Electronic Supplementary Material (ESI) for RSC Advances.

Supplementary Information for *Unsupervised Deep Learning for Molecular Dynamics Simulations: A Novel Analysis of Protein-Ligand Interactions in SARS-CoV-2 Mpro*

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Kenji Yasuoka, Alfonso Gautieri, and Noriyoshi Arai

Additional Figures

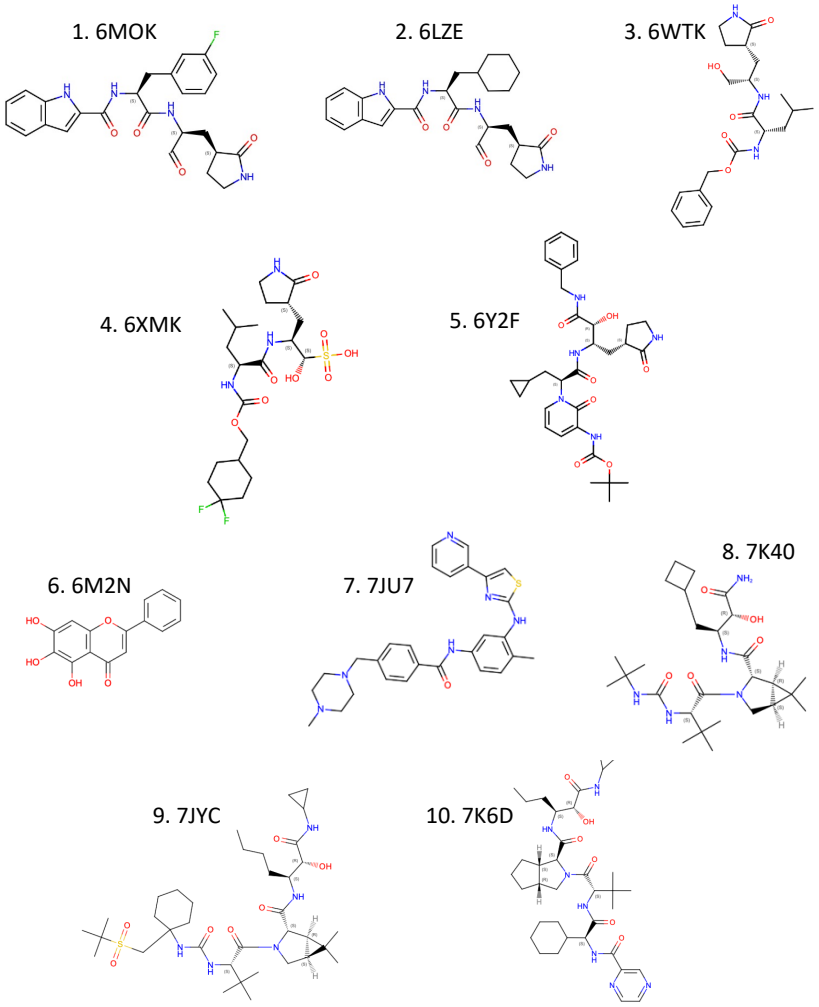


Figure S1: Chemical structure of the ligands. Compounds are labeled with Arabic numerals in descending order of affinity.

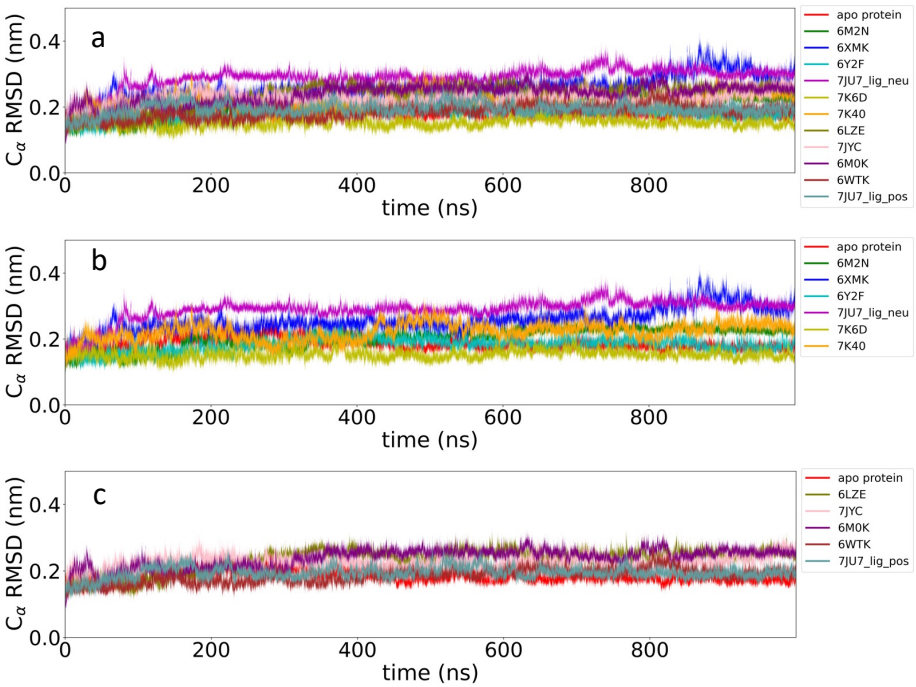


Figure S2: **a** Root mean squared deviation (RMSD) of the protein backbone in the first 1 µs molecular dynamics (MD) simulation for the 12 systems. In figure **b** and **c** the protein-ligand systems have been split for a more clear representation

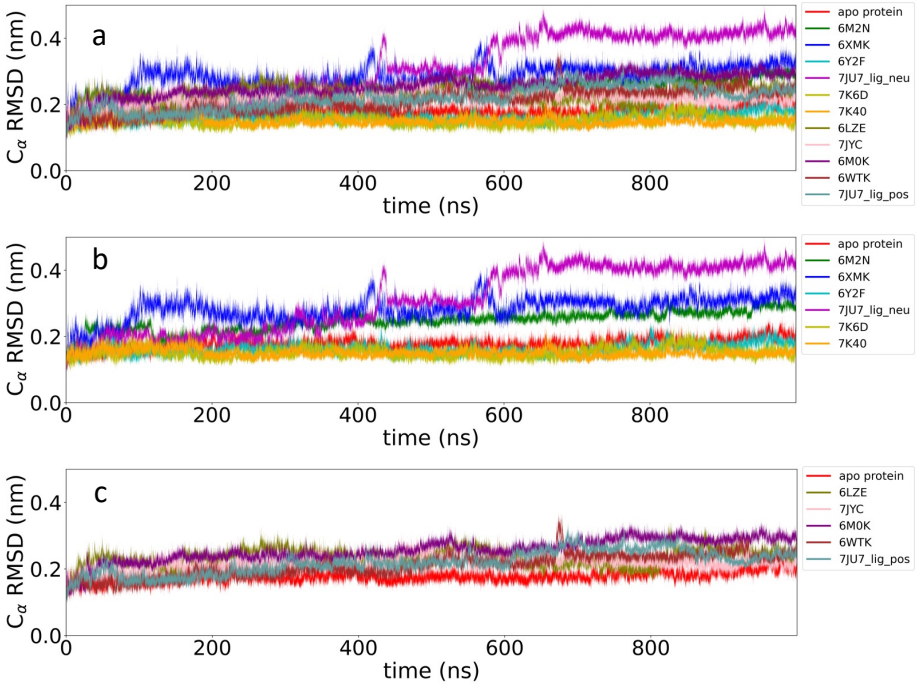


Figure S3: **a** Root mean squared deviation (RMSD) of the protein backbone in the second 1 µs molecular dynamics (MD) simulation for the 12 systems. In figure **b** and **c** the protein-ligand systems have been split for a more clear representation

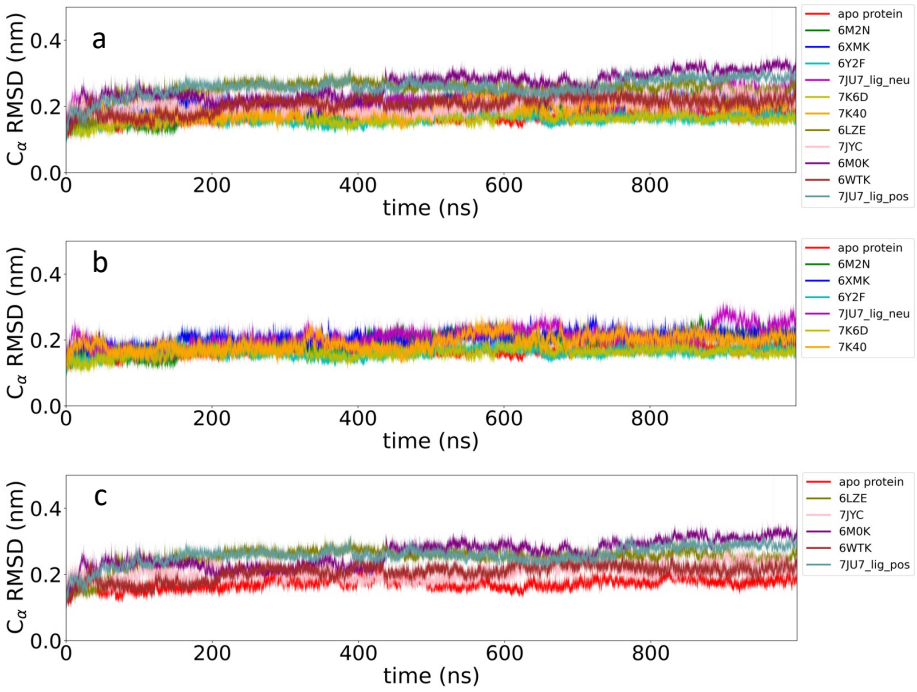


Figure S4: **a** Root mean squared deviation (RMSD) of the protein backbone in the third 1 µs molecular dynamics (MD) simulation for the 12 systems. In figure **b** and **c** the protein-ligand systems have been split for a more clear representation

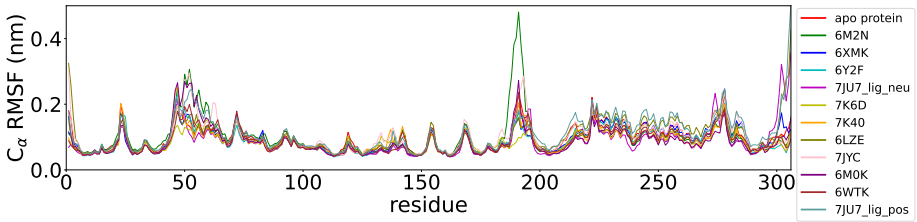


Figure S5: Residue-based root mean squared fluctuation (RMSF) of the protein backbone averaged between monomer A and monomer B in the second 1 µs MD simulation for the 12 systems.

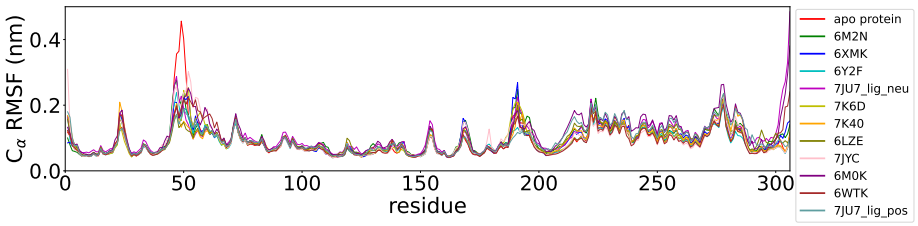


Figure S6: Residue-based root mean squared fluctuation (RMSF) of the protein backbone averaged between monomer A and monomer B in the third 1 µs MD simulation for the 12 systems.

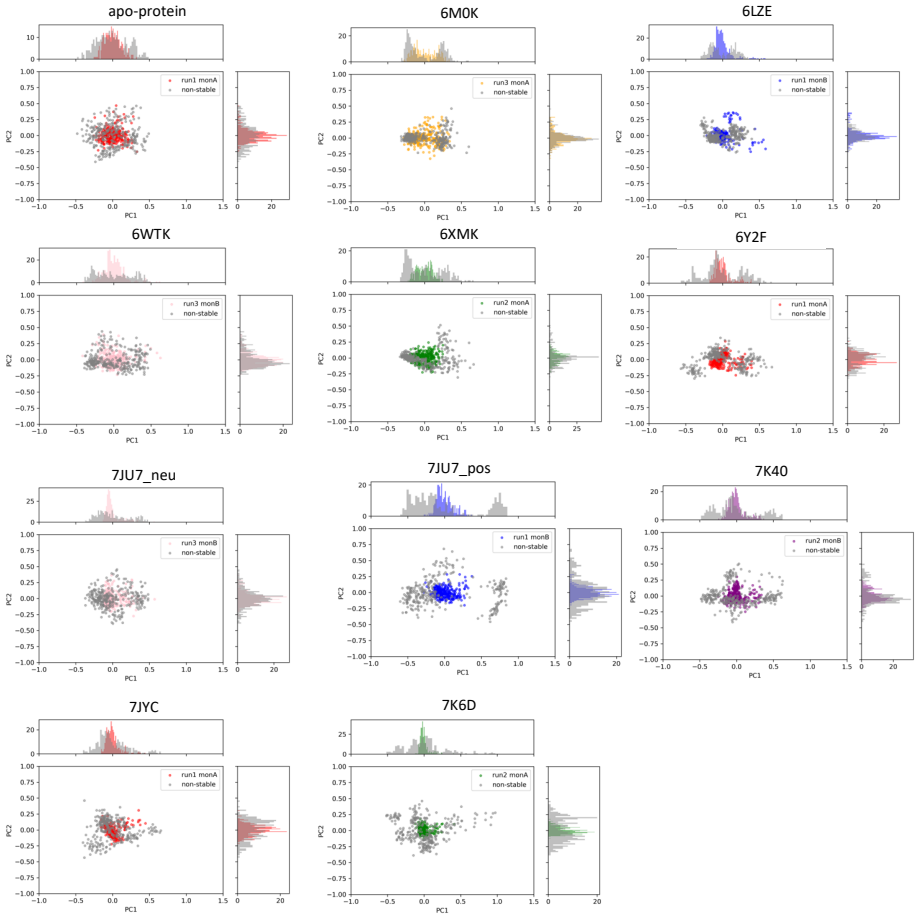
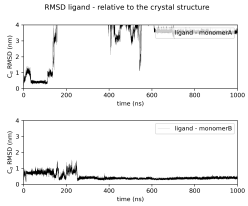
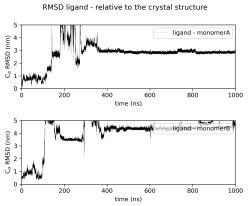


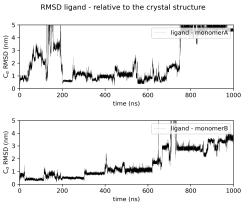
Figure S7: PCA plots of the stable-structure data selected for the generation of the LDEs. In grey, PCA plots of non-stable-structure data for comparison.



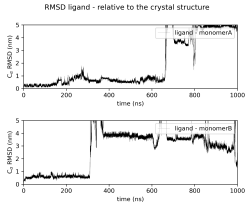
(a) RMSD ligand 6M2N run 1



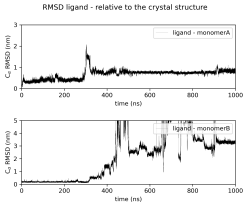
(b) RMSD ligand 6M2N run 2



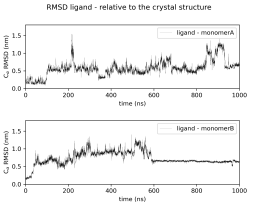
(c) RMSD ligand 6M2N run 3



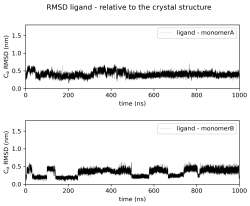
(d) RMSD ligand 6XMK run 1



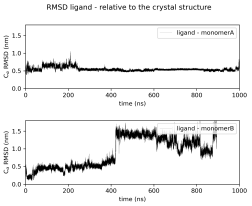
(e) RMSD ligand 6XMK run 2



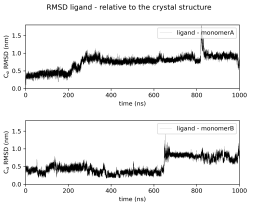
(f) RMSD ligand 6XMK run 3



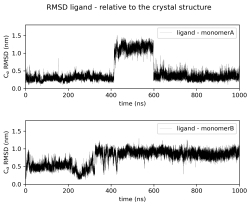
(g) RMSD ligand 6Y2F run 1



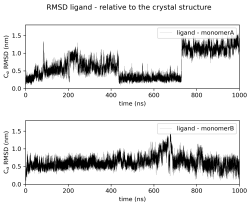
(h) RMSD ligand 6Y2F run 2



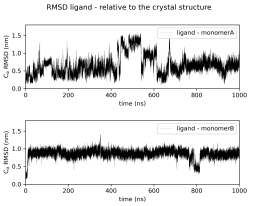
(i) RMSD ligand 6Y2F run 3



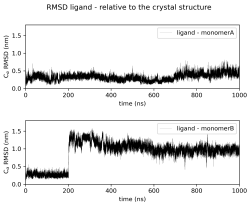
(j) RMSD ligand 7JU7pos run 1



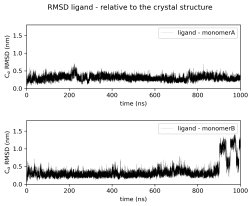
(k) RMSD ligand 7JU7pos run 2



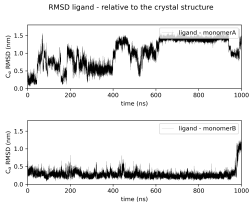
(l) RMSD ligand 7JU7pos run 3



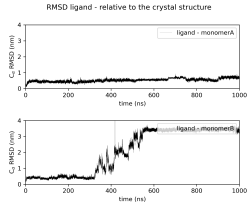
(a) RMSD ligand 7JU7neu run 1



(b) RMSD ligand 7JU7neu run 2



(c) RMSD ligand 7JU7neu run 3



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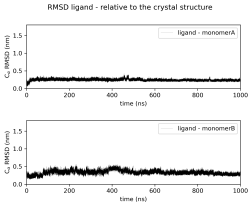

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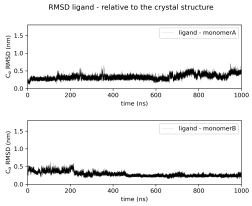
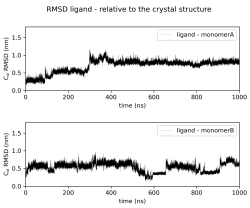
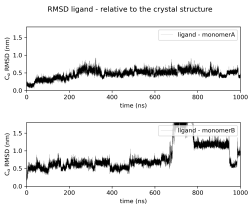


(f) RMSD ligand 7K6D run 3



(g) RMSD ligand 7K40 run 1



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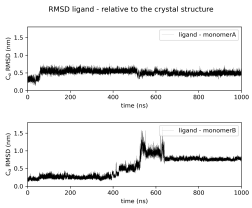

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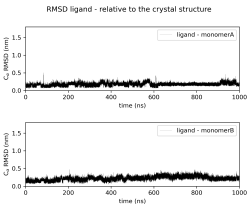

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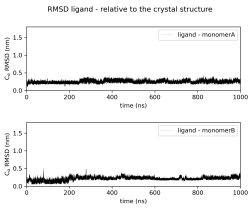
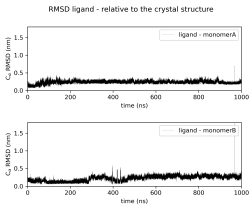


(k) RMSD ligand 6LZE run 2



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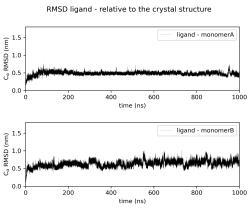
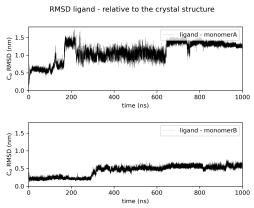
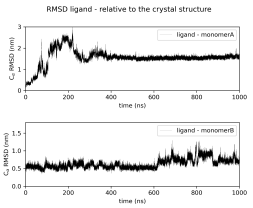


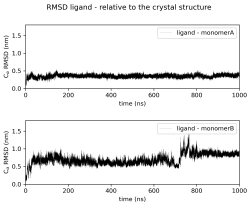
(a) RMSD ligand 7JYC run 1



(b) RMSD ligand 7JYC run 2



(c) RMSD ligand 7JYC run 3



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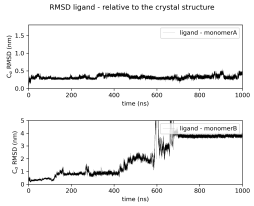
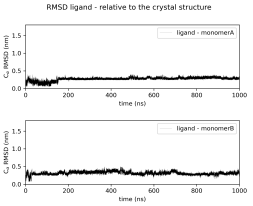
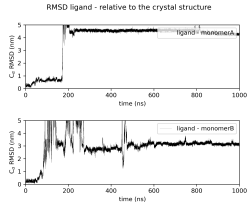


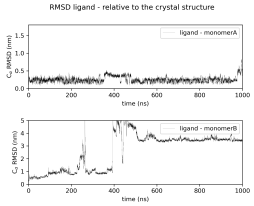
(e) RMSD ligand 6M0K run 2



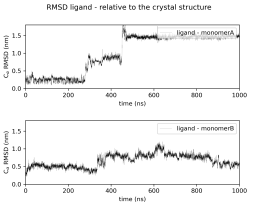
(f) RMSD ligand 6M0K run 3



(g) RMSD ligand 6WTK run 1



(h) RMSD ligand 6WTK run 2



(i) RMSD ligand 6WTK run 3

Figure S8: Ligand RMSD for the 11 systems (vertical) in the three MD simulations (horizontal): movement of the ligand relative to the main protein.

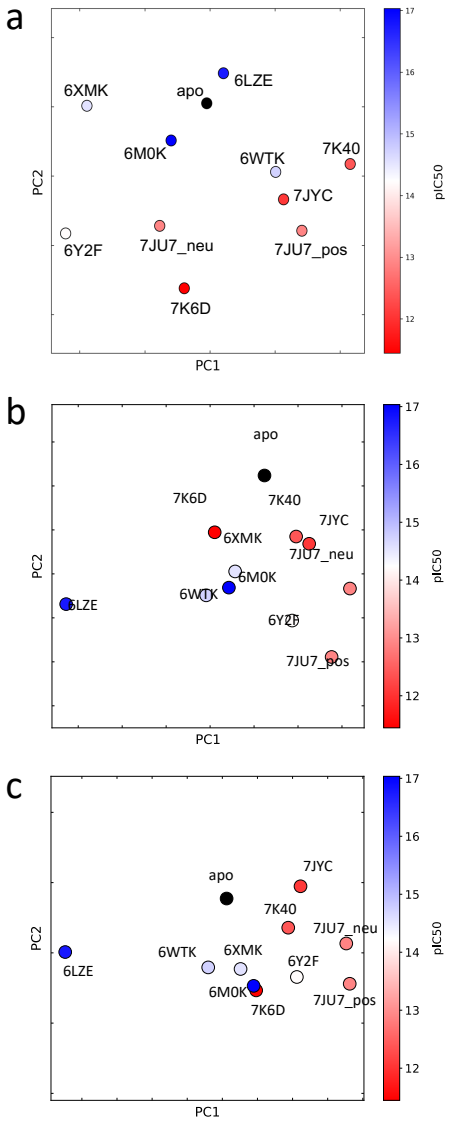


Figure S9: **a** Embedded points of the distance matrix using as input the time-series displacements of residue–pocket center distance **b** Embedded points of the distance matrix using as input the time-series residue–pocket center xyz displacement **c** Embedded points of the distance matrix using as input the time-series displacements of residue–pocket center xyz displacement