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HLA-EpiCheck: A B-cell epitope prediction tool on HLA antigens using molecular dynamics simulation data

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Introduction

In the context of organ transplantation, recipient’s antibodies against donor-specific HLA antigens are the main reason for transplant loss. The prediction of B-cell (antibody) epitopes on HLA antigens is therefore a key challenge on the way to improving the matching step between donor and recipient from a structural point of view. Here, we present HLA-EpiCheck, a B-cell epitope prediction tool that relies on an unprecedented dataset of short Molecular Dynamics (MD) simulations of 207 HLA antigens. We use hydrophobic properties, electrostatic charges, flexibility and solvent accessibility as descriptors calculated on patches sampled from MD trajectories. Then, we train an Extremely Randomized Trees machine learning model. This model outperforms the state-of-the-art DiscoTope 3.0 tool [1] for B-cell epitope prediction on HLA antigens.

MD data:

- 207 HLA antigens (the most prevalent in the European population).
- Initial templates for MD simulations were obtained from PDB [3] or Alphafold2 [4].
- 10ns MD simulations performed for each HLA antigen and 500 frames extracted from the last 5ns of the trajectory.
- NAMD3 software [5], CHARMM36 [6] force field and TIP3P explicit solvent model were used for MD runs.

Dataset generation

- Patch definition
  - Calculated for each frame of each MD run of each HLA antigen
  - Centered on every surface accessible residue (RSASA* ≥ 20%)
  - Composed of the surface accessible residues within a radius of 7Å from the central residue (centers of mass where used to measure distances).
  - 18 descriptors: (8 static and 10 dynamic).
- 2 classes: epitope and non-epitope.
- Epitope labels = confirmed eplets in the HLA Eplet Registry database [2].
- Non epitope = neither confirmed nor putative epitope.
- Patches composed solely of conserved residues (with respect to the locus) were discarded.

Model selection (on Training set)

Feature Importance for the Extra Trees model

Comparison with DiscoTope 3.0 (on Test set)

Conclusions and Perspectives

- Modest contribution of MD descriptors on prediction performance.
- Poor performance of DiscoTope 3.0: no HLA antigen in the dataset used to train DiscoTope.
- Find better descriptors for MD: analyse false negative epitopes.
- Try instance-based predictors such as K-NN.

References


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