# Fast reconstruction of 3D molecular structure from 2D covariance in cryo-EM

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## Goal

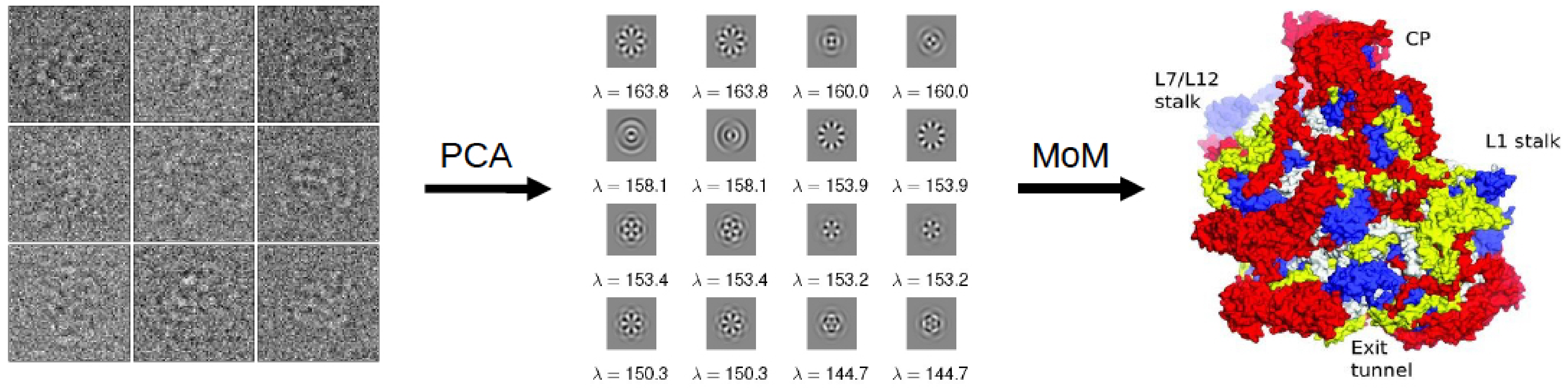
Estimating a 3D *ab initio* model for the molecular structure in cryo-EM. Main requirements are:

- Improving our ability to derive *ab initio* models for small particles via robustness to noise.
- Low computational cost (memory and storage space, complexity and size of data).

## Method of Moments (MoM)

- In the conventional maximum likelihood (ML) approach [1, 2], one iteratively finds a model by repeatedly scanning the data.
- Our method generalizes the method of moments [3, 4] rather than ML, as it requires just one pass over the data.
- In [3, 4], the viewing directions from which the projections are taken was assumed to be uniform. The uniformity assumption is used in an autocorrelation analysis to determine the 3D structure (from third moments).
- We propose a reconstruction procedure that uses the first and second moments of the images, exploiting ***non-uniformity*** of the distribution of viewing directions.
- We derive explicit formulas for the moments and observe that the first and second moments are quadratic and cubic functions of the distribution and the volume. Therefore, determining the volume from the moments is equivalent to solving a polynomial system.
- Non-uniformity assures enough independent equations.

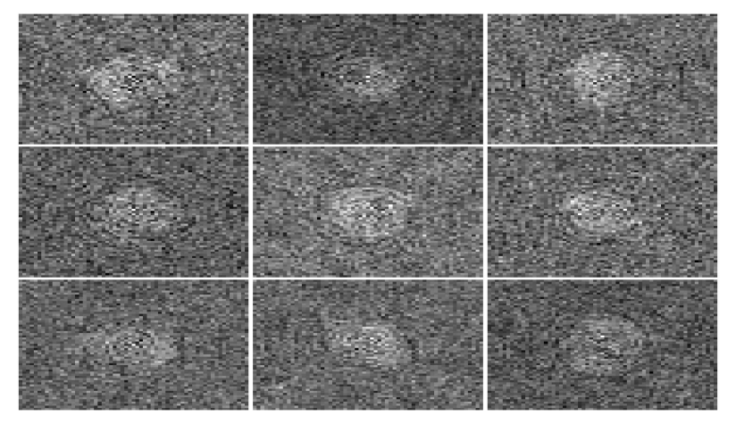
## Reconstruction Overview



## Demonstration of MoM

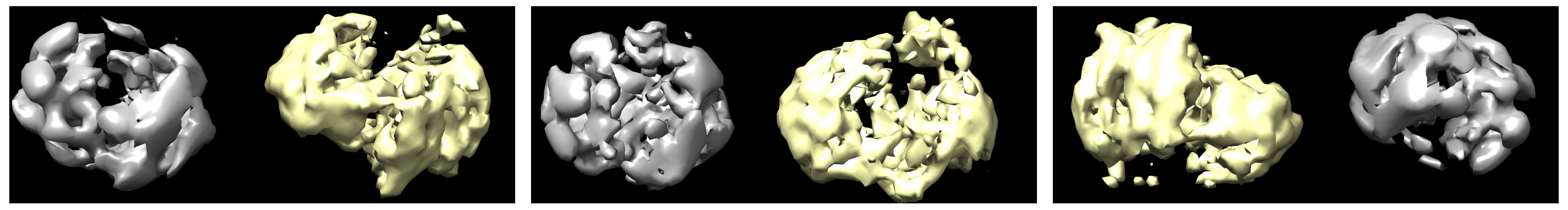
### Simulation

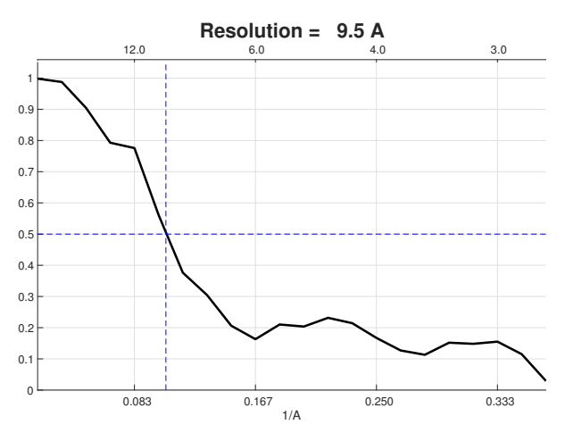
- Ground truth is EMD-4190 (Influenza C polymerase)
- 35k images, SNR $\approx 1/10$



### Results

Visual results using gradient-based optimization:





Estimated model is in gray, ground truth is in yellow.

FSC

The spatial correlation is 76%

## Conclusions

- Establishing an *ab initio* model without explicitly estimating the viewing directions is feasible and allows reconstruction in the low SNR region.
- Non-uniformity of the viewing directions enables 3D reconstruction via low-order statistics.
- The one-pass approach gives rise to ultra-fast reconstruction algorithms with running time mostly dependent on the desired resolution and not the number of images.
- Real data introduces further challenges. e.g., centering, software robustness, CTF denoising, which are being addressed to achieve the full potential of our method.

[1] Sigworth, F. J. *A maximum-likelihood approach to single-particle image refinement*, Journal of Structural Biology 122.3 (1998): 328-339.

[2] Scheres, S. H. *RELION: implementation of a Bayesian approach to cryo-EM structure determination*, Journal of Structural Biology 180.3 (2012): 519-530.

[3] Kam, Z. *The reconstruction of structure from electron micrographs of randomly oriented particles*, Journal of Theoretical Biology, vol. 82, no. 1, pp. 15-39, 1980.

[4] von Ardenne et. al. *Structure determination from single molecule X-ray scattering with three photons per image*, Nature Communications, 9(1), 2375, 2018.