T-Cell Receptor-Peptide Interaction Prediction with Physical Model Augmented Pseudo-Labeling

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Background: Modern Healthcare is a Data-Driven Service
Background: Big Data Enables Precision Medicine

Picture Credit: https://www.nature.com/news/personalized-medicine-time-for-one-person-trials-1.17411
T-Cell Receptor (TCR) Recognition for Precision Immunotherapy
TCR recognition is the holy grail of immunology

TCRs bind with anomalous peptides (viral / cancerous) presented on the surface of cells

If TCR-peptide binding takes place, the immune system can kill cancerous/infected cells
Data-Driven Precision Immunotherapy

Personalized immunotherapy considers genomic variations of patients
CDR3, especially CDR3β, is mainly responsible for recognizing peptide antigens.

TCR recognition is the holy grail of immunology.

T-Cell Receptor (TCR) Recognition of Peptide Antigens

Our task: Given a sequence of CDR3 beta of TCR and a sequence of peptide, predict the interaction (binary, 0/1).

For example, for a machine learning model, the inputs are: TCR: CASSDAGANTEVF and Peptide: IKAVYNFATCG
Output is a binary prediction.

TCR recognition is the holy grail of immunology
Datasets

### McPAS Dataset¹

<table>
<thead>
<tr>
<th>CDR3.beta.aa</th>
<th>Species</th>
<th>Category</th>
<th>Protein.ID</th>
<th>Epitope.peptide</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAS_3DAGANTEVF</td>
<td>Mouse</td>
<td>Pathogens</td>
<td>P09991</td>
<td>KAPYVNIFATCG</td>
</tr>
<tr>
<td>CAS_3DAGAWEQF</td>
<td>Mouse</td>
<td>Pathogens</td>
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</tbody>
</table>

### VDJdb Dataset²

<table>
<thead>
<tr>
<th>CDDYLPQQDDYSPQYQPHF</th>
<th>TRBV13</th>
<th>HomoSapiens</th>
<th>HLA-B*08</th>
<th>E2M</th>
<th>MHC1</th>
<th>FLKEKGGGL</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASSFEAGQGFFSNQPOPHF</td>
<td>TRBV13</td>
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</tr>
<tr>
<td>CASALASLINGFF</td>
<td>TRBV14</td>
<td>HomoSapiens</td>
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<td>MHC1</td>
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</tr>
</tbody>
</table>

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¹ McPAS-TCR: a manually curated catalogue of pathology-associated T cell receptor sequences, Bioinformatics 2017
² VDJdb in 2019: database extension, new analysis infrastructure and a T-cell receptor motif compendium, Nucleic Acids Research 2020
Challenges on Learning Deep Models

1. The dataset are relatively small: 20,000 TCRs in McPAS and 40,000 in VDJdb.

2. The examples in datasets are biased, i.e., there are only 200 and 300 different peptides in McPAS and VDJdb.
Potential Solutions


2. Data-augmentation by physical simulation, e.g., leveraging fast computing of binding energies by physical computation (e.g., Docking).

Especially, there exist millions of TCR sequences in database, like TCRdb\textsuperscript{1}.

\textsuperscript{1}TCRdb: a comprehensive database for T-cell receptor sequences with powerful search function, Nucleic Acids Research 2022
Our Model

- **Our contribution is introducing a universal learning framework with pseudo labeling.**
  - we adapt a simple base model from ERGO\(^1\), which has one encoder for TCR and another one for peptide.

- Our learning framework should be agnostic to different base models.

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\(^1\) Prediction of Specific TCR-Peptide Binding From Large Dictionaries of TCR-Peptide Pairs. Front. Immunol. 2020
Our Learning Losses

1. Supervised learning from limited labeled data.
2. Learning from pseudo-labeled data (by a teacher model pretrained).
3. Learning from data with surrogate labels by physical modeling.
Our Learning Losses

$L_{total} = L_{label} + L_{pseudo} + L_{physical}$

This is standard supervised learning from data from datasets like McPAS or VDJdb.
Our Learning Losses

Suppose we have a model pre-trained on the McPAS and VDJdb, we use this model to pseudo-label TCR and peptide pairs from external TCR database.

For example, \textit{TCR:CASSFRGSETQYF} and \textit{Peptide: IKAVYNFATCG} are labeled by 0.82
Why Pseudo Labeling Works

- The decision boundary should lie in low-density regions in order to improve generalization.
- Unlabeled samples that lie either near or far from labeled samples should be informative for decision boundary estimation.
- Pseudo-labeling generally works by iteratively propagating labels from labeled samples to unlabeled samples using the current model to relabel the data.\(^1\)

Pseudo Labeling is Not a Silver Bullet

- The key lies in the choice of the unlabeled data for pseudo labeling
Physical Augmentation by Docking for Pseudo Labeling

$$L_{total} = L_{label} + L_{pseudo} + L_{physical}$$

We compute **Docking energy** between a TCR and peptide, as the surrogate label, to extend our dataset for pseudo labeling.
Docking by HDock\(^1\)

Docking is a computational method for predicting the structures of protein complex by minimizing an **energy scoring function**.

Docking by HDock\(^1\)

1. For sequences without 3D structures, we run **blastp** for multiple sequence alignment (MSA) to find homologous sequence with known structures.

2. Then, we use MODELLER to build 3D structures of sequences (both TCRs and peptides).

Docking by HDock\textsuperscript{1}

1. We use the minimal energies found during the docking optimization as surrogate labels.

2. Pairs with the least 25 percentile energies are used as positive pairs and top 25 percentile are used as negatives.

Our Proposed Method

\[ L_{\text{labeled}} = \text{BinaryCrossEntropy}(\text{pred}, y) \]
\[ L_{\text{physical}} = \text{BinaryCrossEntropy}(\text{pred}', y') \]
\[ L_{\text{pseudo-labeled}} = \text{KL-div}(\text{pred}', \text{prob}') \]

\[ L_{\text{total}} = \alpha L_{\text{labeled}} + \beta L_{\text{physical}} + \gamma L_{\text{pseudo-labeled}} \]
Our Algorithm

1. Learning from labeled dataset
2. Learning from data-augmented pseudo-labeling
3. Learning from physical modeling
4. Look ahead meta-update
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Our Algorithm

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4. Look ahead meta-update

We will only update parameters of the model if and only if the learning from surrogate labels reduces the loss (on labeled dataset).
Experiments on McPAS Dataset

<table>
<thead>
<tr>
<th>Data size</th>
<th>6K</th>
<th>10K</th>
<th>20K</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERGO</td>
<td>54.4 ± 0.5</td>
<td>56.3 ± 0.5</td>
<td>71.2 ± 0.3</td>
</tr>
<tr>
<td>+ Pseudo</td>
<td>58.5 ± 0.5</td>
<td>62.7 ± 0.4</td>
<td>72.7 ± 0.3</td>
</tr>
<tr>
<td>+ Docking</td>
<td>61.4 ± 0.4</td>
<td>64.8 ± 0.4</td>
<td>72.4 ± 0.4</td>
</tr>
<tr>
<td>ours (3 losses)</td>
<td>62.1 ± 0.4</td>
<td>66.0 ± 0.4</td>
<td>73.2 ± 0.3</td>
</tr>
<tr>
<td>ours + meta-update</td>
<td>63.4 ± 0.4</td>
<td>66.5 ± 0.4</td>
<td>74.2 ± 0.3</td>
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</tbody>
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Experimental results with ERGO-AE (using auto-encoder for TCR and a double-LSTM for Peptides).
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<td>ERGO</td>
<td>67.6 ± 0.4</td>
<td>71.9 ± 0.4</td>
<td>76.6 ± 0.3</td>
</tr>
<tr>
<td>+ Pseudo</td>
<td>69.3 ± 0.4</td>
<td>73.6 ± 0.3</td>
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<tr>
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Experimental results with ERGO-LSTM (using both LSTMs for TCRs and Peptides).
Experiments on VDJdb Dataset

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<td>ERGO</td>
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<td>ours + meta-update</td>
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</tr>
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Experimental results with ERGO-LSTM (using both LSTMs for TCRs and Peptides).
Analysis on Rare Peptides

<table>
<thead>
<tr>
<th>rare peptides</th>
<th>baseline</th>
<th>average</th>
<th>ours</th>
</tr>
</thead>
<tbody>
<tr>
<td>KRWIILGLNK</td>
<td>52.8</td>
<td>54.4</td>
<td>68.1</td>
</tr>
<tr>
<td>KMVAVFYTT</td>
<td>48.9</td>
<td>54.4</td>
<td>65.8</td>
</tr>
<tr>
<td>FPRPWHLHGL</td>
<td>50.2</td>
<td>54.4</td>
<td>58.5</td>
</tr>
</tbody>
</table>

Experiments with AE-LSTM model with McPAS dataset of 6K labeled examples "average" denotes the average AUC for all peptides in this experimental setup
Conclusions

- We propose a general method for training a deep learning model with physical modeling augmented pseudo-labeling:

  1. Physical modeling between TCRs and peptides by docking to select what kind of unlabeled data for pseudo labeling, leveraging domain knowledge and inductive biases
  2. Data-augmented pseudo-labeling of TCR-peptide pairs with a model first trained on the labeled dataset.
  3. Look-ahead meta-update to further remove noise in physical modeling

- We introduce a new dataset that contains over 80,000 unknown TCR-peptide pairs with docking energy scores.
Future Research

- Population-wide TCR characterization and generalization of TCR-peptide interaction prediction

- Incorporate MHC Class I/II sequence/structure information into TCR-peptide-MHC interaction prediction

“Deep learning has instead given us machines with truly impressive abilities but no intelligence. The difference is profound and lies in the absence of a model of reality.”


Studying the synergy between physical modeling and data-driven deep learning
Acknowledgement

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Ohio State University: Ziqi Chen, Xia Ning

Yale University: Murilo Dorion, Prashant Emani, Tianxiao Li, Mark Gerstein

University of Hong Kong: Tung-Chi IP, Jun Yang
Questions?

Orchestrating a brighter world

https://www.nec-labs.com/research/machine-learning/