy.

In this work, we evaluated the use of transfer learning from TAPE, ProtBert-BFD, and ESM2, for PPI prediction of peptides and MHC-I. We will evaluate six pre-trained BERT architectures (four models from ESM-2) followed by BiLSTM layers. Furthermore, we will evaluate our results using Anthem dataset [1]. Finally, we will deploy a Web platform for the prediction of bindings between peptides and MHC-I.

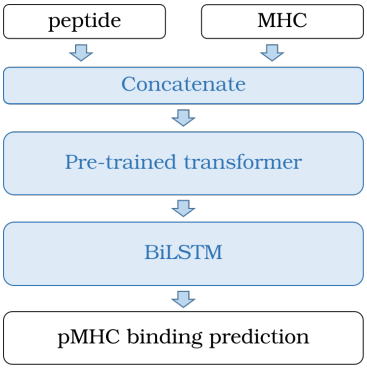
2 Proposal and methodology

We propose the development of a Web platform for PPI prediction of peptides and MHC. This project is based on previous works, where we performed a review of peptide-MHC interactions [38], and implemented a model using transformers and transfer learning for peptide-MHC bindings [39]. Consequently, we will use Transformers and transfer learning from BERT models pre-trained on large protein datasets. These pre-trained models are TAPE [33], ProtBert-BFD [37] and ESM-2 [40]; furthermore, in Table 1, we present the major difference between these models.

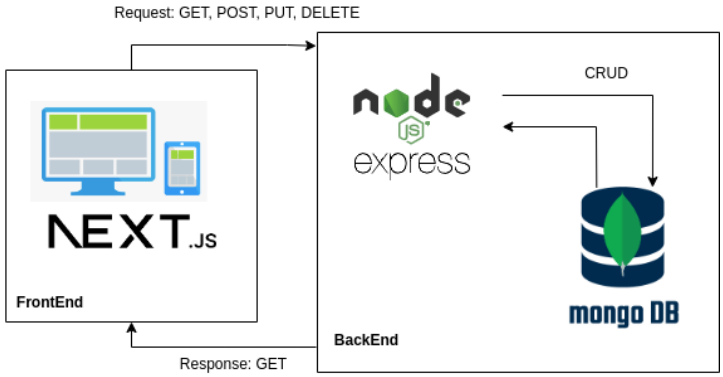
Table 1: Major differences between TAPE, ProtBert-DFB, and ESM-2.

Model	**Dataset**	**Samples**	**Layers**	**Hidden size**	**Att. heads**	**Params.**
TAPE	Pfam	30M	12	768	12	92M
ProtBert-BFD	BFD	2122M	30	1024	16	420M
ESM-2 (6 layers)	Uniref50	60M	6	320	20	8M
ESM-2 (12 layers)	Uniref50	60M	12	480	20	35M
ESM-2 (30 layers)	Uniref50	60M	30	640	20	150M
ESM-2 (33 layers)	Uniref50	60M	33	1280	20	650M

For fine-tuning, we will stack in cascade a BiLSTM at the end of the pre-trained model. The BiLSTM is based on HLAB [24] and has two layers with 768 units. In Figure. 1a, we present our proposal. This model takes the aminoacid sequences of a peptide and the MHC; then these sequences are concatenated and encoded using one-hot; then it feed-forward the pre-trained transformers and the BiLSTM model; finally, we will predict 1 for physical binding and 0 for no binding. Furthermore, we will use Anthem dataset [1] for fine-tuning.



(a) Transformer model.



(b) Web platform architecture.

Figure 1: (a) The proposed model for PPI prediction of peptides and MHC. (b) The Web architecture.

3 Infrastructure

4 Limitations

5 Expected results and their impact

6 Ethics

7 Gantt chart

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