Zernike3Deep: Combining classic analytics and deep learning for flexibility analysis and resolution enhancement

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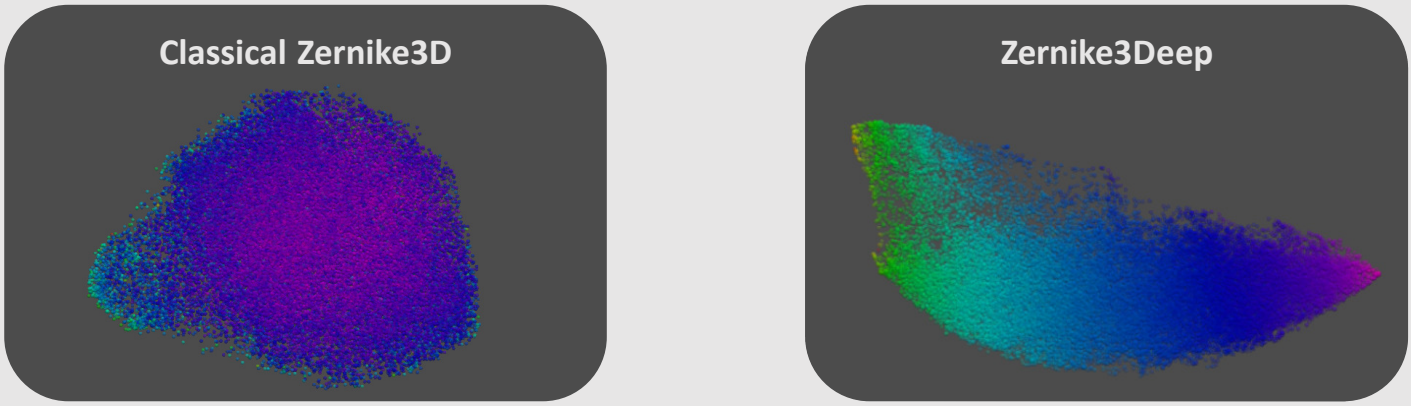
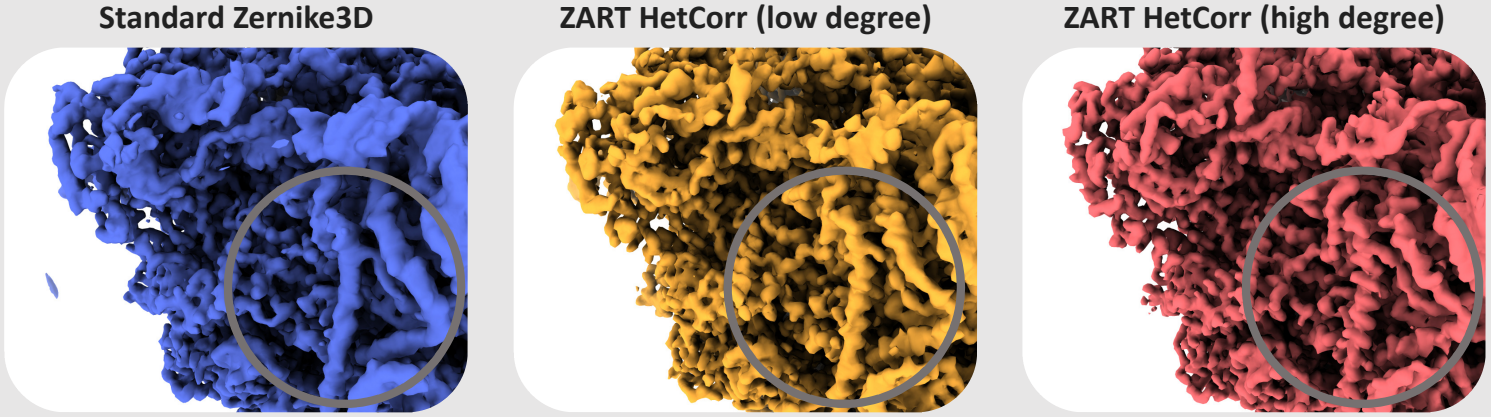
(a)



(b)



Introduction

- Conformational variability analysis supposes a significant step in the understanding of how macromolecular structure and function meet
- In our previous works [1,2] we introduced the Zernike3D method, a versatile tool to estimate molecular motions from CryoEM particles
- Here we present the extension of the Zernike3D basis into the deep learning, combining the strengths of classical and AI worlds into a semi-classical neural network for flexibility analysis

Methods

- The Zernike3Deep neural network is designed following an autoencoder architecture able to learn how to produce meaningful expansions of functions into the Zerniike3D basis
- Therefore, only the encoder becomes an optimization black box. The latent space and the physical decoder follow classical principles so that they can take advantage of the Zernike3D basis properties and applications

Zernike3Deep vs Zernike3D

- Zernike3Deep produces more meaningful expansions in the Zernike3D basis thanks to the advanced optimization algorithms applied in Deep Learning applications as shown in **(a)**
- Zernike3Deep can recover better missing information along the projection direction compared to classical Zernike3D
- Zernike3Deep coefficients can be further refine by the per-particle conformational search that characterizes the classical Zernike3D approach to improve accuracy
- Zernike3Deep performance improvements allows for estimating larger basis degrees with almost no impact on execution times
- Improved Zernike3D expansions in combination with ZART flexible refinement leads to improved heterogeneity corrected maps as shown in **(b)** (even in cases of significant blurring)
- Zernike3Deep conformational search can be coupled with structural models, particle pose refinements...

ZART flexible refinement

- ZART heterogeneity correction can now be applied into flexible refinement workflows
- Flexible refinements produce more meaningful conformational landscapes, and can improve resolution of areas with a significant level of motion blurring
- ZART performance has been greatly improved with its new GPU implementation (around 100x-1000x faster than the current CPU version)
- ZART GPU version allows for correcting more accurately estimated deformation fields **(b)**

References

1. D. Herreros, et al. IUCR J, 8: 992-1005 (2021)
2. D. Herreros, et al. Nat. Comm., 14: 154 (2023)
3. D. Herreros, et al. JMB, 9: 435 (2023)