Introduction:
# Computational methods for single-particle electron microscopy

CS/CME/Biophys/BMI 371

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Single-particle electron (cryo) microscopy

- We want the structure of a "particle": a molecule (e.g., protein) or a well-defined complex composed of many molecules (e.g., a ribosome)
- We spread identical particles out on a film, and image them using an electron microscope
- The images are two-dimensional (2D), and each particle is positioned at a different, unknown angle.
- Given enough 2D images of particles, we can computationally reconstruct the 3D shape of the particle

Electron beam

Particles

Images

Image from Joachim Frank
http://biomachina.org/courses/structures/091.pdf
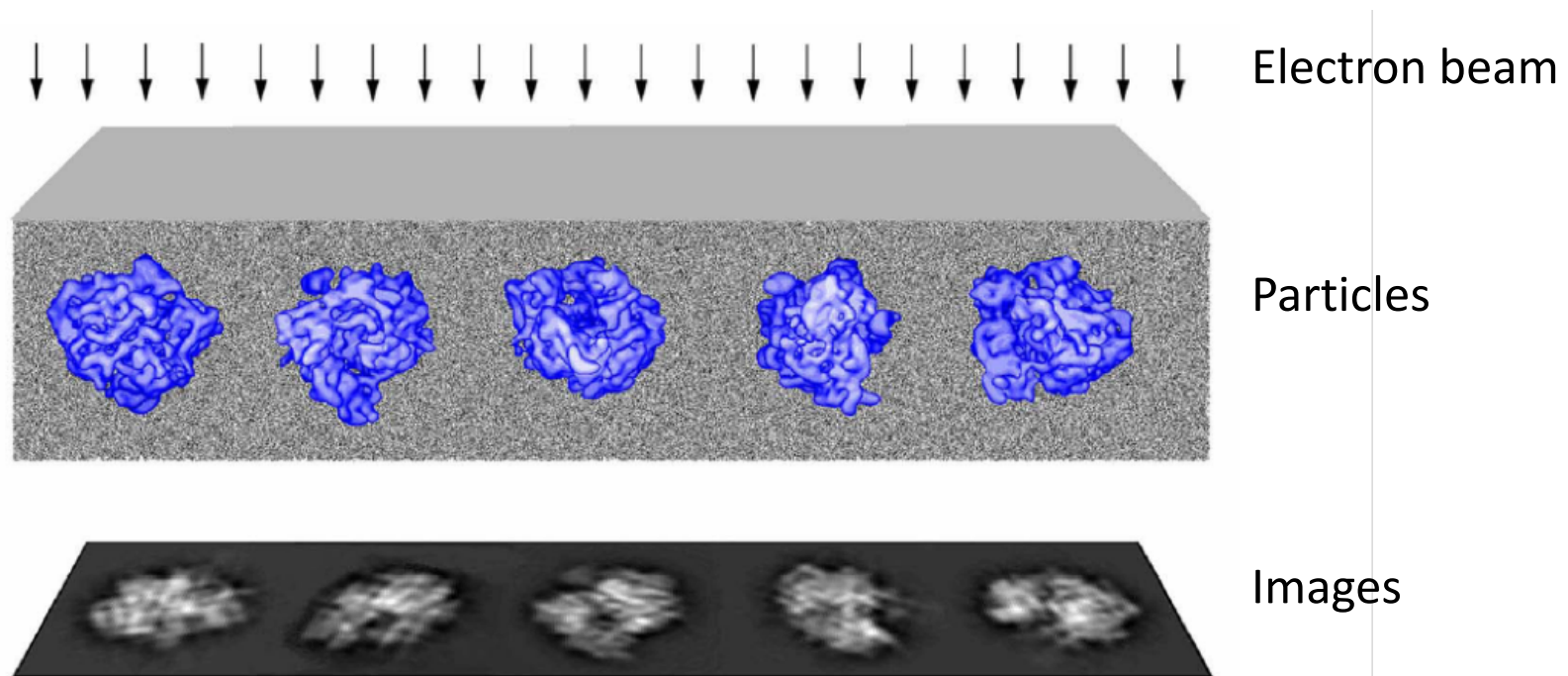
Improved computational method for reconstructing 3D particle shape

- Raw electron microscopy (EM) images are *very* noisy
- A new software package (Relion) that uses Bayesian statistics to prevent overfitting to noise has substantially improved cutting-edge single-particle results
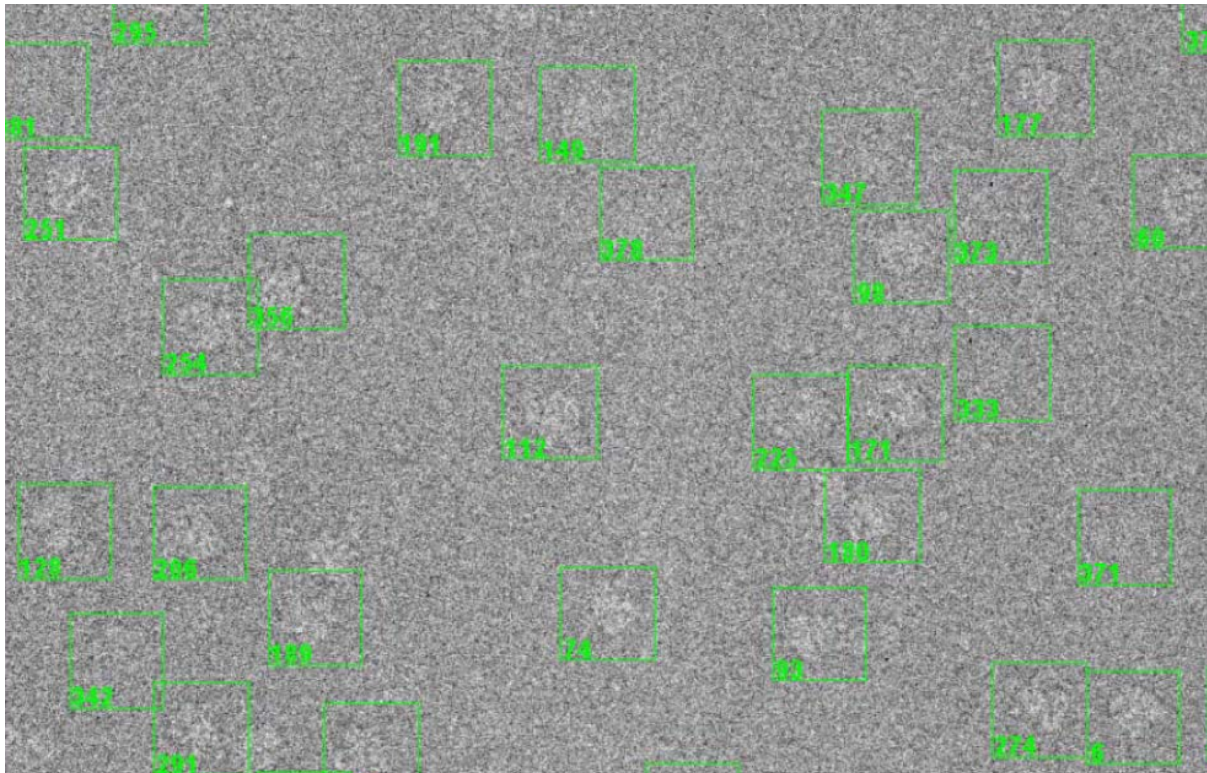

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Recovering a conformational *ensemble* from EM images

- Real biomolecules (and complexes) don't exist in just a single conformation. They interchange rapidly between different conformations.

  – Each EM image reflects just one conformation

- Usually one reconstructs just a single 3D structure from a collection of images

  – Or, perhaps, two or three 3D structures

- One of Wednesday's papers aims to recover a full ensemble (that is, the full range of conformations — essentially a "movie")

  – Uses manifold embedding methods

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Background information

- My slides on single-particle electron microscopy from CS/CME/Biophys/BMI 279:

    – http://web.stanford.edu/class/cs279/lectures/lecture13.pdf

- My slides on Fourier transforms and convolution from CS/CME/Biophys/BMI 279:

    – http://web.stanford.edu/class/cs279/lectures/lecture8.pdf

- For more detail, see the paper "A Primer to Single-Particle Cryo-Electron Microscopy" (listed on the course website as an "additional paper" for Wednesday)