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Supporting Information

Improved Antibody-Specific Epitope Prediction Using AlphaFold and AbAdapt**

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The RMSD of CDRs and paratope in the LOOCV set

		CDR-H1	CDR-H2	CDR-H3	CDR-L1	CDR-L2	CDR-L3	Paratope
AlphaFold2	Median	0.61	0.64	2.88	0.59	0.49	0.78	1.76
	Mean	0.93	0.89	3.44	0.84	0.64	1.15	2.08
	Stdev	0.89	0.98	2.42	0.90	0.82	1.08	1.28
Repertoire Builder	Median	0.81	0.81	4.01	0.67	0.57	0.92	2.44
	Mean	1.14	1.07	4.38	0.95	0.72	1.37	2.69
	Stdev	0.97	1.03	2.31	0.90	0.79	1.24	1.20

The RMSD of CDRs and paratope in the holdout set

		CDR-H1	CDR-H2	CDR-H3	CDR-L1	CDR-L2	CDR-L3	Paratope
AlphaFold2	Median	0.67	0.74	2.86	0.62	0.55	0.25	1.80
	Mean	1.14	1.04	3.62	0.88	0.60	1.31	2.12
	Stdev	1.06	0.86	2.88	1.01	0.41	1.17	1.17
Repertoire Builder	Median	0.85	1.07	4.07	0.72	0.61	0.28	2.59
	Mean	1.34	1.31	4.44	1.05	0.74	1.53	2.83
	Stdev	1.12	1.01	2.19	1.09	0.79	1.15	1.18

Supplementary Table 1. The RMSD (Å) of CDRs and paratope in the LOOCV and holdout set.

Initial epitope prediction of LOOCV set

	Prediction	Median	Mean	Stdev
AbAdapt/AbAdapt-AF	TRAIN ROC AUC	0.863	0.854	0.048
	TEST ROC AUC	0.694	0.687	0.147
	TEST PR AUC	0.165	0.200	0.137
	TEST Recall	0.625	0.599	0.241
	TEST Precision	0.149	0.157	0.088

Initial epitope prediction of holdout set

	Prediction	Median	Mean	Stdev
AbAdapt/AbAdapt-AF	TEST ROC AUC	0.695	0.690	0.146
	TEST PR AUC	0.162	0.212	0.159
	TEST Recall	0.571	0.593	0.224
	TEST Precision	0.150	0.159	0.092

Supplementary Table 2. The initial epitope prediction of AbAdapt and AbAdapt-AF in LOOCV and holdout set.

	Prediction	Median	Mean	Stdev
AbAdapt	TEST ROC AUC	0.721	0.705	0.152
	TEST PR AUC	0.189	0.226	0.151
	TEST Sensitivity	0.684	0.621	0.246
	TEST Precision	0.155	0.159	0.084
AbAdapt-AF	TEST ROC AUC	0.756	0.727	0.172
	TEST PR AUC	0.204	0.276	0.214
	TEST Sensitivity	0.775	0.708	0.250
	TEST Precision	0.162	0.161	0.090
AbAdapt-AF (AF's Ab/Ag models)	TEST ROC AUC	0.745	0.715	0.168
	TEST PR AUC	0.195	0.259	0.206
	TEST Sensitivity	0.771	0.691	0.258
	TEST Precision	0.158	0.160	0.096

Supplementary Table 3. Comparison of the performance of antibody-specific epitope prediction between AbAdapt and AbAdapt-AF. Analysis of the antibody-specific epitope prediction performance of the AbAdapt-AF pipeline that was trained by antigen models from Spanner and antibody models from AlphaFold2 versus using antibody and antigen models both from AlphaFold2 as input.

The RMSD of CDR-H3 and paratope in the LOOCV set

		Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
CDR-H3	Median	2.88	2.90	2.95	2.90	3.18
	Mean	3.44	3.45	3.51	3.53	3.69
	Stdev	2.42	2.42	2.38	2.42	2.49
Paratope	Median	1.76	1.78	1.86	1.83	1.96
	Mean	2.08	2.10	2.12	2.15	2.21
	Stdev	1.28	1.27	1.31	1.29	1.29

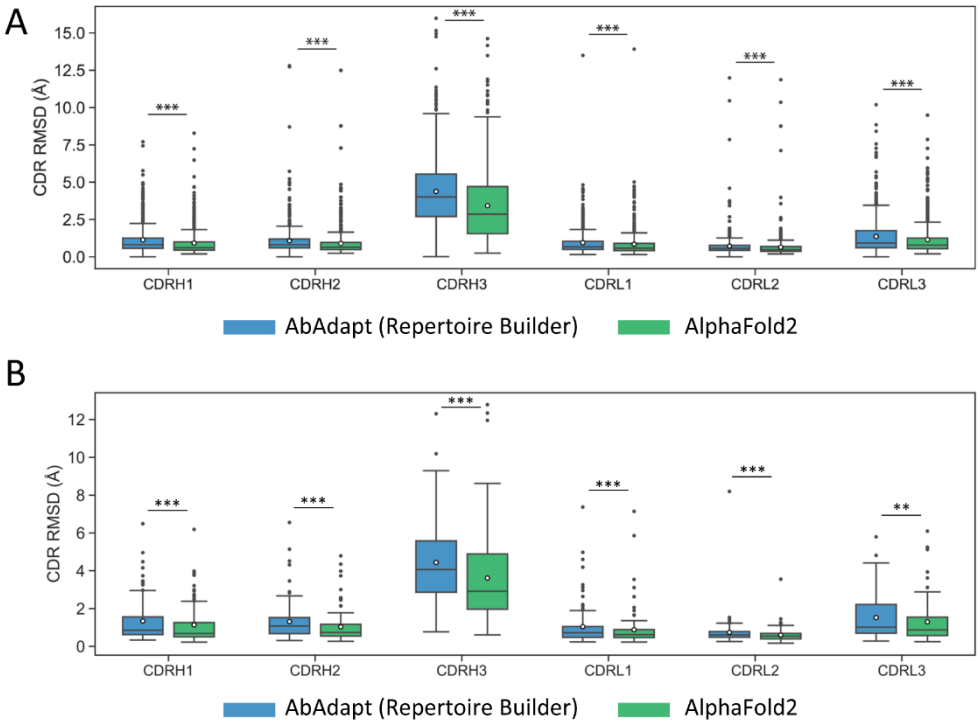
The RMSD of CDR-H3 and paratope in the holdout set

		Rank 1	Rank 2	Rank 3	Rank 4	Rank 5
CDR-H3	Median	2.86	3.04	2.95	3.04	3.41
	Mean	3.62	3.74	3.80	3.83	3.86
	Stdev	2.88	2.84	2.89	2.82	2.80
Paratope	Median	1.80	1.97	1.91	1.84	1.98
	Mean	2.12	2.17	2.20	2.23	2.28
	Stdev	1.17	1.15	1.19	1.26	1.30

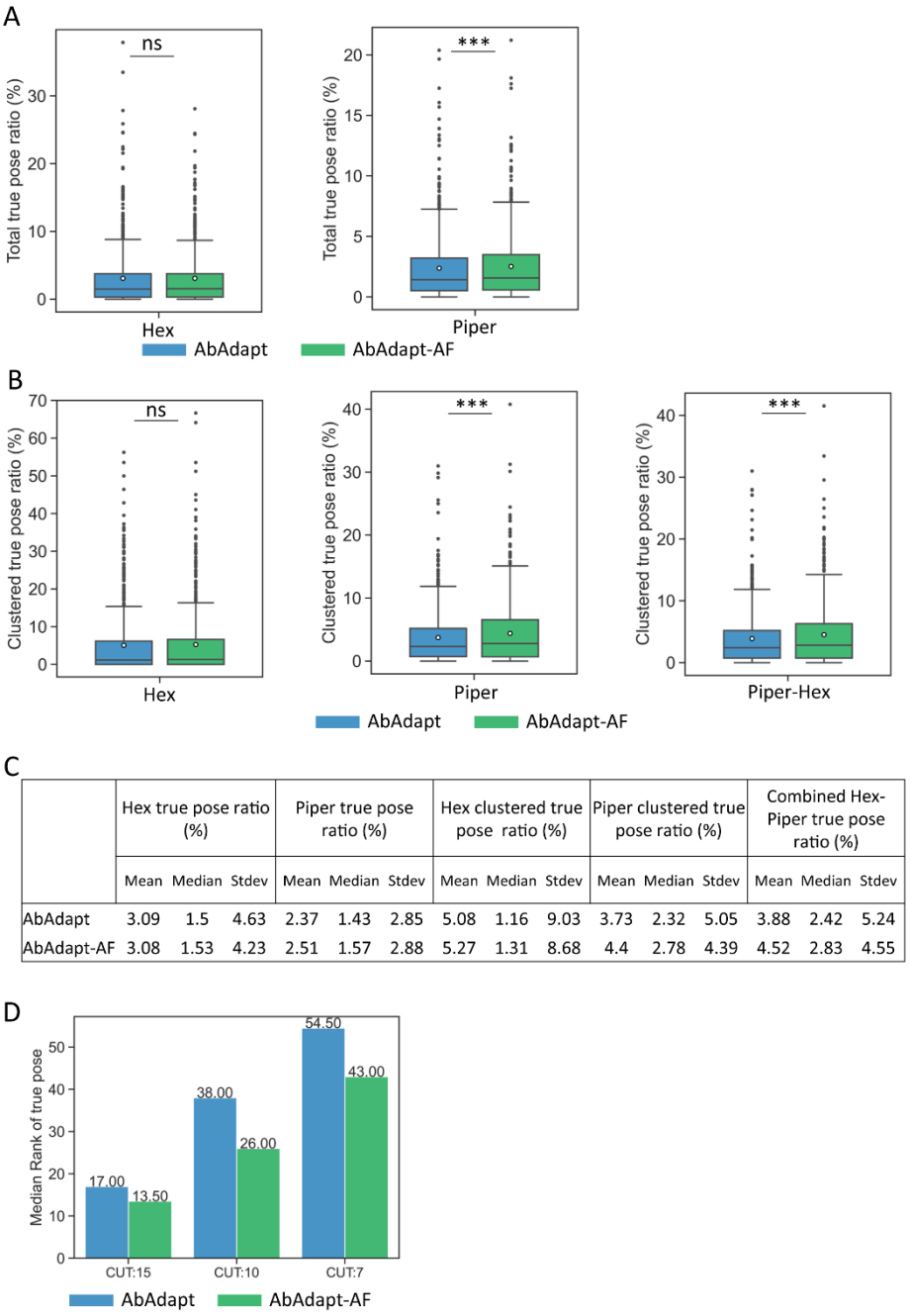
Supplementary Table 4. Comparison of the quality of top 5 antibody models by AlphaFold2.

Name	Description
Initial_Paratope	DNN binary classifier to predict paratope (1) or not (0) based on Antibody sequence and structure
Initial_Epitope	DNN binary classifier to predict epitope (1) or not (0) based on Antigen sequence and structure
Piper_Docking and Hex_Docking	Boosted Tree binary classifier to predict of a pose is True (1) or not (0) based on pose sequence and structure
Piper_Hex_Docking	Boosted Tree regressor to predict $IRMSD^{-2}$, based on AbAdapt docking Score, the number of clashes, Hex or Piper docking energy, the fraction of Piper poses in a cluster, and cluster size
Final_Epitope	DNN binary classifier to predict epitope (1) or not (0) based on Antigen sequence and structure as well as docking contact statistics

Supplementary Table 5. Description of machine learning models in AbAdapt and AbAdapt-AF pipelines.



Supplementary Figure 1. Comparison of the modeling performance of antibodies between AbAdapt and AlpahFold2. The RMSD of six CDRs of antibody model in LOOCV training set with 620 queries (A) and Holdout set with 100 queries (B) by AbAdapt powered by Repertoire Builder (blue) or AlphaFold2 (green). The Wilcoxon matched-pairs signed rank test was performed to compare the corresponding performance between AbAdapt and AbAdapt-AF (**$P \leq 0.01$; ***$P \leq 0.001$). The empty circle in each box indicated the average value.

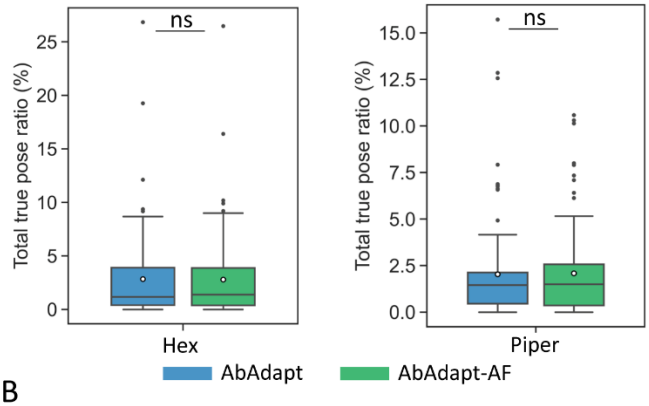


C

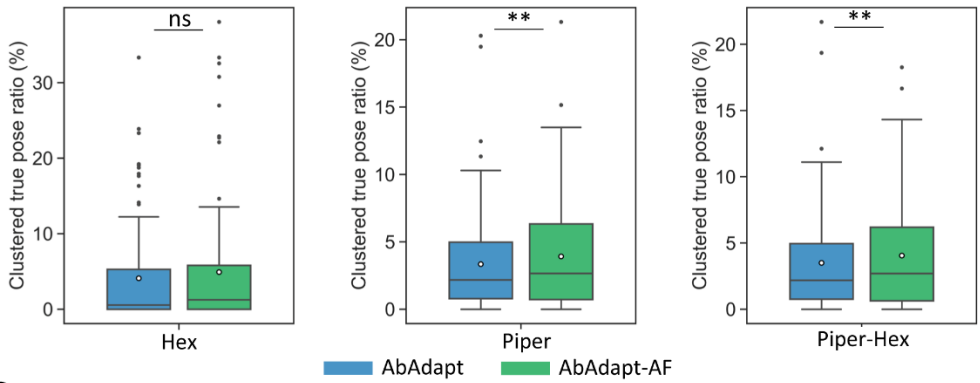
	Hex true pose ratio (%)			Piper true pose ratio (%)			Hex clustered true pose ratio (%)			Piper clustered true pose ratio (%)			Combined Hex-Piper true pose ratio (%)		
	Mean	Median	Stdev	Mean	Median	Stdev	Mean	Median	Stdev	Mean	Median	Stdev	Mean	Median	Stdev
AbAdapt	3.09	1.5	4.63	2.37	1.43	2.85	5.08	1.16	9.03	3.73	2.32	5.05	3.88	2.42	5.24
AbAdapt-AF	3.08	1.53	4.23	2.51	1.57	2.88	5.27	1.31	8.68	4.4	2.78	4.39	4.52	2.83	4.55

Supplementary Figure 2. Comparison of docking performance and pose combination between AbAdapt and AbAdapt-AF in LOOCV set. (A) The total true pose that produced by Hex (left) and Piper (right) by AbAdapt and AbAdapt-AF. (B) The true pose ratio after clustering the pose from Hex (left) and Piper (middle) separately and a combination of them (right). The Wilcoxon matched-pairs signed rank test was performed to compute the significance (***$P \leq 0.001$, ns: not significant). (C) The average and median values of each true pose ratio that related to (A) and (B). (D) The median rank of true poses after the combination of Hex-Piper clusters for the sharing of successful queries among AbAdapt and AbAdapt-AF. The true pose was defined by the cutoff value indicated on the x-axis (15, 10, or 7 Å) for the RMSD of the interface residues (IRMSD) with minimum epitope and paratope accuracies of 50%.

A



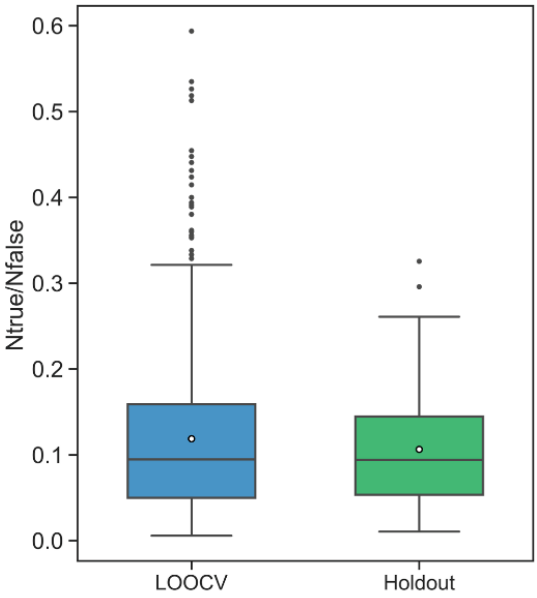
B



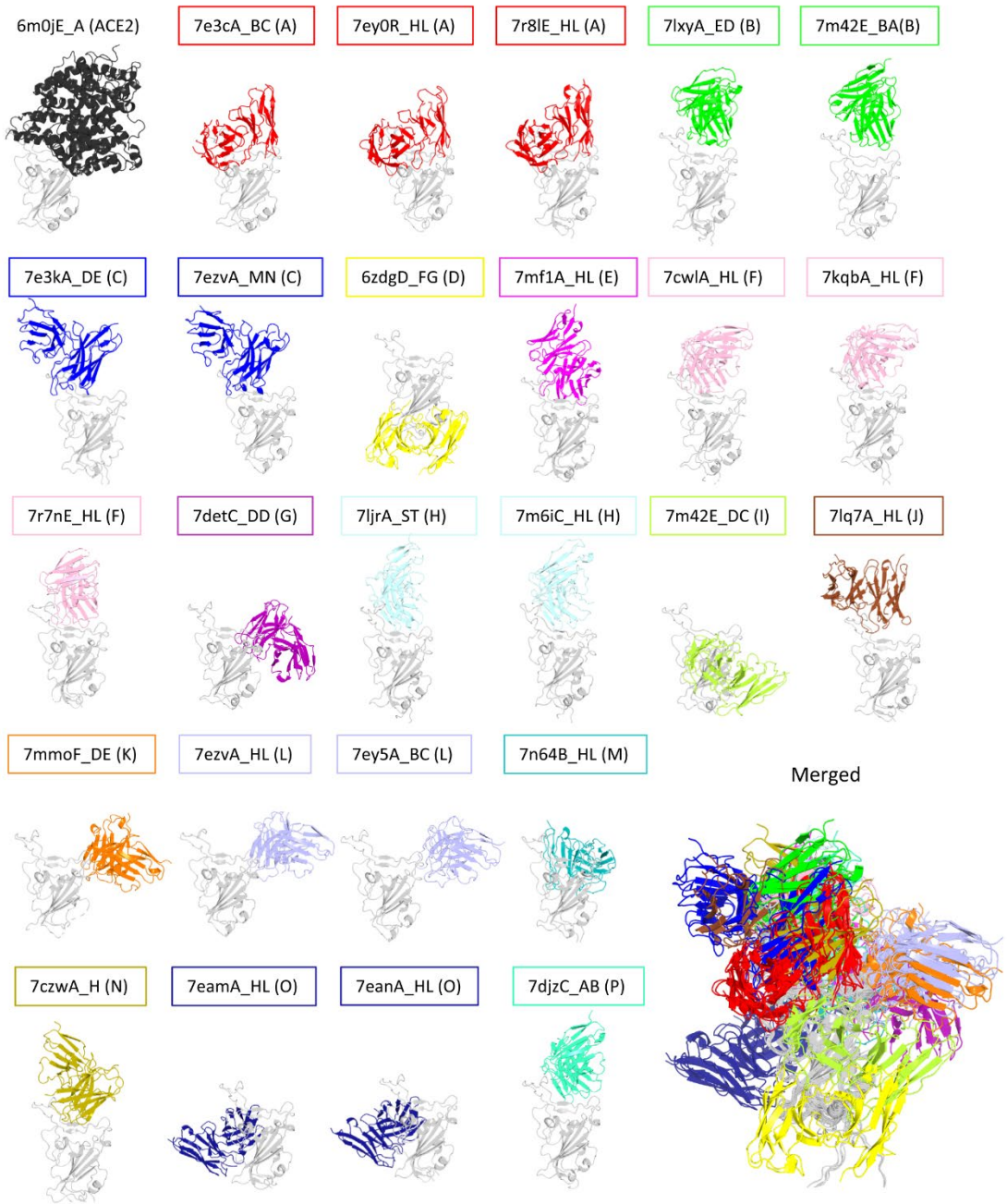
C

	Hex true pose ratio (%)			Piper true pose ratio (%)			Hex clustered true pose ratio (%)			Piper clustered true pose ratio (%)			Combined Hex-Piper true pose ratio (%)		
	Mean	Median	Stdev	Mean	Median	Stdev	Mean	Median	Stdev	Mean	Median	Stdev	Mean	Median	Stdev
AbAdapt	2.83	1.17	3.82	2.03	1.45	2.34	4.11	0.56	8.15	3.35	2.18	3.97	3.5	2.18	4.12
AbAdapt-AF	2.79	1.39	4.02	2.09	1.5	2.7	4.92	1.25	6.69	3.92	2.66	3.72	4.05	2.7	3.9

Supplementary Figure 3. Comparison of docking performance and pose combination between AbAdapt and AbAdapt-AF in holdout set. (A) The total true pose that produced by Hex (left) and Piper (right) by AbAdapt and AbAdapt-AF. (B) The true pose ratio after clustering the pose from Hex (left) and Piper (middle) separately and a combination of them (right). The Wilcoxon matched-pairs signed rank test was performed to compute the significance (**$P \leq 0.01$, ns: not significant). (C) The average and median values of each true pose ratio that related to (A) and (B).



Supplementary Figure 4. PR ROC baseline of LOOCV and holdout sets. The baseline is based on the ratio of epitope and non-epitope amino acid residue. The “Ntrue” indicate the number of epitope residue and “Nfalse” indicate the number of non-epitope residue in each antigen from the LOOCV set (blue) and the holdout set (green).



Supplementary Figure 5. The visualization of 25 SARS-Cov-2 RBD-antibody complexes. The epitope cluster is given followed by the query name. Each RBD in the complex was aligned as the orientation of the RBD in RBD-ACE2 binding pose.