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Leveraging Zernike polynomials for peptide conformer identification

Diego Amaya-Ramirez, Bernard Maigret, Etienne Corman, Jean-Luc Taupin,
Marie-Dominique Devignes

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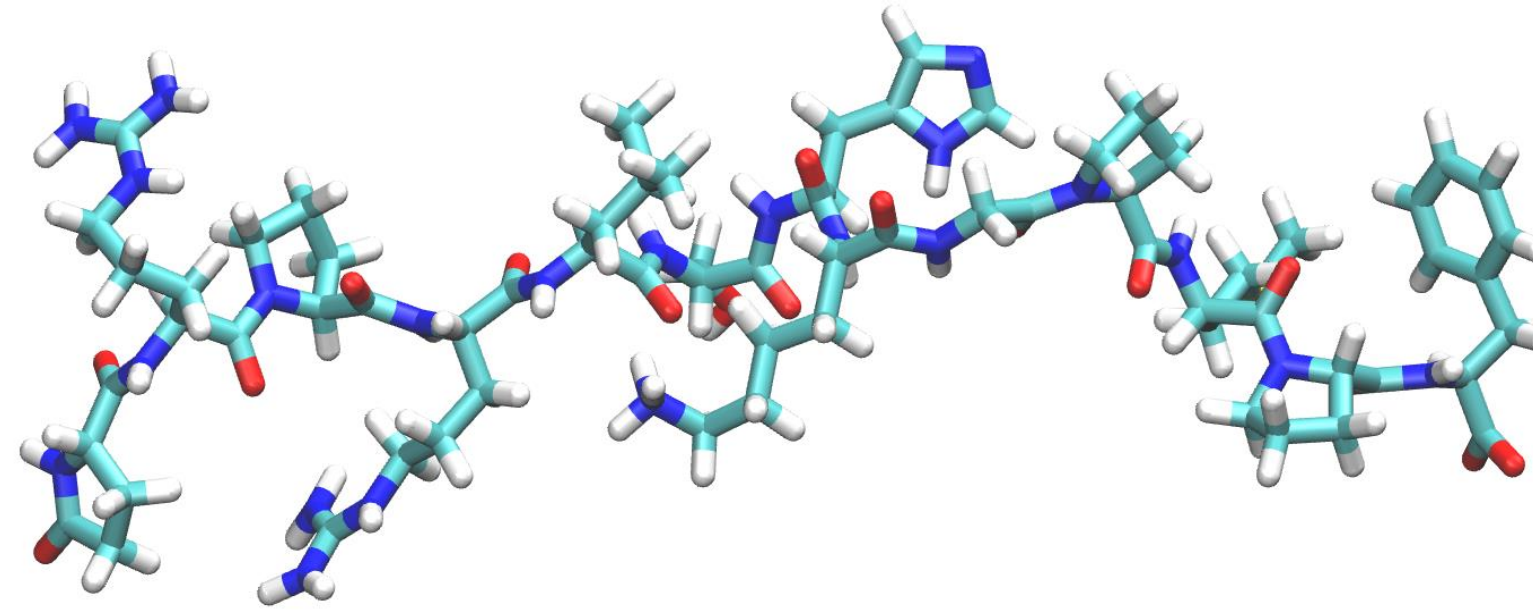
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Introduction

Peptides play a key role in multiple biological processes. For this reason, peptides have gained relevance in recent years as pharmacological agents¹. However, peptides are highly flexible leading to diverse three-dimensional (3D) conformers that can modify their specificity and efficacy in binding to their targets. Identifying and understanding such 3D-conformers is therefore fundamental. This can be achieved by analysis of molecular dynamics (MD) runs. However, classical methods such as RMSD maps are difficult to process automatically and manual interpretation can be subjective.

Materials and Methods



Peptide [Pyr1]apelin-13

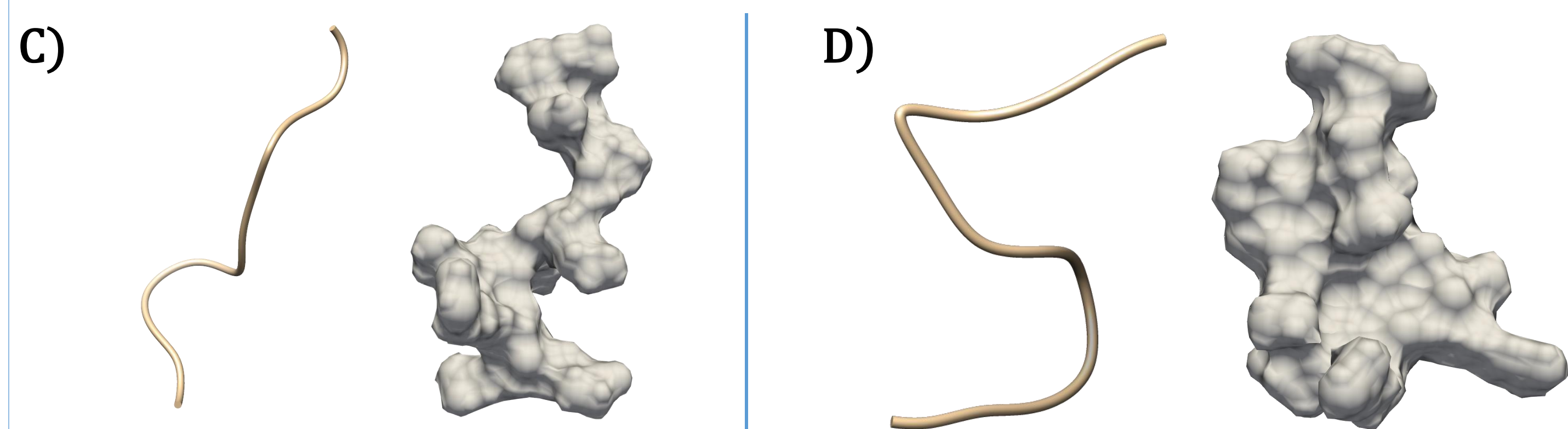
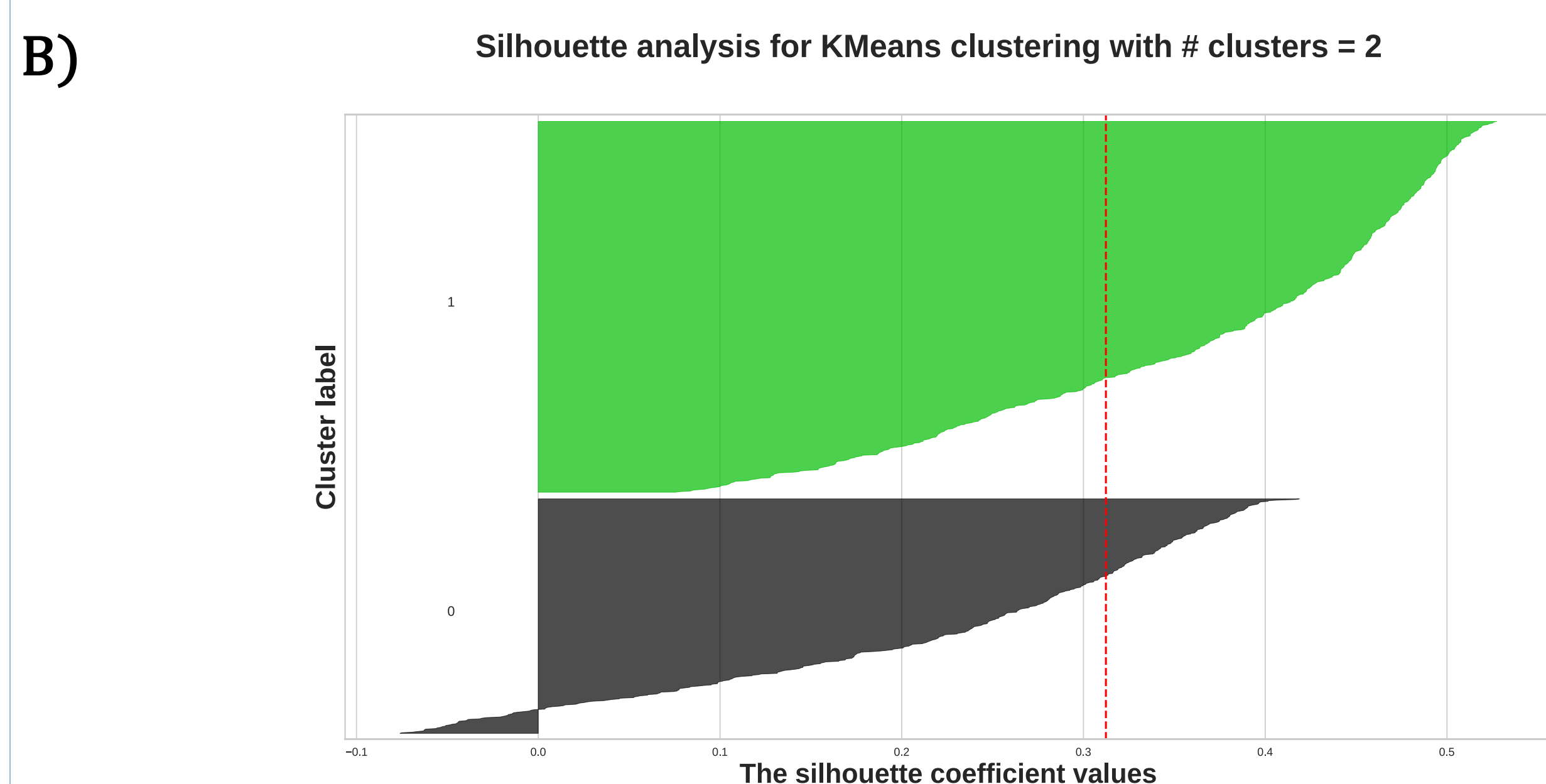
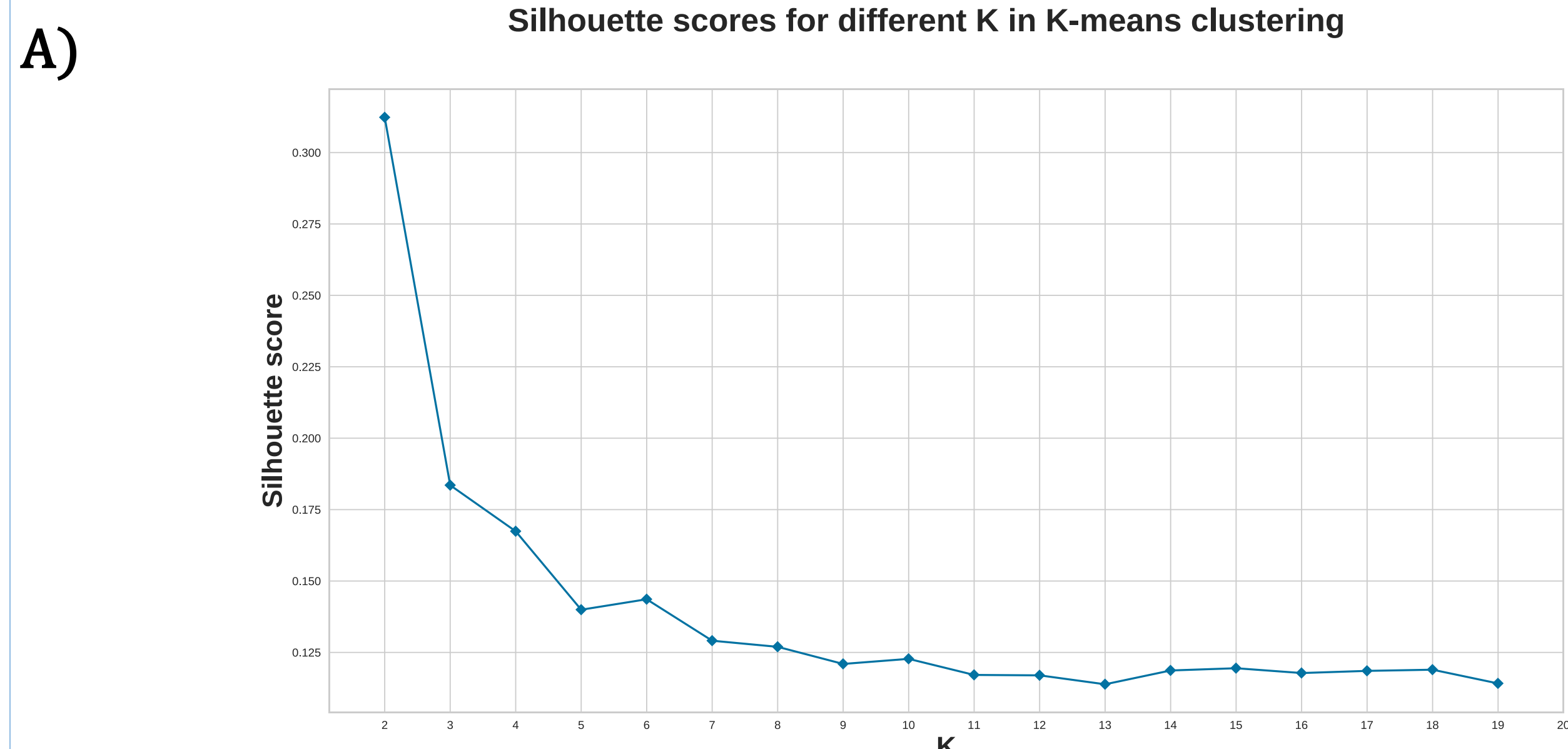
- Peptide [Pyr1]apelin-13² of sequence : pE-R-P-R-L-S-H-K-G-P-M-P-F.
- 1000 frames from a MD simulation of 100ns : using NAMD³, CHARMM36⁴ force field and TIP3P (Transferable Intermolecular Potential with 3 Points) explicit solvent model.

For each frame, a 3D Zernike descriptor^{5,6} is used to represent the 3D shape of the peptide as a vector of invariants representing a series of orthogonal polynomials. The 3D shape is the solvent-accessible surface, constructed from the Van der Waals radius sphere associated with each atom type and obtained using Chimera⁷. The MindBoggle⁸ python library is then adapted to calculate the 3D Zernike descriptor relying on 121 invariants.

Conformer identification is performed by clustering the previously calculated 3D Zernike descriptors, using the K-means and silhouette analysis algorithms to identify the optimal number of clusters. For each cluster, the conformation closest to its centroid is chosen as a representative.

Results

According to silhouette analysis, two main clusters are discernable. The representative conformers correspond to frames 748 and 840.



A) Silhouette scores for different number of clusters. B) Silhouette analysis for K-means clustering of 3D Zernike descriptors. The dashed line corresponds to the average silhouette score of 0,312. C) Backbone (on the left) and surface (on the right) visualization of the representative conformer for the Cluster #0 (frame 840). D) Backbone (on the left) and surface (on the right) visualization of the representative conformer for the Cluster #1 (frame 748).

Conclusion

The 3D Zernike descriptors have already been used for protein tertiary structure comparison but to our knowledge, not to identify 3D-conformers from MD runs. The Zernike vector format allows using a variety of clustering methods to process MD frames and to automatically determine the optimal number of clusters/conformers. This strategy could be promising for other biomolecules such as proteins or nucleic acids.

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