Mapping antigenic variation in HIV-1 envelope

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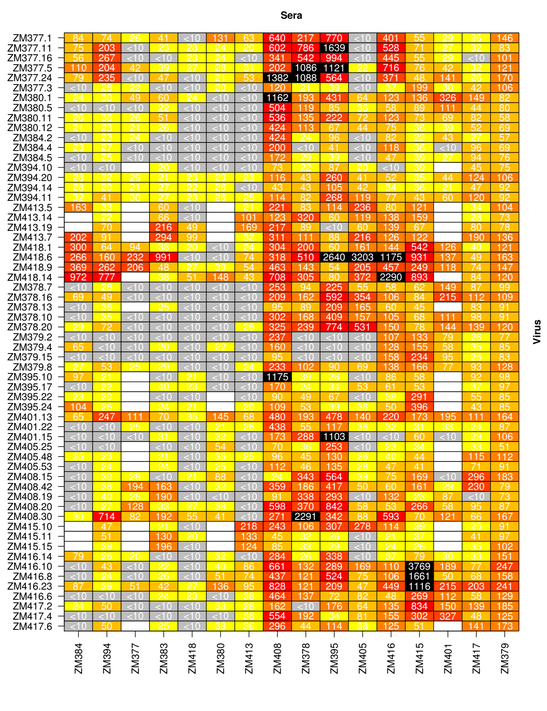
Background

- Recombinant-virus based assays of neutralisation of HIV-1 envelope are routinely used to measure the sensitivity of viruses to neutralisation, and the ability of sera to neutralise viral isolates.
- It is difficult to visualise antigenic differences, especially when the number of viruses and sera are large.
- **I present a statistical model to map viruses and sera into antigenic space, and apply it to data from five published studies of HIV-1 neutralisation.**

Materials and Methods

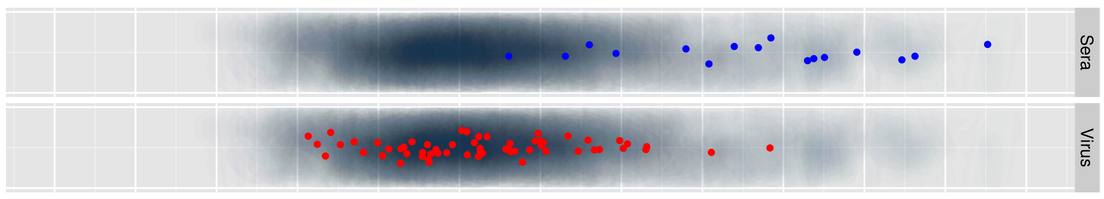
- Data on neutralisation were from published studies were analysed using Bayesian unfolding multidimensional scaling:
  - The model estimates X, a n by p matrix of coordinates in antigenic space of viruses, and Y, a k by p matrix of coordinates in antigenic space of plasma samples.
  - Let y_{ij} denote the $\log_2$ transformed IC_{50} neutralization titer between virus i and plasma j
  - The observed dissimilarity measure, d_{ij}, was obtained by normalizing the data using the maximum neutralization for each titer, $d_{ij} = \max y_{i\cdot} - y_{ij}$
  - d_{ij} is assumed to follow a truncated normal distribution, $d_{ij} \sim N(\delta_{ij}, \tau),\ I(d_{ij} > 0)$, where $i = 1, \ldots, n,\ j = 1, \ldots, k$
  - δ_{ij} was calculated assuming a two dimensional map.

Analysis of Kirchherr et al. (2011)



60 viruses (including multiple isolates from the same patients), 16 sera

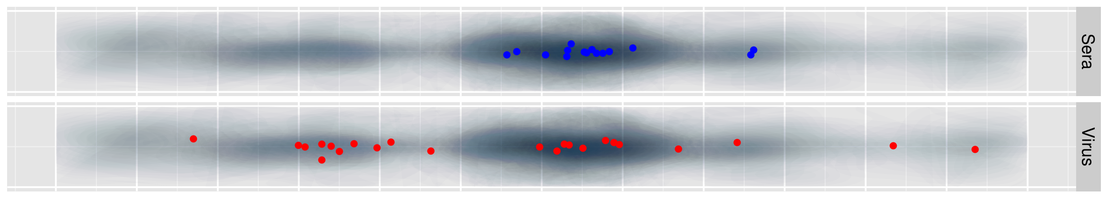
- Hard to see patterns in the data
- Missing data
- Measurements below the limit of detection



- Interpretation of antigenic map
  - Each large square represents a 2-fold difference in neutralisation
  - Distance between viruses represents similarity in neutralisation sensitivity
  - Distance between sera represents similarity in their ability to neutralise diverse viruses (controlling for magnitude)
  - Distances between viruses and sera represent similarity in sensitivity to specific sera, relative to the most sensitive virus in the panel

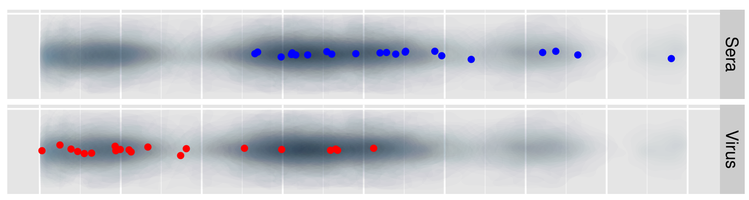
Van Gils et al. (2010)

- 23 viruses, subtypes A-D, 15 subtype B sera
- Some apparent clusters of viruses, but *not* related to subtype

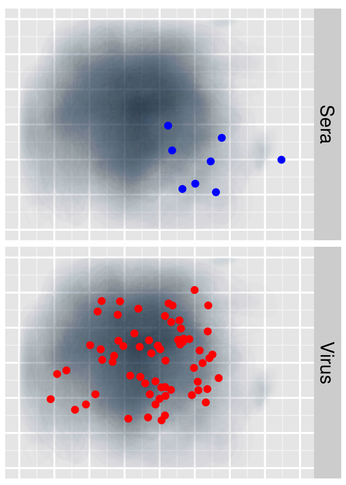


Georgiev et al. (2013)

- 21 viruses, 22 sera
- Some clustering of viruses, less antigenic variation than Van Gils et al. (2010)



Ping et al. (2013)



- 65 viruses, 9 sera (including two immunoglobulin pools)
- Higher resolution than other datasets; significant two-dimensional variation in the map

Conclusions

- Differences in neutralisation of HIV-1 can be mapped into 1-2 dimensions without significant loss of information
  - This approach removes confounding of breadth by the overall magnitude of the response
  - Without knowing the number of antibodies in a sample, we cannot compare sera without normalisation
- 'Broadly-reactive' sera exhibit similar patterns of neutralisation across viral isolates.
- Extensive, often continuous, antigenic distances between viruses.
  - Not related to subtype, and only weakly associated with specific positions.

References

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