KVFinderMD: a Python package to detect and describe binding sites in molecular dynamics trajectories

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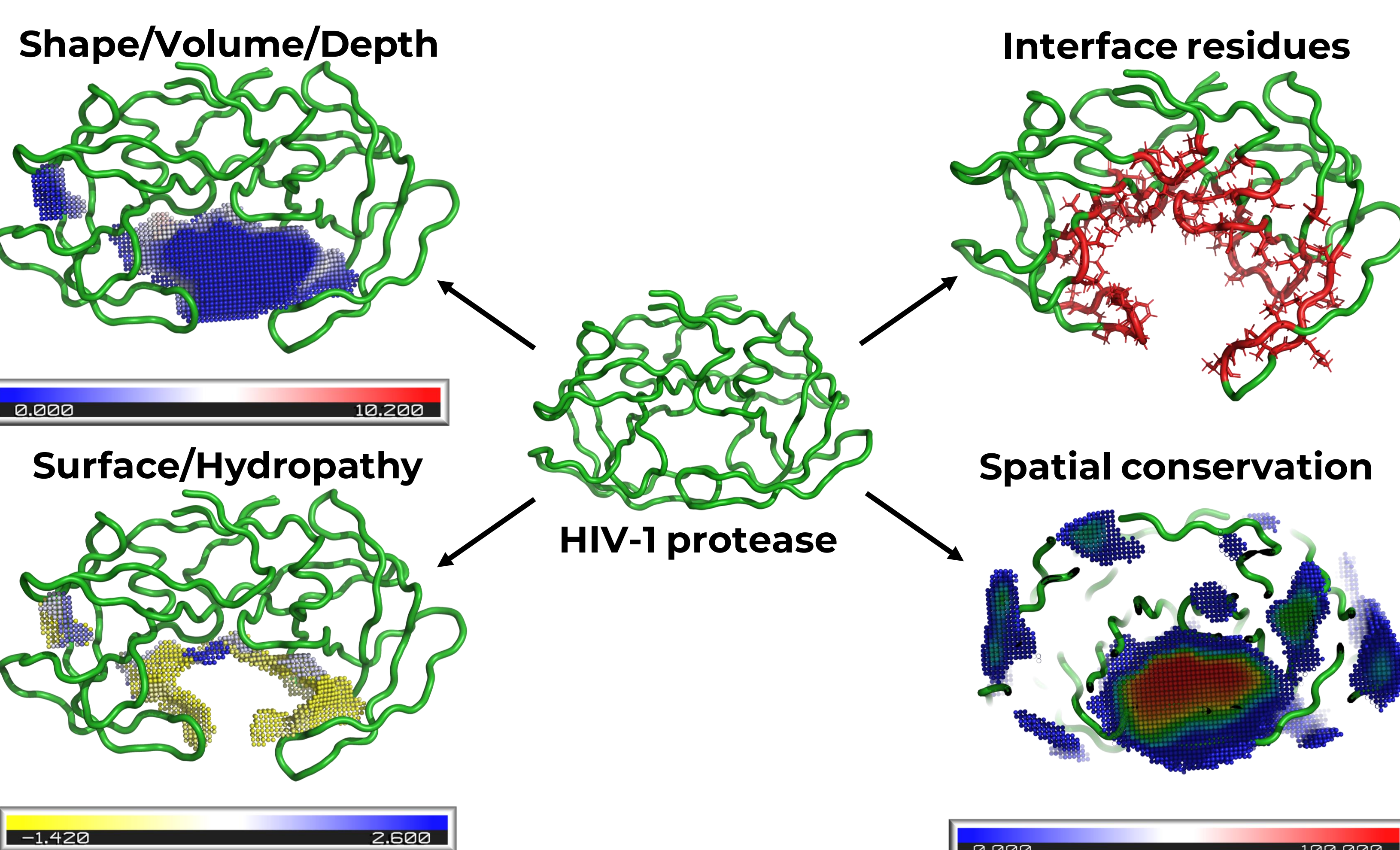
Background

Biomolecular interactions dictate many biological processes, which mainly occur by receptors interacting with other molecules. These ligands usually interact in specific binding sites formed by cavities. The protein-protein and protein-ligand interactions rely on the intrinsic dynamics of the target receptor, in which the classical lock and key model fails, and more recent binding models, e.g., conformational selection and induced-fit, thrive [1]. Thus, molecular dynamics (MD) is applied to understand the biomolecular function.

Lock and key

Induced Fit

Conformational selection
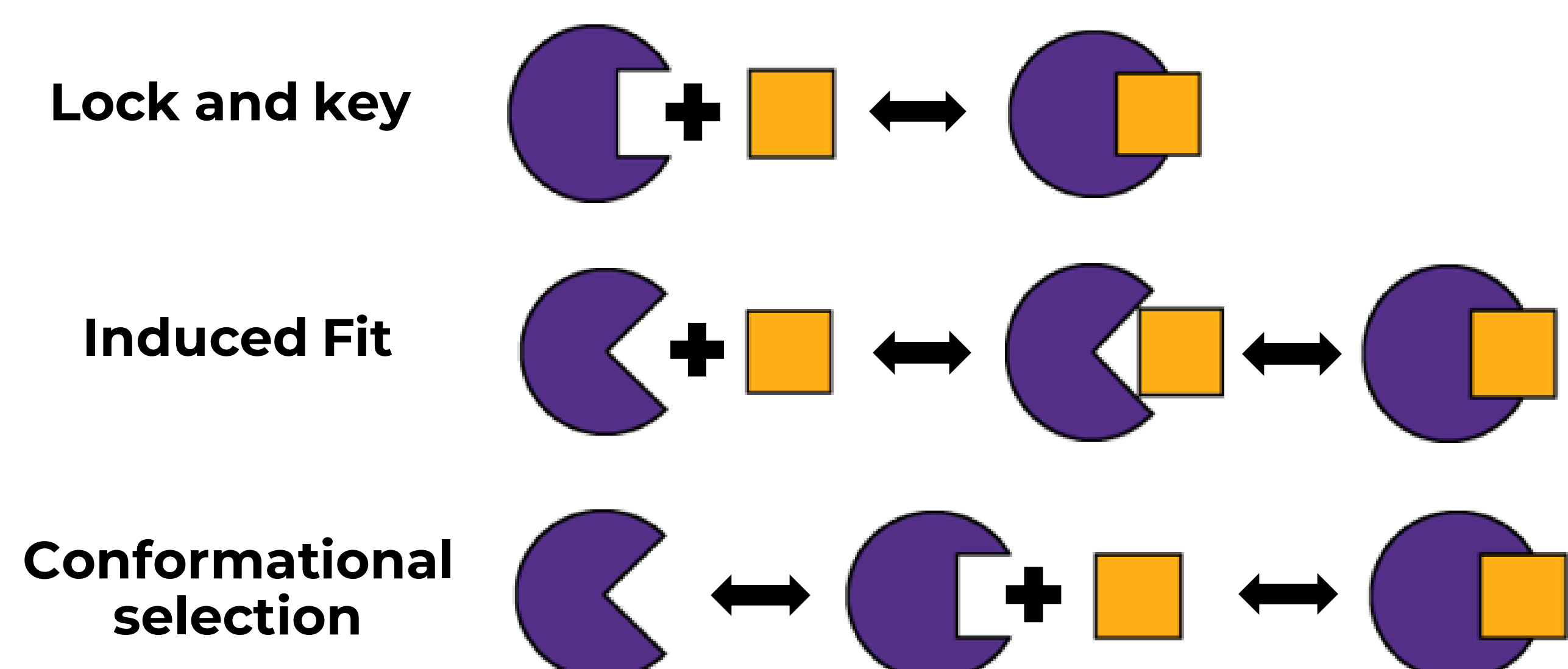
Methodology

Using pyKVFinder, recently developed by our group, as a building block, we developed <u>KVFinder</u> for <u>M</u>olecular <u>D</u>ynamics analysis (KVFinderMD), to explore binding site dynamics in biomolecular structures of interest. Since the intrinsic MD may change characteristics over time, KVFinderMD describe cavities in respect to:
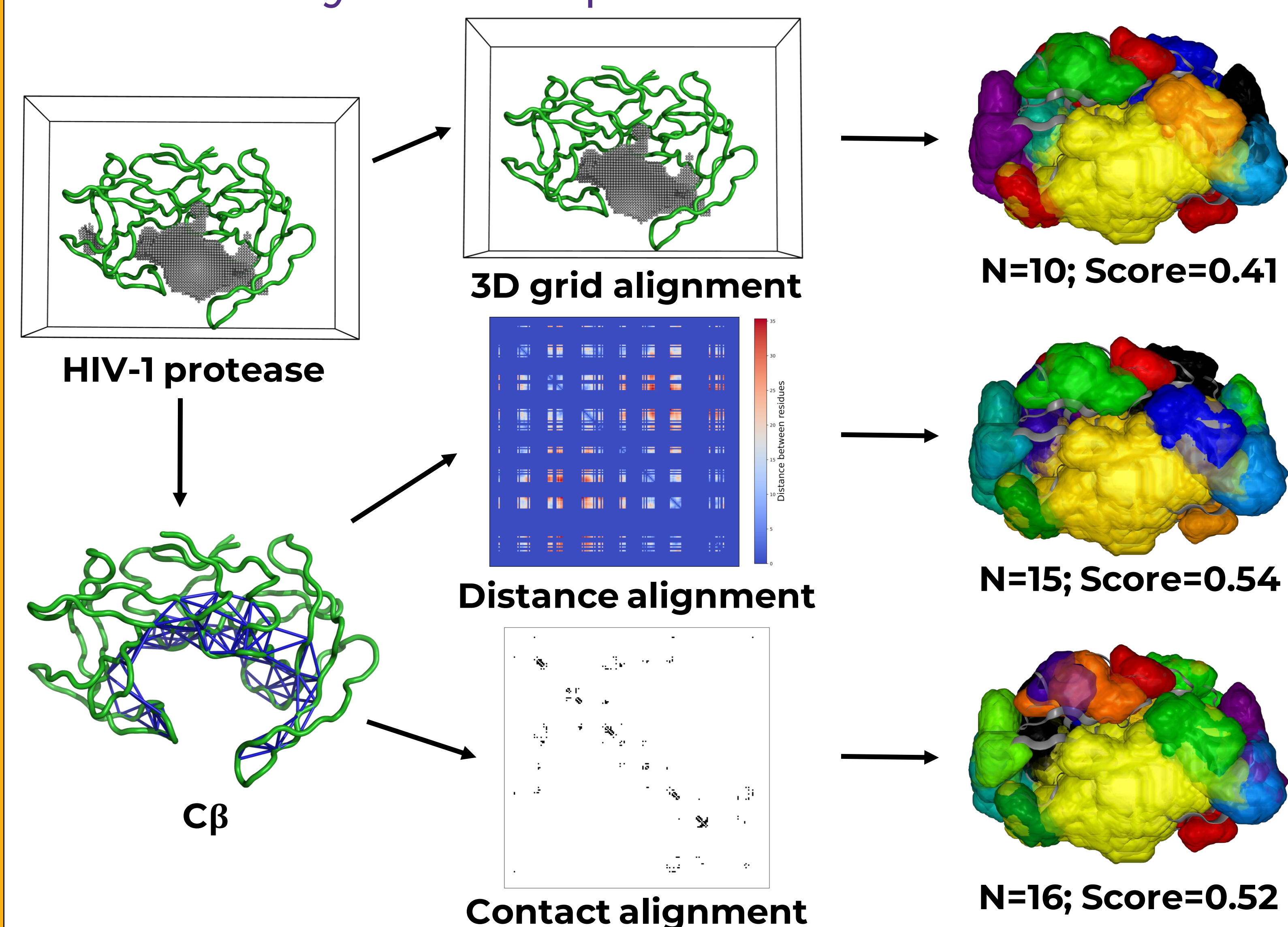
Shape/Volume/Depth

0.000   10.200

Surface/Hydropathy

−1.420   2.600

HIV-1 protease

Interface residues

Spatial conservation

0.000   100.000

Besides that, we also implemented a graph-based algorithm that considers distances from Cα, Cβ or any atom to topologically describe the binding site.
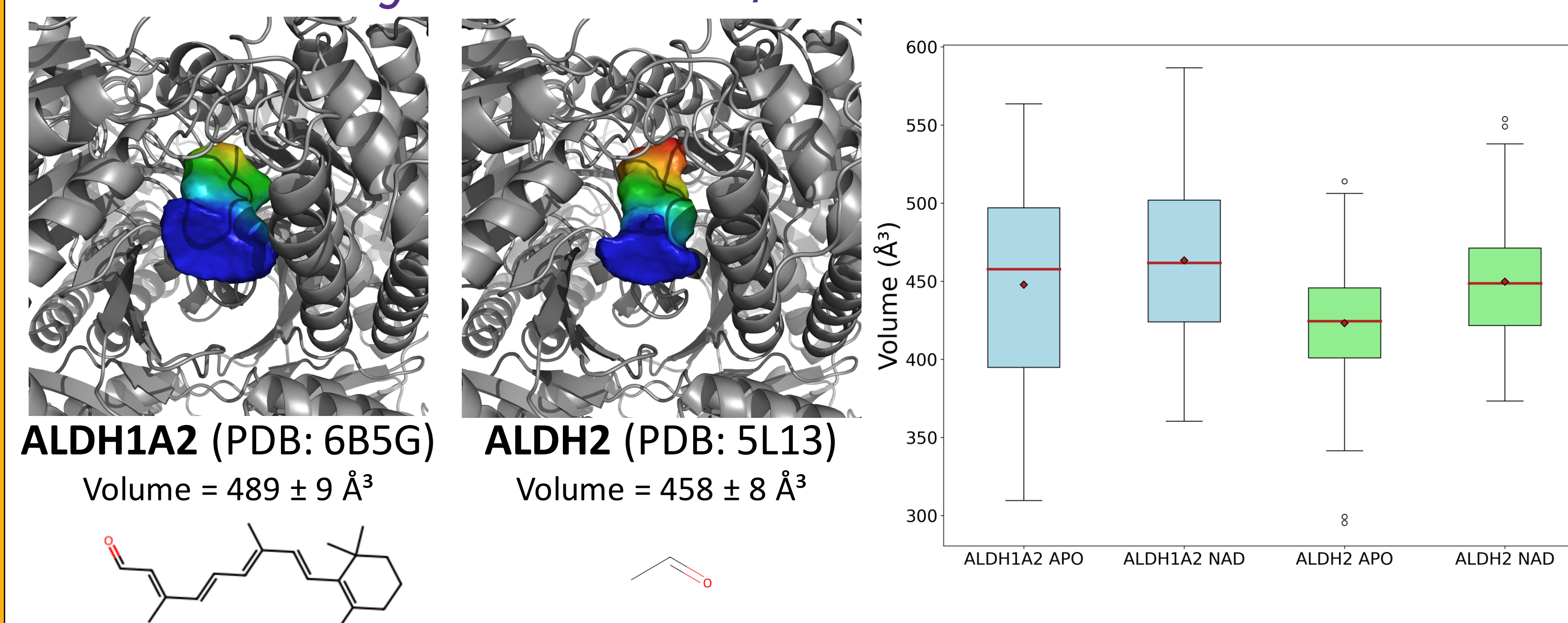
Cα   **Cβ**   **Any atom**
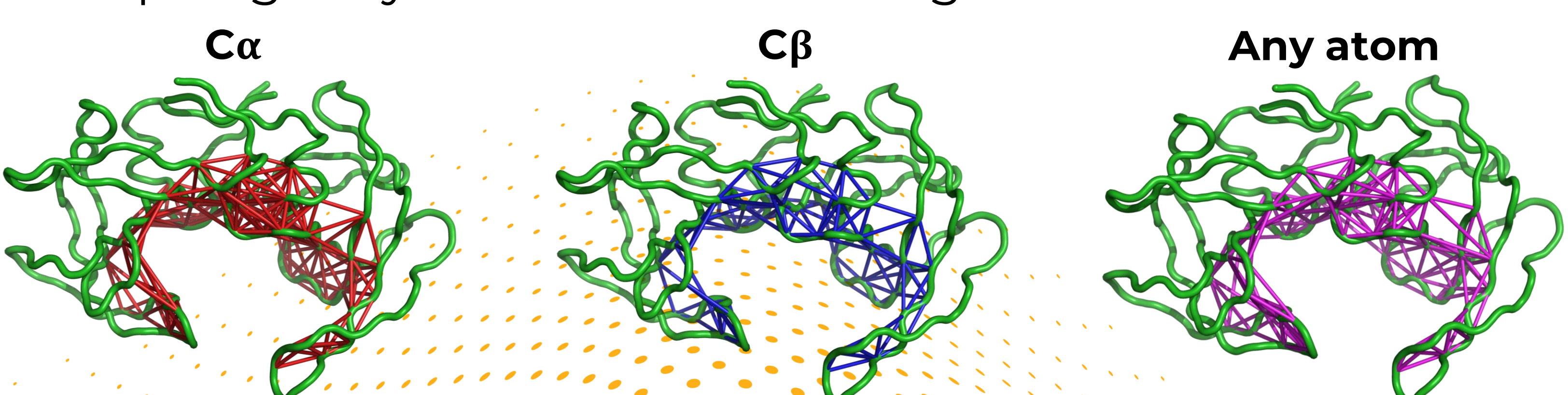
Results & Discussion

As case studies, we applied KVFinderMD with important therapeutic targets, i.e., HIV-1 protease [3] and ALDH1/2 [4].

Case study I: HIV-1 protease

HIV-1 protease

3D grid alignment

N=10; Score=0.41

Distance alignment

Distance between residues

N=15; Score=0.54

Cβ

Contact alignment

N=16; Score=0.52

Case study II: ALDH 1/2

ALDH1A2 (PDB: 6B5G)
Volume = 489 ± 9 Å³

ALDH2 (PDB: 5L13)
Volume = 458 ± 8 Å³

Volume (Å³)

ALDH1A2 APO   ALDH1A2 NAD   ALDH2 APO   ALDH2 NAD

Conclusion

We successfully developed a useful tool to describe the molecular dynamics of binding sites in biomolecular structures of relevant therapeutic targets, e.g., HIV-1 protease and ALDH 1/2.

References

[1] Holyoak, T. Molecular Recognition: Lock-and-Key, Induced Fit, and Conformational Selection. Encyclopedia of Biophysics 1584–1588 (2013)

[2] Guerra, J. V. da S. et al. pyKVFinder: an efficient and integrable Python package for biomolecular cavity detection and characterization in data science. BMC Bioinformatics vol. 22 (2021).

[3] Guerra, J. V. da S. et al. ParKVFinder: A thread-level parallel approach in biomolecular cavity detection. SoftwareX vol. 12 100606 (2020).

[4] Sobreira, T. J. P. et al. Structural shifts of aldehyde dehydrogenase enzymes were instrumental for the early evolution of retinoid-dependent axial patterning in metazoans. PNAS. vol. 108 226–231 (2010).

Acknowledgments

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