MAPPING THE ANTIGENIC AND GENETIC EVOLUTION OF INFLUENZA VIRUS

Article: Smith et al.

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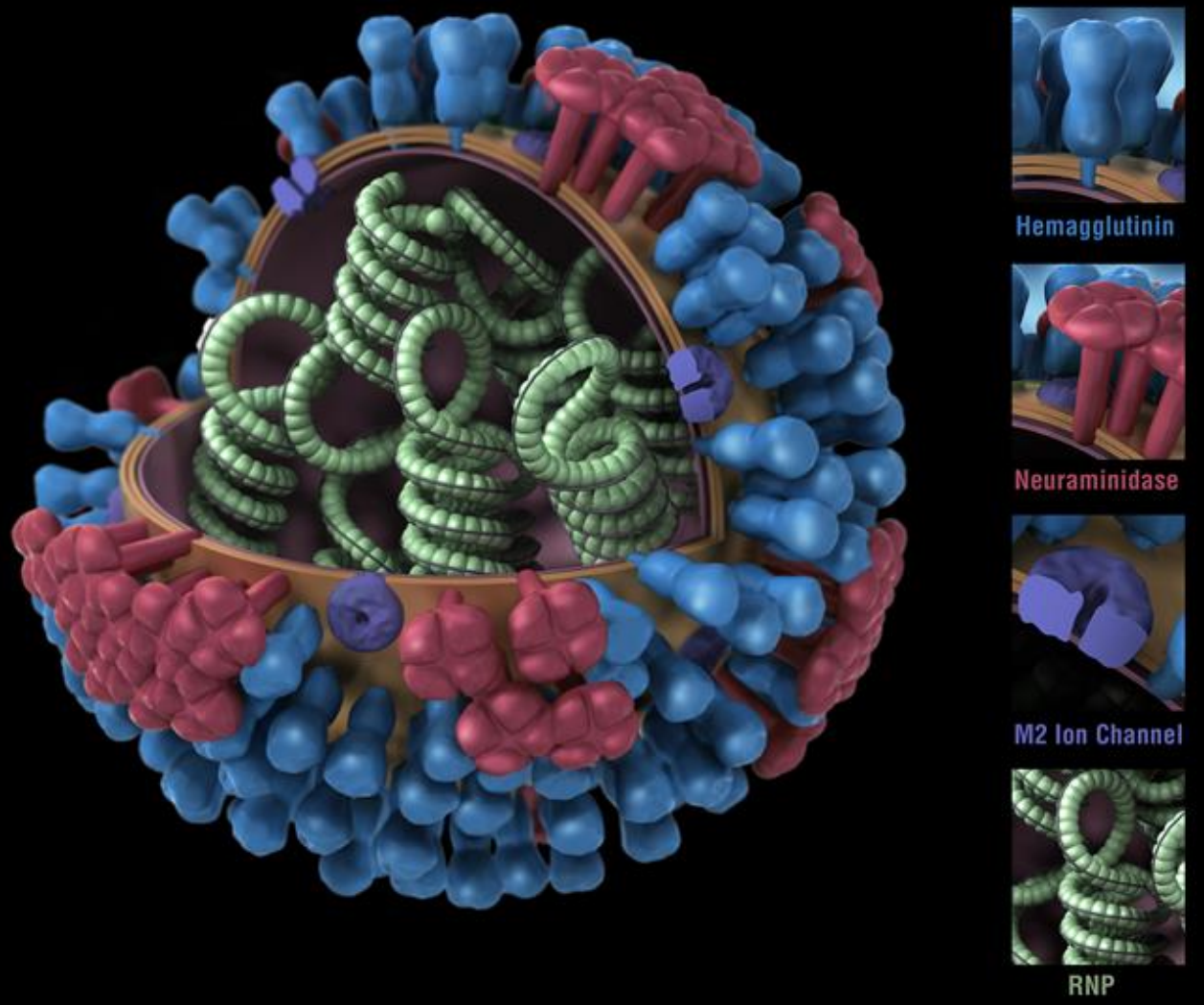
BACKGROUND

- Virus: Influenza A (H3N2).
- 2 proteins on the surface of virus: Hemagglutinin (H) and Neuraminidase(N)[4]
- 18 different H subtypes and 11 different N subtypes.[1]

- Antigenic evolution: mutation overtime of antigen-binding sites on a virus. When mutated, immune system's antibodies have a harder time detecting the virus.[2]

INFLUENZA A



https://www.cdc.gov/flu/images/h1n1/3D_Influenza_black_key_pieslice_med.jpg

MAIN POINTS

- Smith et al.'s purpose for mapping the antigenic and genetic evolution:
  - Monitor antigenic difference in vaccine and circulating strains.
  - Estimate the effectiveness of vaccines.
  - May also help predict the success of an emerging strains.

- Create a method that analyzes phenotypes similar to phylogenetic algorithms.

VIROLOGY AND IMMUNOLOGY

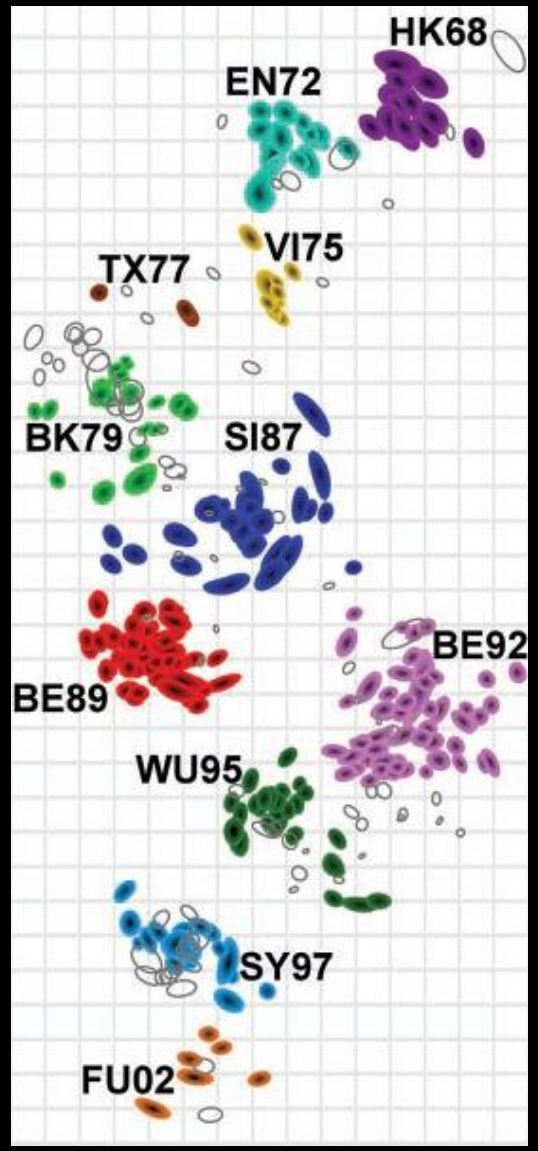
- Lapedes and Farber's "shape space": represents antibody/antigen binding.
- Two characteristics considered: coordinates and distance.
- Coordinates in the space represents binding attributes such as geometric shape, charge, hydrophobicity.
- Distance in the spaces between points represents binding affinity. Less space, greater affinity, stronger bind.[3]

VIROLOGY AND IMMUNOLOGY

- Antigenic drift: small changes in virus's genes that happen over time during replication. Small changes lead to viruses closely related and usually share antigenic properties.
- Antigenic shift: major change in virus. Usually results in hemagglutinin and/or hemagglutinin and neuraminidase protein combination.[2]

- Glycoprotein Hemagglutinin (HA): Antigen on surface of virus. Antibodies attach to these glycoproteins.
- HA evolves with antigenic drift.

ANTIGENIC MAP



- Different strains of Influenza A organized in clusters.
- Vaccine is updated when there is a 2-unit difference between the vaccine strain and next season's expected strain.
- Reason why each cluster has at least one vaccine strain.

ANTIGENIC AND GENETIC EVOLUTION

Cluster transition	Genetic distance (aa changes)	Antigenic distance (units)	Genetic antigenic ratio	Cluster-difference substitutions					
				Site A	Site B	Site C	Site D	Site E	Other
HK68-EN72	12.1	3.4	3.6	T122N G144D	T155Y* N188D		R207K		
EN72-VI75	14.6	4.4	3.3	N137S*† S145N‡	L164Q Q189K S193D‡	N53D I278S	F174S R102K‡ I213V I217V I230V		
V175-TX77	14.8	3.4	4.4	S137Y*†	G158E‡ Q164L D193N‡	K50R† D53N	S174F K201R‡ V213I V230I	E82K M260I	
TX77-BA79	16.0	3.3	4.8	N133S‡ P143S G146S	K156E‡ T160K Q197R‡	N53D N54S	D172G† V217I V244L	162K K82E	
BA79-SI87	11.9	4.9	2.4	G124D‡	Y155H* K189R				
SI87-BE89	6.9	4.6	1.5	N145K‡					
BE89-BE92	13.7	7.8	1.8	S133D‡ K145N‡	E156K‡ E190D*‡			T262N‡	
BE92-WU95	9.9	4.6	2.2	N145K‡					
WU95-SY97	16.0	4.7	3.4		K156Q‡ E158K‡ V196A†	N276K†		K62E	
SY97-FU02	16.0	3.5	4.5	A131T	H155T* Q156H‡	R50G†		H75Q E83K	L25I V202I W222R G225D*
Total	131.9	44.6							
Average	13.2	4.5	3.2						
SD	2.9	1.3	1.1						

- Correlation between antigenic distance and number of amino acids was 0.81.
- On average 2.9 amino acid substitutions result in one unit change in distance.
- Rate of antigenic evolution per amino acid substitution was slower within cluster.

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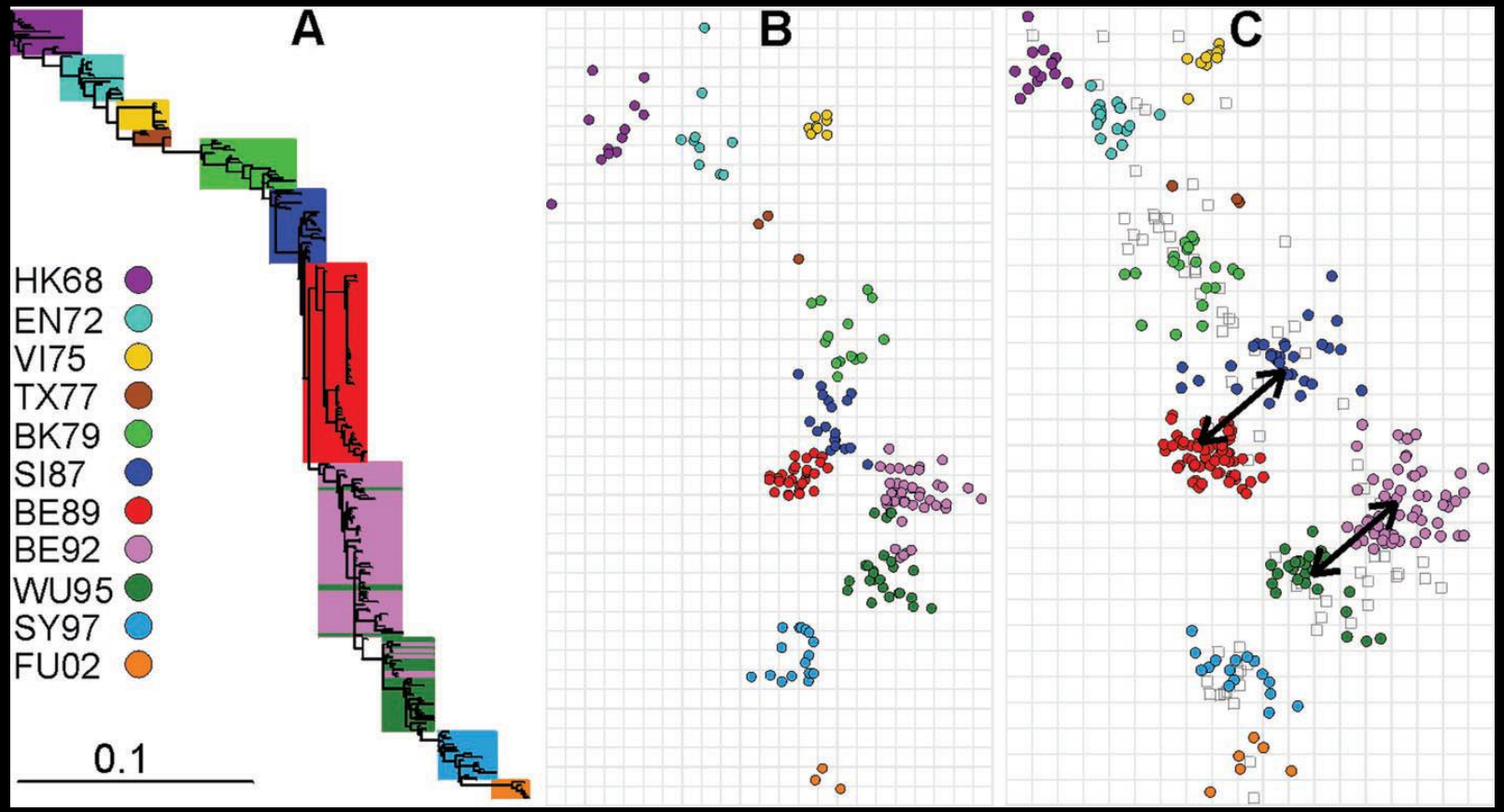
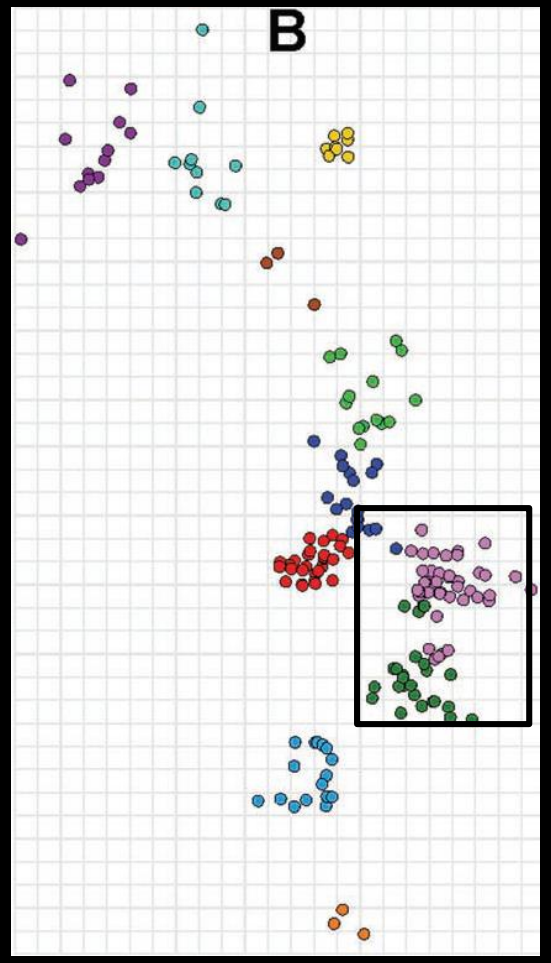
- SI87 to BE89 and BE92 to WU95 has one amino acid substitution.
- Suggests that the substitution has a major antigenic effect and can create a cluster transition on its own.

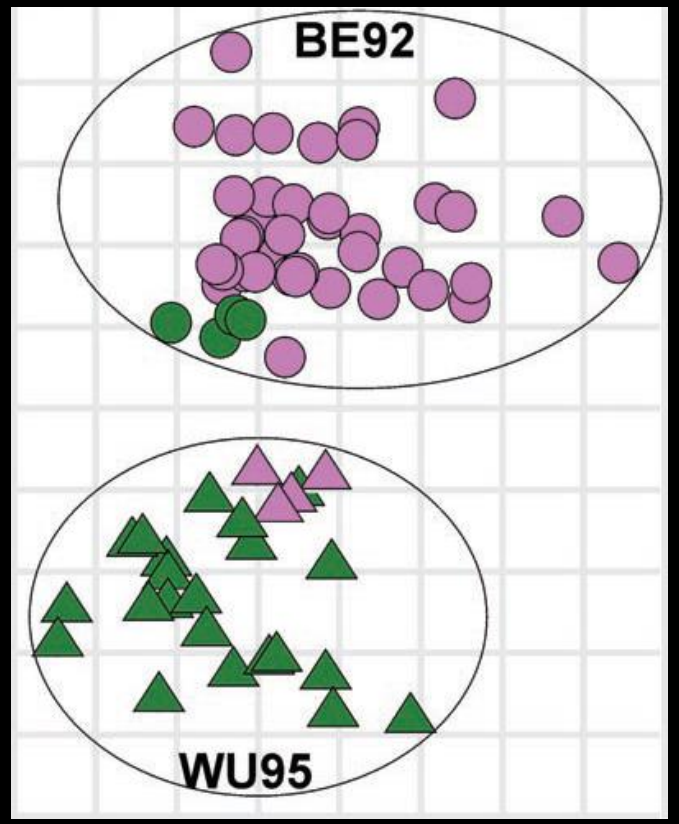
COMPARING ANTIGENIC AND GENETIC EVOLUTION



- A: phylogenetic tree of HA1 nucleotide sequences.
- B: Genetic map of HA1 amino acid sequences.
- C: Antigenic map (similar to previous map on previous slide)

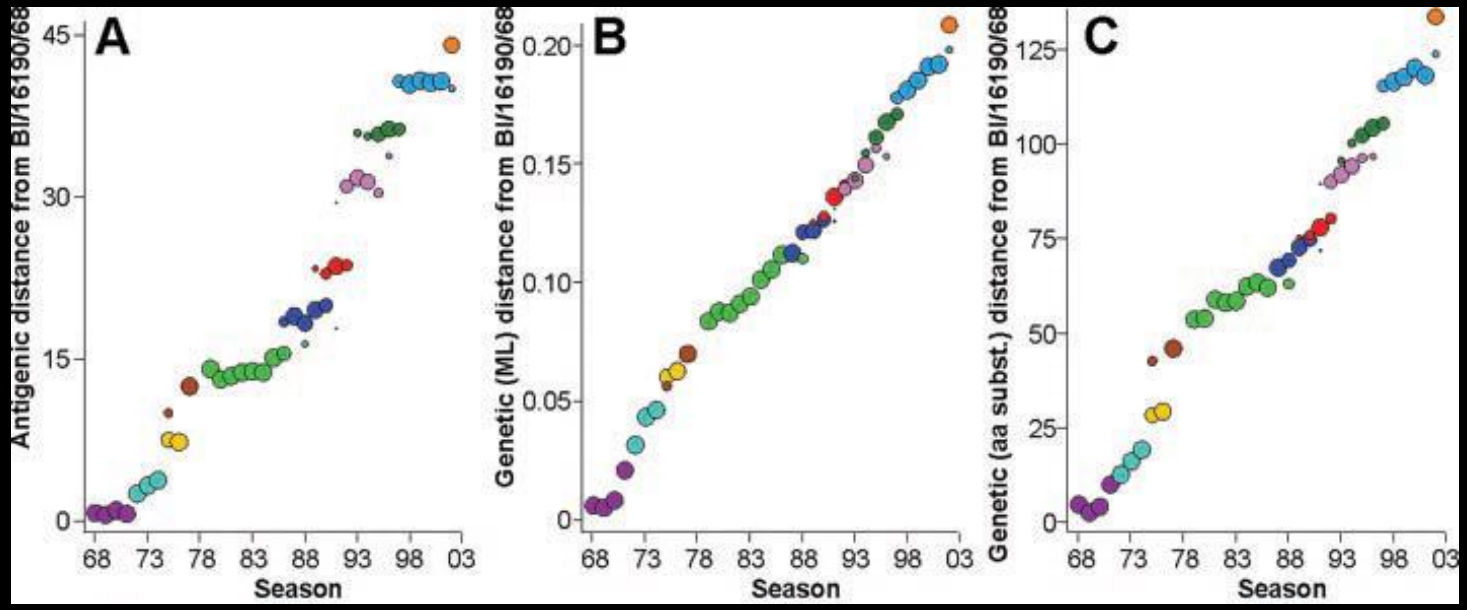
COMPARING ANTIGENIC AND GENETIC EVOLUTION

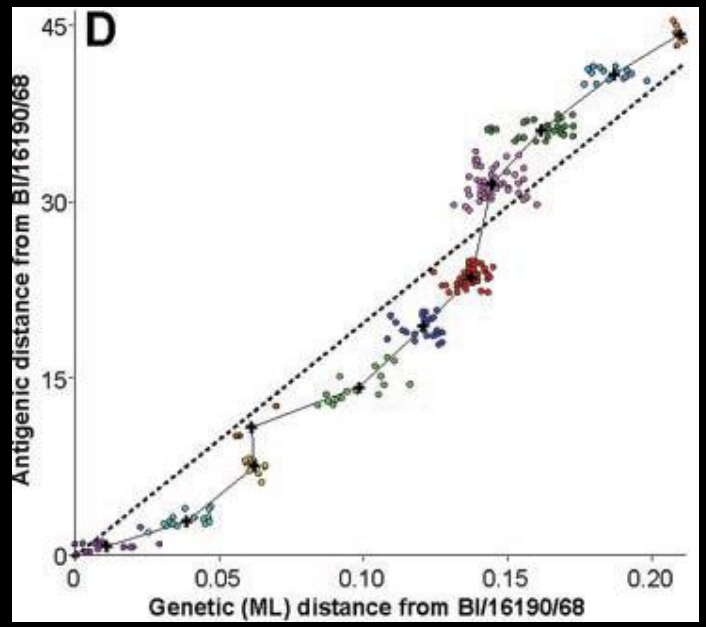




- Rate of antigenic evolution was, at times, faster than genetic evolution or vice versa.
- We can calculate the genetic difference between the center of each cluster.

GRADUAL GENETIC EVOLUTION AND PUNCTUATED ANTIGENIC EVOLUTION





- Take note the punctuated nature of the antigenic distance graph and the linear nature of the genetic distance graph.

CONCLUSION

- Antigenic evolution is clustered.
- Higher rate of antigenic evolution between clusters rather than within clusters.
- Antigenic maps can potentially quantify the extent that emerging strains can escape the immune system.

REFERENCES

1. "Types of Influenza Viruses," *CDC (2016)*. *https://www.cdc.gov/flu/about/viruses/types.htm*
2. "How the Flu Virus Can Change: 'Drift' and 'Shift'," *CDC (*2014). https://www.cdc.gov/flu/about/viruses/change.htm
3. Lapedes and Farber. "The geometry of shape space: application to influenza." *Journal of Theoretical Biology* 7.212 (2001): 57-69.
4. Liu et al. "Antigenic Patterns and Evolution of the Human Influenza A (H1N1) Virus." *Scientific Reports* 5.14171 (2015).
5. Smith et al. "Mapping the Antigenic and Genetic Evolution of Influenza Virus," *Science* 305.371 (2014): 371-376.