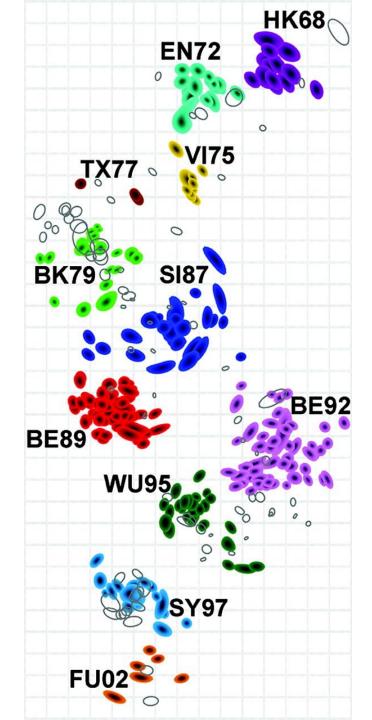
Introduction to antigenic cartography

August 2024

Antonia Netzl (she/her) <u>an604@cam.ac.uk</u>
Centre for Pathogen Evolution, University of Cambridge

Antigenic data

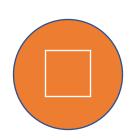
	STRAIN DESIGNATION						REFERENC	E FERRET AN	TISERA							
	3 TRAIN DESIGNATION		Date	Α	В	С	D	E	F	G	н	- 1	J	К	L	М
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2 NZ	A/WELLINGTON/01/2004	2004729358	1/26/04	160	1280	640	1280	640	30	160	320	160	640	640	160	64
3 CA	A/CALIFORNIA/07/04	2005705486	9/16/04	160	160	640	2560	1280	320	320	320	160	640	640	160	32
4 CA	A/CA/07/04 x PR/8 CDC	2005712034	REASS	320	320	1280	2560	2560	640	640	1280	320	1280	1280	160	12
5 AS	A/VICTORIA/500/2004	2005707652	8/13/04	160	160	320	1280	640	80	160	160	80	320	320	80	32
6 AS	A/SINGAPORE/37/2004 IVR-140	2005707637	REASS	160	160	640	1280	640	640	1280	640	160	640	640	80	32
7 WI	A/WISCONSIN/19/2004	2005705540	11/6/04	160	320	1280	2560	640	320	1280	1280	160	640	640	160	64
8 NY	A/NEW YORK/55/2004	2005705561	1] (20 (04						222			222				64
9 NY	A/NY/55/04 A/PR/8/34 X-157	2005711905										_				12
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14 TH	02-504942 ORIGINAL	2005707539	— a	IJII	86	? /]]	\mathbf{C}	dali	LO	212	10	M	a 9			64
15 TH	02-504957 ORIGINAL	2005707540			0		_ '			Ο.,	- P	7		-		64
16 TH	02-505107 ORIGINAL	2005707542			_					_	_	_				32
17 MS	05020500027 ORIGINAL	2005712779	2/			_	•	•	_		_	_	•			64
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Antigenic cartography

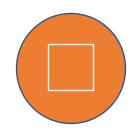
Antigenic map of influenza H3N2 from 1968 –
 2002 by Smith et al Science 305, 371-376, 2004

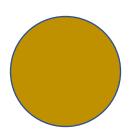
	Antigen 1	Antigen 2	Antigen 3	Antigen 4
Titer	160	40	80	40
Log2(Titer/10)	4	2	3	2
Log2(maxTiter/10) – Log2(Titer/10)	4 - 4 = 0	4 -2 = 2	4 – 3 = 1	4 -2 = 2
Fold change (FC) from max titer	160/160 = 1	160/40 = 4	160/80 = 2	160/40 = 4
Log2(FC)	0	2	1	2





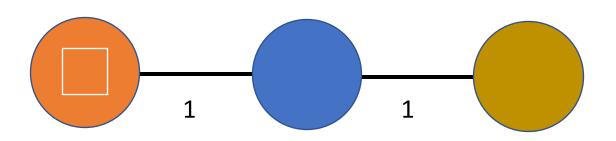
	Antigen 1	Antigen 2	Antigen 3	Antigen 4
Titer	160	40	80	40
Log2(Titer/10)	4	2	3	2
Log2(maxTiter/10) – Log2(Titer/10)	4 - 4 = 0	4 -2 = 2	4 – 3 = 1	4 -2 = 2
Fold change (FC) from max titer	160/160 = 1	160/40 = 4	160/80 = 2	160/40 = 4
Log2(FC)	0	2	1	2







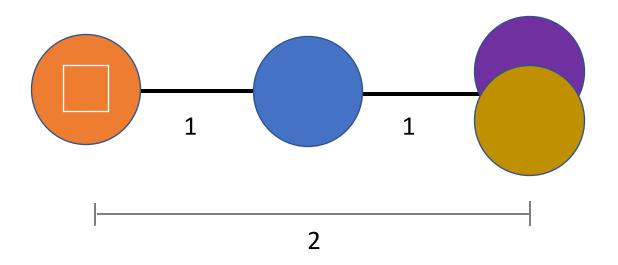
	Antigen 1	Antigen 2	Antigen 3	Antigen 4
Titer	160	40	80	40
Log2(Titer/10)	4	2	3	2
Log2(maxTiter/10) – Log2(Titer/10)	4 - 4 = 0	4 -2 = 2	4 – 3 = 1	4 -2 = 2
Fold change (FC) from max titer	160/160 = 1	160/40 = 4	160/80 = 2	160/40 = 4
Log2(FC)	0	2	1	2





2

	Antigen 1	Antigen 2	Antigen 3	Antigen 4
Titer	160	40	80	40
Log2(Titer/10)	4	2	3	2
Log2(maxTiter/10) – Log2(Titer/10)	4 - 4 = 0	4 -2 = 2	4 – 3 = 1	4 -2 = 2
Fold change (FC) from max titer	160/160 = 1	160/40 = 4	160/80 = 2	160/40 = 4
Log2(FC)	0	2	1	2





	Serum 1	Serum 2		Serum 1	Serum 2
Antigen 1	160	160	Antigen 1	0	1
Antigen 2	40	80	Antigen 2	2	2
Antigen 3	80	320	Antigen 3	1	0
Antigen 4	40	160	Antigen 4	2	1

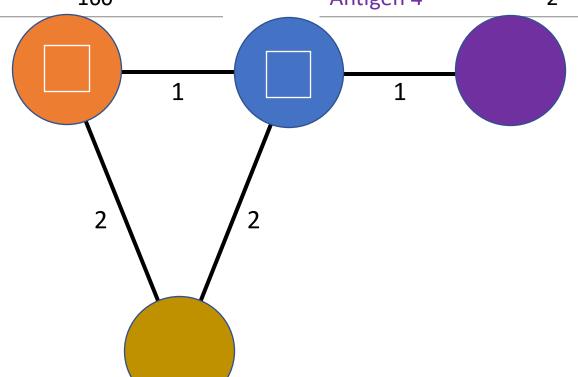


	Serum 1	Serum 2
Antigen 1	160	160
Antigen 2	40	80
Antigen 3	80	320
Antigen 4	40	160

Serum

Antigen

	Serum 1	Serum 2
Antigen 1	0	1
Antigen 2	2	2
Antigen 3	1	0
Antigen 4	2	1



	Serum 1	Serum 2	•••	Serum n
Antigen 1	Titer _{1,1}	Titer _{1,2}		Titer _{1,n}
Antigen 2	Titer _{2,1}	Titer _{2,2}		Titer _{2,n}
Antigen i	Titer _{i,1}	Titer _{i,2}		Titer _{i,n}

Log2 transform calculate distances

Table with target distances D

Optimize map distances d for each serum, antigen pair

Minimize map stress $s = \sum_{i,n} (D_{i,n} - d_{i,n})^2$

Where D = log2(maxTiter/LOD) for titers below the limit of detection (LOD) and d>D without penalty

Antigenic map

Key Points

- Antigenic cartography is a geometric interpretation of neutralization data
- Map distance corresponds to neutralization titers
- Variants that elicit the same titers in the same sera are close together in map, and vice versa
- Different serum types are necessary to resolve different areas of antigenic space
- Map distance reflects antigenic relationship

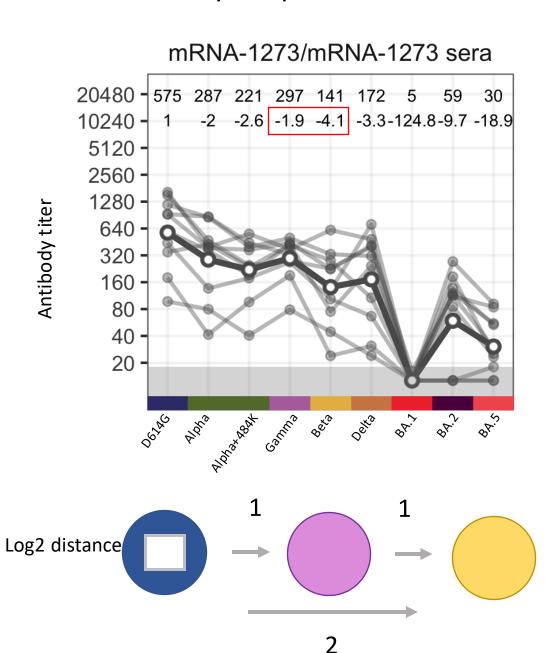
What about multiple exposures?

From antigenic maps to antibody landscapes

The data used in the next section is from the publication by Rössler, Netzl, et al. (2022) DOI: 10.1038/s41467-022-35312-3

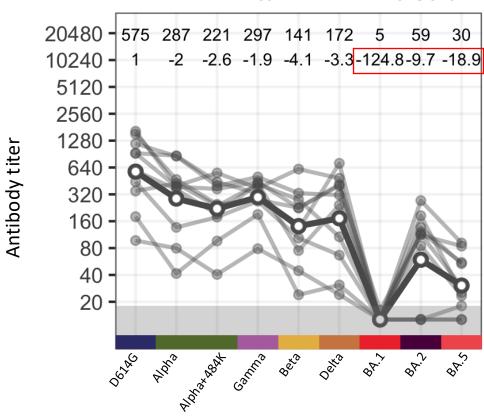
The original publication on antibody landscape is by Fonville, Wilks, et al. (2014) DOI: 10.1126/science.1256427

Secondary exposures overshadow underlying relationships

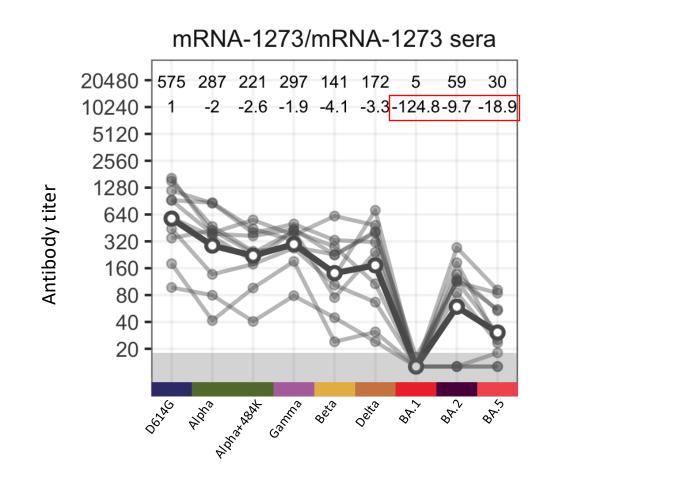


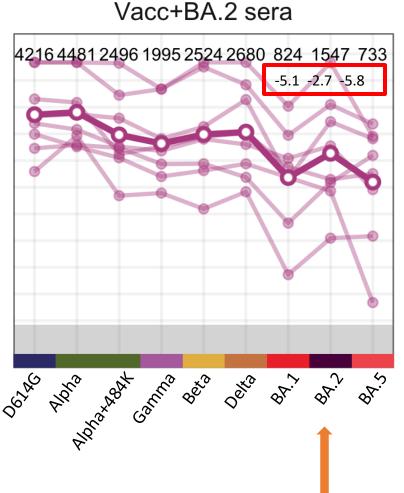
Secondary exposures overshadow underlying relationships



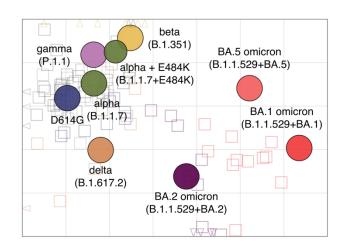


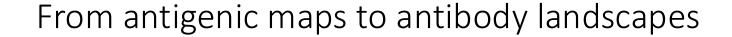
Secondary exposures overshadow underlying relationships

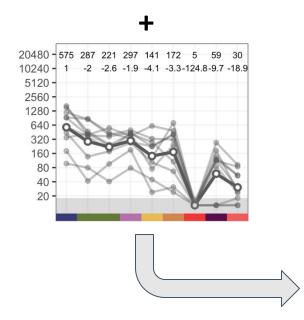


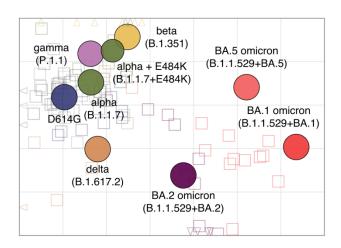


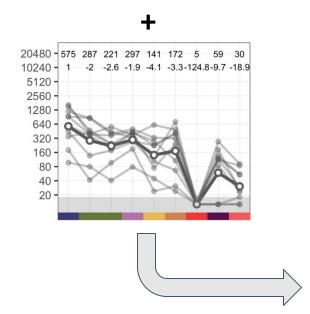
Multiple (distinct) exposures increase cross-neutralization and therefore decrease antigenic distance (log2 fold changes). It is not, however, the variants' antigenic properties that change with multiple exposures but the antibody composition in the serum \rightarrow Antibody landscapes on top of a single exposure serum map



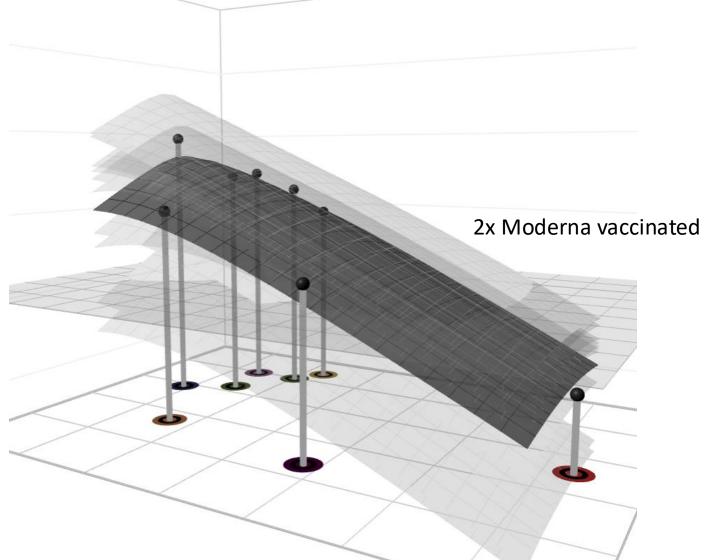


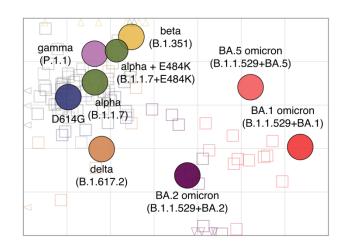






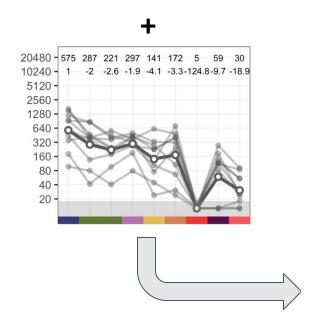
From antigenic maps to antibody landscapes

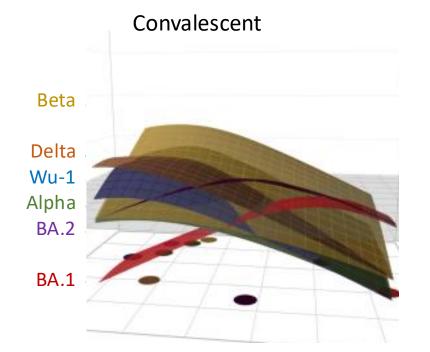


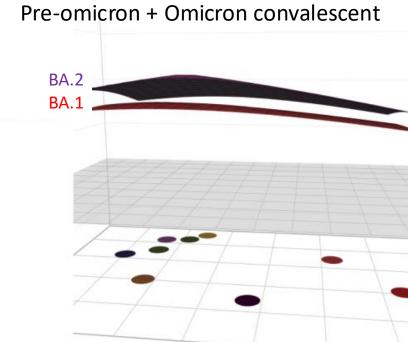


From antigenic maps to antibody landscapes

Multiple (distant) exposures broaden immune profiles







Key Points

- Multiple exposures broaden immune response and decrease titer fold changes
- Multiple exposures change the neutralizing properties of the serum, not the antigenic properties of the variants
- Antibody landscapes show titers across a mapped antigenic space
- Antibody landscapes show titer magnitude as well as breadth
- Antibody landscapes show how serum properties change over time without changing the antigenic relationships of mapped variants

References

- Antigenic cartography: Smith et al., Science (2004) DOI: 10.1126/science.1097211
- Antibody landscapes: Fonville et al., Science (2014) <u>DOI:</u> 10.1126/science.1256427
- Racmacs R package for map making: Wilks S (2023). *Racmacs: Antigenic Cartography Macros*. R package version 1.2.9, https://github.com/acorg/Racmacs/, https://acorg.github.io/Racmacs/.
- Antibody landscapes R package: Wilks S (2021). _ablandscapes: Making Antibody landscapes Using R_. R package version 1.1.0,
 https://github.com/acorg/ablandscapes.
- Map diagnostics in supplementary material of these publications:

Rössler, A., Nat Commun 13, 7701 (2022). https://doi.org/10.1038/s41467-022-35312-3
Rössler, A., Nat Commun 14, 5224 (2023). https://doi.org/10.1038/s41467-023-41049-4