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APPLE Picking: Particles without Templates

Joakim Andén[1], Ayelet Heimowitz[2], Amit Singer[2]

April 10, 2018

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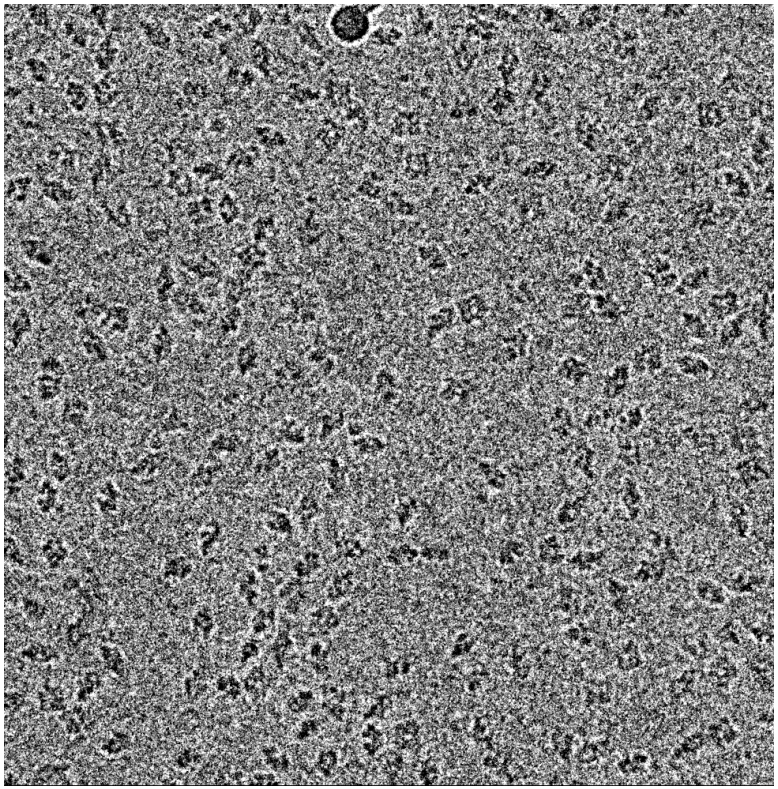
[2]Program in Applied and Computational Mathematics (PACM), Princeton University

Particle Picking in Cryo-EM



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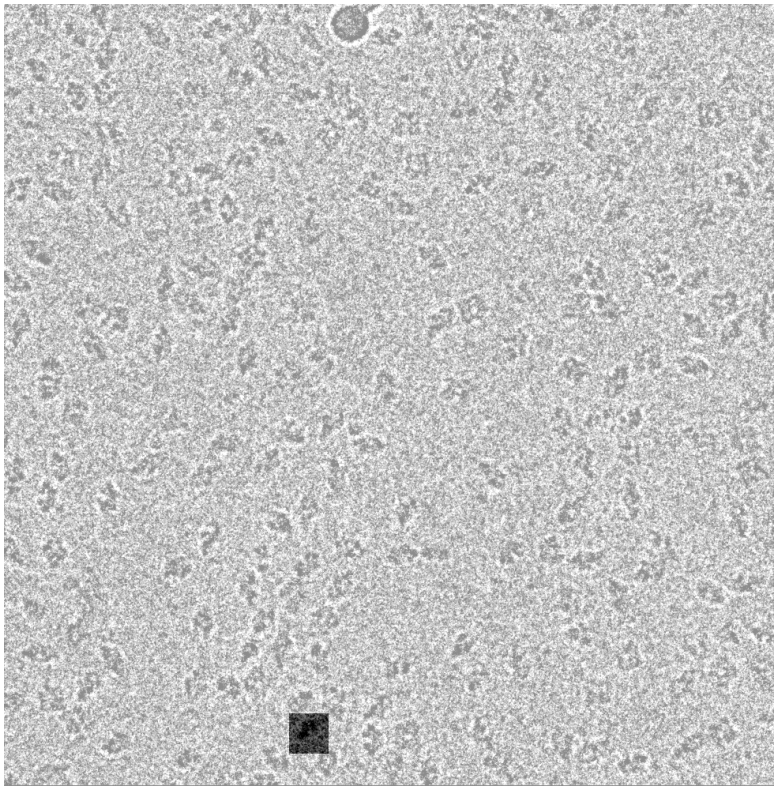

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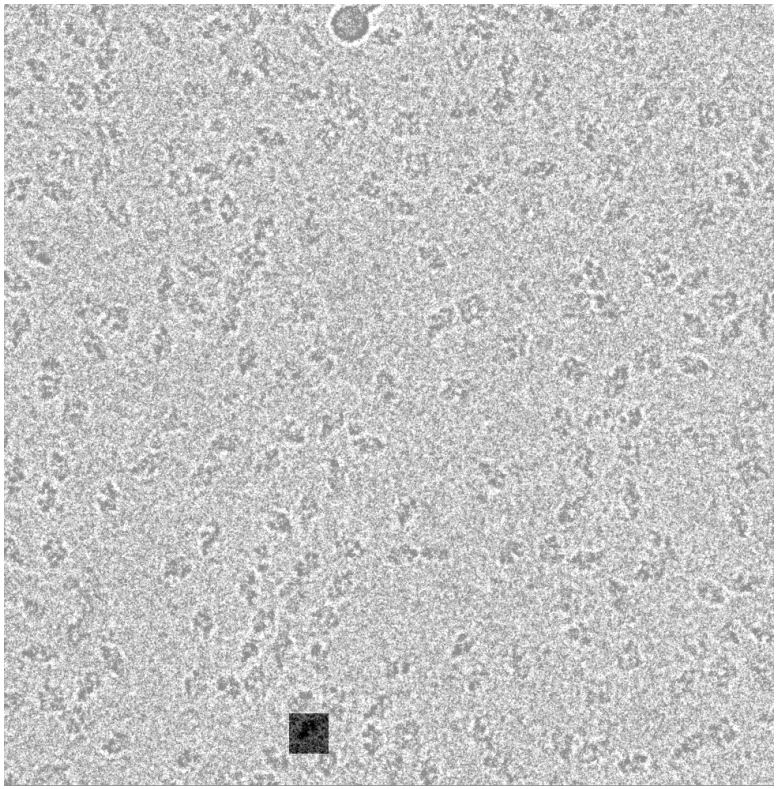

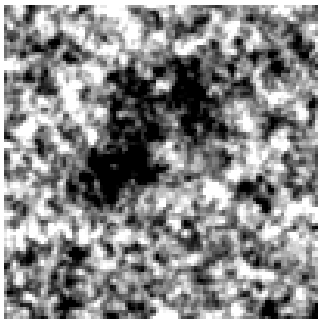

Template Matching

- Query window $f[n, m]$, template $g[n, m]$, cross-correlation:[1]

$$\max_{n,m} \sum_{n',m'} f[n - n', m - m']g[n', m']$$

[1] Frank & Wagenknecht, 1983

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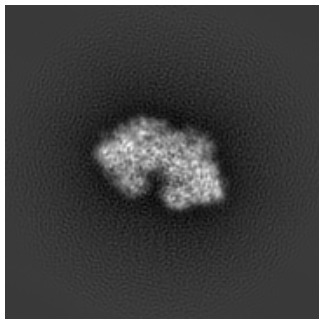

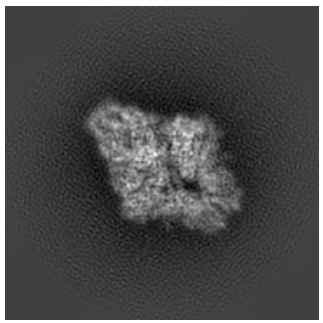

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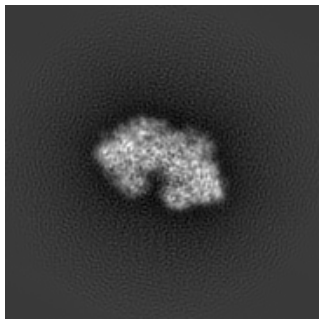

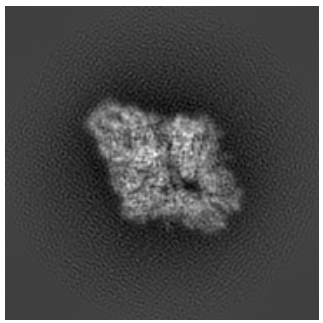

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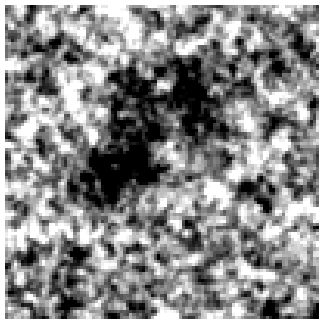

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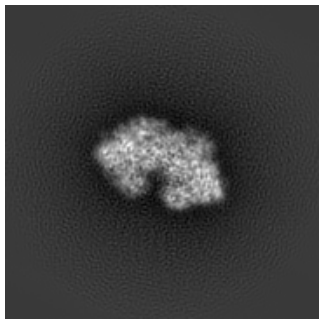

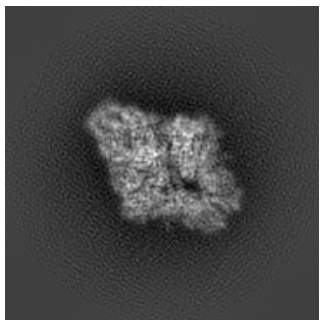

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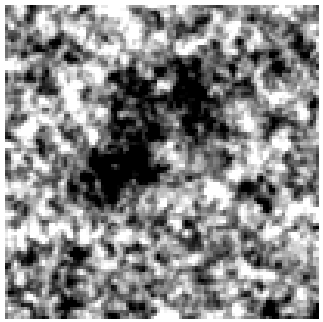

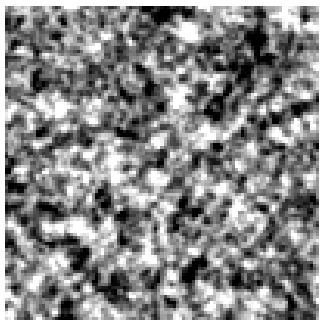

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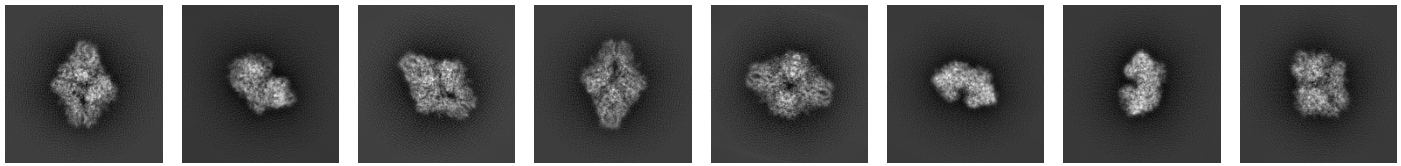
What Templates?

- Simulated projections of particles



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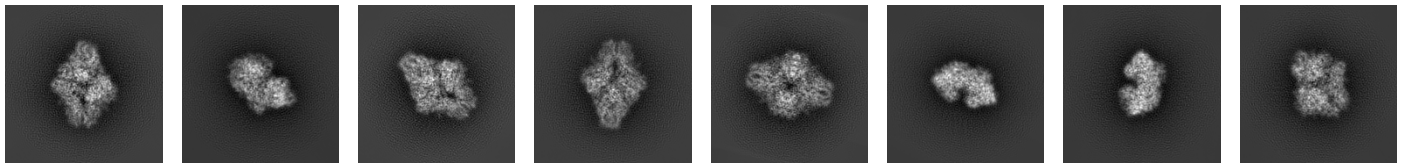
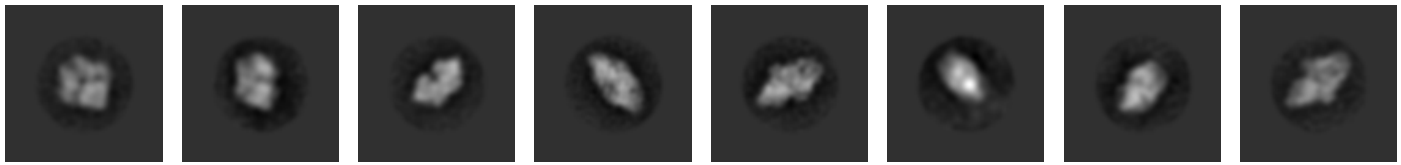


- Class averages from micrograph[2]



[2]Scheres, 2015

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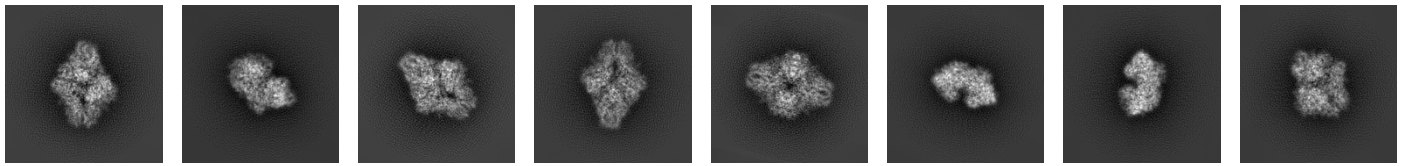

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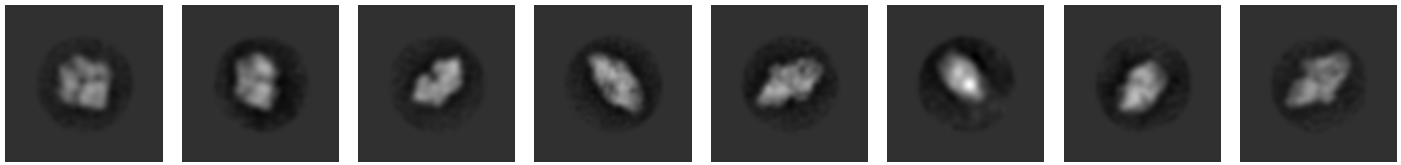
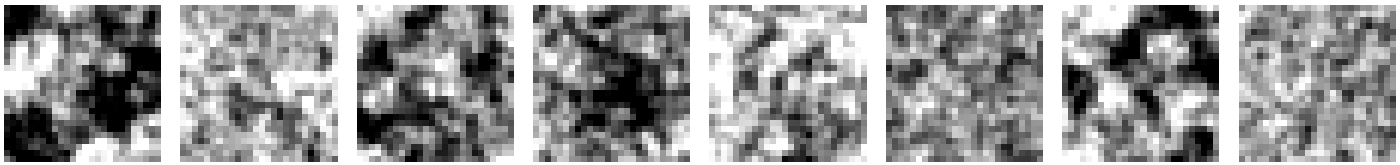


- Difference of Gaussians[3], disks[4]

[2]Scheres, 2015
[3]Voss et al., 2009
[4]Langlois et al., 2014

Template-Free Matching

- Randomly select *reference* windows from micrograph



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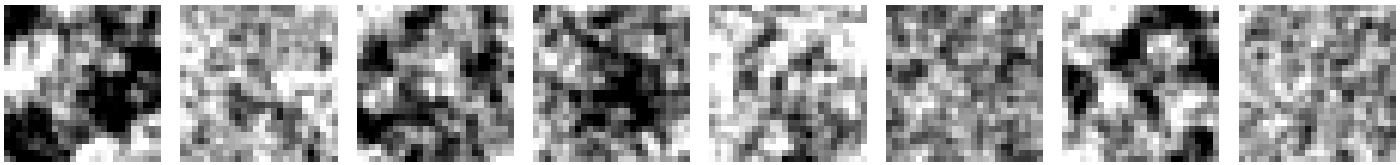

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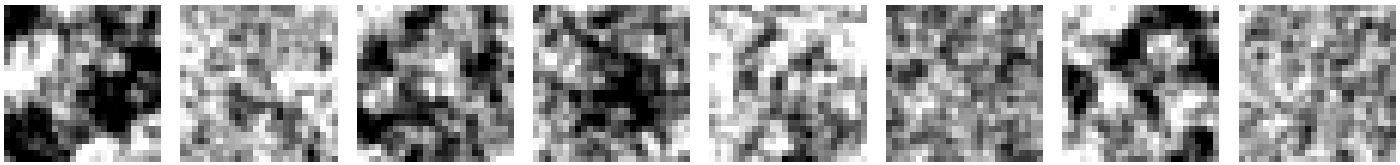

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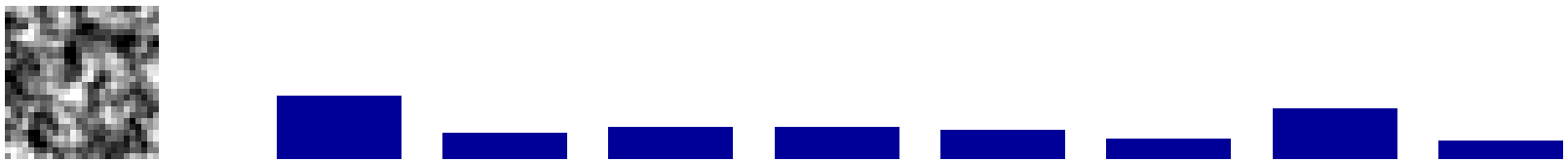

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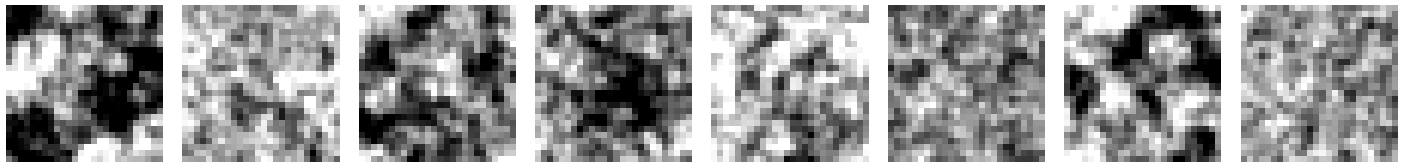

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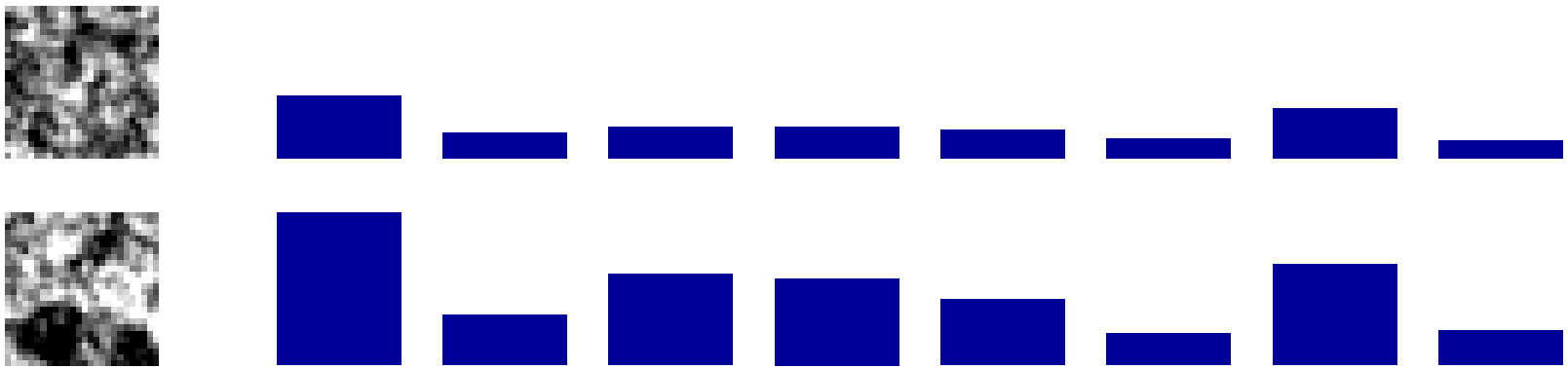

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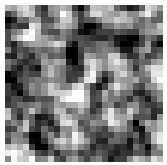
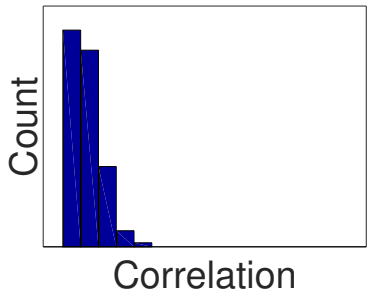
Correlation Distribution

- Empty window correlates badly with all





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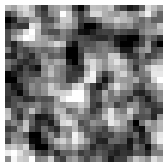
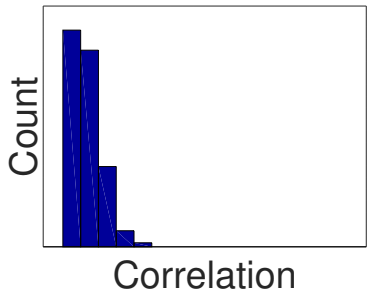
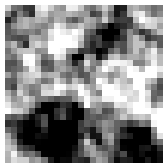
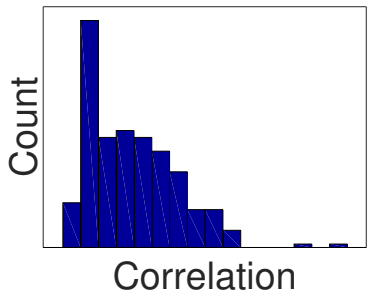




- Window with particle correlates well with some





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Window Score

- Count number k of correlations above threshold

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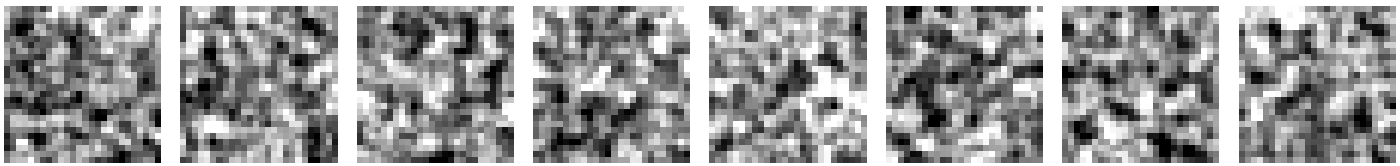

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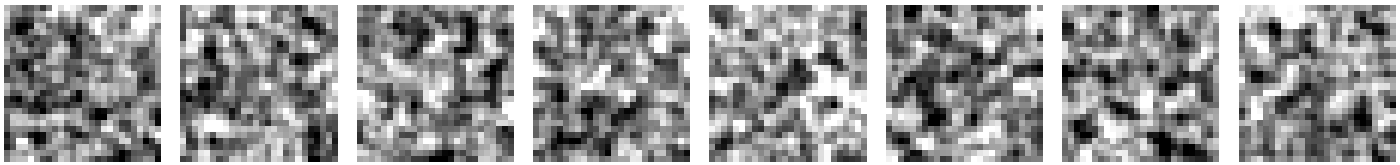
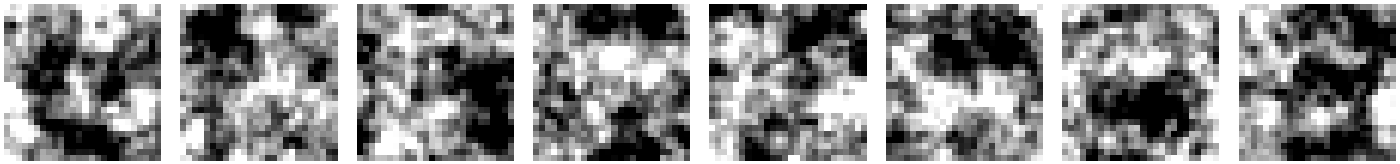
$k = 30$ 

$k = 168$ 

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- Good indicators, but expensive

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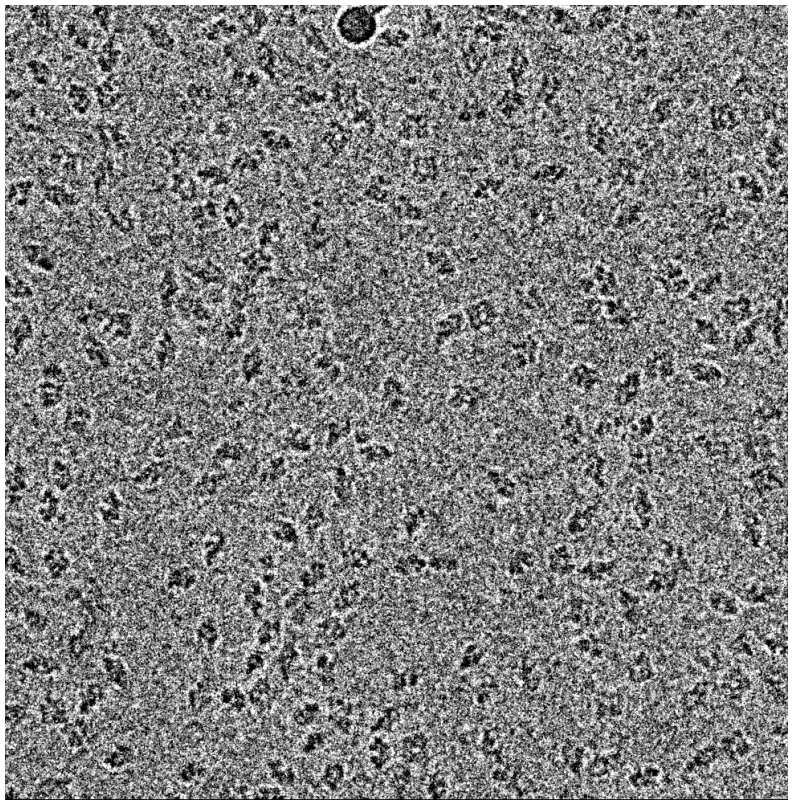
Micrograph



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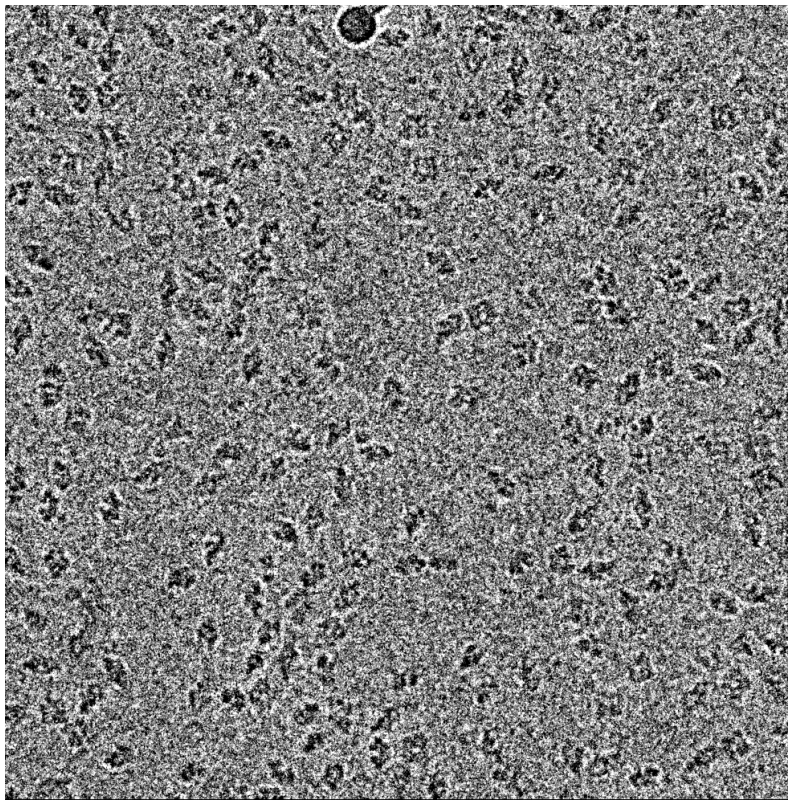

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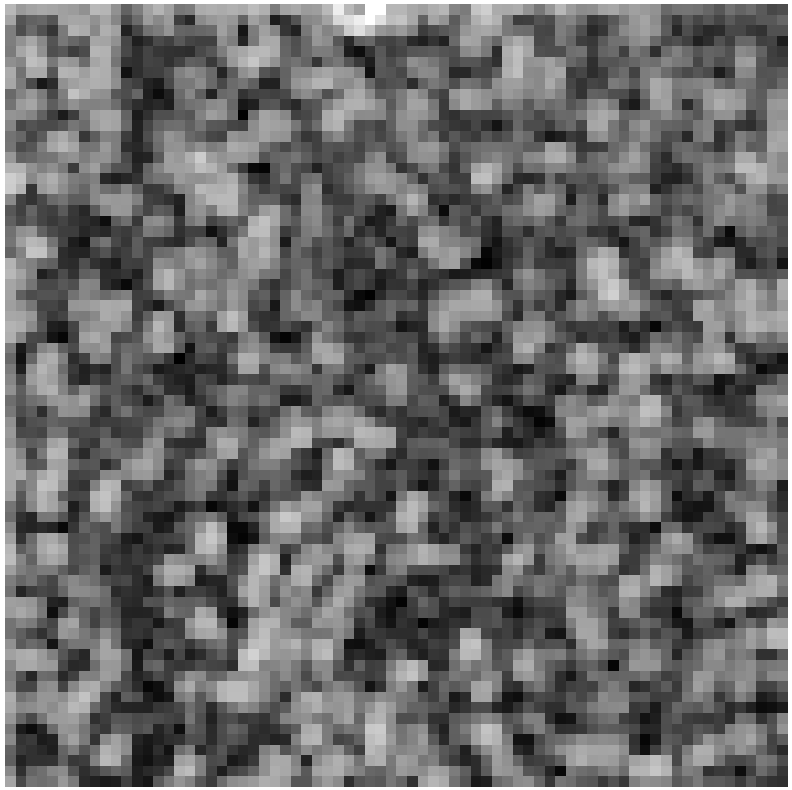

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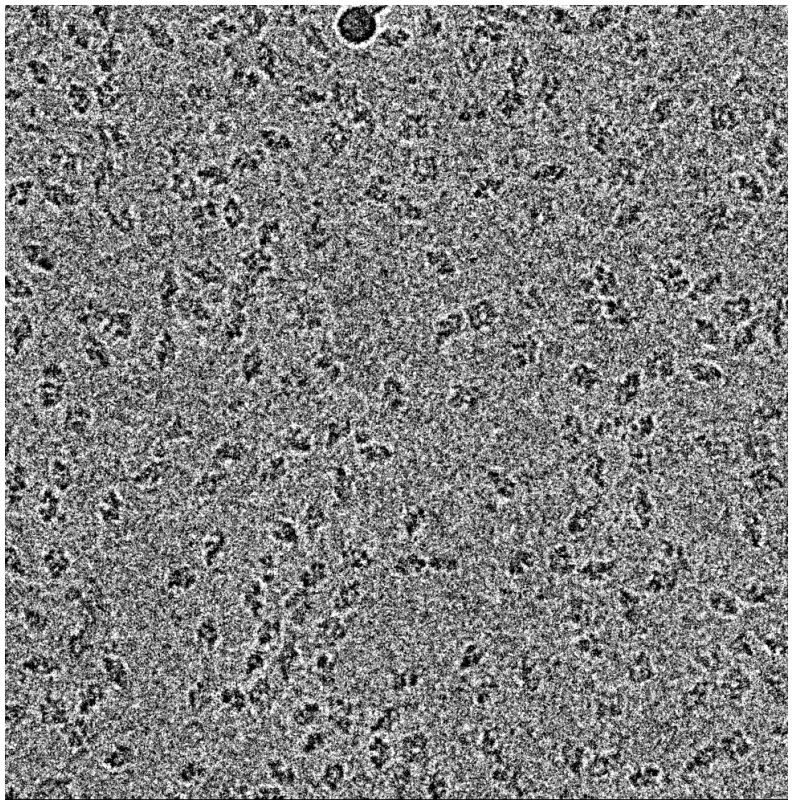

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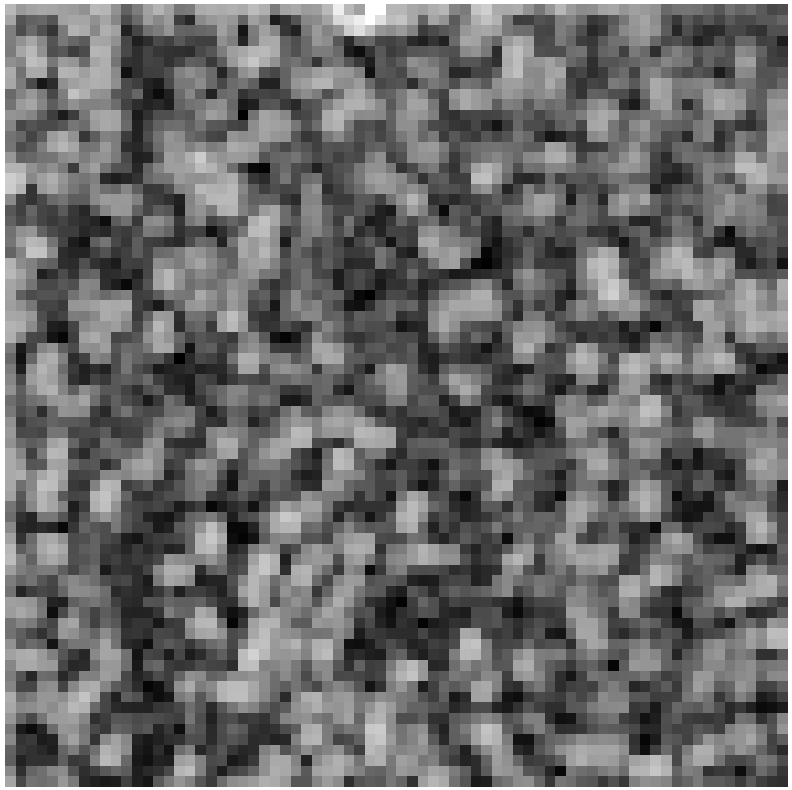

- Need denser sampling

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Localization

- Mean (μ) and standard deviation (σ) can discriminate

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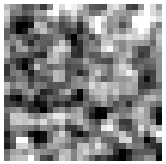
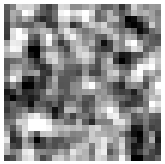
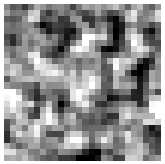
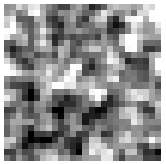
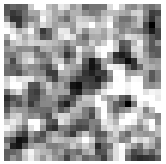
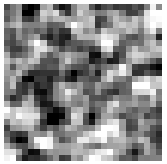
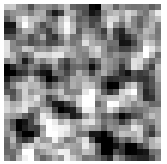
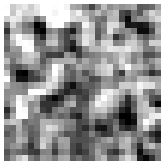
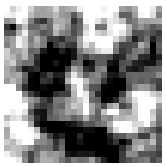
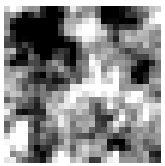
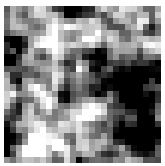
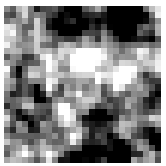
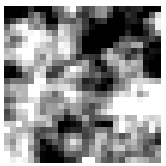
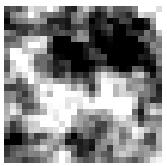
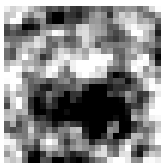
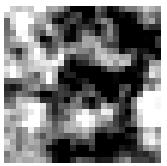
$k = 30$								
μ	-6.2	10	11	10	57	2.0	6.2	25
σ	141	140	140	140	140	150	150	150
$k = 168$								
μ	-10	-22	-35	-41	1.6	-18	-23	-61
σ	230	210	220	220	220	220	220	220

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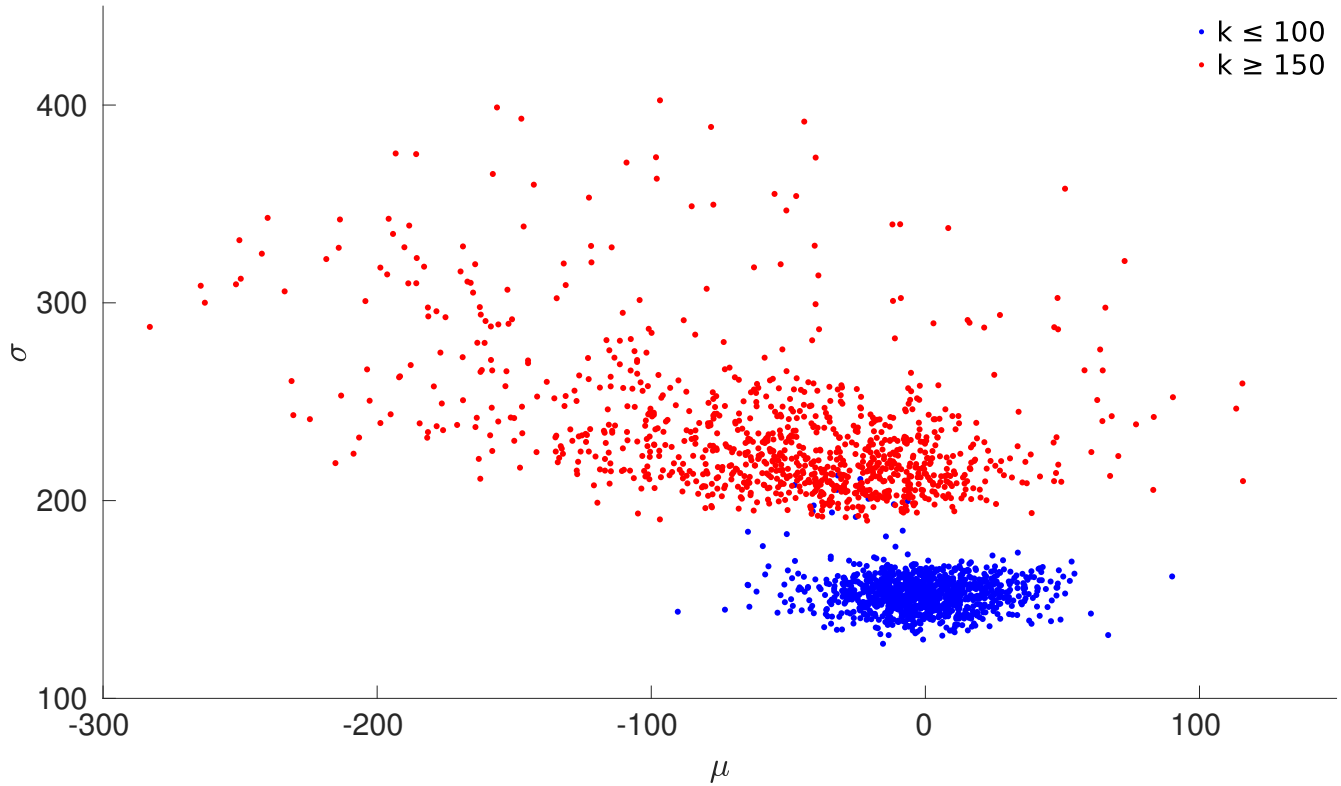
Localization

- Mean (μ) and standard deviation (σ) can discriminate



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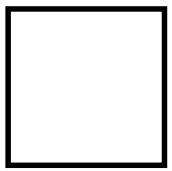
Localization (cont.)

- Train support vector machine[5] (SVM) on μ and σ from high and low k windows

[5] Cortes & Vapnik, 1995

Localization (cont.)

- Train support vector machine[5] (SVM) on μ and σ from high and low k windows
- Both μ and σ may be calculated fast



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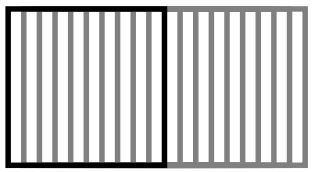

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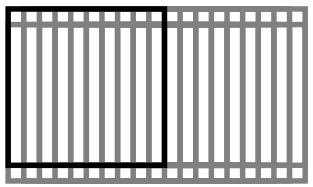

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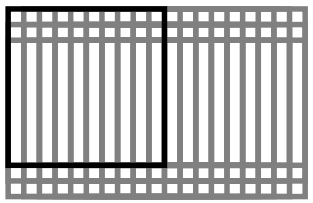

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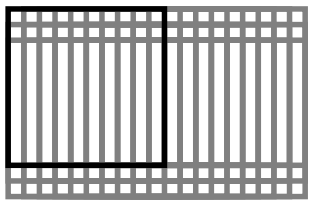

- Calculate μ and σ for dense sampling of windows

[5] Cortes & Vapnik, 1995

Localization (cont.)

- Train support vector machine[5] (SVM) on μ and σ from high and low k windows
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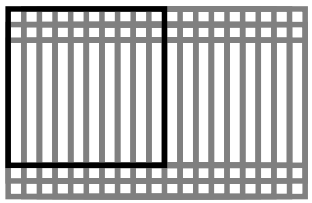
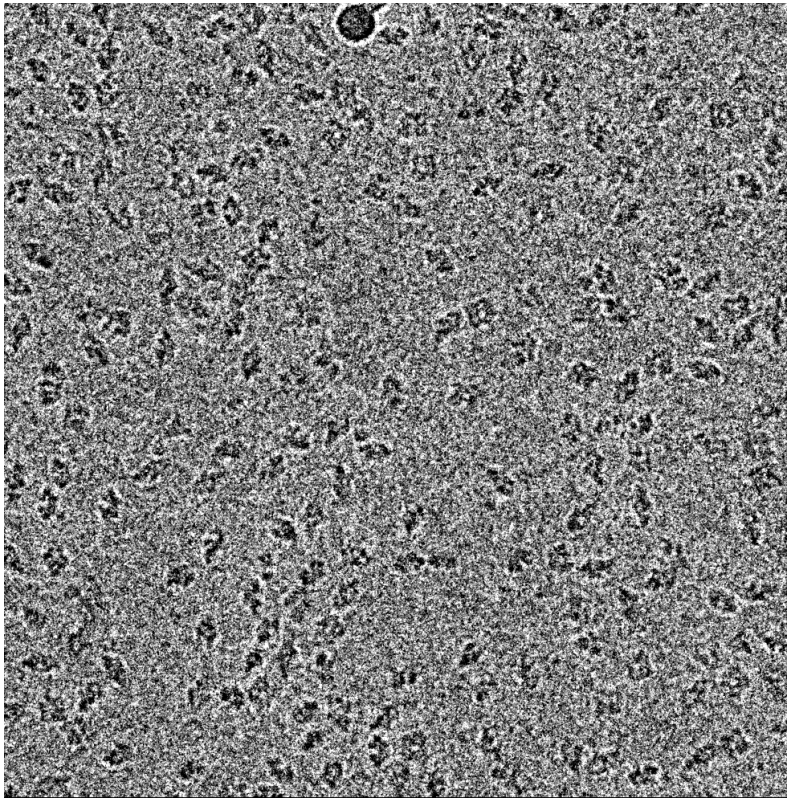


- Calculate μ and σ for dense sampling of windows
- Use SVM to predict

[5] Cortes & Vapnik, 1995

Results



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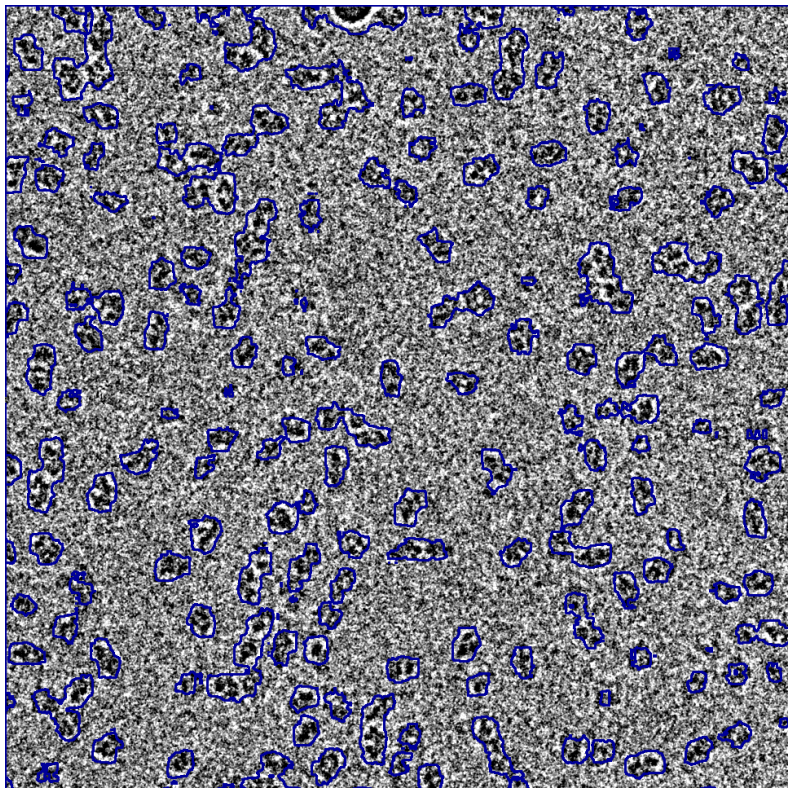

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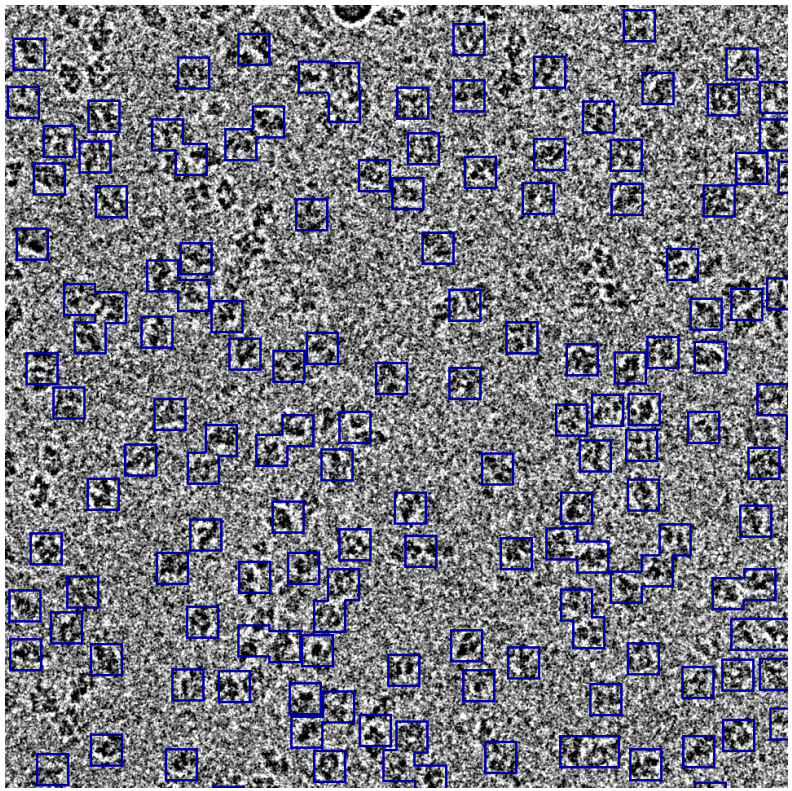

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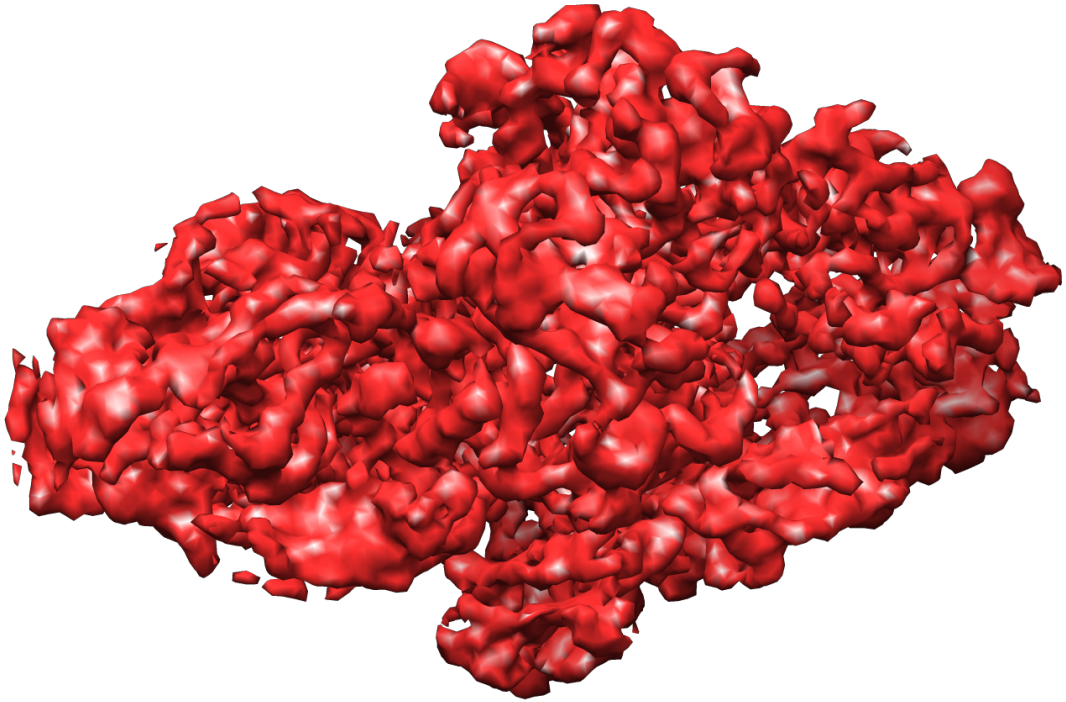
Results (cont.)

- Pick particles from 84 micrographs and reconstruct using RELION



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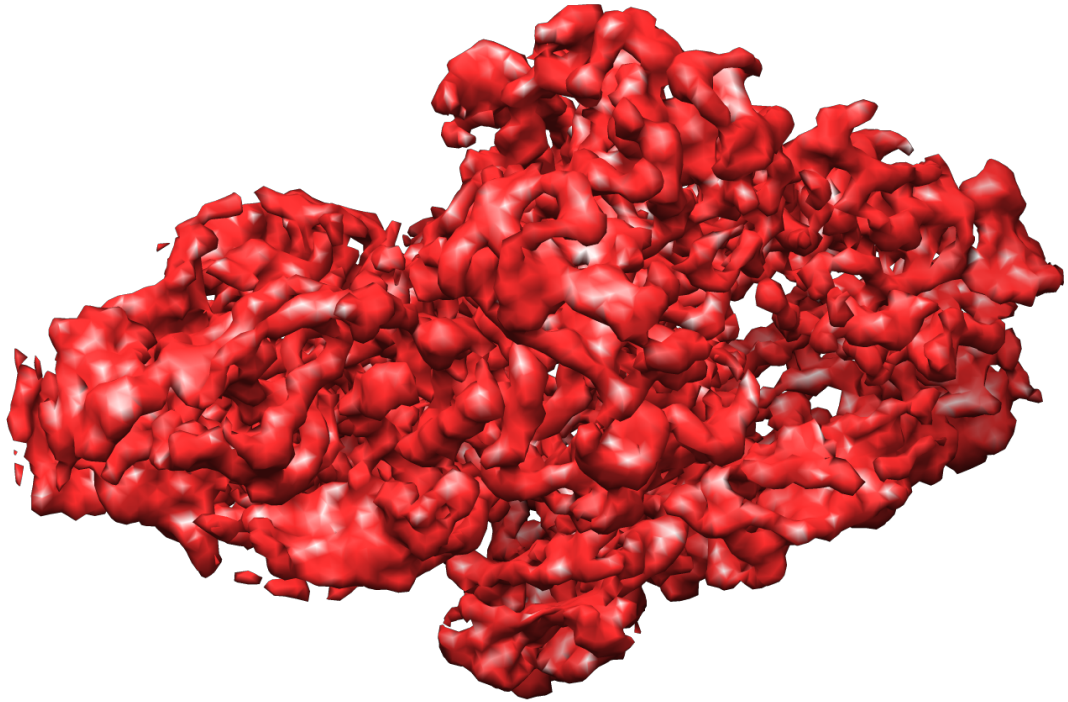

- Agrees up to 6.7 Å with published EMD-2824

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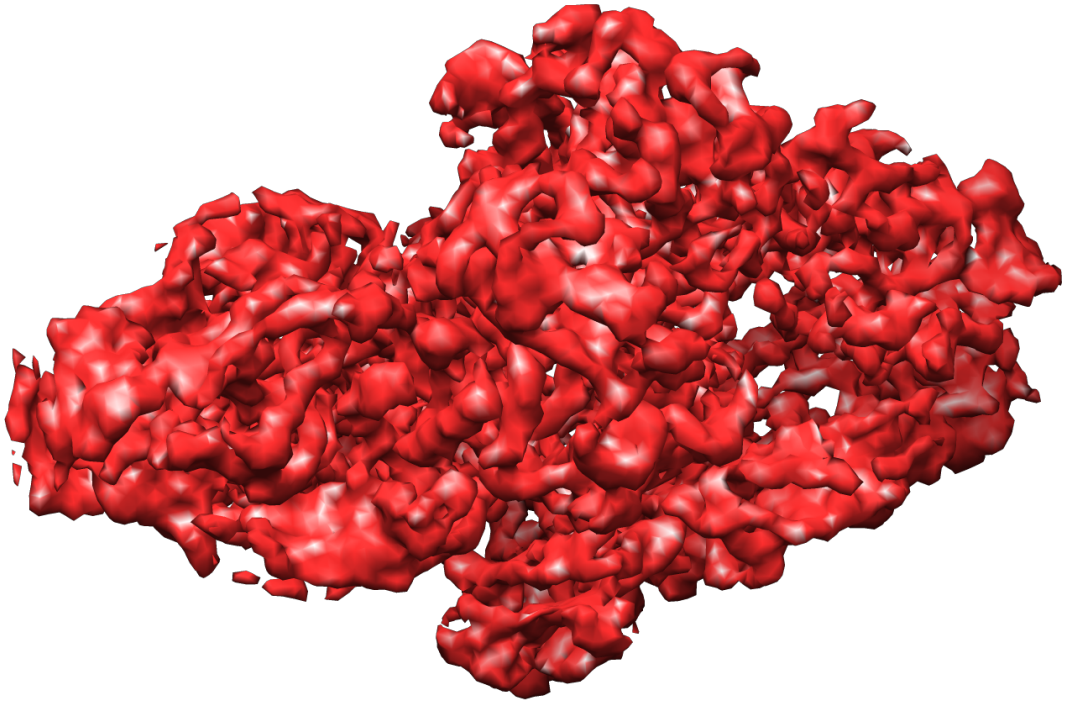

- Agrees up to 6.7 $\mathrm{\AA}$ with published EMD-2824
- Fully automatic, template-free particle picking, 15 $\mathrm{minutes}$

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Conclusion

- Cross-correlation within micrograph strong signal

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Future Work

- How to extract more information from cross-correlation? Distance on histograms? Moments of distributions? Separate identification of non-particles?

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- Score function on densely spaced windows. Fast calculation? Smoothness? Efficient interpolation?

- More discriminative features for SVM? Large-scale gradients? Wavelet moments? Other classifiers? Training for deep networks?

Thank you!

Paper:
`https://arxiv.org/abs/1802.00469`

Software:
`https://github.com/PrincetonUniversity/APPLEpicker`

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NIGMS R01GM090200, BSF 2014401, AFOSR FA9550-12-1-0317, Simons Investigator Award, Simons Collaboration on Algorithms and Geometry, and Moore Data-Driven Discovery Investigator Award

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