Prediction of TCR-pMHC interactions using sequence embeddings and recurrent neural networks

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https://github.com/HenriettaHolze/TCR-pMHC-prediction

Introduction

- Recent advances within biological sequencing and deep learning methods have made it possible to investigate key interactions of the immune system computationally.
- The adaptive immune system is a key element for fighting diseases and the T-cells are responsible for cell-mediated immune response via their surface T-cell receptors (TCR).
- TCRs bind to peptide-Major Histocompatibility Complexes (pMHC) to form a complex that triggers an immune response.

Problem: Predict TCR-pMHC binding using molecular modeling and recurrent neural networks (RNN).

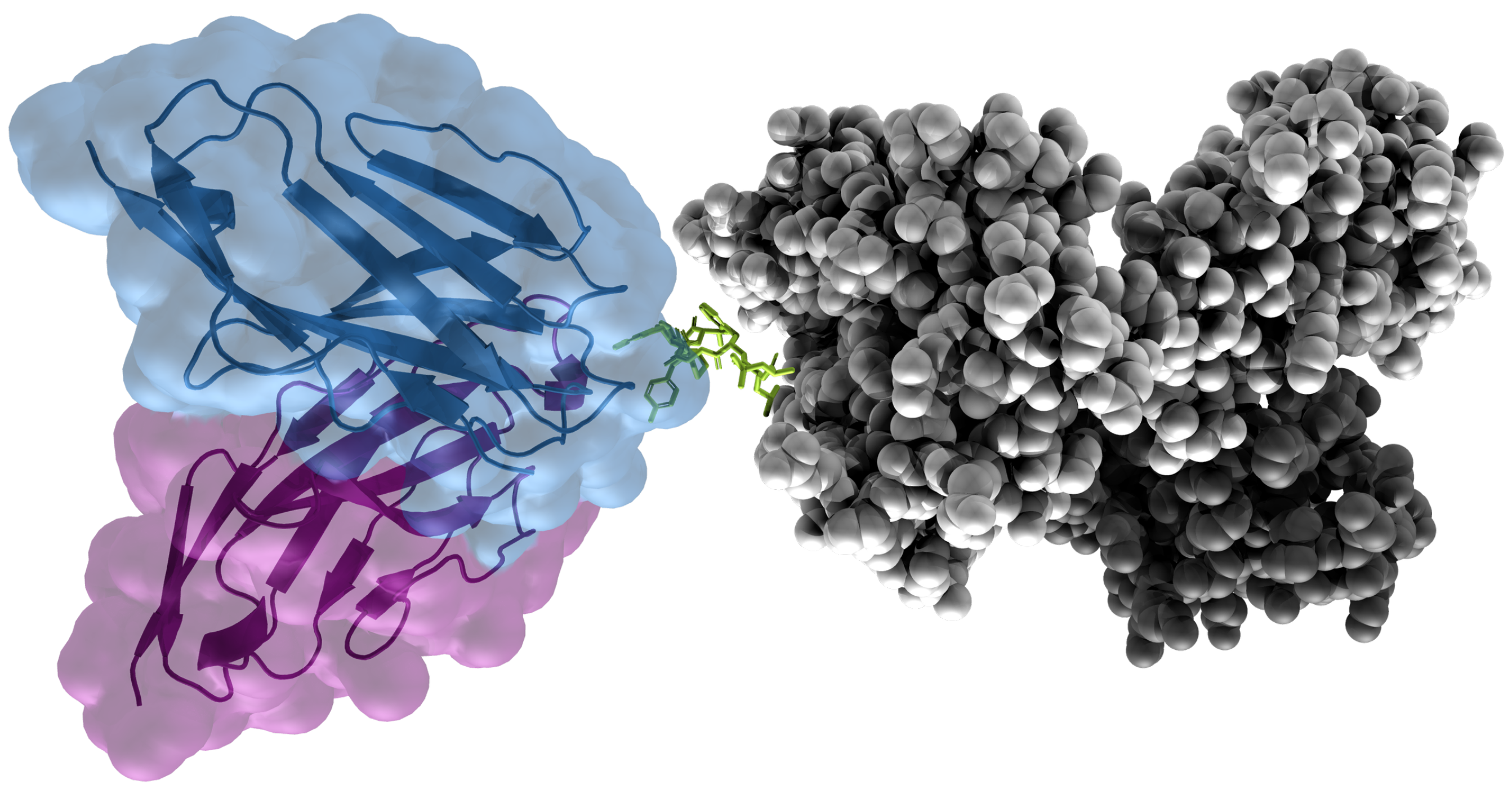


Figure 1. 3D-visualization of the TCR-pMHC complex. Blue and purple: TCR α and β chain, Green: Peptide, Grey: MHC.

Input data[1,3]

- Protein sequence of TCR, peptide, MHC (one-hot-encoding)
- Per-residue energy terms (one value per row)
- Global energy terms (constant, one value per column)

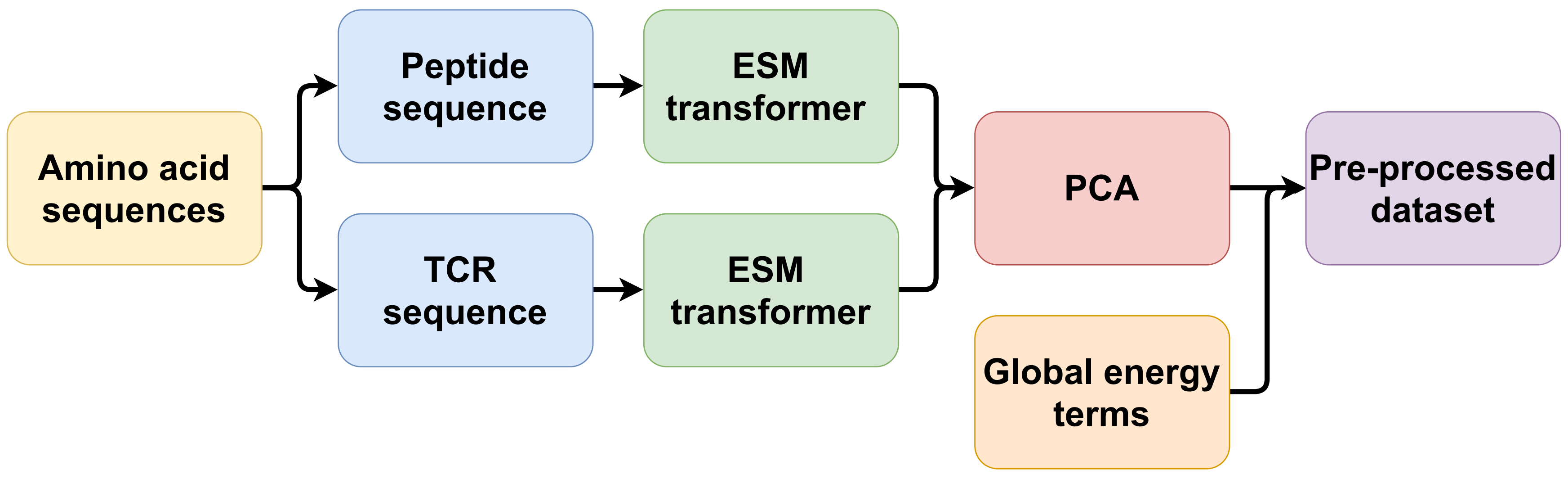
Input dimensions

- 6913 observations (4180 training, 1526 validation, 1207 test)
- 419 peptide positions (zero-padding where sequences are shorter)
- 54 channels (including sequence embedding and energy terms)

Methods

Pre-processing with protein embedding

- **BLOSUM (BLOcks SUbstitution Matrix):** Captures the biochemical properties of amino acids and turns one-hot encoding into a non-sparse vector.
- **ESM (Evolutionary Scale Modeling)[2]:** A transformer, i.e. a series of blocks that alternate self-attention with feed-forward connections. The ESM model was pre-trained with 250 million sequences and has 650 million weights. The output is a vector of size 1280 for each amino acid position.



Amino acid sequences

Peptide sequence

TCR sequence

ESM transformer

ESM transformer

PCA

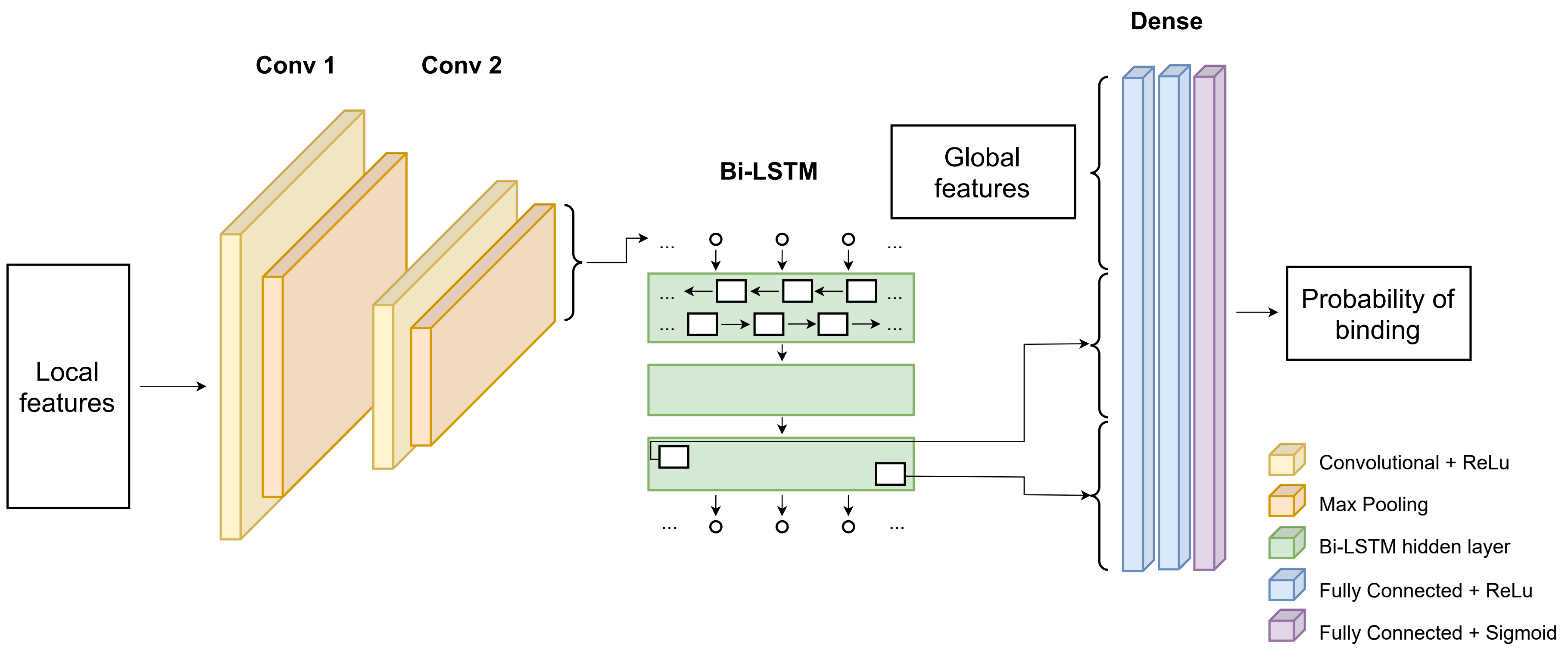
Global energy terms

Pre-processed dataset

Figure 2. Pipeline for embedding the peptide and TCR protein sequences to generate the pre-processed dataset.

Neural network architecture and training

- Early stopping, Adam optimizer with weight decay
- **Improvements:** More dense layers, division into local and global features, more drop out, additional batch normalization, weighted binary cross-entropy loss, more CNN filters for ESM embeddings



Local features

Conv 1

Conv 2

Bi-LSTM

Global features

Dense

Probability of binding

Convolutional + ReLu

Max Pooling

Bi-LSTM hidden layer

Fully Connected + ReLu

Fully Connected + Sigmoid

Figure 3. Architecture of the neural network. 2 convolutional layers with max pooling followed by Long short-term memory (LSTM) and dense feed forward neural network.

Results

Network architecture	AUC	MCC	Precision	Recall	F1
Vanilla architecture	0.82	0.473	0.572	0.658	0.612
Improved architecture	0.86	0.469	0.5	0.794	0.614
Improved architecture with BLOSUM encoding	0.87	0.559	0.623	0.738	0.676
Improved architecture with ESM encoding	0.87	0.584	0.678	0.700	0.689

Table 1. Comparison of the performance on the test set between different data preprocessing methods and network architectures.

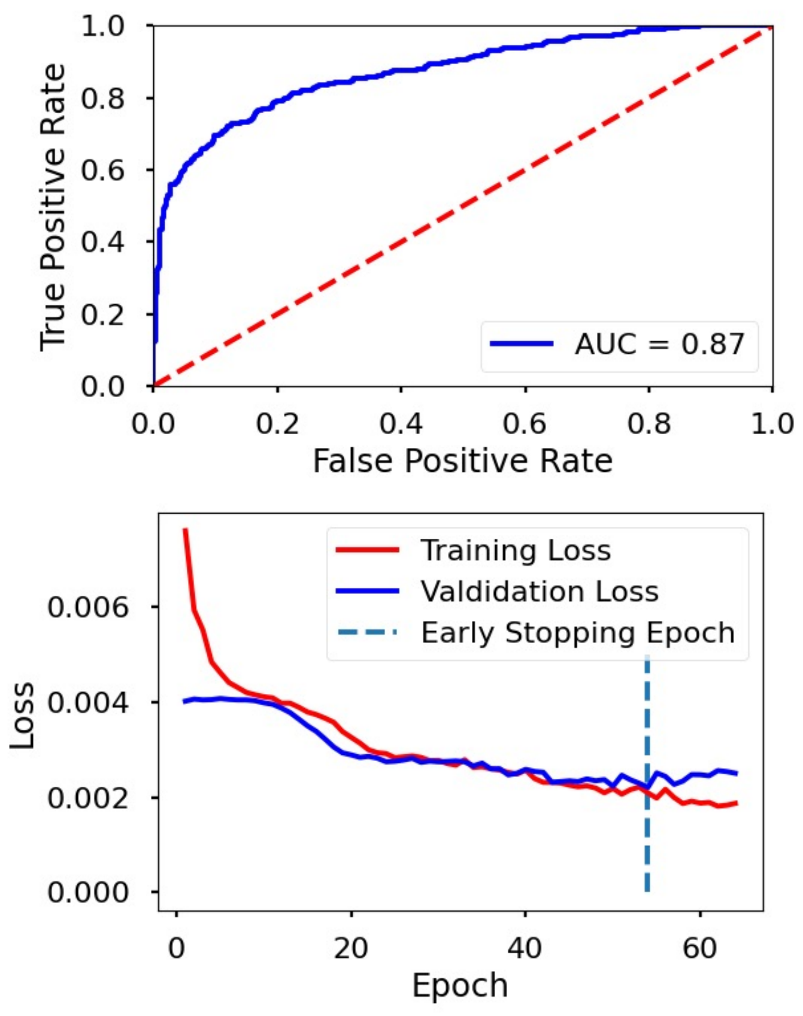


Figure 4. Evaluation of training and performance of improved architecture model with ESM embedding. Top: Receiver operating characteristic (ROC) curve on the test set. Bottom: Cross entropy loss of training and validation set and point of early stopping.

	Predicted: Negative	Predicted: Positive
Actual: Negative	806	100
Actual: Positive	90	211

Table 2. Confusion matrix on the test set for model with improved architecture and ESM embeddings with threshold 0.7, determined by optimal MCC.

- Both changes in network architecture and protein sequence embeddings improve prediction of TCR-pMHC binding
- The optimal threshold of 0.7 is calibrated based on the MCC of the validation set

Discussion

- The class imbalance of the dataset (75% negatives) is addressed by using a weighted loss function and calibrating the threshold based on the MCC. MCC and F1 score are still preferred over accuracy and AUC as evaluation metrics. Alternatively, positive examples could be oversampled by interpolation, generating more training examples in addition to the artificial negative swapped examples.
- The here used ESM Transformer is trained on diverse protein sequences. TCR-specific embeddings as generated by the TCR-BERT[4] model could improve our performance.

References

[1] Magnus H. Høie. (2021). T-cell binding prediction challenge (TCR-pMHC). Github repository, https://github.com/CBH2021/tcr-pmhc

[2] Rives, A. et al. (2021). Biological structure and function emerge from scaling unsupervised learning to 250 million protein sequences. *Proceedings of the National Academy of Sciences, 118(15).*

[3] Ida Kristine Sandford Meitil. (2021). Using deep learning for improving TCR homology modeling and its application to immunogenicity prediction [Master's Thesis, DTU]

[4] Wu, K. et al. (2021). TCR-BERT: learning the grammar of T-cell receptors for flexible antigen-xbinding analyses. *bioRxiv*.