Extended Data

Slip-catch-slip binding of SARS-CoV-2 spike variants to ACE2

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Extended Data Table EDT1: **Experimentally collected and tabulated data sets for Omicron-ACE2 interaction.**

Force F $\pm$ 0.1 $\cdot$ F (pN)	Lifetime $\tau \pm \Delta\tau$ (s)	N_{curves}	n_{events}	p_{events} (%)
5 $\pm$ 0.5	0.3357 $\pm$ 0.0251	1416	150	10.593
7 $\pm$ 0.7	0.1058 $\pm$ 0.0213	1402	149	10.628
10 $\pm$ 1.0	0.0742 $\pm$ 0.0261	1800	239	13.278
12 $\pm$ 1.2	0.0605 $\pm$ 0.0279	1810	219	12.099
15 $\pm$ 1.5	0.0624 $\pm$ 0.0225	956	152	15.899
17 $\pm$ 1.7	0.0949 $\pm$ 0.0223	3906	614	15.719
20 $\pm$ 2.0	0.1730 $\pm$ 0.0269	508	69	13.583
22 $\pm$ 2.2	0.1974 $\pm$ 0.0265	1102	133	12.069
25 $\pm$ 2.5	0.2090 $\pm$ 0.0249	1887	274	14.520
30 $\pm$ 3.0	0.1598 $\pm$ 0.0265	1212	248	20.465
35 $\pm$ 3.5	0.1449 $\pm$ 0.0298	1011	98	9.693
40 $\pm$ 4.0	0.1207 $\pm$ 0.0271	1120	198	17.679
45 $\pm$ 4.5	0.1055 $\pm$ 0.0269	1501	282	18.787
50 $\pm$ 5.0	0.1134 $\pm$ 0.0241	888	132	14.865

Force-dependent bond lifetimes $\tau(\mathrm{F})$, total amount of experimentally measured curves N_{curves}, number of specific binding events n_{events} observed and the resulting event/binding frequency $p_{events} = \frac{n_{events}}{N_{curves}}$ for each pull-trigger force F.

Extended Data Table EDT2: **Experimentally collected and tabulated data sets for Delta-ACE2 interaction.**

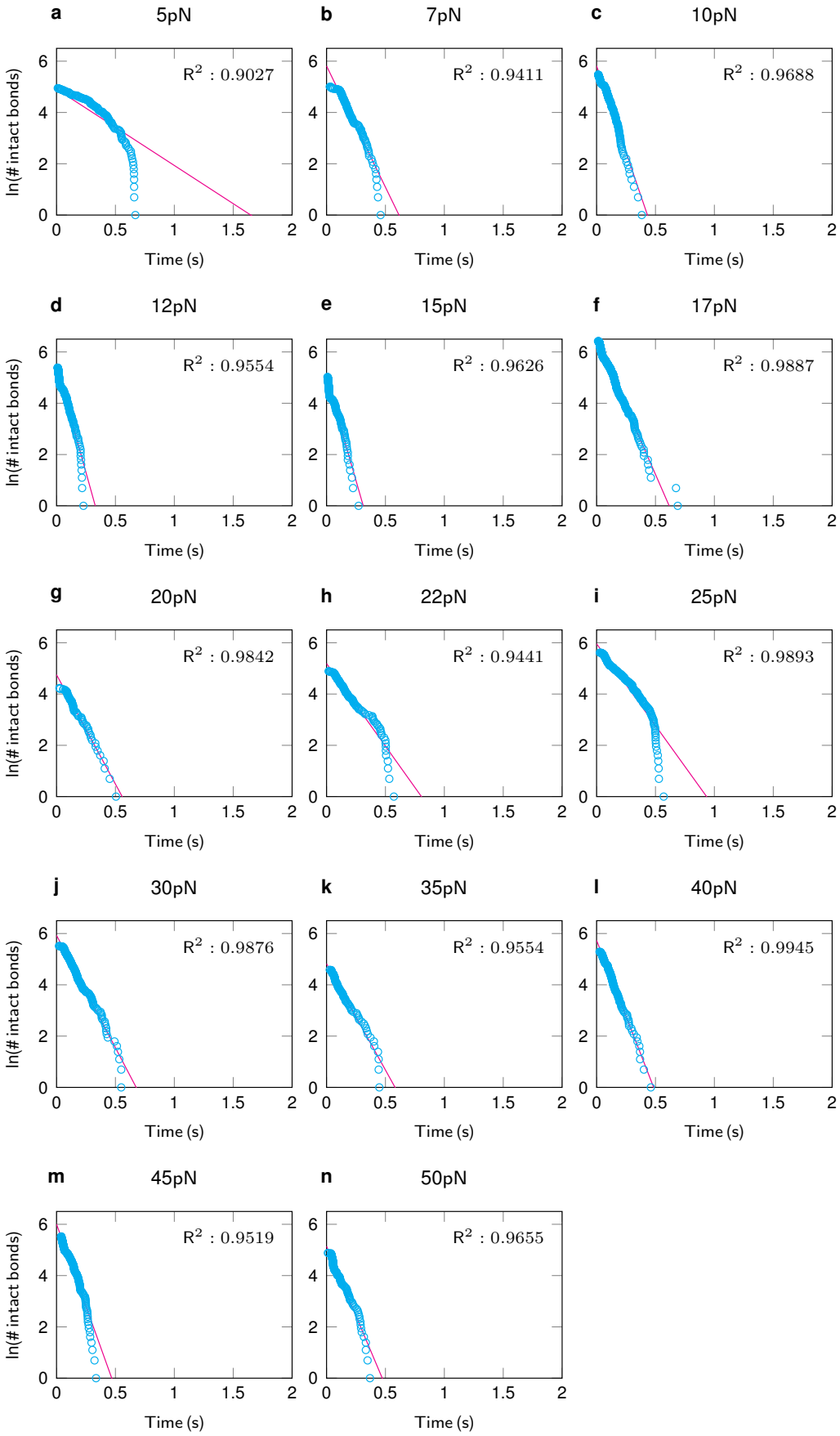
Force F $\pm$ 0.1 $\cdot$ F (pN)	Lifetime $\tau \pm \Delta\tau$ (s)	N_{curves}	n_{events}	p_{events} (%)
10 $\pm$ 1.0	0.470 $\pm$ 0.025	1011	105	10.386
15 $\pm$ 1.5	0.270 $\pm$ 0.015	1059	115	10.859
20 $\pm$ 2.0	0.257 $\pm$ 0.011	1121	115	10.259
22 $\pm$ 2.2	0.333 $\pm$ 0.013	1072	151	14.086
25 $\pm$ 2.5	0.399 $\pm$ 0.011	1032	201	19.477
27 $\pm$ 2.7	0.258 $\pm$ 0.023	1157	80	6.914
30 $\pm$ 3.0	0.204 $\pm$ 0.006	1397	144	10.308
35 $\pm$ 3.5	0.115 $\pm$ 0.007	1148	138	12.021
40 $\pm$ 4.0	0.116 $\pm$ 0.005	1010	191	18.911
45 $\pm$ 4.5	0.121 $\pm$ 0.005	1020	137	13.431
50 $\pm$ 5.0	0.151 $\pm$ 0.008	1055	151	14.313

Force-dependent bond lifetimes $\tau(F)$, total amount of experimentally measured curves N_{curves}, number of specific binding events n_{events} observed and the resulting event/binding frequency $p_{events} = \frac{n_{events}}{N_{curves}}$ for each pull-trigger force F.

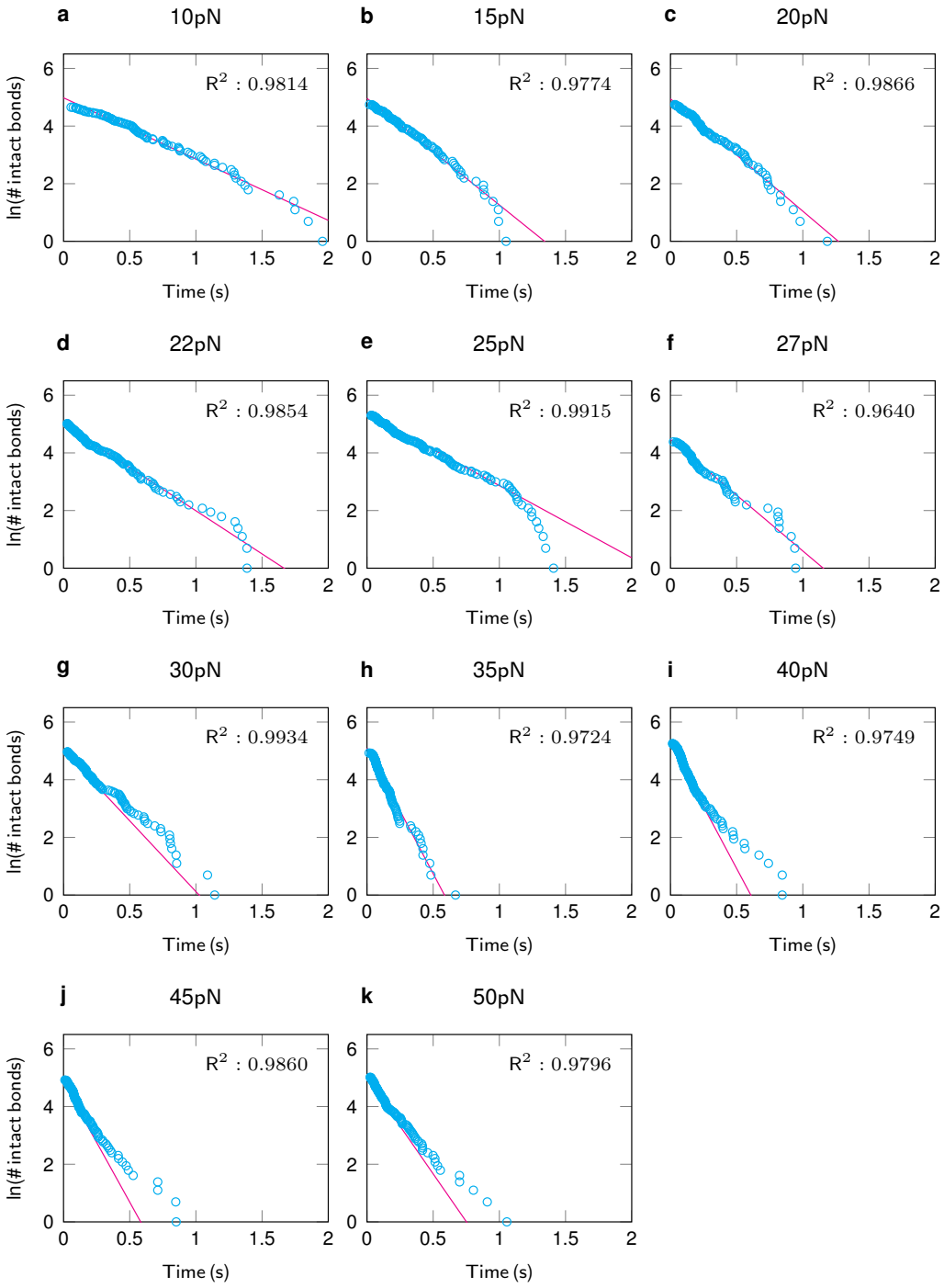
Extended Data Table EDT3: **Experimentally collected and tabulated data sets for Alpha-ACE2 interaction.**

Force F $\pm$ 0.1 $\cdot$ F (pN)	Lifetime $\tau \pm \Delta\tau$ (s)	N_{curves}	n_{events}	p_{events} (%)
7 $\pm$ 0.7	0.1780 $\pm$ 0.0163	1447	142	9.813
8 $\pm$ 0.8	0.1762 $\pm$ 0.0136	1117	85	7.609
10 $\pm$ 1.0	0.1171 $\pm$ 0.0040	1489	162	10.879
12 $\pm$ 1.2	0.0993 $\pm$ 0.0032	1001	115	11.489
15 $\pm$ 1.5	0.1197 $\pm$ 0.0061	1225	177	14.449
20 $\pm$ 2.0	0.1060 $\pm$ 0.0043	1502	112	7.457
25 $\pm$ 2.5	0.0573 $\pm$ 0.0014	1488	137	9.207
30 $\pm$ 3.0	0.0287 $\pm$ 0.0005	1368	136	9.942
35 $\pm$ 3.5	0.0390 $\pm$ 0.0009	1451	246	16.954
40 $\pm$ 4.0	0.0477 $\pm$ 0.0006	1591	370	23.256
45 $\pm$ 4.5	0.0300 $\pm$ 0.0005	1202	182	15.141

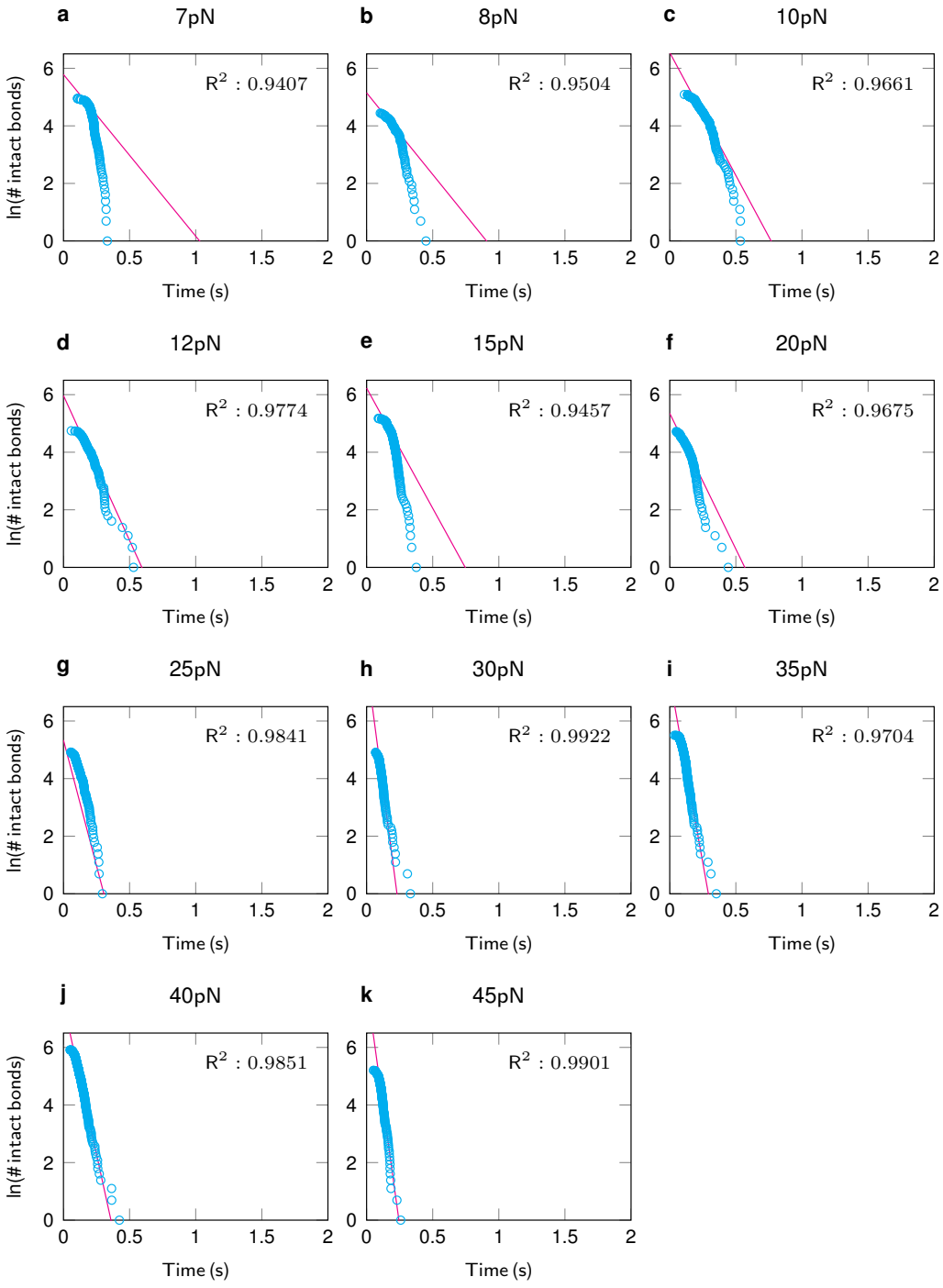
Force-dependent bond lifetimes $\tau(F)$, total amount of experimentally measured curves N_{curves}, number of specific binding events n_{events} observed and the resulting event/binding frequency $p_{events} = \frac{n_{events}}{N_{curves}}$ for each pull-trigger force F.



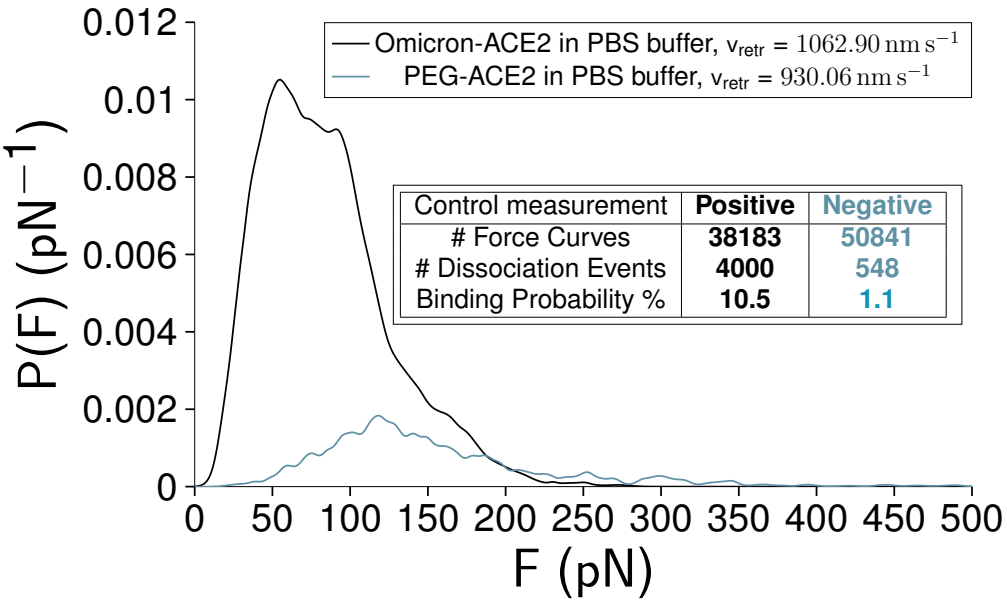
Extended Data Figure EDF1: **Full set of** $\ln(\mathrm{N})$ **vs. time** t **graphs for *slip-catch-slip* dissociation of first Omicron-ACE2 interaction (see Table EDT1).** The natural logarithm of intact bonds is plotted vs. time (open blue circles) for different pull-trigger forces (see titles of subplots **a**-**n**). The decay curves are approximated by a single linear (magenta line) according to Eq.(1). The negative inverse slope of the steep regime accounts for the lifetime of the Omicron-ACE2 dimer. The shallow, long lifetime regime in some plots can probably be assigned to unspecific adhesion. The R^2-value specifies the coefficient of determination (COD).



Extended Data Figure EDF2: Full set of $\ln(\mathrm{N})$ vs. time t graphs for *slip-catch-slip* dissociation of second Delta-ACE2 interaction (see Table EDT2). Approximation of τ-values and determination of R^2 were carried out as described above.



Extended Data Figure EDF3: **Full set of $\ln(N)$ vs. time t graphs for *slip-catch-slip* dissociation of second Alpha-ACE2 interaction (see Table EDT3).** Approximation of τ-values and determination of R^2 were carried out as described in Figure **EDF1**.



Extended Data Figure EDF4: **Series of (positive and negative) control experiments performed exemplarily on the Omicron-ACE2 for differently prepared cantilever tips.** The experiments were conducted in dynamic force spectroscopy mode at a pulling speed of $\approx 1000\,\mathrm{nm\,s^{-1}}$ (see legend entries for exact velocity values) estimating the distribution of dissociation forces $\mathrm{P(F)}$. The dissociation probability distributions are scaled for the absolute binding frequency. Experiments with Omicron-spike modified AFM cantilever and sample substrate functionalized with ACE2 (black). The background of unspecific adhesion was tested with a readily modified cantilever lacking the Omicron spike protein (cyan), i.e. only the Ald-Ph-PEG($n = 24$)-NHS-ester linker was attached to the cantilever tip, and a regularly immobilized ACE2-substrate. The number of force curves, dissociation events and binding probabilities are listed in the table in the colours of the corresponding plots.