

Introduction to antigenic cartography

August 2024

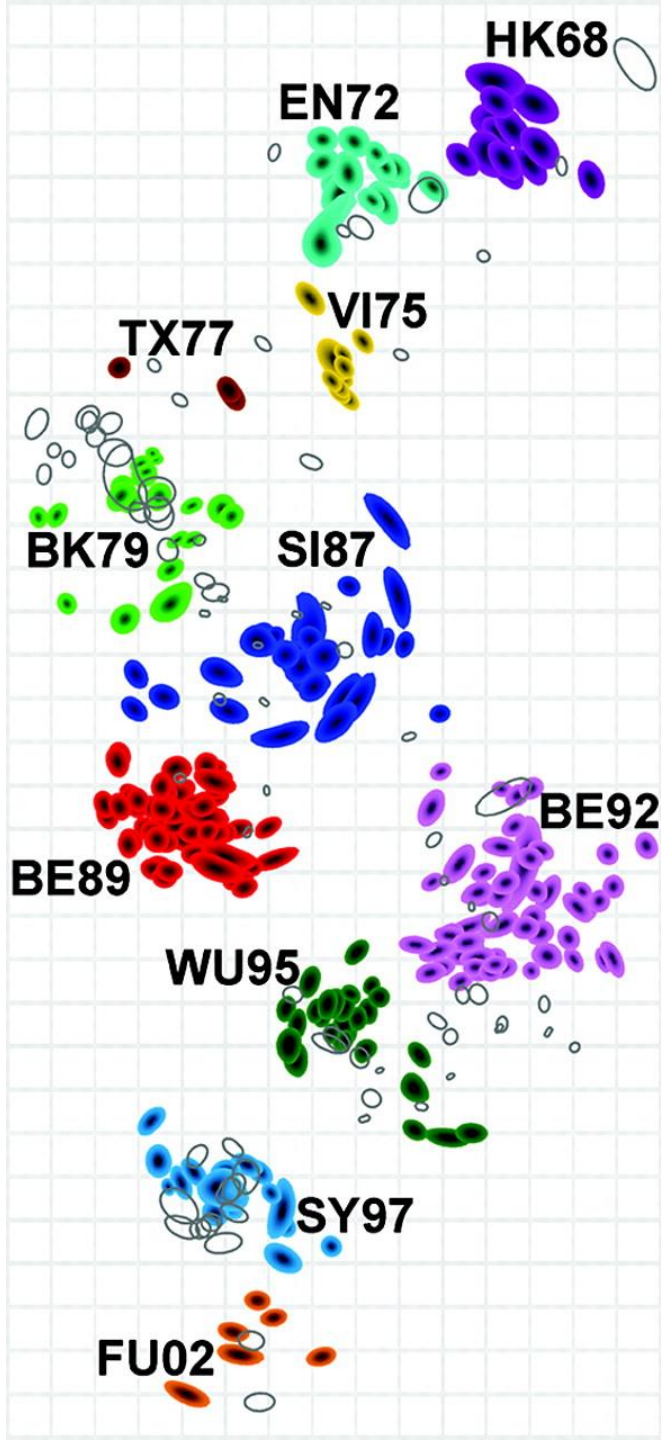
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Antigenic data

HEMAGGLUTINATION INHIBITION REACTIONS OF INFLUENZA H3 VIRUSES (08/11/05)																
STRAIN DESIGNATION			REFERENCE FERRET ANTISERA													
REFERENCE ANTIGENS	CDC ID#	Date collected	A WY/03 REASS	B WEL/01	C CA/7	D CA/7 REASS	E VIC/500	F SN/37 REASS	G WI/19	H NY/55	I NY/55 REASS	J HK/4593	K NH/14	L HK/2831 NEW	M MS/5 NEW	
1 WY A/WYOMING/03/2003 X-147	2003715730	REASS	1280	80	160	320	320	40	80	80	40	80	320	40	160	
2 NZ A/WELLINGTON/01/2004	2004729358	1/26/04	160	1280	640	1280	640	30	160	320	160	640	640	160	640	
3 CA A/CALIFORNIA/07/04	2005705486	9/16/04	160	160	640	2560	1280	320	320	320	160	640	640	160	320	
4 CA A/CA/07/04 x PR/8 CDC	2005712034	REASS	320	320	1280	2560	2560	640	640	1280	320	1280	1280	160	1280	
5 AS A/VICTORIA/500/2004	2005707652	8/13/04	160	160	320	1280	640	80	160	160	80	320	320	80	320	
6 AS A/SINGAPORE/37/2004 IVR-140	2005707637	REASS	160	160	640	1280	640	640	1280	640	160	640	640	80	320	
7 WI A/WISCONSIN/19/2004	2005705540	11/6/04	160	320	1280	2560	640	320	1280	1280	160	640	640	160	640	
8 NY A/NEW YORK/55/2004	2005705561	11/16/04	160	160	1280	1280	1280	320	640	640	320	640	640	160	640	
9 NY A/NY/55/04 A/PR/8/34 X-157	2005711905															1280
10 HK A/HONG KONG/4593/04	2005710182	10/1/04														640
11 NH A/NEW HAMPSHIRE/14/04	2005710231	12/1/04														640
12 HK A/HONG KONG/2831/05	2005743649	5/31/05														160
13 MS A/MISSISSIPPI/5/04	2005707679	12/1/04														640
TEST ANTIGENS	REPEATS															
14 TH 02-504942 ORIGINAL	2005707539															640
15 TH 02-504957 ORIGINAL	2005707540															640
16 TH 02-505107 ORIGINAL	2005707542															320
17 MS 05020500027 ORIGINAL	2005712779	2/1/05														640
18 UR A/KHABAROVSK/9/05	2005714223	1/2/05														320
19 DJ 2004914389	2005714244	12/1/04														640
20 DJ 2005900911	2005714283	1/2/05														640
21 DJ 2005900992	2005714289	1/2/05														640
22 DJ 2005901307	2005714306	2/1/05														320
23 DJ 2005901309	2005714307	2/1/05														1280
24 DJ 2005901315	2005714308	2/1/05														1280
25 DJ 2005901330	2005714309	2/4/2005	2560	640	2560	5120	5120	2560	2560	2560	640	5120	5120	640	5120	
26 DJ 2005902082	2005714334	2/12/2005	320	640	1280	2560	2560	1280	1280	1280	320	2560	2560	320	2560	
27 DJ 2005902100	2005714335	2/14/2005	640	320	1280	5120	2560	640	1280	2560	320	2560	1280	320	1280	
28 DJ 2005902111	2005714336	2/24/2005	320	160	640	2560	2560	640	640	640	320	640	1280	160	640	
29 PN 490730	2005740130	6/22/2005	320	160	640	2560	1280	640	640	1280	160	1280	640	160	640	
30 PN 490728	2005740131	6/21/2005	20	80	160	640	160	80	40	80	80	80	160	160	160	
31 PN 490714	2005740132	6/18/2005	320	320	1280	5120	2560	1280	1280	1280	320	1280	2560	320	1280	
32 UR A/EKATERINBURG/1/05	2005740144	1/14/2005	160	40	320	320	80	80	80	160	80	160	160	80	80	
33 UR A/YAROSLAVL/13/05	2005740147	2/1/2005	640	320	640	2560	640	1280	640	640	640	1280	2560	320	640	
34 UR A/OMSK/23/04	2005740149	1/20/2004	160	160	320	640	640	160	40	80	80	160	160	160	320	
35 UR A/VLADIMIR/37/05	2005740150	2/17/2005	160	80	320	640	320	80	320	320	160	320	320	160	320	
36 UR A/KHABAROVSK/51/05	2005740151	3/5/2005	5	5	5	5	5	5	5	5	5	5	5	5	5	
37 UR A/TOMSK/27/04	2005740153	1/7/2004	160	160	160	320	320	80	40	80	80	80	160	80	320	
38 HK A/HONG KONG/4421/05	2005740176	6/8/2005	80	20	160	160	20	40	40	160	80	80	160	160	40	
39 HK A/HONG KONG/4281/05	2005740177	6/16/2005	40	20	80	160	20	40	40	40	80	40	80	160	40	
40 HK A/HONG KONG/4241/05	2005740179	6/16/2005	80	40	320	160	80	80	80	160	160	160	320	640	80	
41 HK A/HONG KONG/4607/05	2005740181	6/14/2005	40	10	40	40	20	10	20	40	40	40	20	40	10	
42 EG 2005904864	2005740677	4/20/2005	80	20	160	160	80	40	80	80	80	160	160	80	80	
43 OM 2005906943	2005740704		80	20	160	160	10	20	40	80	80	160	80	80	40	
44 SN A/SINGAPORE/03/05	2005741146	2/16/2005	320	160	640	640	320	160	160	320	160	320	640	160	320	
45 SN A/SINGAPORE/07/05	2005741152	3/13/2005	80	10	80	80	20	20	40	80	80	40	80	40	20	
46 SN A/SINGAPORE/34/05	2005741162	5/31/2005	40	20	160	160	20	20	40	80	80	80	160	160	80	
47 SN A/SINGAPORE/35/05	2005741164	5/31/2005	40	10	20	40	10	10	10	20	40	20	40	80	20	

Difficult to interpret →
antigenic cartography as
geometric interpretation

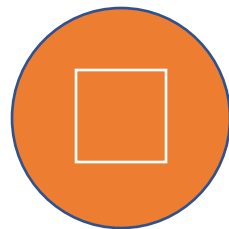




Antigenic cartography

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

From titers to a map

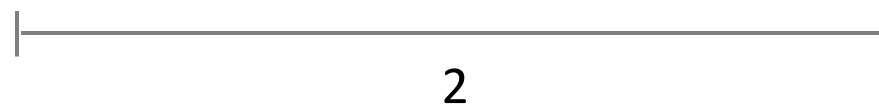
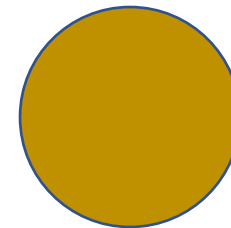
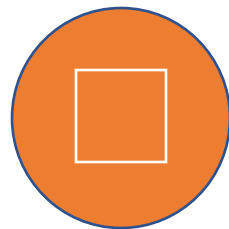
	Antigen 1	Antigen 2	Antigen 3	Antigen 4
Titer	160	40	80	40
$\text{Log}_2(\text{Titer}/10)$	4	2	3	2
$\text{Log}_2(\text{maxTiter}/10) - \text{Log}_2(\text{Titer}/10)$	$4 - 4 = 0$	$4 - 2 = 2$	$4 - 3 = 1$	$4 - 2 = 2$
Fold change (FC) from max titer	$160/160 = 1$	$160/40 = 4$	$160/80 = 2$	$160/40 = 4$
$\text{Log}_2(\text{FC})$	0	2	1	2



 Serum
 Antigen

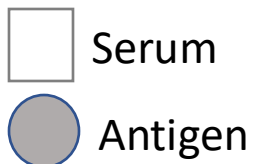
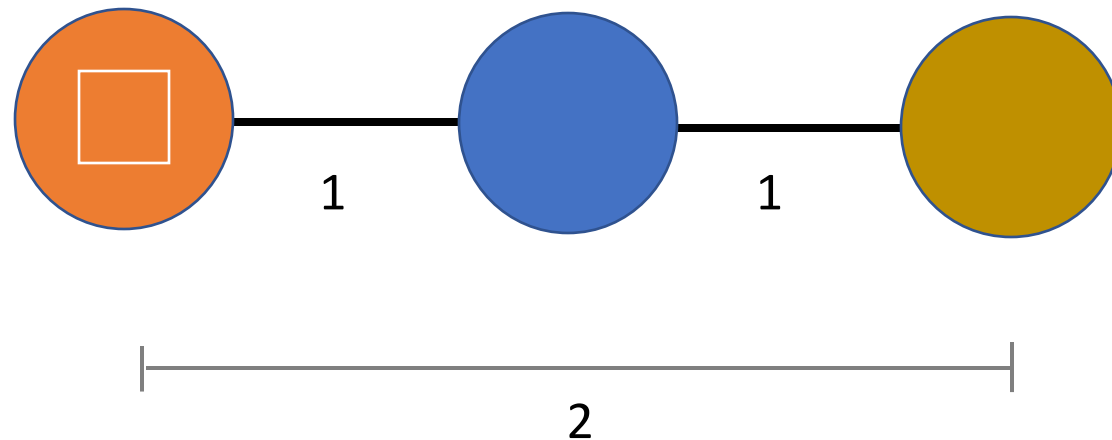
From titers to a map

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$\text{Log}_2(\text{FC})$	0	2	1	2



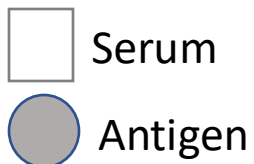
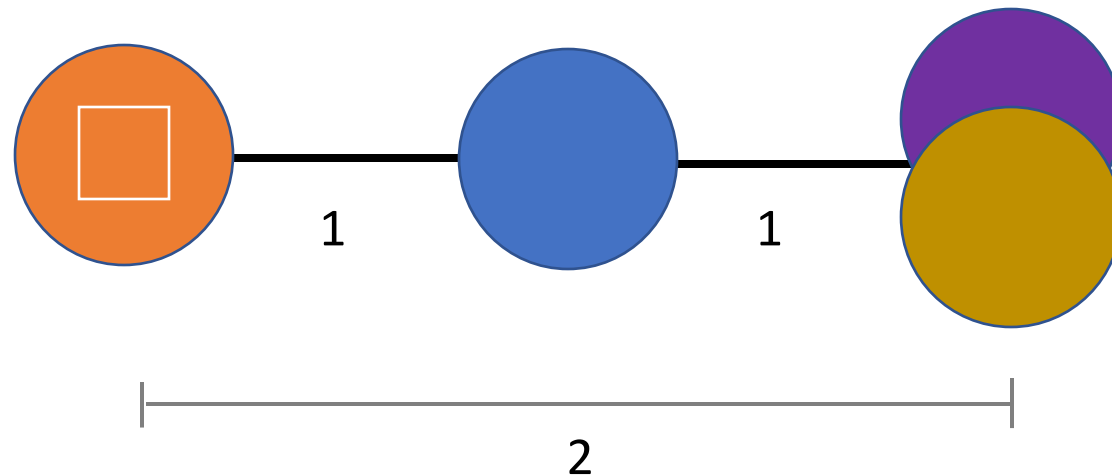
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Fold change (FC) from max titer	$160/160 = 1$	$160/40 = 4$	$160/80 = 2$	$160/40 = 4$
$\text{Log}_2(\text{FC})$	0	2	1	2



From titers to a map

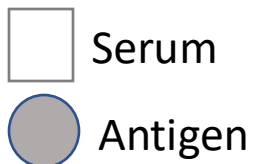
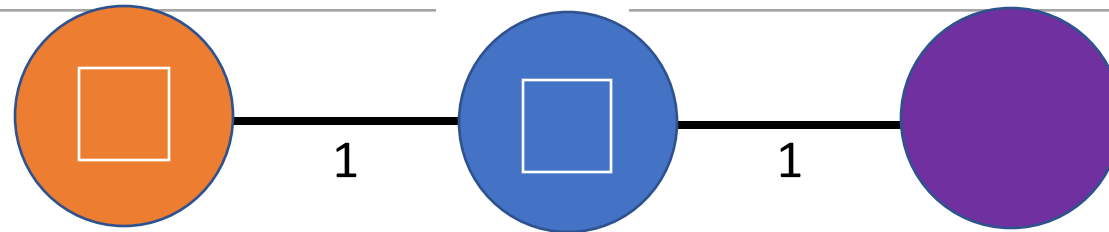
	Antigen 1	Antigen 2	Antigen 3	Antigen 4
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$\text{Log}_2(\text{maxTiter}/10) - \text{Log}_2(\text{Titer}/10)$	$4 - 4 = 0$	$4 - 2 = 2$	$4 - 3 = 1$	$4 - 2 = 2$
Fold change (FC) from max titer	$160/160 = 1$	$160/40 = 4$	$160/80 = 2$	$160/40 = 4$
$\text{Log}_2(\text{FC})$	0	2	1	2



From titers to a map

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

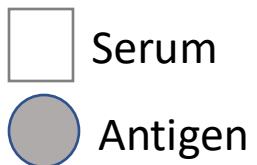
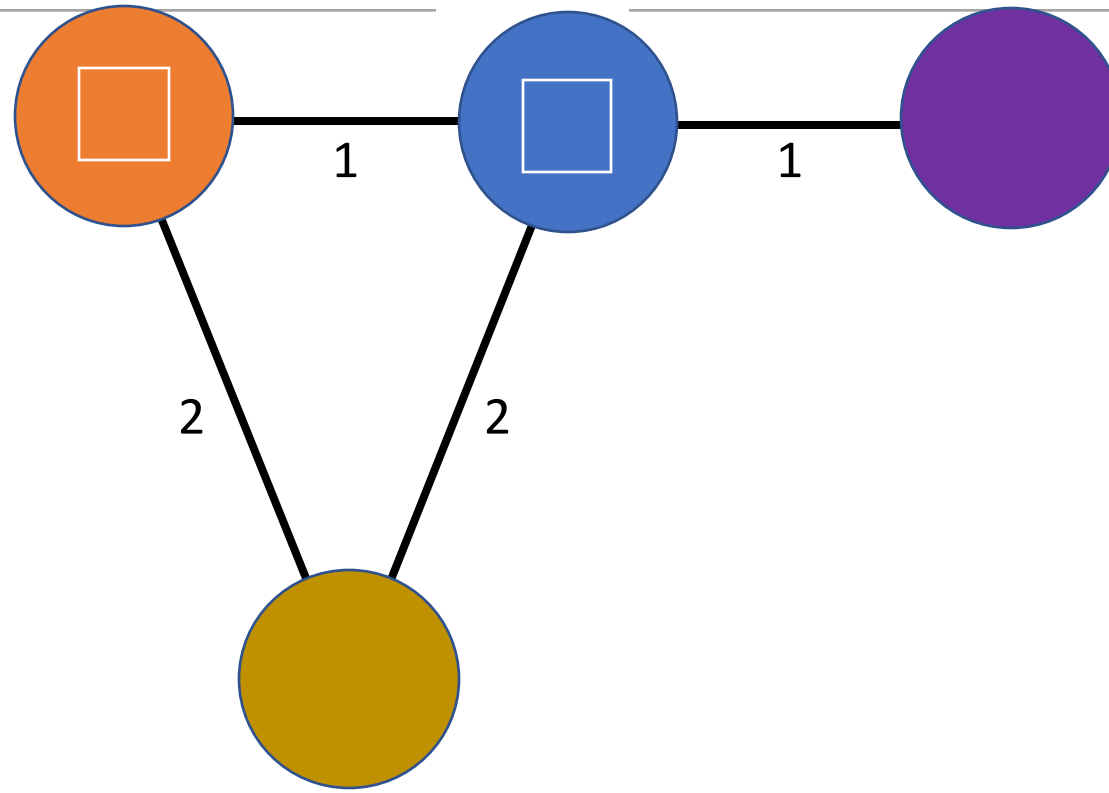
	Serum 1	Serum 2
Antigen 1	0	1
Antigen 2	2	2
Antigen 3	1	0
Antigen 4	2	1



From titers to a map

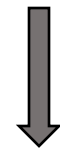
	Serum 1	Serum 2
Antigen 1	160	160
Antigen 2	40	80
Antigen 3	80	320
Antigen 4	40	160

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



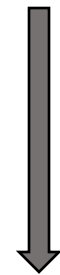
From titers to a map

	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 $D = \log_2(\max\text{Titer}/\text{LOD})$ 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

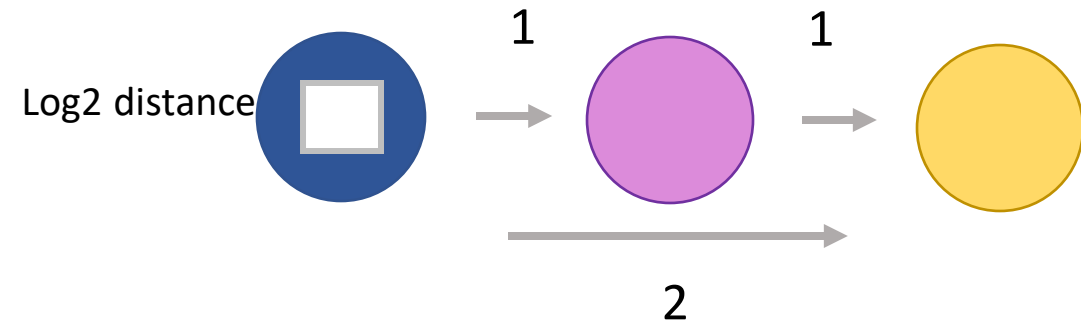
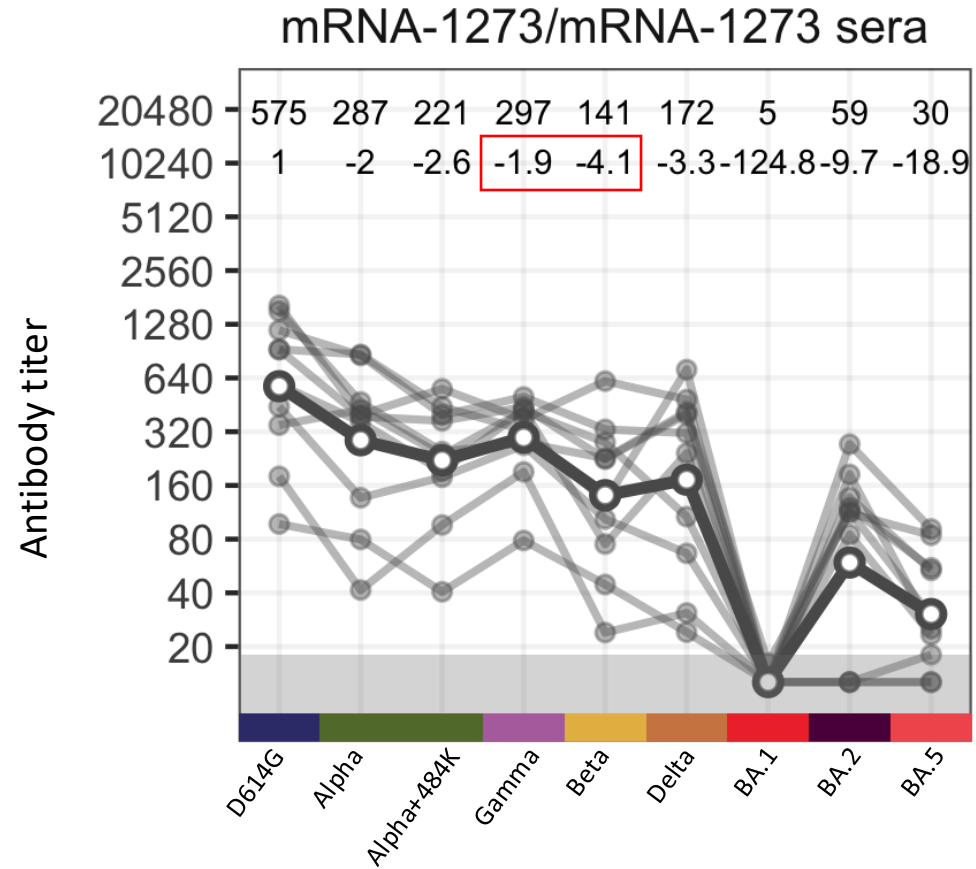
What about multiple exposures?

From antigenic maps to antibody landscapes

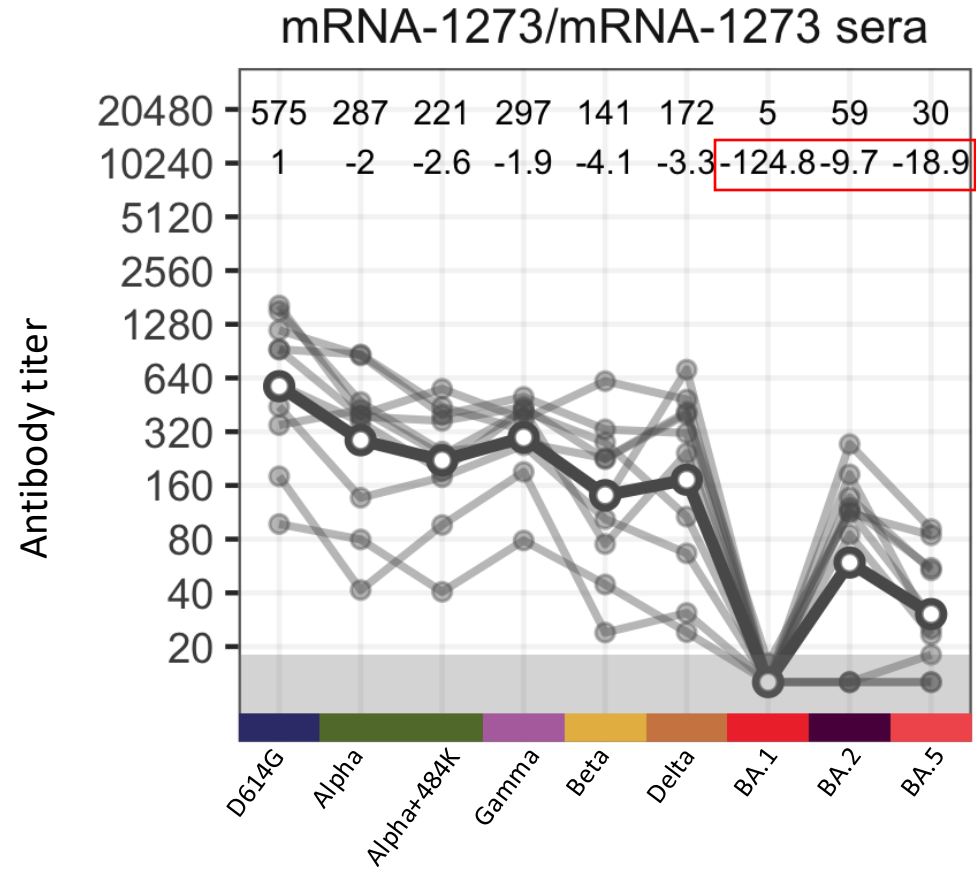
The data used in the next section is from the publication by Rössler, Netzl, et al. (2022) DOI: [10.1038/s41467-022-35312-3](https://doi.org/10.1038/s41467-022-35312-3)

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

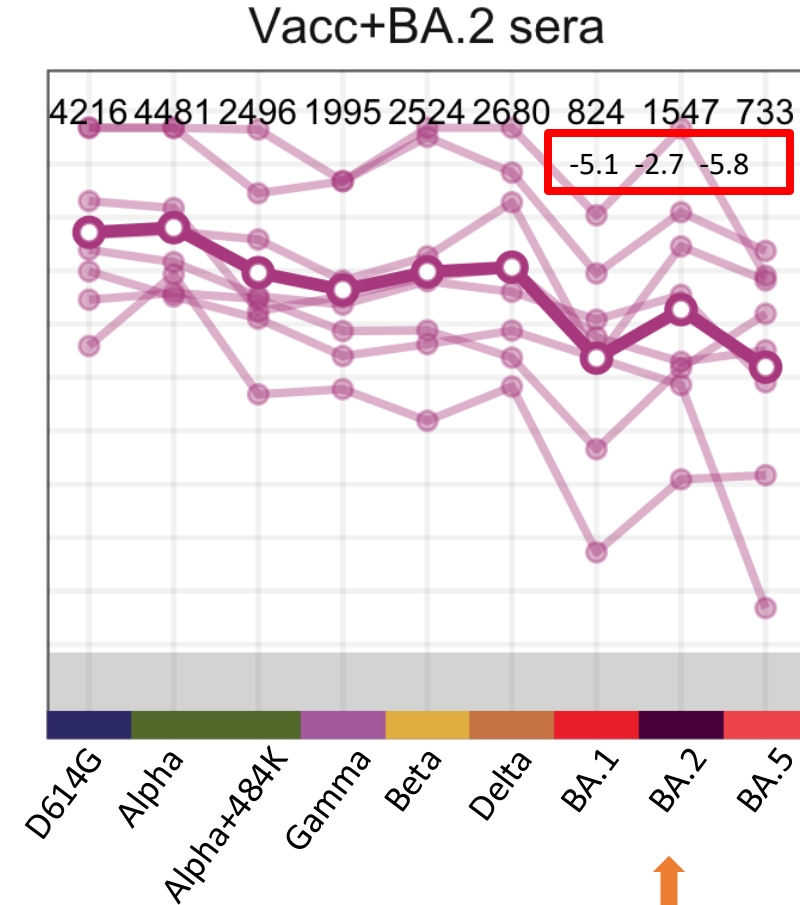
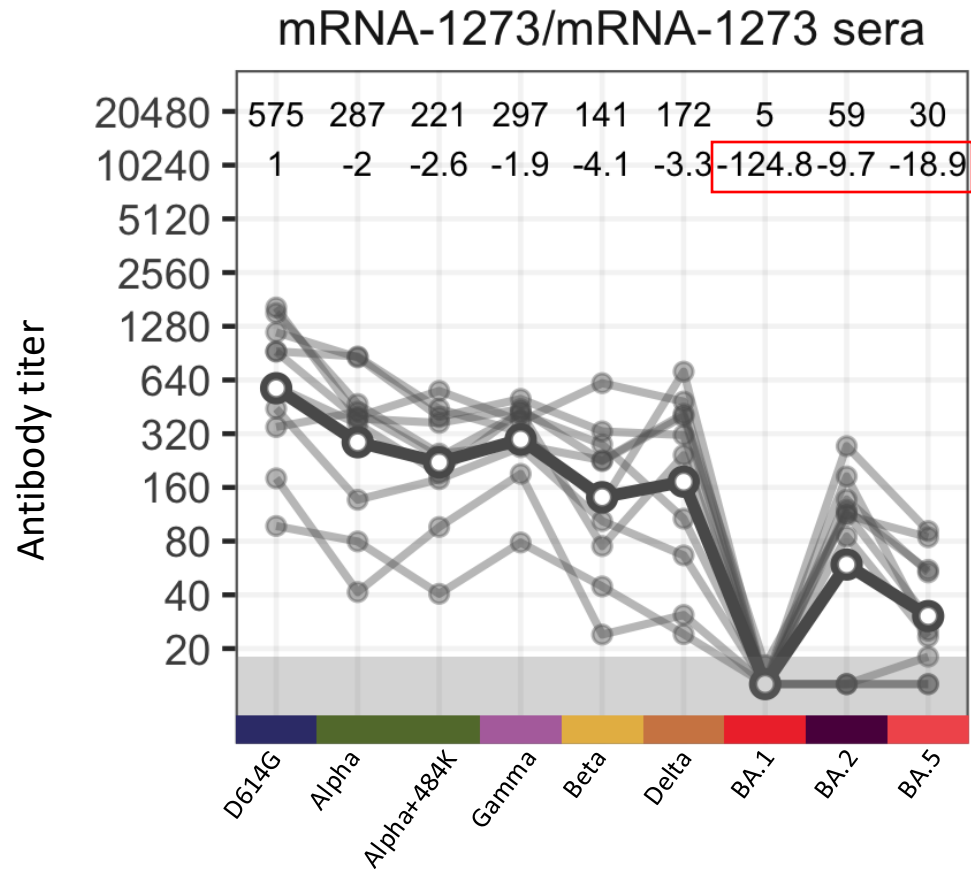
Secondary exposures overshadow underlying relationships



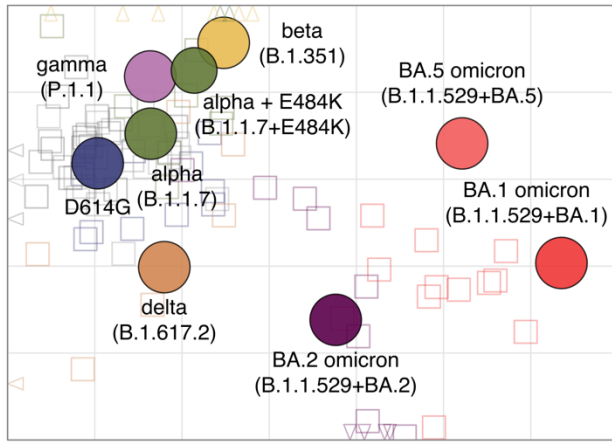
Secondary exposures overshadow underlying relationships



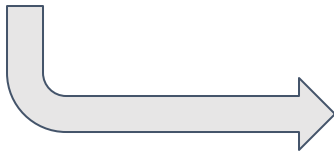
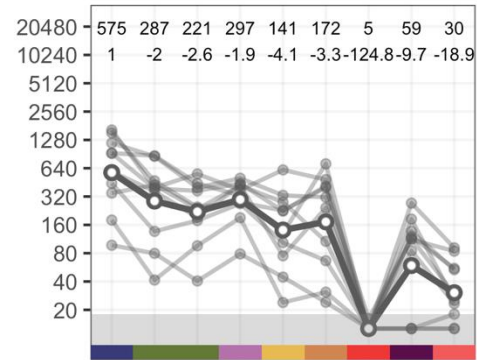
Secondary exposures overshadow underlying relationships



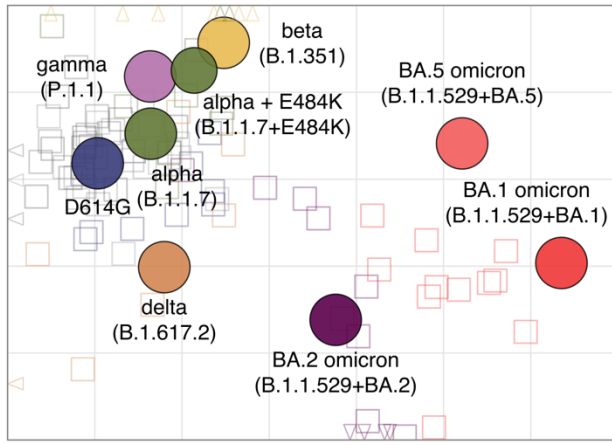
Multiple (distinct) exposures increase cross-neutralization and therefore decrease antigenic distance (log2 fold changes). **It is not, however, the variants' antigenic properties that change with multiple exposures but the antibody composition in the serum → Antibody landscapes on top of a single exposure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



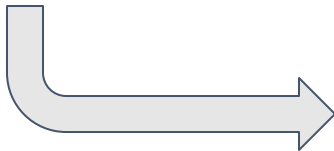
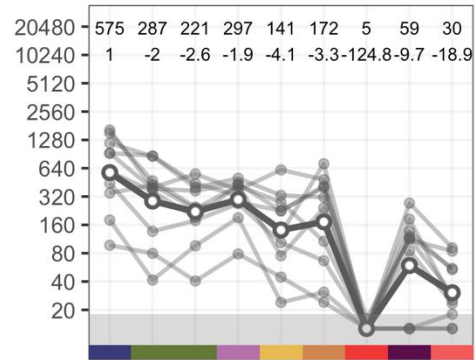
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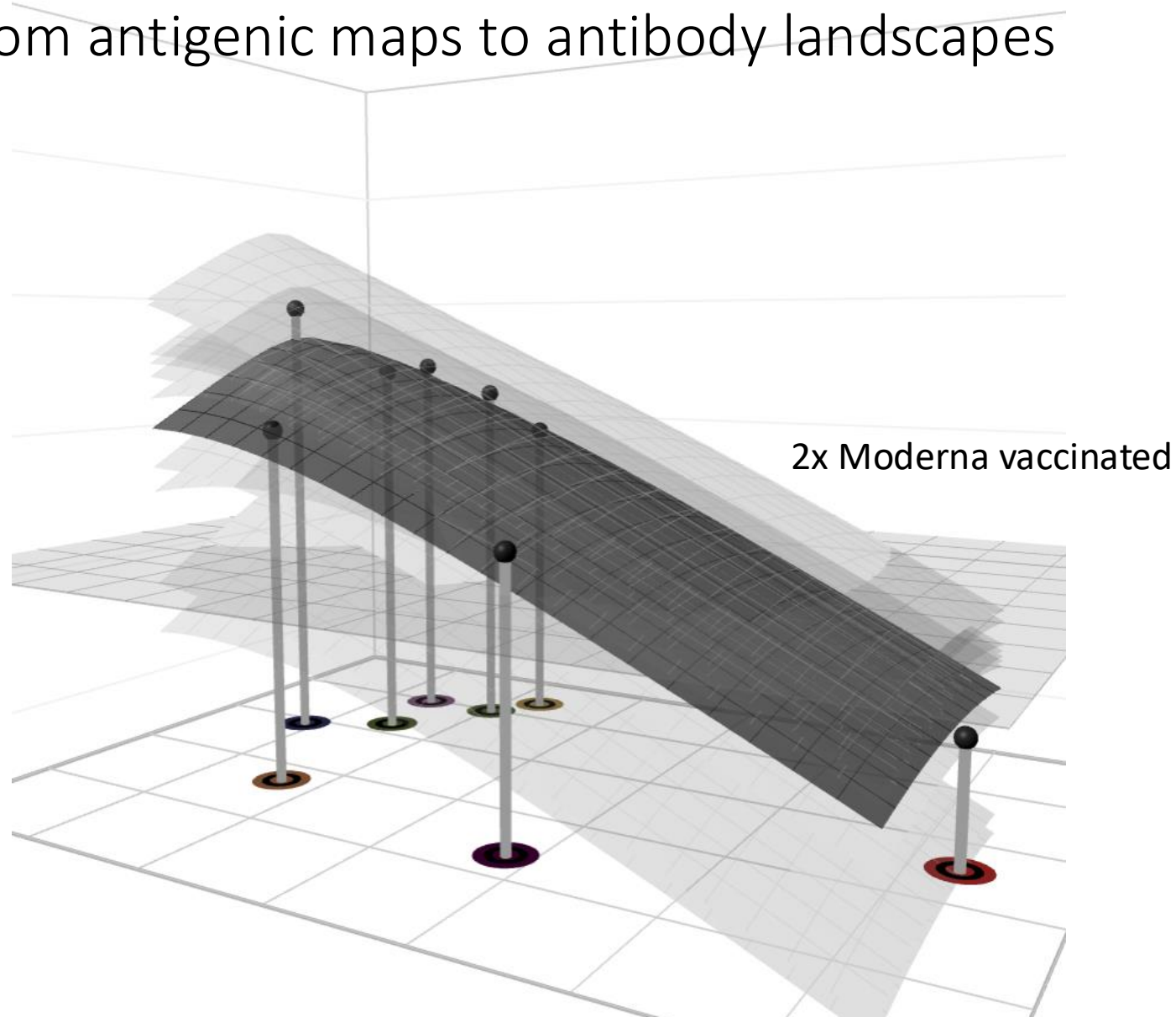
From antigenic maps to antibody landscapes

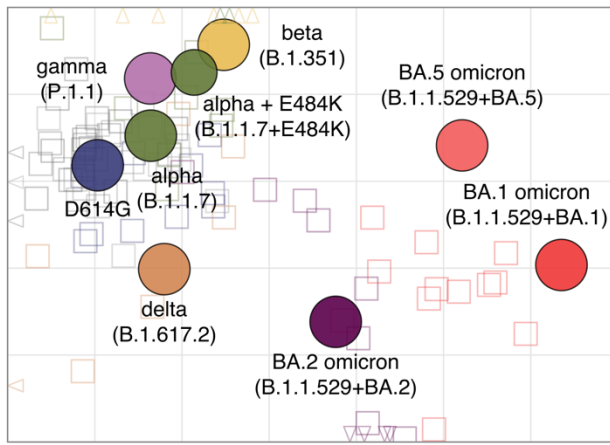


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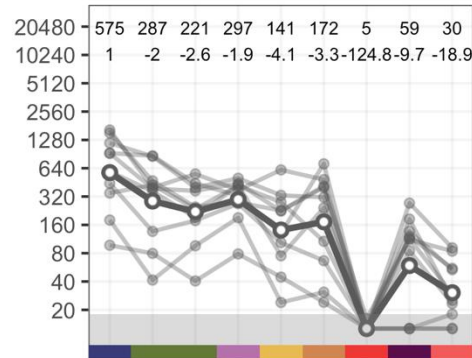


From antigenic maps to antibody landscapes





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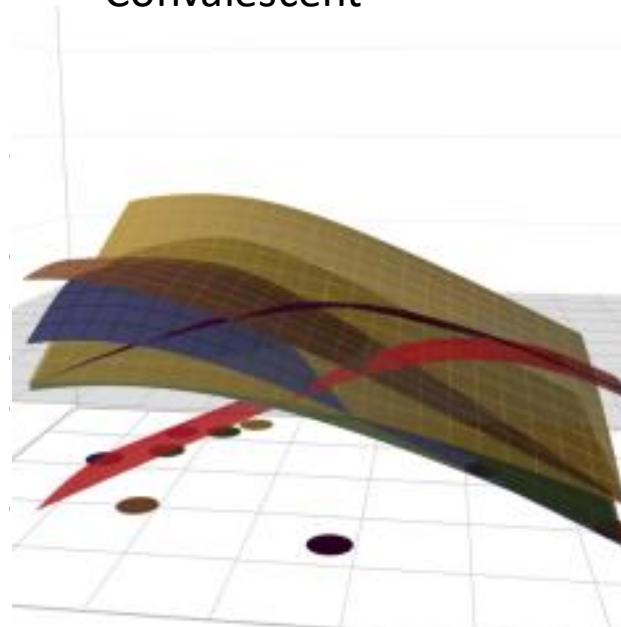


From antigenic maps to antibody landscapes

Multiple (distant) exposures broaden immune profiles

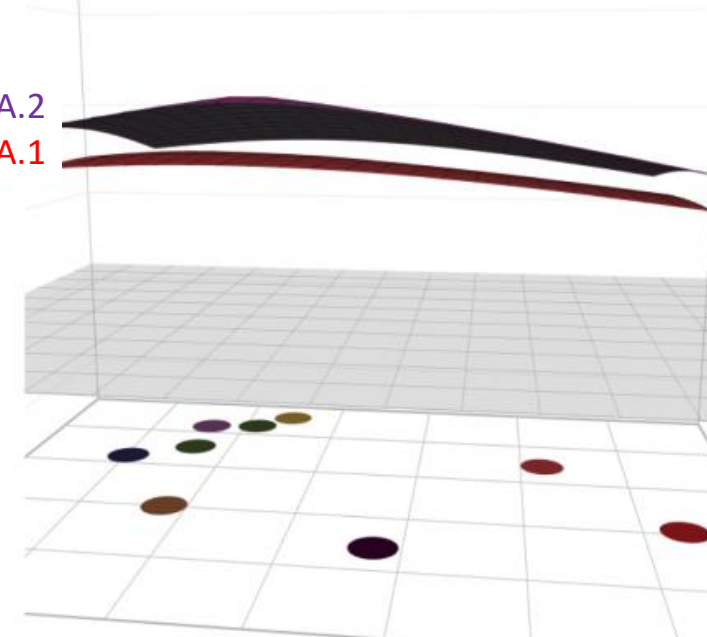
Convalescent

Beta
Delta
Wu-1
Alpha
BA.2
BA.1



Pre-omicron + Omicron convalescent

BA.2
BA.1



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](https://doi.org/10.1126/science.1097211)
- Antibody landscapes: Fonville et al., Science (2014) [DOI: 10.1126/science.1256427](https://doi.org/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>