SUPPLEMENTARY MATERIAL

Domino effect in allosteric signaling of peptide binding

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Residue 1	Residue 2	Mutual Information	KS test value	KL divergence (Å)	Correlation
Gly23	Lys79	-	0.59808	-	0.31662
Phe24	Lys79	0.03008	0.49532	18.07	0.32063
Asn25	Asp31	-	0.61054	-	0.28958
Asn25	Glu33	-	0.57146	22.27	0.29099
Asn25	Ile35	-	0.64436	18.93	0.35772
Asn25	Phe36	-	0.66421	48.25	0.38374
Asn25	Ile37	-	0.54305	35.11	0.32529
Asn25	Ser38	-	-	26.37	0.32914
Asn25	Leu41	0.04424	0.70128	32.49	-0.34922
Asn25	Ala42	-	0.6361	29.20	-0.33893
Asn25	Gly43	0.03840	-	33.92	-0.36436
Asn25	Gln57	-	0.64150	35.32	0.33154
Asn25	Lys79	0.03268	0.50425	-	-
Asn25	Lys92	-	0.54884	19.53	0.34175
Asn25	Glu94	-	0.55058	25.86	0.34518
Asn25	Glu95	-	0.62693	34.93	0.36738
Asn25	Tyr96	-	0.61221	32.07	0.36486
Asn25	Ser97	-	-	-	0.33147
Ile26	Lys79	0.03855	0.49003	-	-
Ile37	Lys79	0.03073	0.48914	-	0.31323
Ser38	Lys79	0.03792	0.48722	-	-
Ile40	Lys79	0.03197	0.50300	-	0.30330
Arg53	Lys79	0.02928	0.48817	-	0.26781
Gly55	Lys79	0.03123	0.49293	-	-
Asp56	Lys79	0.03118	0.49490	-	-
Gln57	Lys79	0.03239	0.50499	-	-
Ile58	Lys79	0.03021	0.48665	-	0.26505
Leu78	Glu9	-	-	27.23	0.28767
Leu78	Leu41	-	-	-	-0.33846
Leu78	Gln57	-	-	21.74	-
Leu78	Ile58	-	-	19.43	-
Leu78	Leu59	-	-	19.24	0.28927
Leu78	Leu66	-	-	18.00	-
Leu78	Arg67	-	-	18.12	-
Leu78	Gln90	-	-	20.57	0.28648
Leu78	Tyr91	-	-	27.79	-
Gln90	Lys79	0.03744	0.49704	-	-
Tyr91	Lys79	0.03955	0.49671	-	0.31159
Lys92	Lys79	0.03691	0.49695	-	-
Pro93	Lys79	0.03654	0.48892	-	-

Table S 1. PDZ3 residue pairs for which Mutual Information, Kolmogorov-Smirnov (KS) test value, or Kullback-Leibler (KL) divergence between first (bound) and last (unbound) basins, or Pearson correlation to u_1 reaction coordinate is on the 99.9 percentile of all distances

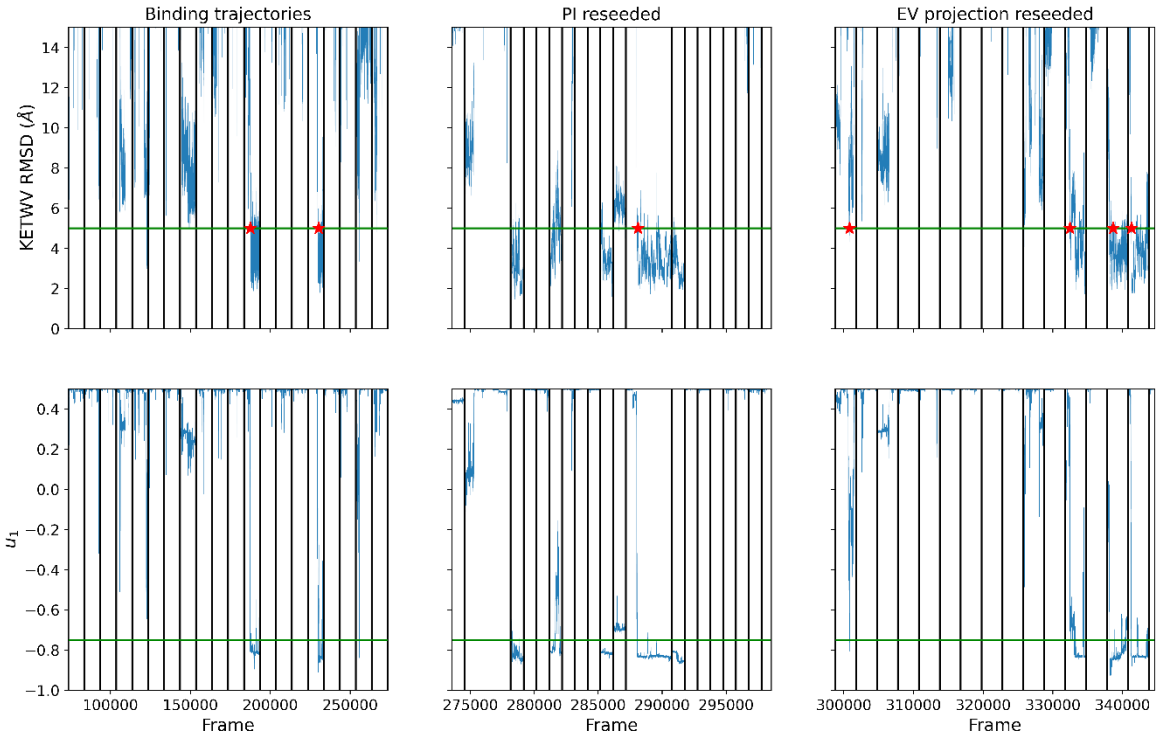


Figure S 1. Definition of binding events. Threshold of peptide RMSD = 5 Å (top) and eigenvector projection u_1 = -0.75 (bottom) for binding and reseeded trajectories. Binding events considered are shown with a red star. Reseeded trajectories were not considered if the trajectory was initially bound (below threshold in the first frame), and therefore some trajectories seem below the threshold but no red star is shown. Vertical lines separate the independent trajectories.

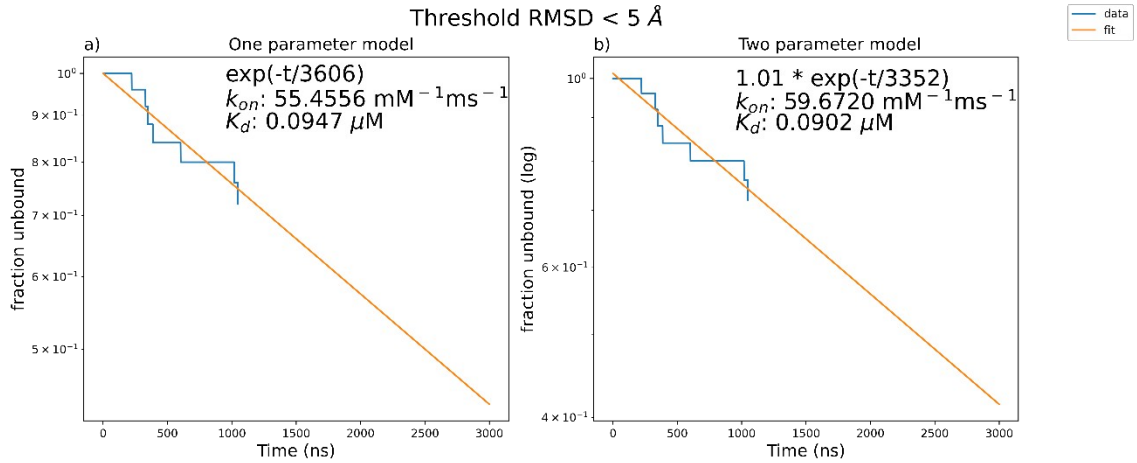
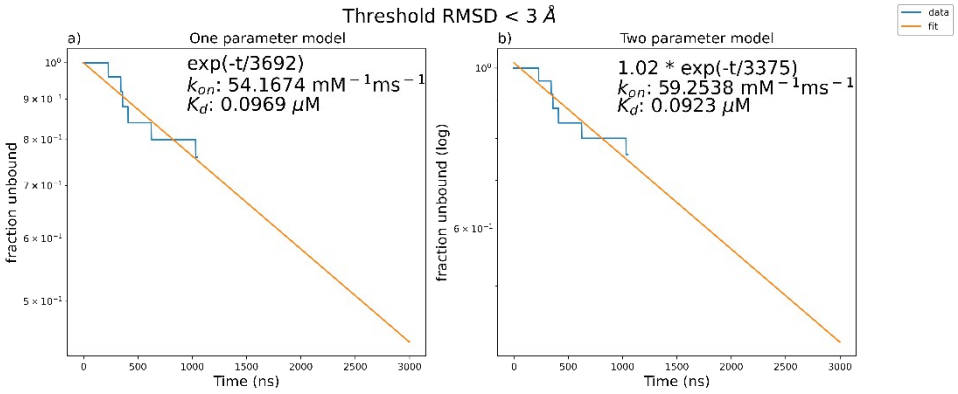
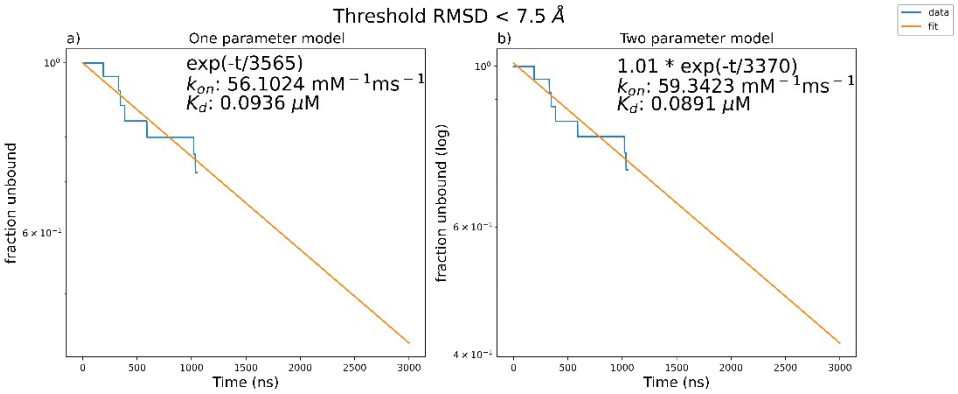
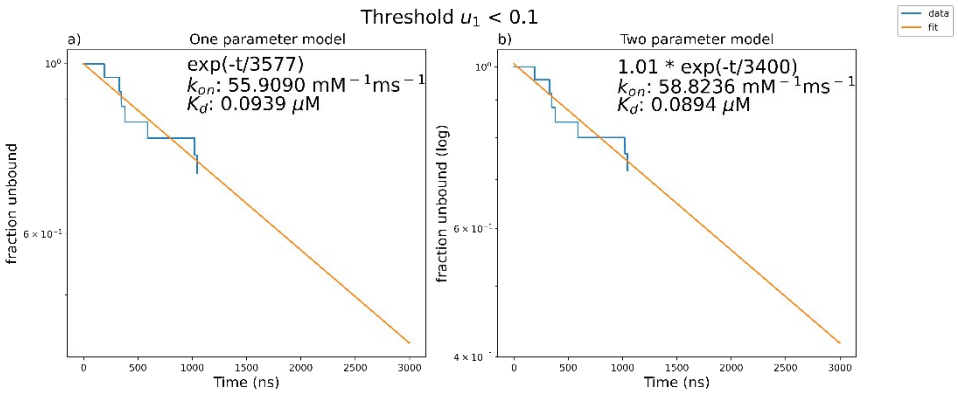


Figure S 2. Kinetic analysis of binding events. (a) Fitting of fraction of trajectories with peptide unbound to a one-parameter model where f(t) = exp(-1/τ). Probability was obtained by averaging binary vectors of length 1050 ns. Corresponding to the seven binding events observed, seven vectors were flipped to zero (bound) at the time of binding. (b) Fitting according to a two-parameter model where f(t) = α*exp(-1/τ).


Threshold RMSD < 3 Å
a)
One parameter model
exp(-t/3692)
k_{on}: 54.1674 mM^{-1}ms^{-1}
K_d: 0.0969 μM
b)
Two parameter model
1.02 * exp(-t/3375)
k_{on}: 59.2538 mM^{-1}ms^{-1}
K_d: 0.0923 μM
fraction unbound
fraction unbound (log)
Time (ns)
data
fit


Threshold RMSD < 7.5 Å
a)
One parameter model
exp(-t/3565)
k_{on}: 56.1024 mM^{-1}ms^{-1}
K_d: 0.0936 μM
b)
Two parameter model
1.01 * exp(-t/3370)
k_{on}: 59.3423 mM^{-1}ms^{-1}
K_d: 0.0891 μM
fraction unbound
fraction unbound (log)
Time (ns)
data
fit


Threshold u_1 < 0.1
a)
One parameter model
exp(-t/3577)
k_{on}: 55.9090 mM^{-1}ms^{-1}
K_d: 0.0939 μM
b)
Two parameter model
1.01 * exp(-t/3400)
k_{on}: 58.8236 mM^{-1}ms^{-1}
K_d: 0.0894 μM
fraction unbound
fraction unbound (log)
Time (ns)
data
fit

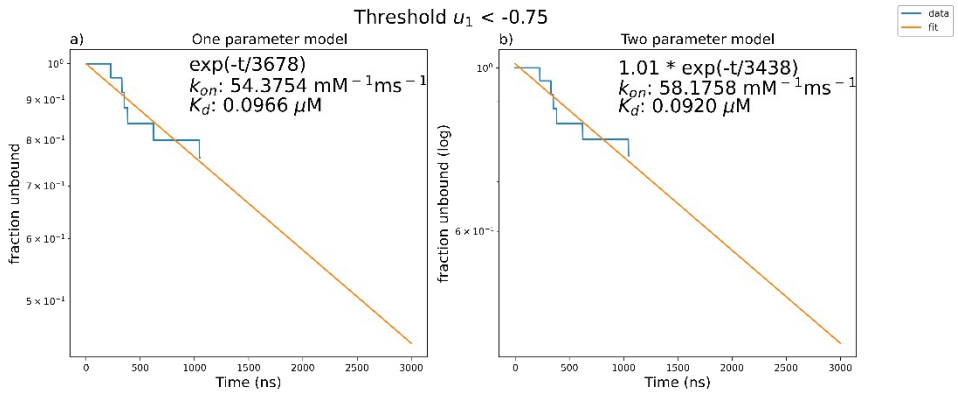

Threshold u_1 < -0.75
a)
One parameter model
exp(-t/3678)
k_{on}: 54.3754 mM^{-1}ms^{-1}
K_d: 0.0966 μM
b)
Two parameter model
1.01 * exp(-t/3438)
k_{on}: 58.1758 mM^{-1}ms^{-1}
K_d: 0.0920 μM
fraction unbound
fraction unbound (log)
Time (ns)
data
fit

Figure S 3. Robustness of the kinetic analysis with respect to the definition of the threshold for bindings. From top to bottom: RMSD of peptide Cα < 3 Å, RMSD < 7.5 Å, optimized RC u_1 < 0.1, optimized RC u_1 < -0.75

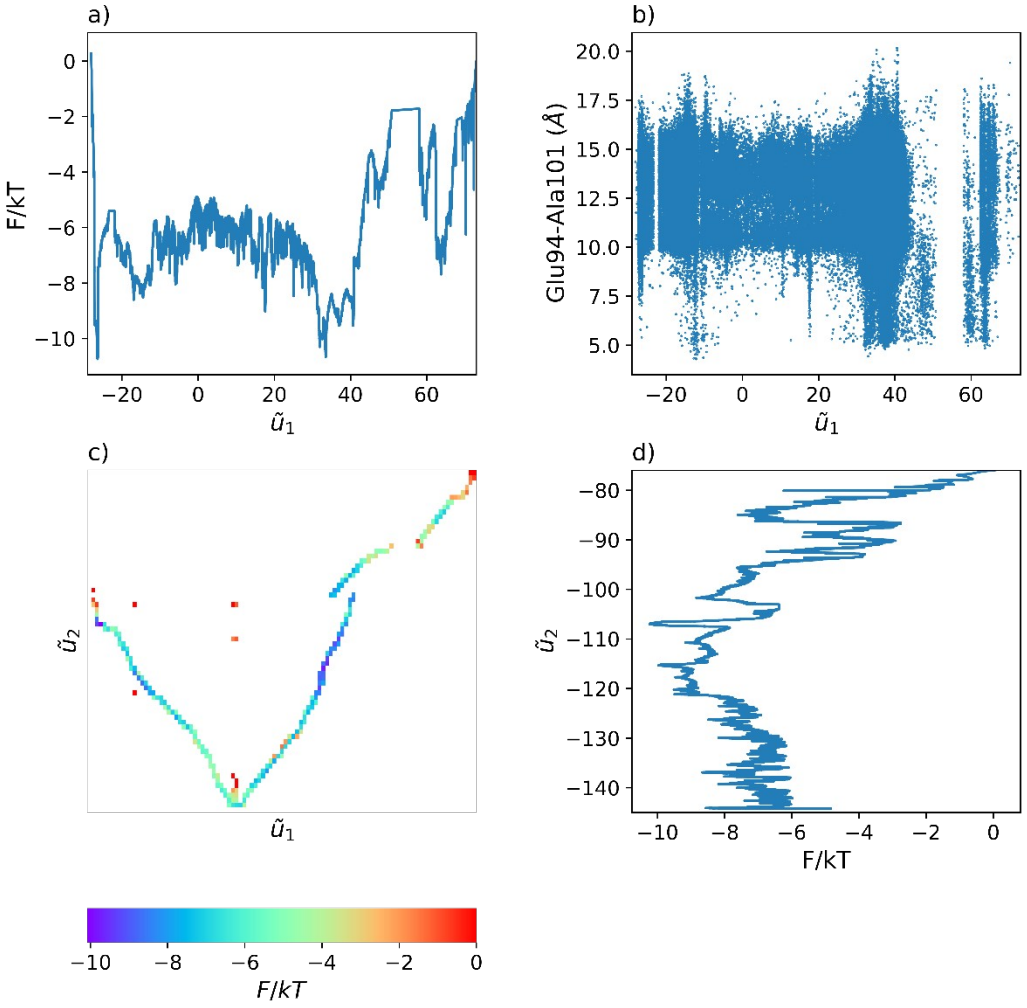


Figure S 4. Projection of trajectory on natural reaction coordinates. These plots are similar to those in Figure 7Error: Reference source not found, but with the coordinates transformed such that the diffusion coefficient is unitary. (a) Projection of the free energy on the slowest-relaxation eigenvector $\tilde{u}_1$. The Free Energy Profile shows the different basins from the bound state at around $\tilde{u}_1 \approx$ -25 to the unbound states at about $\tilde{u}_1 \approx$ 60. (b) Distribution of distances between the Cα of residues Glu94 and Ala101 in the C-terminal region projected on the $\tilde{u}_1$ natural coordinate. (c) Two-dimensional histogram of trajectory frames. (d) Projection of the free energy on the second eigenvector $\tilde{u}_2$

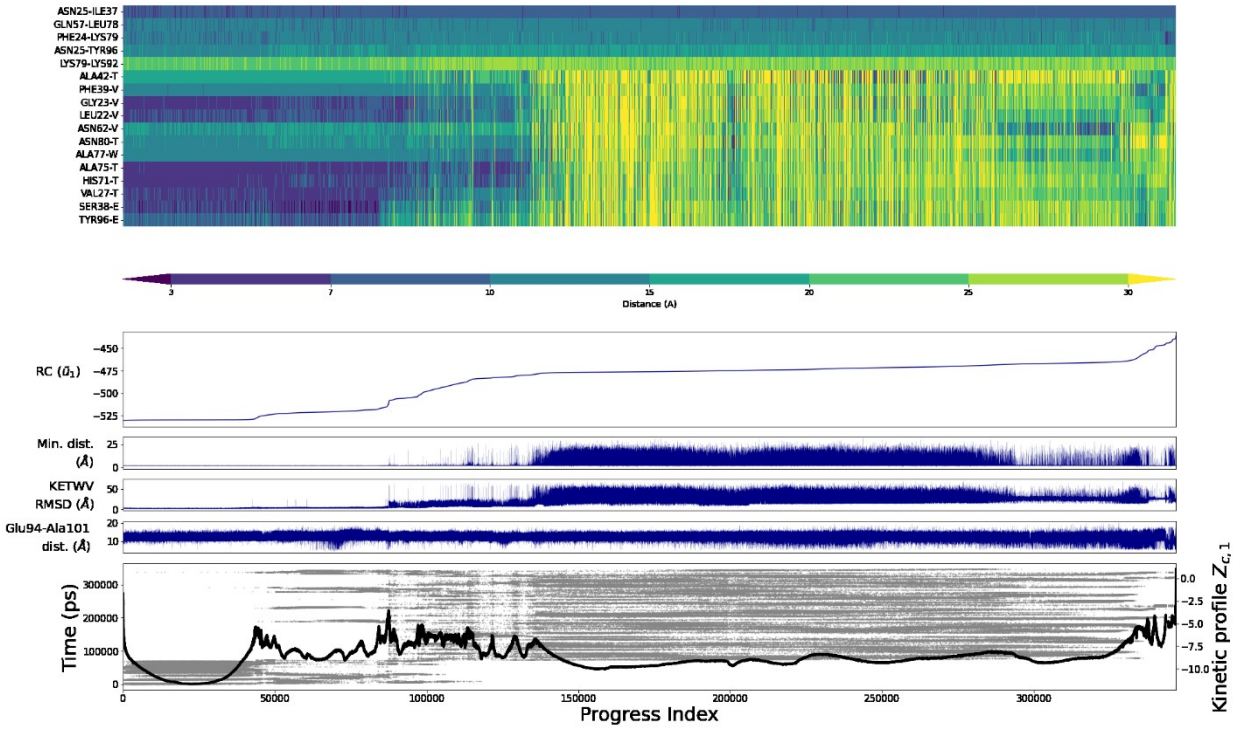


Figure S 5. SAPPHIRE plot of trajectory projected on natural reaction coordinate. Analogous to Figure 8Error: Reference source not found. From top to bottom: structural annotation with interatomic distances. Value of $\tilde{u}_1$: first eigenvector RC. Minimum distance between peptide and protein (Å), RMSD of peptide Cα with respect to crystal structure (Å). Distance between residues Glu94-Ala101, Kinetic and temporal annotation.

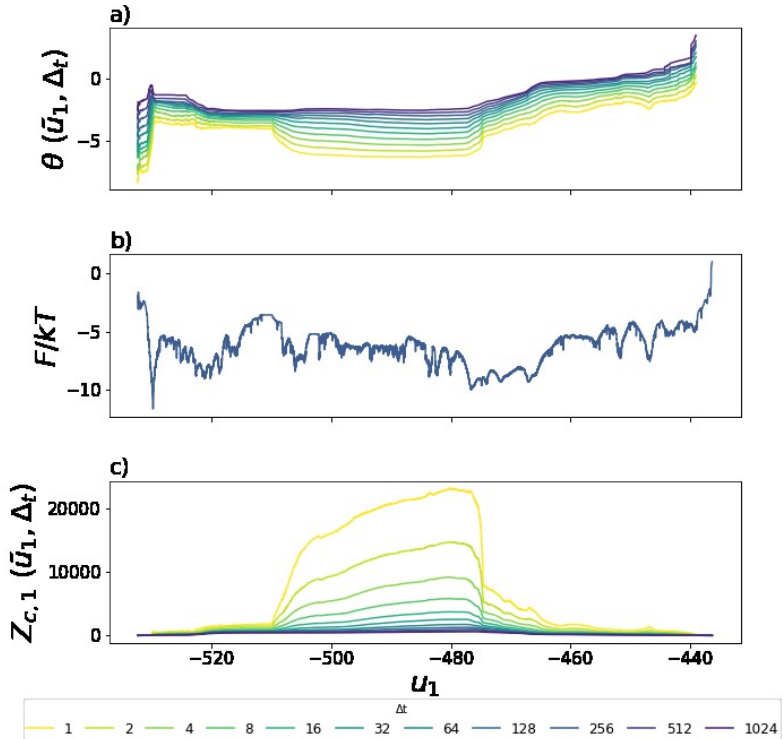


Figure S 6. Reaction coordinate (RC) quality metrics for the natural coordinate $\tilde{u}_1$. (a) eigenvector optimality criterion $\theta(\tilde{u}_1, \Delta t)$. (b) Free energy profile projected on the natural RC. (c) Committor optimality criterion $Z_{C,-1}$.

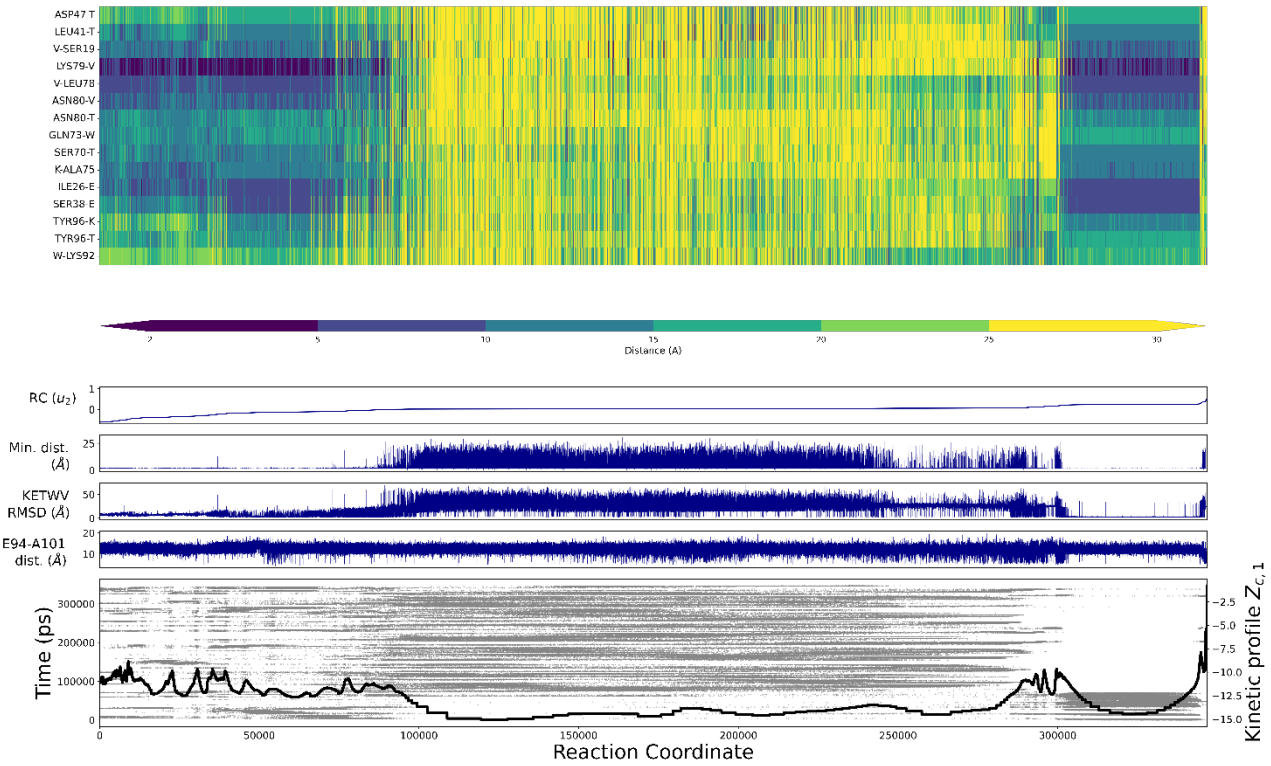


Figure S 7. SAPPHIRE plot of RC u_2. From top to bottom: Structural annotation, u_2 RC, minimum distance (Å), KETWV RMSD (Å), distance between Glu94-Ala101 (Å), temporal and kinetic annotation.

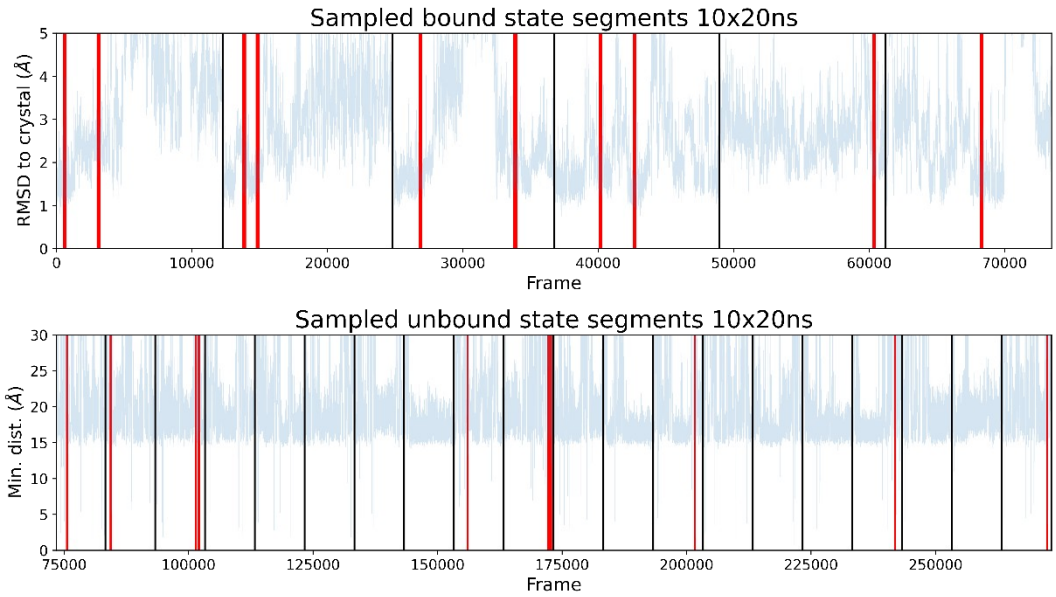


Figure S 8. Definition of bound and unbound states. Top: selected stretches of 20 ns with RMSD below 2.5 Å. Bottom: stretches of 20 ns where the peptide is completely unbound, meaning a minimum distance greater than 10 Å.

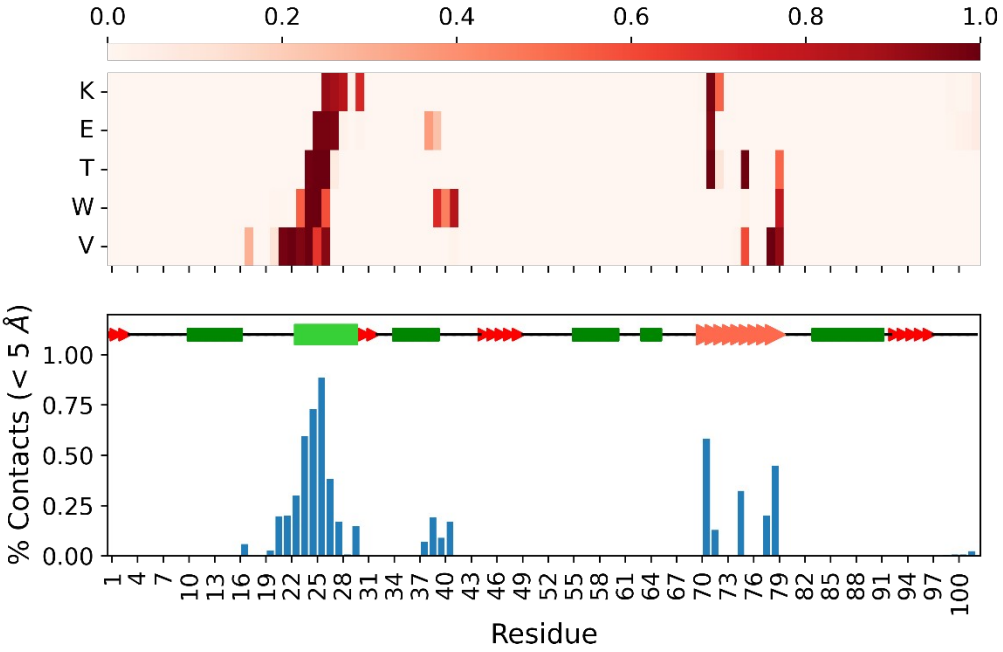


Figure S 9. Protein-peptide interactions in the bound state (u_1 < -0.912) Top: peptide/PDZ3 contact map. Bottom: sequence profile of cumulative number of contacts. The bottom panel shows the sum of each column on the contact map.

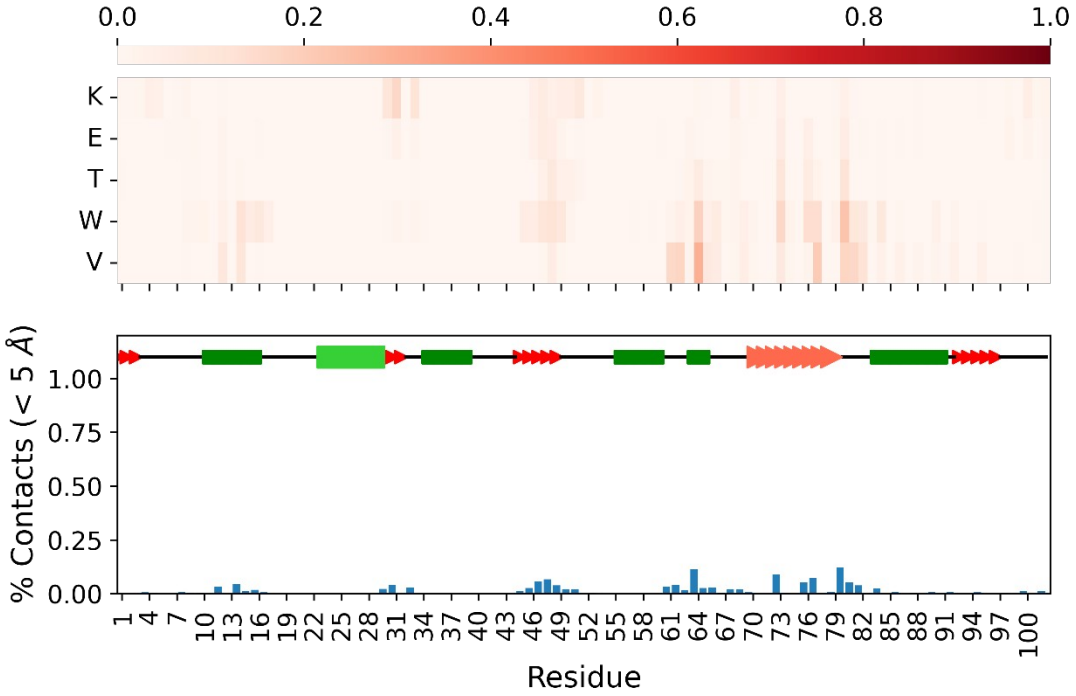


Figure S 10. Same as Figure S 9 for the non-natively bound sections of the trajectory, with 0.573 < u_1 < 0.621.

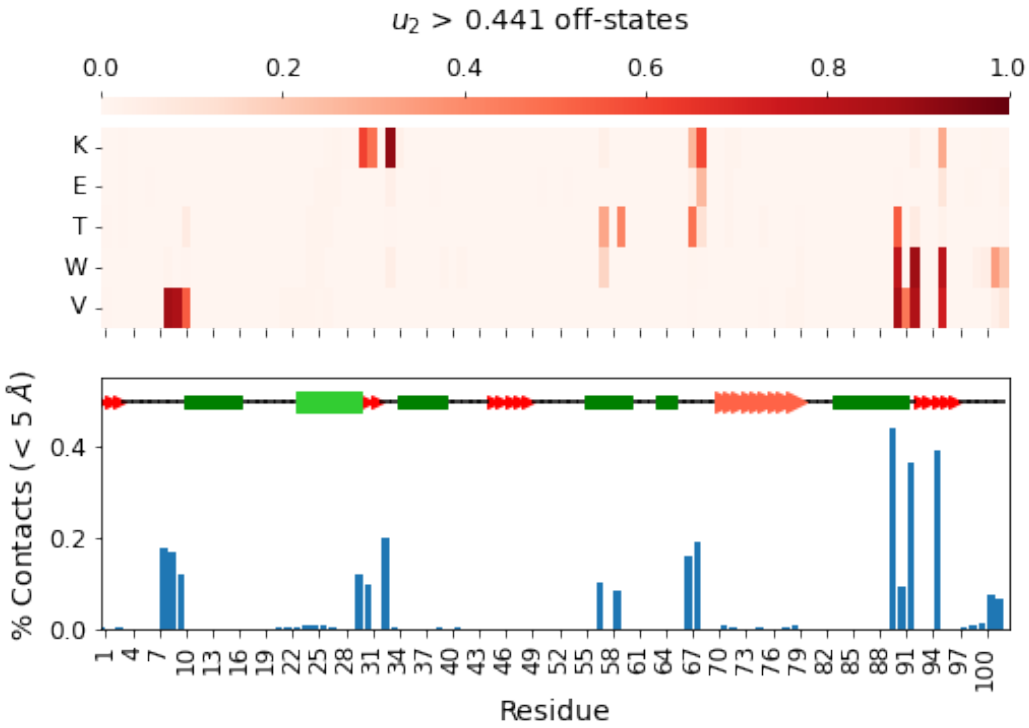


Figure S 11. Same as Figure S 9 for the u_2 > 0.441 off states. The basin consists of a nonnative association of the peptide to the C-terminal region of the protein.

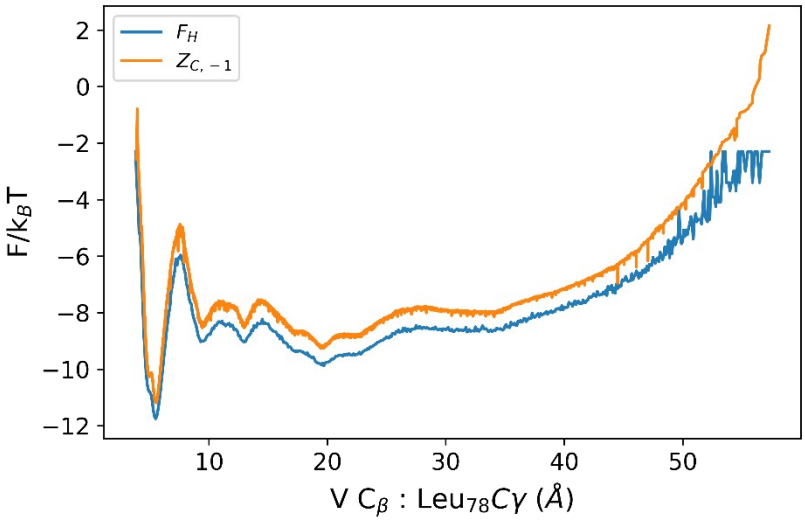


Figure S 12. Free Energy Profiles along peptide-protein distance Reaction Coordinate. Figure shows the histogram-based and cut-based free energy profiles of the trajectory along the distance between the V C_β and the Leu78 C_γ atoms. Both profiles show that the main barrier is around a distance of 8 Å, in consistence with the profile shown by [20].

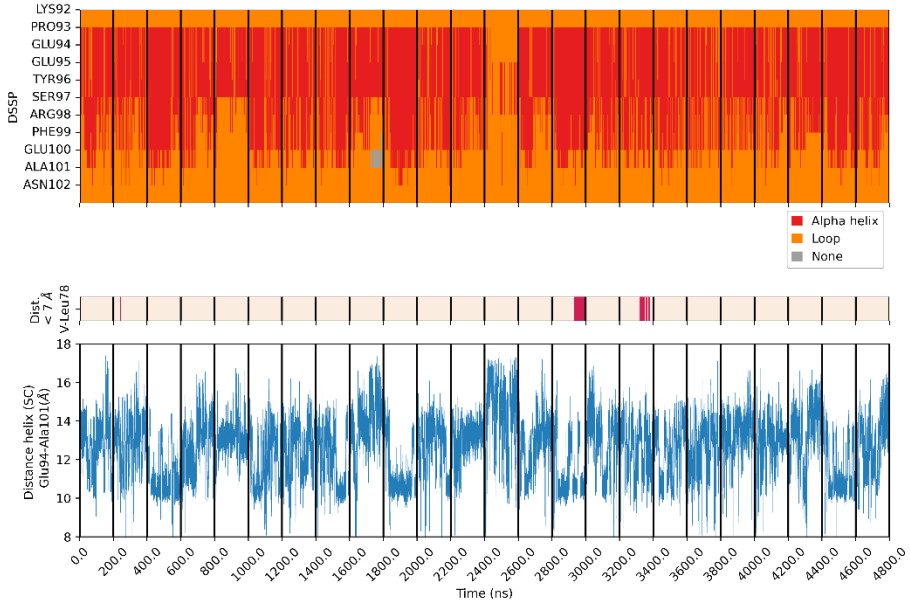


Figure S 13. Structural features of Ile37Ala-PDZ3 simulations. First panel: *dssp* analysis of α3 helix region. Middle panel: V-Cβ to Leu78-Cγ distance, marker of peptide position, white (unbound) or pink (bound). Last panel: Glu94-Ala101 distance

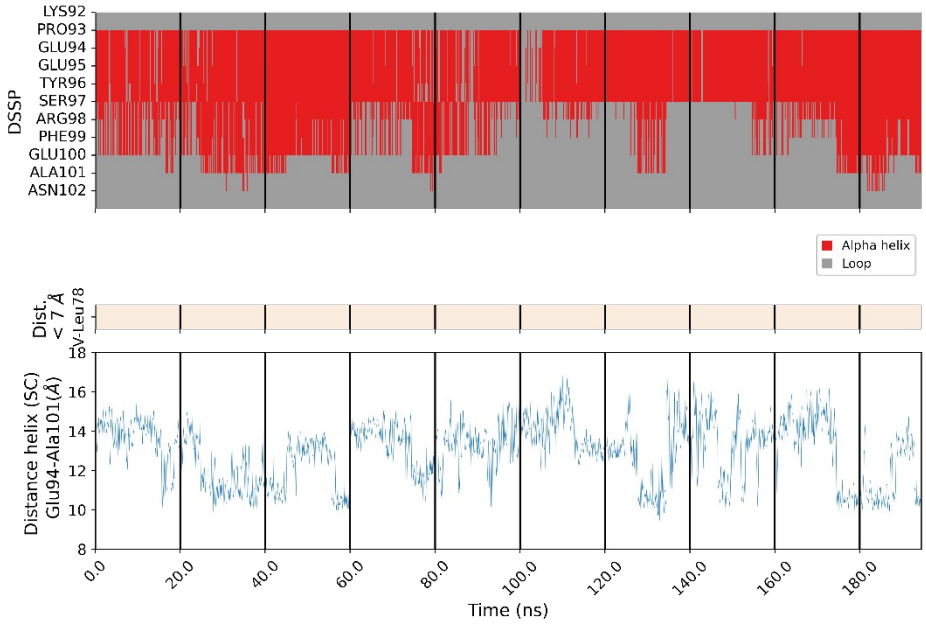


Figure S 14. Structural features of C-terminal region of WT PDZ3 unbound trajectory segments. Top panel: dssp analysis of C-terminal region. Middle panel: V-Cβ to Leu78-Cγ distance reporting on peptide unbound (white). Bottom panel: Glu94-Ala101 distance

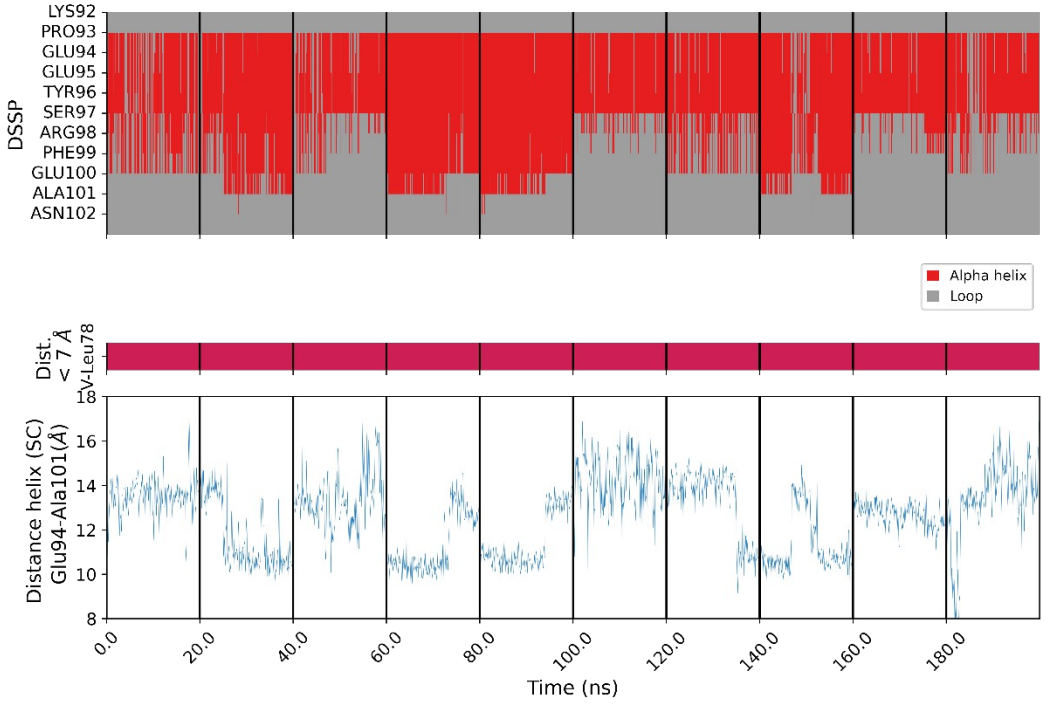


Figure S 15. Structural features of C-terminal region of WT PDZ3 bound trajectory segments. Top panel: dssp analysis of C-terminal region. Middle panel: V-Cβ to Leu78-Cγ distance reporting on peptide bound (red). Bottom panel: Glu94-Ala101 distance