Estimating and Visualizing HIV-1 Susceptibility to Broadly Neutralizing Antibodies

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Motivation
In HIV-1 treatment, clinicians still have to face drug-resistant viral strains, while the number of available drugs and drug targets remains limited. Recently, combination therapy with potent broadly neutralizing antibodies (bNAbs) was introduced as a viable new option in antiretroviral treatment against HIV-1 that is capable of reducing viral load under detectable levels for up to 60 days in humanized mice\textsuperscript{1} and primates\textsuperscript{2}. However, similar as with the well-established highly active antiretroviral therapy (HAART), the emergence of neutralization resistant strains might be a major problem in the selection of an efficient combination therapy of bNAbs for an individual patient. Prior to the administration of an antiretroviral bNAb combination therapy to a patient, it has to be ensured that the patient’s viral strains are susceptible to the respective bNAbs.

Methods
1. Learning

- Input
  - Viral ID
  - AA Sequence (Env)

- Kernel
  - SVM

- Choice

2. Predicting

Unseen viral Env sequence

- $^{\text{D-FNISSTR}}_{\text{Y}}$

Black Box

\[ P(\text{susceptible}) = 0.9 \]
\[ P(\text{resistant}) = 0.1 \]

3. Understanding

3.1 Classifier

- bNAbs: PG9, PGT121, VRC01

- Discriminant residues x position

- By definition of the oligo kernel\textsuperscript{4}, positional information can be retrieved from the classifier

3.2 Classification Result

- Additional to the classification result, we can
  - Visualize the relationship between the training sequences and the test sequence
  - Retrieve contribution of the most discriminative residues to the classification result for a test sequence

Results
1. Prediction Performance

- Fig. 3: Prediction performance of the final classifiers for each bNAb using the oligo kernel. The classifiers for the V3 loop-dependent antibodies achieved an AUC performance of up to 84%. In general, classifiers for antibodies targeting similar epitopes yield similar performances.

2. Learnt Parameter Settings

- Table 1: Learnt parameter settings for the final classifiers using the oligo kernel for each dataset. The oligo kernel defines the similarity between two sequences by the similarity of their common substrings of a certain size. The width parameter determines the allowed positional variation.

Material
- neutralization assays for seven different bNAbs targeting three major epitopes\textsuperscript{3,4}
  - CD4bs: VRC01, VRC-PG04
  - V1/V2 loop: PG9, PGT16
  - V3 loop: PGT121, 10-996, 10-1074

- 115-1187 HIV-1 envelope sequences per neutralization assay with corresponding IC\textsubscript{50} titers

- Susceptibility is defined as IC\textsubscript{50} values below 50 $\mu$g/mL. IC\textsubscript{50} values above indicate resistance to the antibody

Conclusion
- Well performing prediction models (up to 84% AUC)
- Useful in the selection of bNAbs combination therapy
- Extendable to new HIV bNAbs or HCV bNAbs
- Reliable classifiers identifying potential binding site residues
- Useful for epitope recognition
- Visualization of data relationships and motif logos improve biological understanding of the classification result

References
- Maisonnat et al. 2013. PNAS. Complete-type epitope recognition by broadly neutralizing HIV antibodies.

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\textsuperscript{4} Maisonnat et al. 2013. PNAS. Complete-type epitope recognition by broadly neutralizing HIV antibodies.

Fig. 1: The four epitopes of the envelope proteins gp120 and gp41 of HIV-1.

Fig. 2: Motif logo for the test sequence H9469973 using the PG9 classifier based on 3% of the strongest discriminant signals. The height of the letters is proportional to the contribution to the classification result. The corresponding amino acid positions of Env in the HIV-1 reference sequence HXB2 are shown on the x-axis.

Fig. 3: Prediction performance of the final classifiers for each bNAb using the oligo kernel. The classifiers for the V3 loop-dependent antibodies achieved an AUC performance of up to 84%. In general, classifiers for antibodies targeting similar epitopes yield similar performances.