Antigenic flux in the influenza virus population

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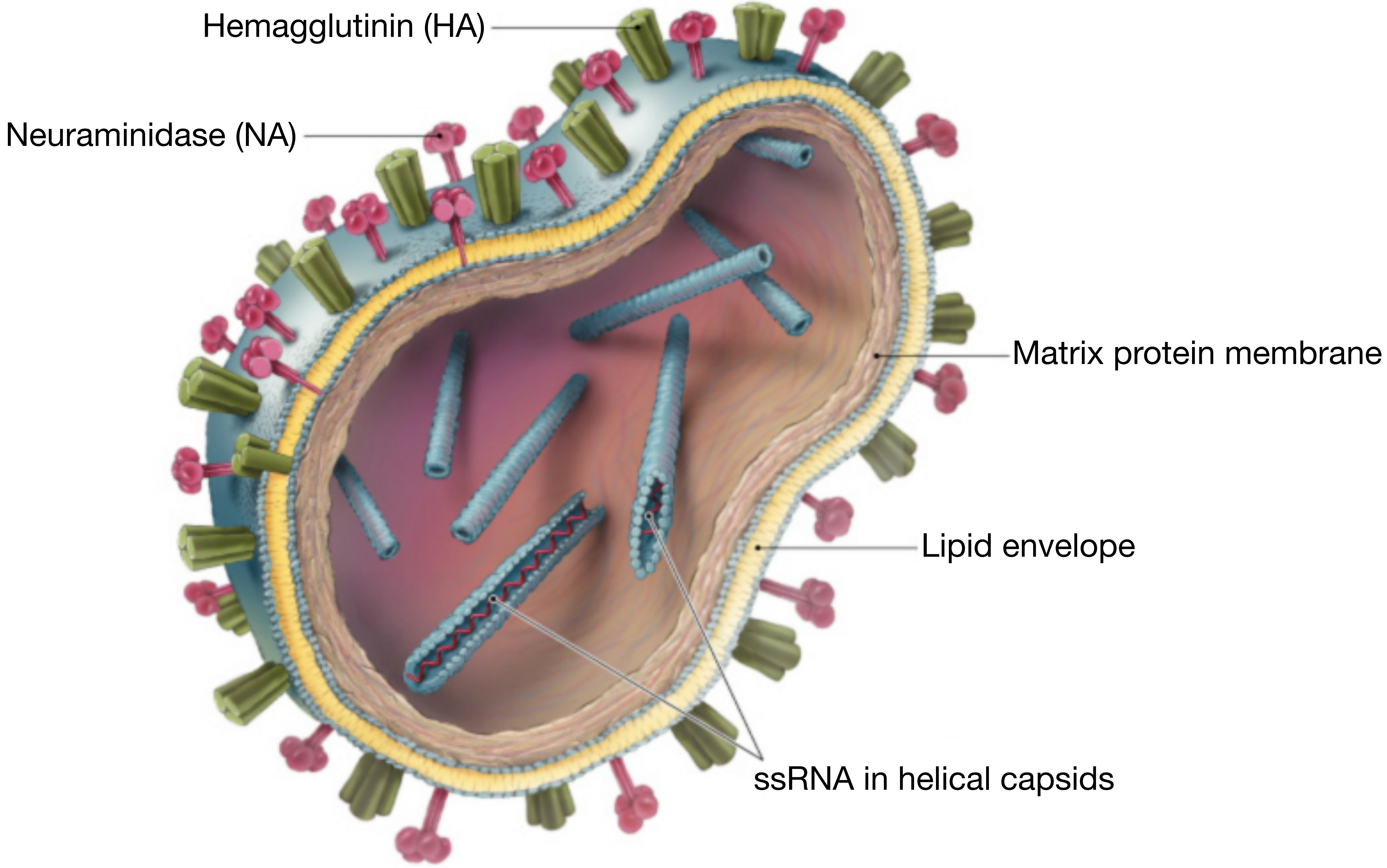
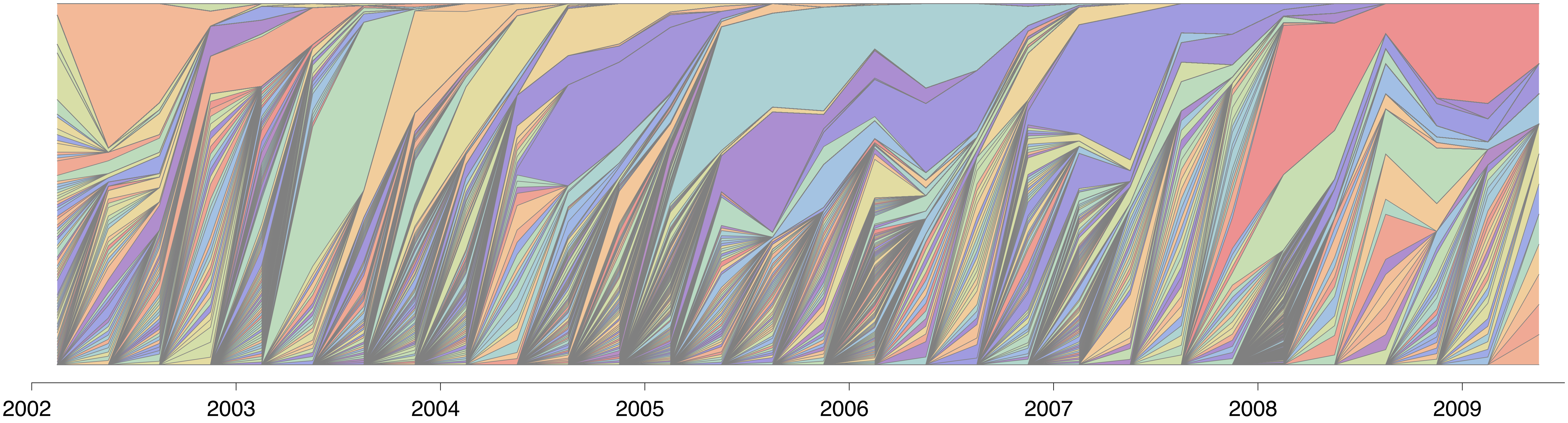
The influenza virus



Gene flow in the influenza population

HA amino acid sequences taken from H3N2 influenza at 2 month intervals



Approximately 1 in 20 sites change over the course of 10 years

Provides a chronological record of evolution

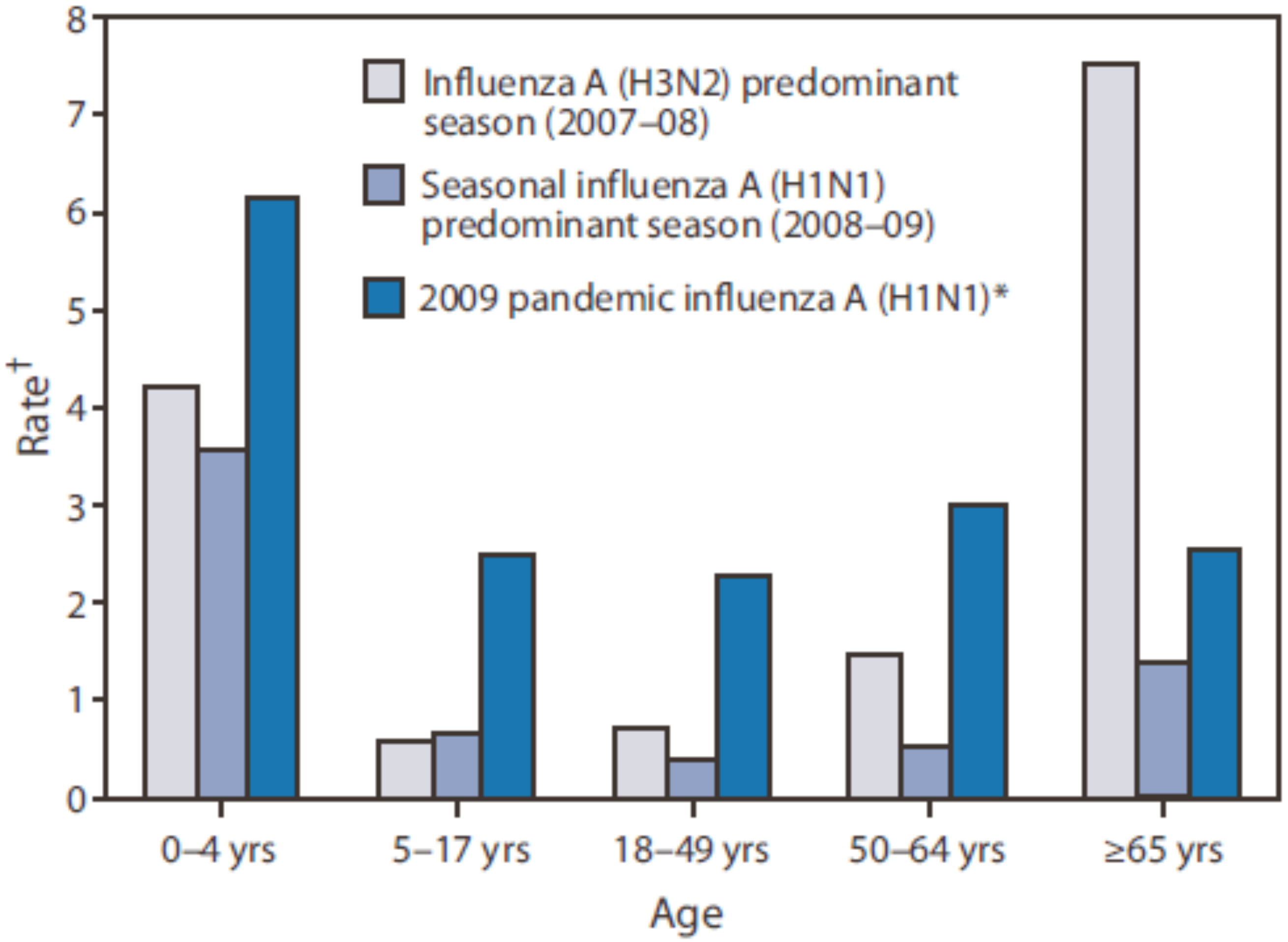
Influenza and measles differ in prevalence and age of infection

Seasonal influenza

Overall incidence ≈ 8% per year

Overall prevalence ≈ 0.1%

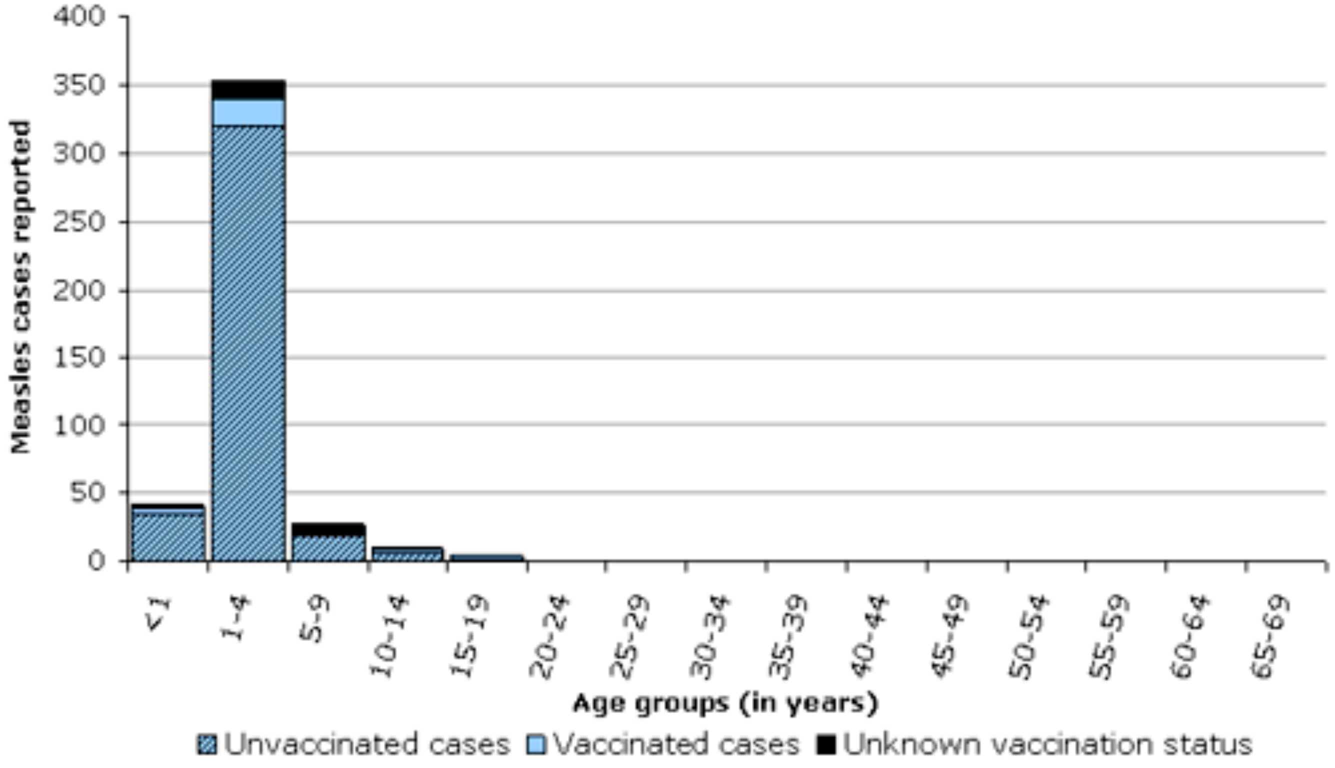
Cumulative hospitalization rate



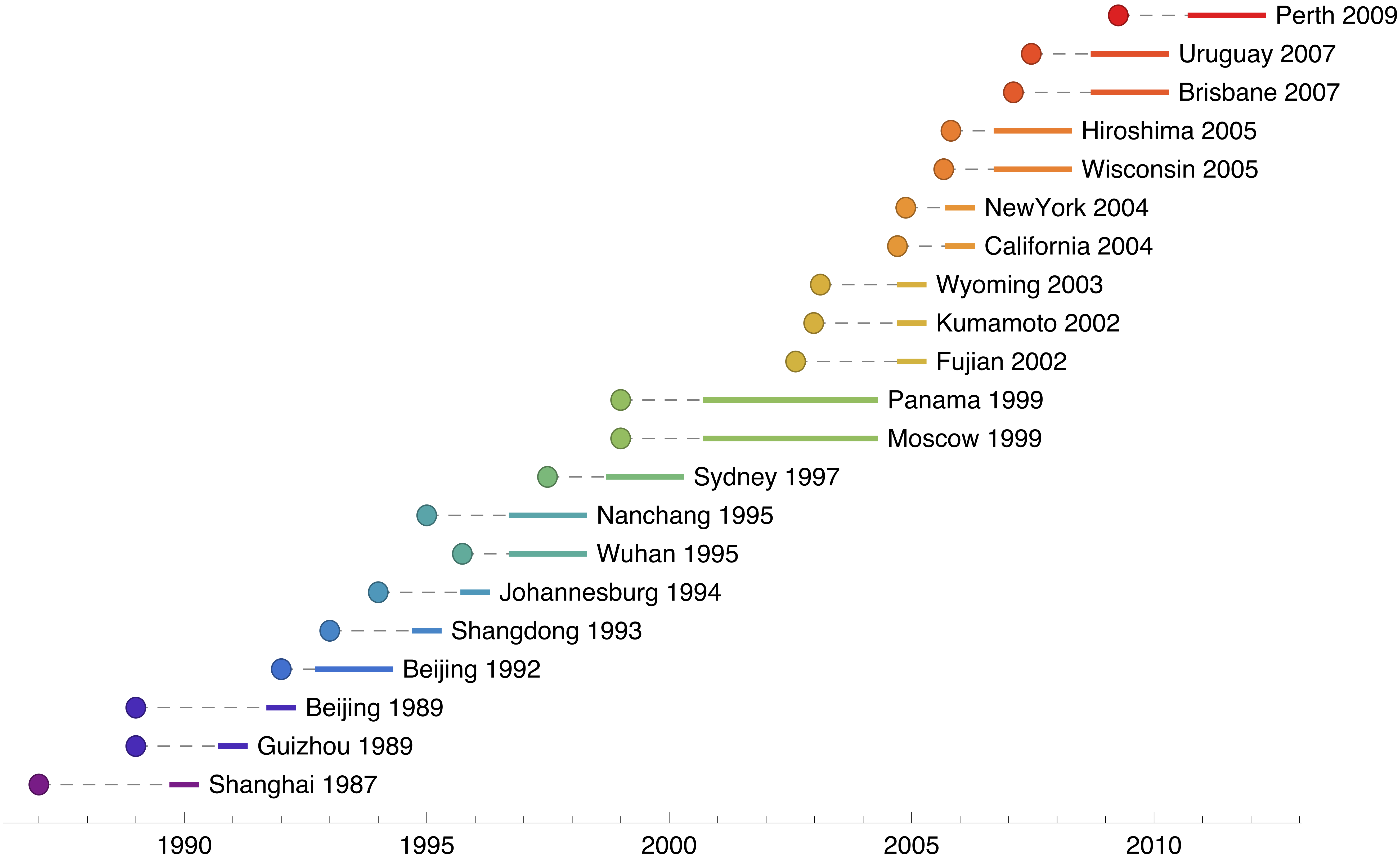
Measles (prior to vaccination)

Overall incidence ≈ 0.5% per year

Overall prevalence ≈ 0.01%



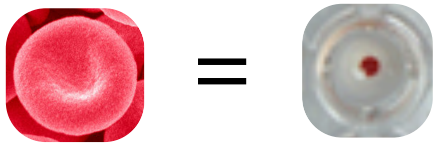
Antigenic drift results in almost yearly influenza vaccine strain updates



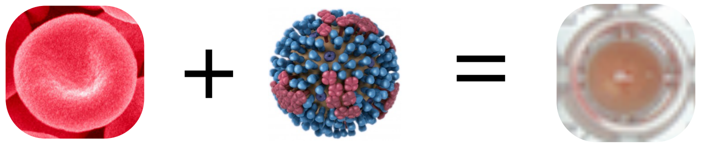
Modeling antigenic phenotype

Influenza hemagglutination inhibition (HI) assay

Hemagglutination assay:

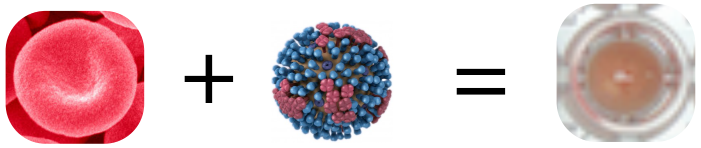


Without virus, red blood cell sink to bottom of well

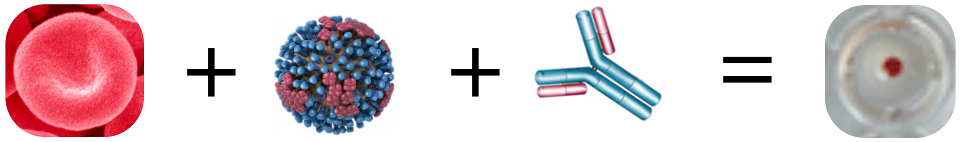


With virus, cells form diffuse lattice

Hemagglutination inhibition assay:

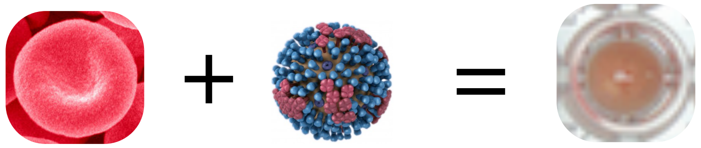


Without antibodies, agglutination of virus to RBC



Antibodies bind viruses, preventing agglutination

Influenza hemagglutination inhibition (HI) assay



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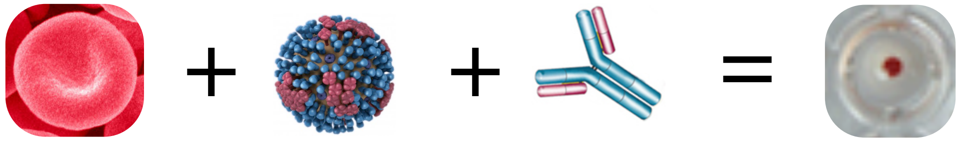
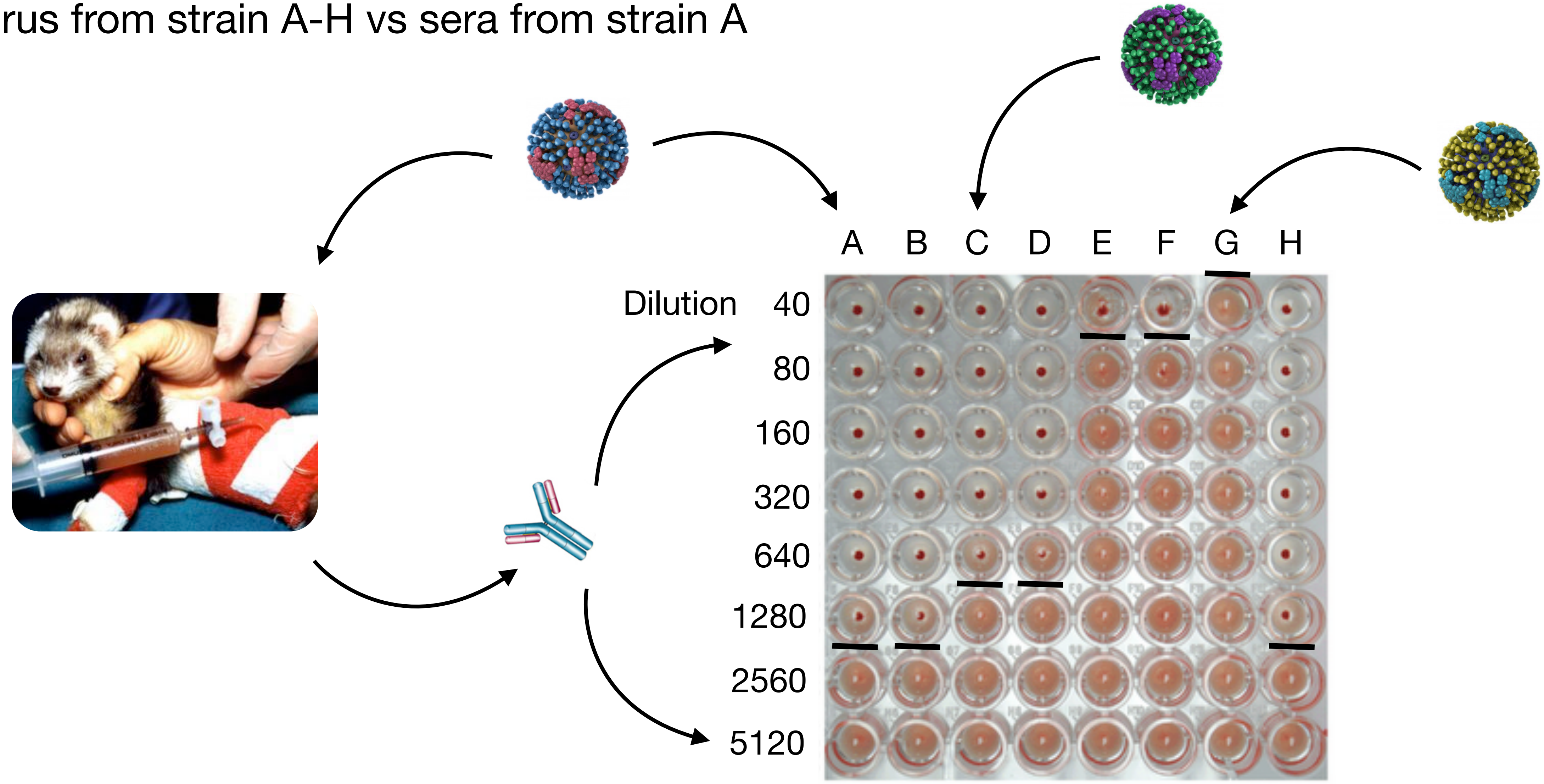


Antibodies bind viruses, preventing agglutination

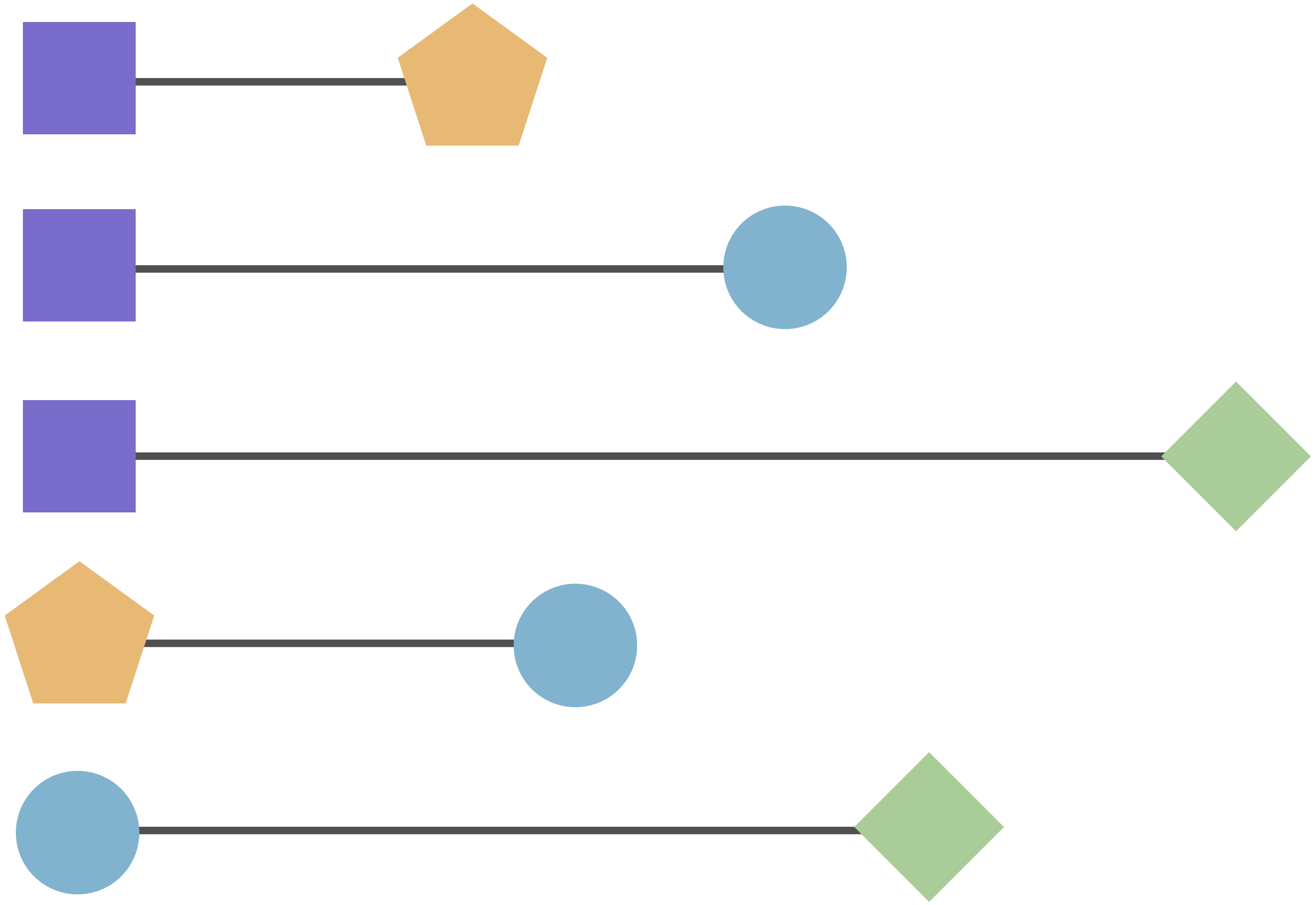
Reacting virus from strain A-H vs sera from strain A



Antigenic cartography

Developed by Derek Smith and colleagues

Uses multidimensional scaling (MDS) to position viruses in 2D space such that the distances in this space best fit the HI assay titres.



Smith et al. 2004. Mapping the antigenic and genetic evolution of the influenza virus. Science.

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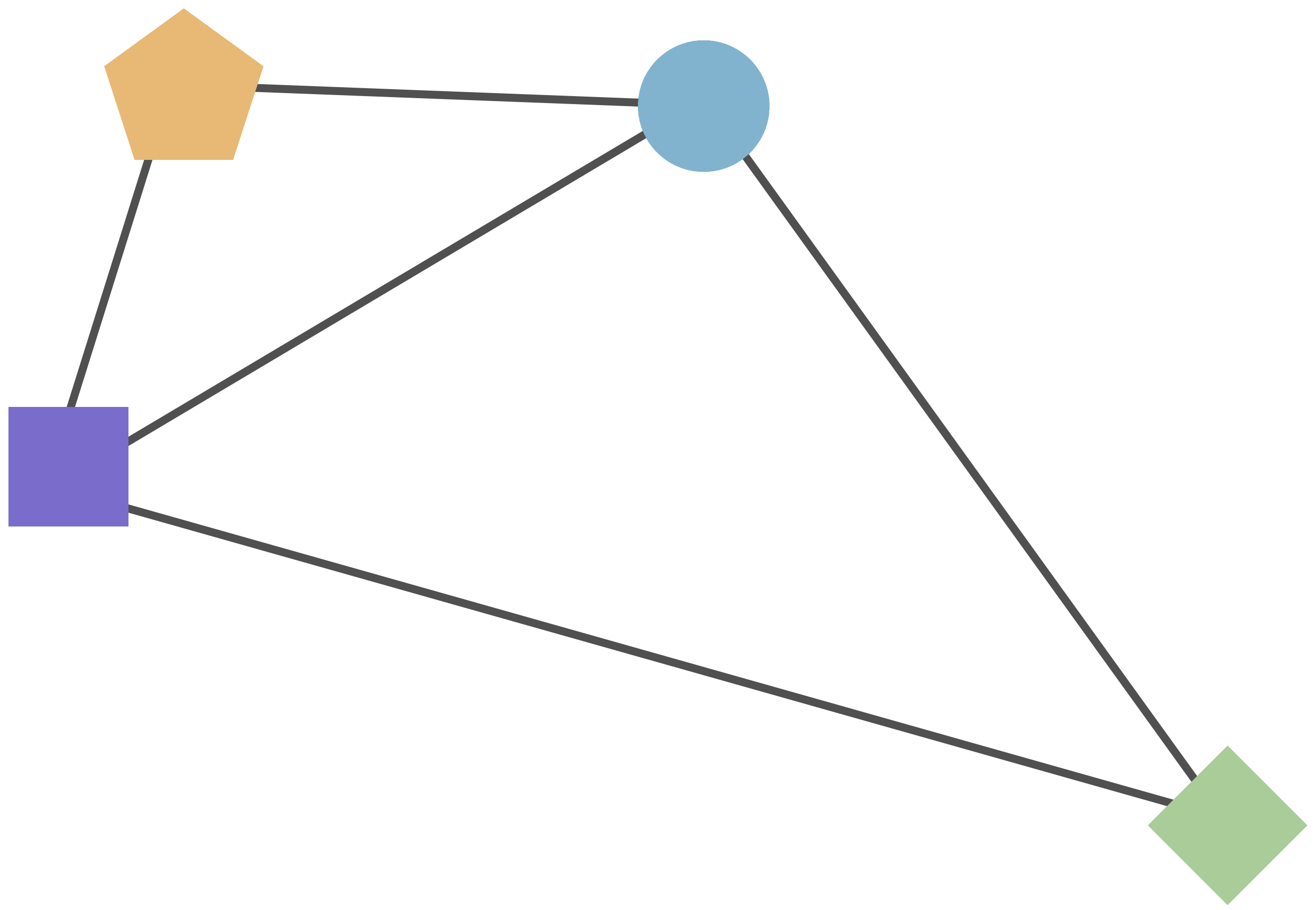


Smith et al. 2004. Mapping the antigenic and genetic evolution of the influenza virus. Science.

Multidimensional scaling (MDS)

Maximum titer (in log2 space) of serum *j*

$$s_j$$

HI titer of virus *i* vs serum *j*

$$H_{ij}$$

Observed HI distance between virus *i* and serum *j*

$$d_{ij} = s_j - H_{ij}$$

Map distance between virus *i* at X_i and serum *j* at Y_j

$$\delta_{ij} = ||X_i - Y_j||_2$$

The goal of **MDS** is to find locations that minimize the difference between HI distance and map distance

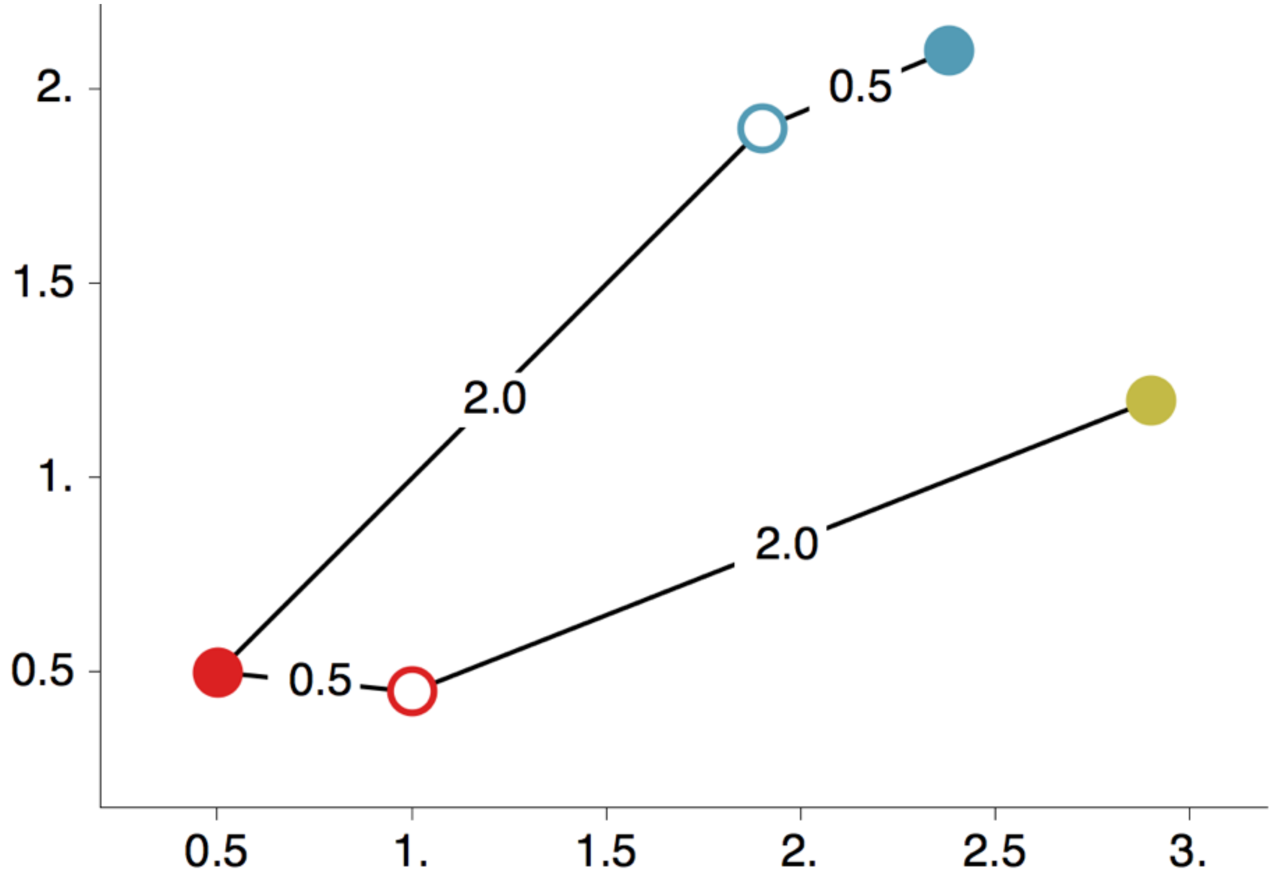
$$\sum_{(i,j)\in\mathcal{I}} (\delta_{ij} - d_{ij})^2$$

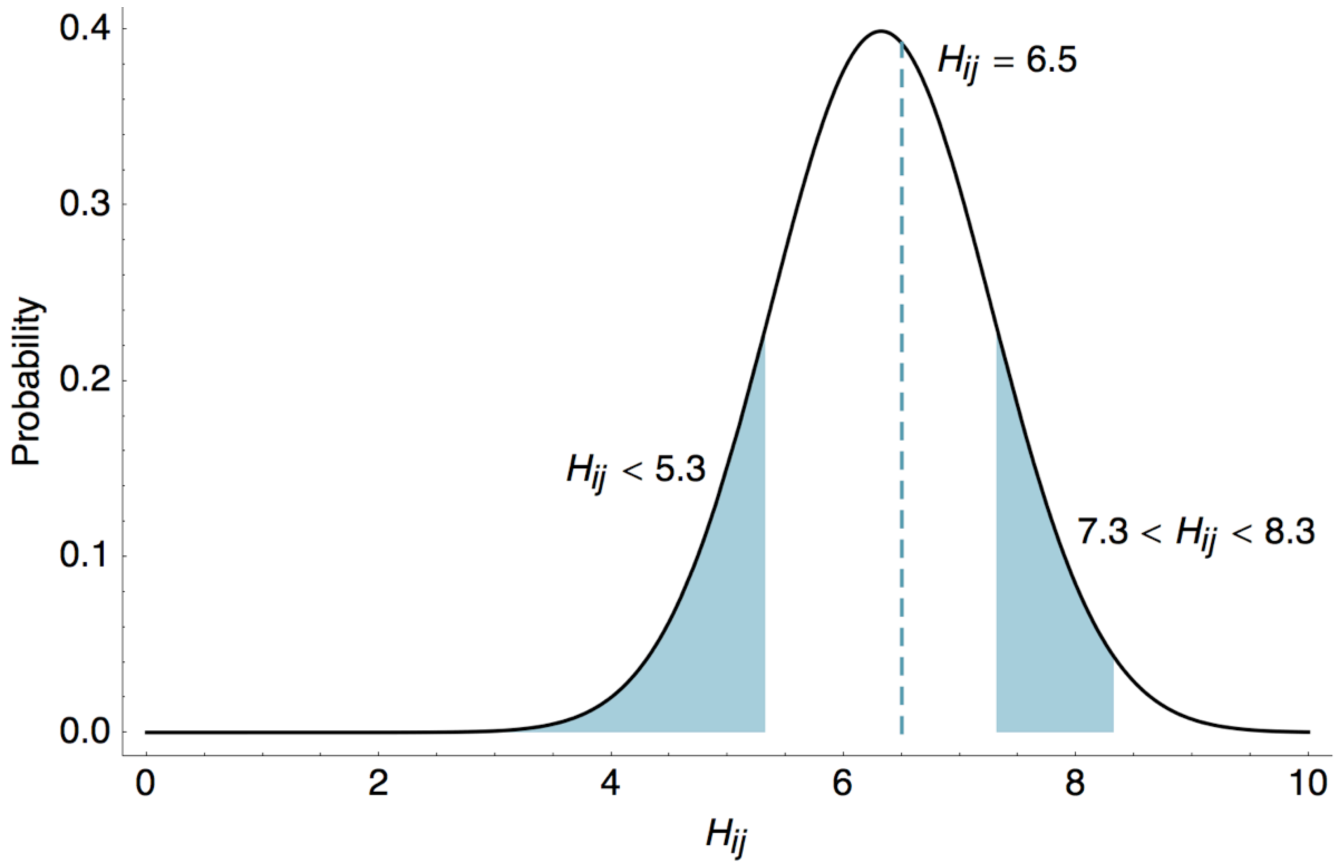
Bayesian multidimensional scaling (BMDS)

In **Bayesian MDS**, this is probabilistically reformulated as

$$H_{ij} \sim \mathrm{Normal}(s_j - \delta_{ij}, \varphi^2)$$

For example, given $\delta_{ij} = 2$ and $s_j = 8.3$





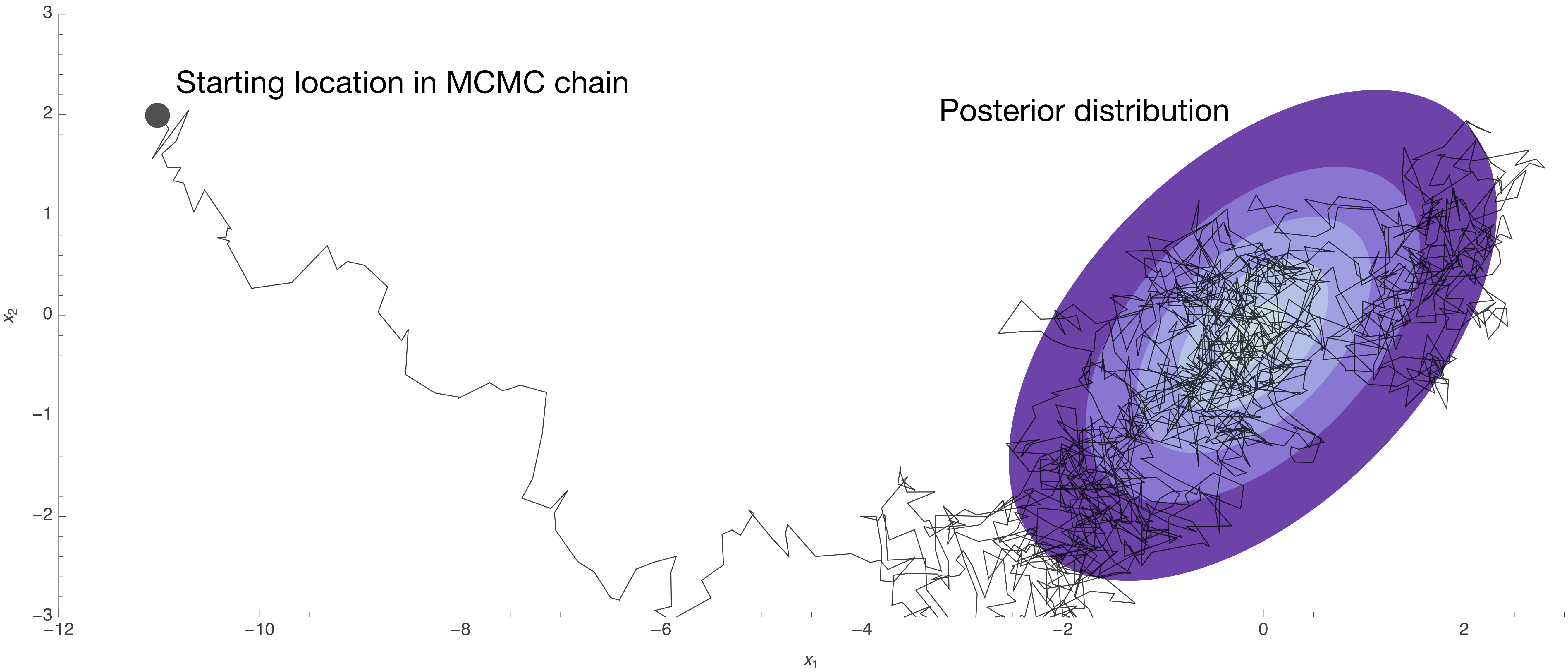
Likelihood of observing HI data

$$L(\mathbf{X},\mathbf{Y}) = \prod_{(i,j)\in\mathcal{I}} f(H_{ij})$$

Oh and Raftery. 2001. Bayesian multidimensional scaling and choice of dimension. J Am Stat Assoc.

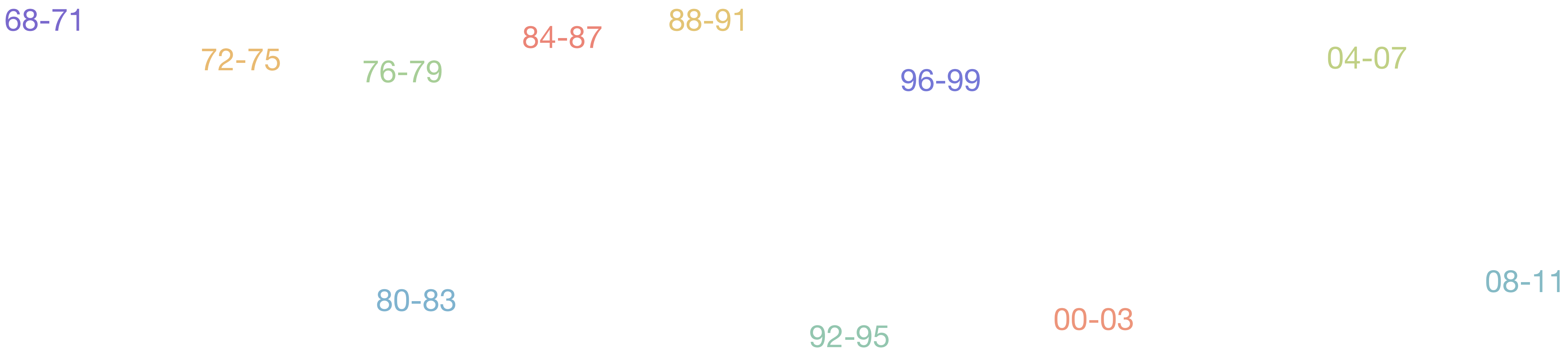
$$p(\mathbf{X}, \mathbf{Y} | \mathbf{H}) \propto p(\mathbf{H} | \mathbf{X}, \mathbf{Y}, \varphi)\; p(\mathbf{X}, \mathbf{Y}, \varphi)$$

Integration through Markov chain Monte Carlo (MCMC)



Bayesian MDS results

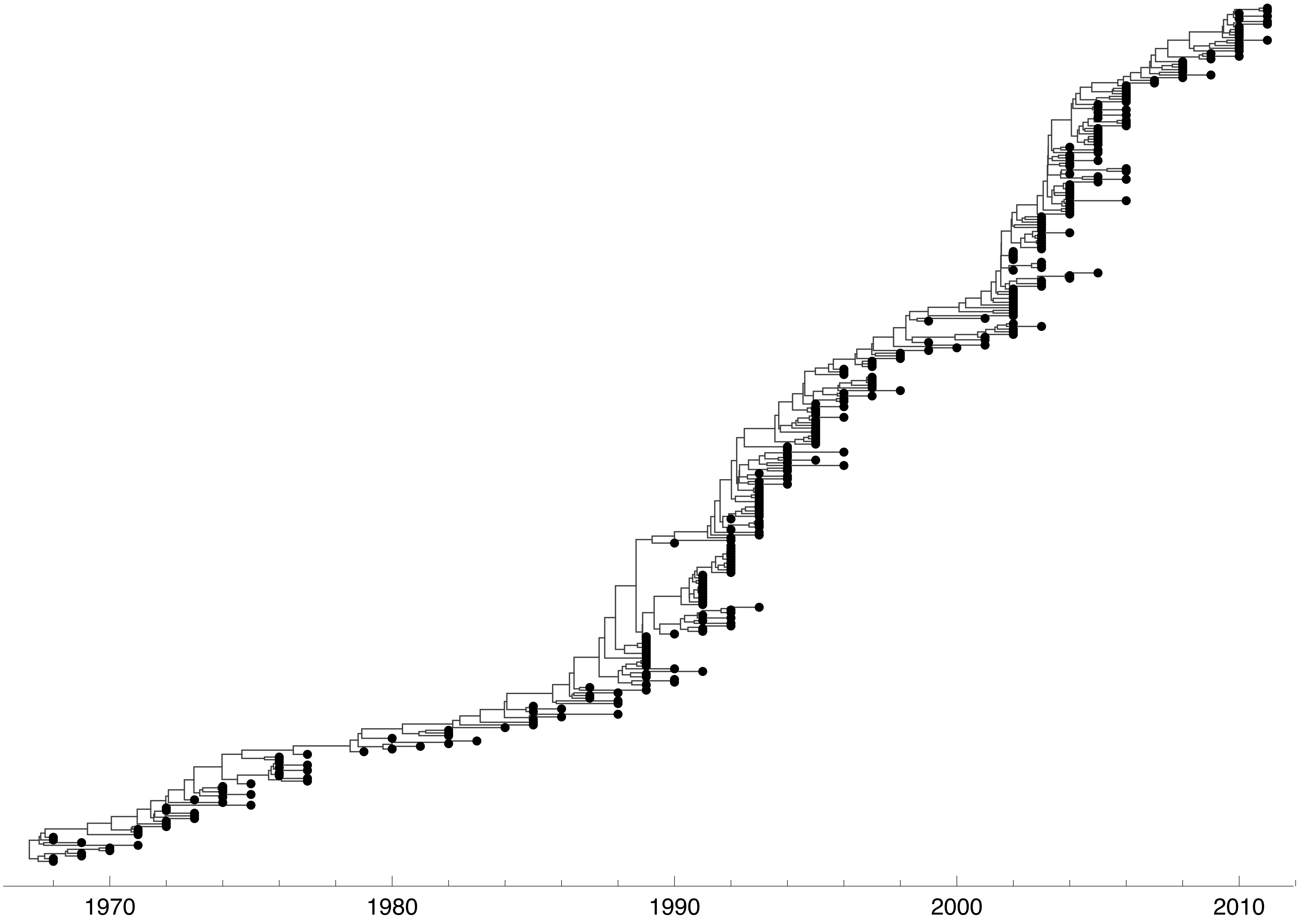
Antigenic map of H3N2 influenza from 1968 to 2011



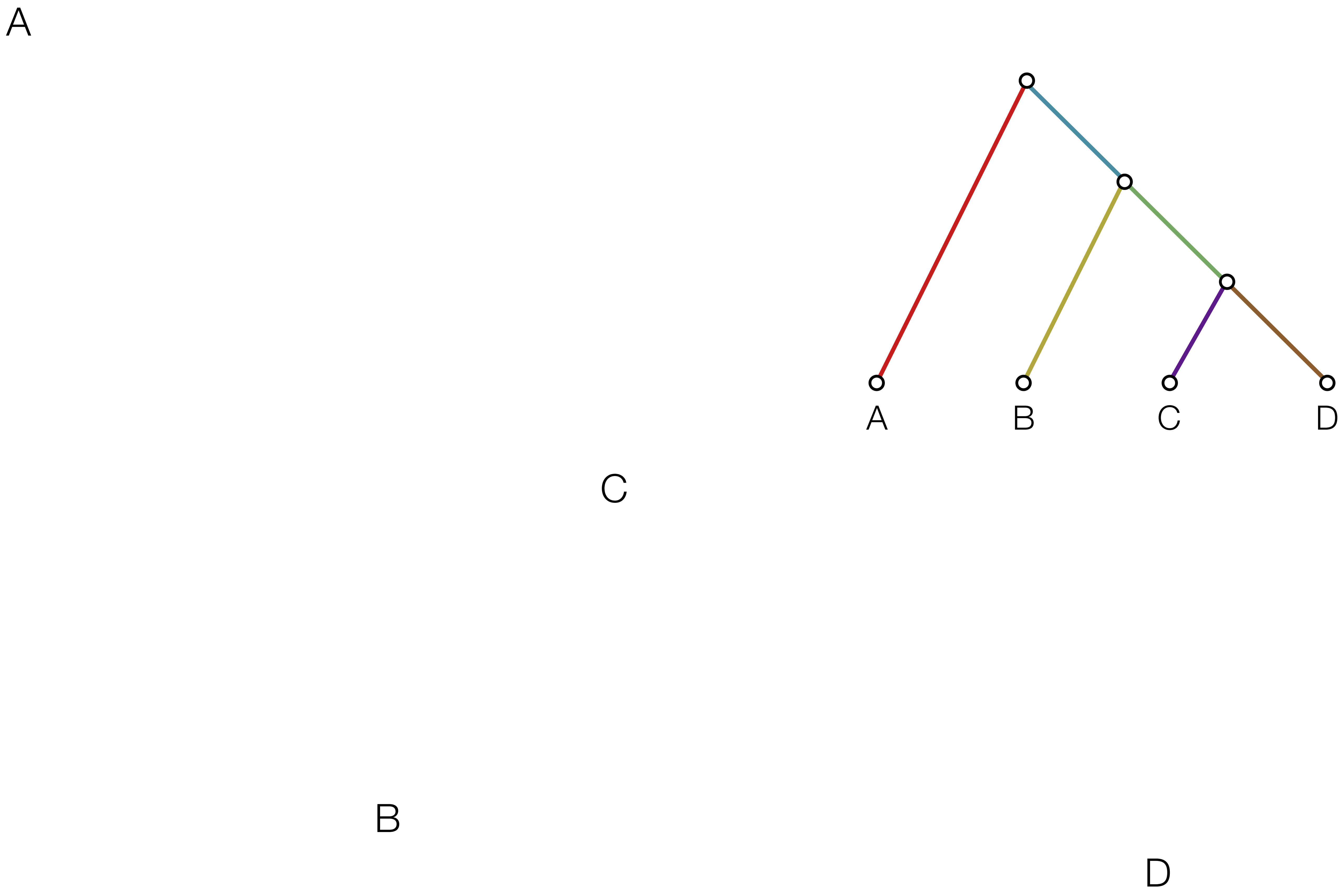
Antigenic drift of H3N2 influenza

Integrating phylogeny and cartography

Phylogeny of H3N2 virus sequences



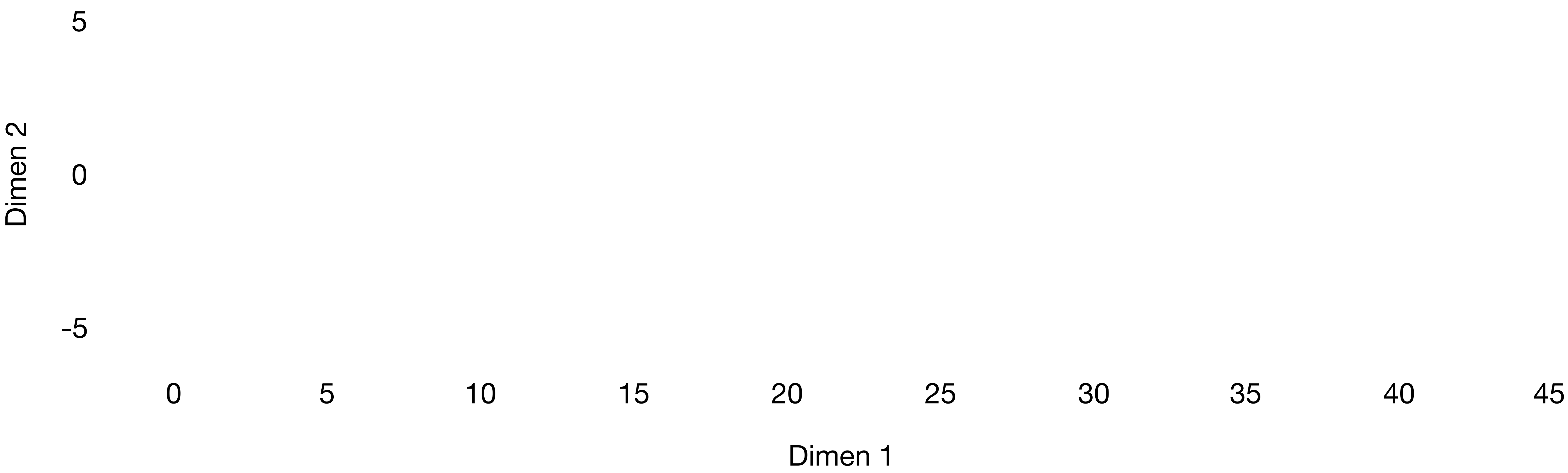
Modeling a continuous character as Brownian motion diffusion



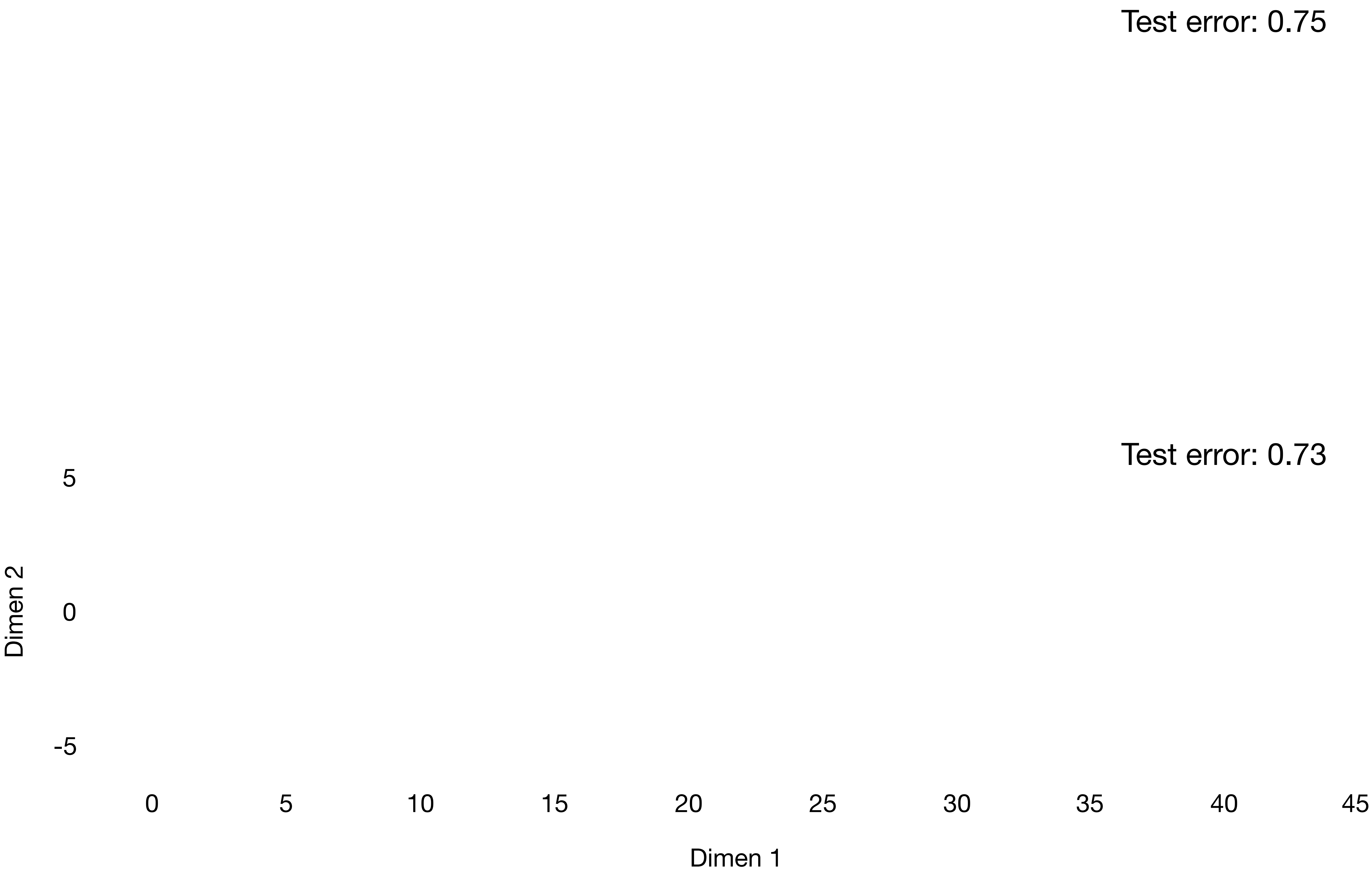
Lemey et al. 2010. Phylogeography takes a relaxed random walk in continuous space and time. Mol Biol Evol.

$$p(\mathbf{X}, \mathbf{Y} | \mathbf{H}) \propto p(\mathbf{H} | \mathbf{X}, \mathbf{Y}, \varphi)\, p(\mathbf{X} | \sigma, \tau)\, p(\mathbf{Y}, \varphi, \sigma, \tau)$$

Comparison of MDS and diffusion models



Comparison of MDS and diffusion models



Antigenic drift driven by trunk lineage

Antigenic drift driven by trunk lineage

Trunk: 1.00 AG / year

Side branches: 0.23 AG / year

Ratio: 4.35×

Linking genetic and phenotypic change

Acknowledgements

Data sources:

- WHO Global Influenza Surveillance Network • WHO Collaborating Centres for Influenza

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- Derek Smith (Cambridge University) • Colin Russell (Cambridge University)
- Gytis Dudas (University of Edinburgh) • Philippe Lemey (Katholieke Universiteit Leuven)
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Papers:

- Bedford T, Suchard MA, Lemey P, Dudas G, Gregory V, Hay AJ, McCauley JW, Russell CA, Smith DJ, Rambaut A. 2013. Integrating influenza antigenic dynamics with molecular evolution. arXiv: 1304.3637.

Source code:

- code.google.com/p/beast-mcmc/