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AntigenMap 3D: an online antigenic cartography resource

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ABSTRACT

Summary: Antigenic cartography is a useful technique to visualize and minimize errors in immunological data by projecting antigens to 2D or 3D cartography. However, a 2D cartography may not be sufficient to capture the antigenic relationship from high-dimensional immunological data. AntigenMap 3D presents an online, interactive, and robust 3D antigenic cartography construction and visualization resource. AntigenMap 3D can be applied to identify antigenic variants and vaccine strain candidates for pathogens with rapid antigenic variations, such as influenza A virus.

Availability and implementation: http://sysbio.cvm.msstate.edu/AntigenMap3D

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1 INTRODUCTION

Antigenic variation is a common strategy for an infectious pathogen to evade its host immunological response. The infectious pathogen can alter its surface protein(s) so that it will not be recognized by specific host antibody. As a result, the pathogen can reinfect the same host. Antigenic variation can be either antigenic drift from accumulating mutations or antigenic shift from exchanging surface proteins from two different strains. For influenza A virus, antigenic drift leads to seasonal epidemics and antigenic shift to pandemics.

Rapid detection of antigenic variant events and accurate quantification of antigenic variant extent are essential for selection of an effective vaccine strain and development of a prompt vaccination program. This has been especially important for influenza A virus, as vaccination is the primary option for reducing the impacts of influenza. The antigenic characterization in influenza virus are performed using immunological assays, such as hemagglutinin inhibition, microneutralization and enzyme-labeled immunosorbent assays. However, analyses of these immunological data are not trivial for the following reasons: (i) these assays are very crude and much noise is present in these datasets; (ii) it is not uncommon that there are empty entries in the resulting immunological tables; and (iii) the data distribution in these datasets is unique, and unobserved values are not distributed randomly in the tables, especially for datasets that contain viruses with large isolation time intervals.

Antigenic cartography is an analog of geographic cartography in presenting the antigens as 2D or 3D maps (Cai *et al.*, 2010; Cai *et al.*, 2011; Liao *et al.*, 2009; Smith *et al.*, 2004). Antigenic cartography has been shown to effectively detect influenza antigenic drift events; therefore, cartography is useful in antigenic characterization and vaccine strain selection (Ducatez *et al.*, 2011; Smith *et al.*, 2004; Wan *et al.*, 2011). Antigenic cartography has become a standard tool in influenza surveillance of the World Health Organization influenza reference laboratories. Because 2D cartography may not be sufficient to capture the antigenic relationship from the high-dimensional immunological data, we developed an antigenic cartography tool, AntigenMap 3D, to construct 3D antigenic cartography.

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2 METHODS

2.1 Antigenic cartography construction

Antigenic cartography construction was implemented in Java based on the matrix completion-multiple dimensional scaling (MC-MDS) algorithm that we described earlier (Cai *et al.*, 2010). Briefly, the missing values and error correlation was performed on the input immunological datasets using an alternating gradient descent low rank matrix completion method. If a temporal model is used, temporal regulation will be applied. Usually a temporal model is used only when antigenic data span long temporal ranges, such as H3N2 human influenza antigenic data described in Cai *et al.*, (2010).

2.2 Advantages of 3D maps

With multiple dimensional scaling, the 2D antigenic cartography reduces the dimension number to two from immunological data (Cai *et al.*, 2010; Cai *et al.*, 2011; Liao *et al.*, 2009; Smith *et al.*, 2004). However, 2D antigenic cartography has a limitation in information retrieval, especially when the dimension of two is not sufficient to capture major components from the high-dimensional immunological data. As a result, 2D may not be able to position the antigens correctly, especially for those antigens with similar properties in 1D but different properties in other dimensions. By moving to 3D space, antigenic cartography will have a much greater capability to optimize the positions on the map, thus a better accuracy in the resulting maps. In Figure 1, the 2D antigenic cartography was not able to display properly the antigenic relationship for antigenic clusters SY97 and FU02, which can be displayed properly in the 3D cartography by AntigenMap 3D. In addition, compared with 2D cartography, AntigenMap 3D is interactive also, thus allowing greater flexibility in display and analysis. Because AntigenMap 3D generates dynamic graphs, the user can refine and zoom the view without generating a new map. To facilitate the antigenic analysis, AntigenMap 3D provides additional functions such as distance measurement, advanced grouping, and view exporting to facilitate rapid analysis and antigenic variant detection.

2.3 Implementation and availability

AntigenMap 3D is written in Java and PHP and uses Jmol (jmol.sourceforge.net) (Herraez, 2006) to display the 3D graph by MC-MDS (Cai *et al.*, 2010). The front-end uses the XHTML 1.0 and CSS 3 standards to ensure a consistent display across different platforms. PHP is used to generate the dynamic pages and for data handling. The computational backend implementing the MC-MDS algorithm is written in

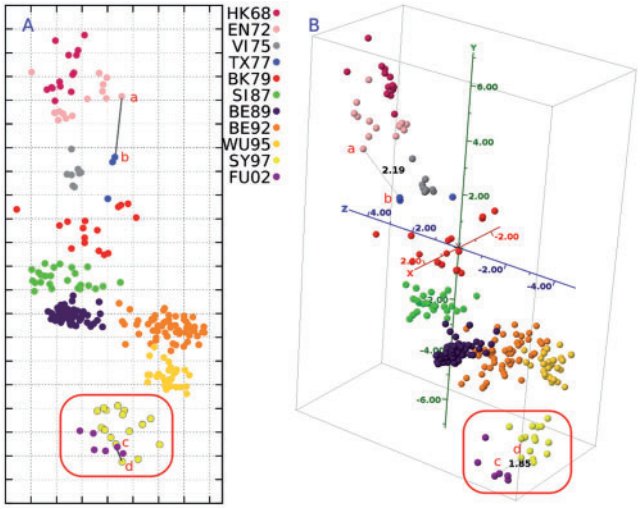

Fig. 1. The influenza antigenic 2D (A) and 3D (B) cartography for H3N2 viruses from 1968 to 2003. The viruses labeled with the cluster names HK68, EN72, VI75, TX77, BK79, SI87, BE89, BE92, WU95, SY97 and FU02 were adapted from Smith *et al.* (2004). One grid in 2D map or one unit in 3D map corresponds to a two-fold change in HI assay. The distance between antigen a and b in 2D cartography is similar to that in 3D cartography. However, the distance between antigenic c and d is at least 1 unit shorter than that in 3D cartography.

Java. Also, AntigenMap 3D is designed with security in mind from the start and includes strict input checking and sanitation.

AntigenMap 3D provides various options to construct antigenic maps, including five normalization methods, ranks for optimization process, low reactor cutoff and as to which modeling process. A temporal model is also provided as an option. Users will input data and select the options they chose and submit the information to the system. Users will select the colorization and grouping of the antigens before proceeding to the display of the 3D map. After the data have been processed, the user will be presented with the antigenic map and the user can proceed to analyze and save the data.

AntigenMap 3D uses a customized version of Jmol to visualize the 3D data generated by MC-MDS. The major changes to Jmol were in the user interface, such as menu and display functions. The custom loading scripts are generated based on the user's input and instructs Jmol on how to load and display correctly the 3D data. The input file format is raw immunological table/matrix and is processed by MC-MDS creating a customized Chemical Markup Language (CML) file. The CML format was adapted to handle antigenic data and is saveable by the user for later analysis.

AntigenMap 3D has been tested in Firefox, Chrome, and Internet Explorer on Windows and Firefox and Chrome on Linux.

3 SUMMARY

In summary, AntigenMap 3D provides a user-friendly and robust online resource for antigenic map construction using immunological datasets. Besides influenza viruses, AntigenMap 3D is also potentially applicable in antigenic cartography construction for other infectious antigens with significant antigenic variations.

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Conflict of Interest: none declared.

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