Introduction: Computational methods for single-particle cryoelectron microscopy

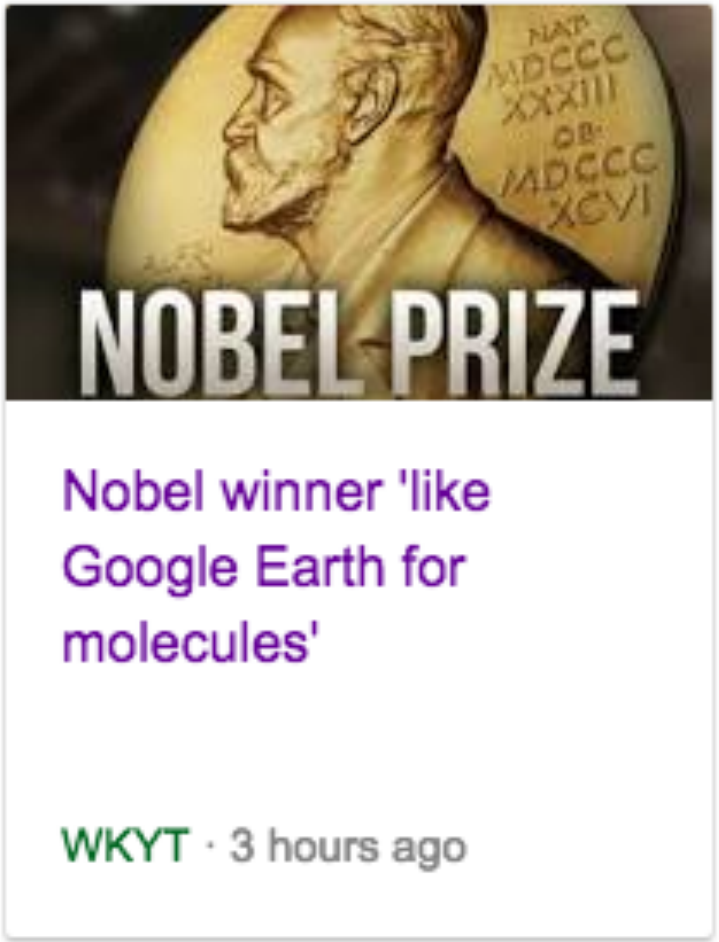
CS/CME/Biophys/BMI 371

Feb. 15, 2018

Ron Dror

October’s Nobel Prize in Chemistry

Awarded to Jacques Dubochet, Joachim Frank and Richard Henderson and "For developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution"



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

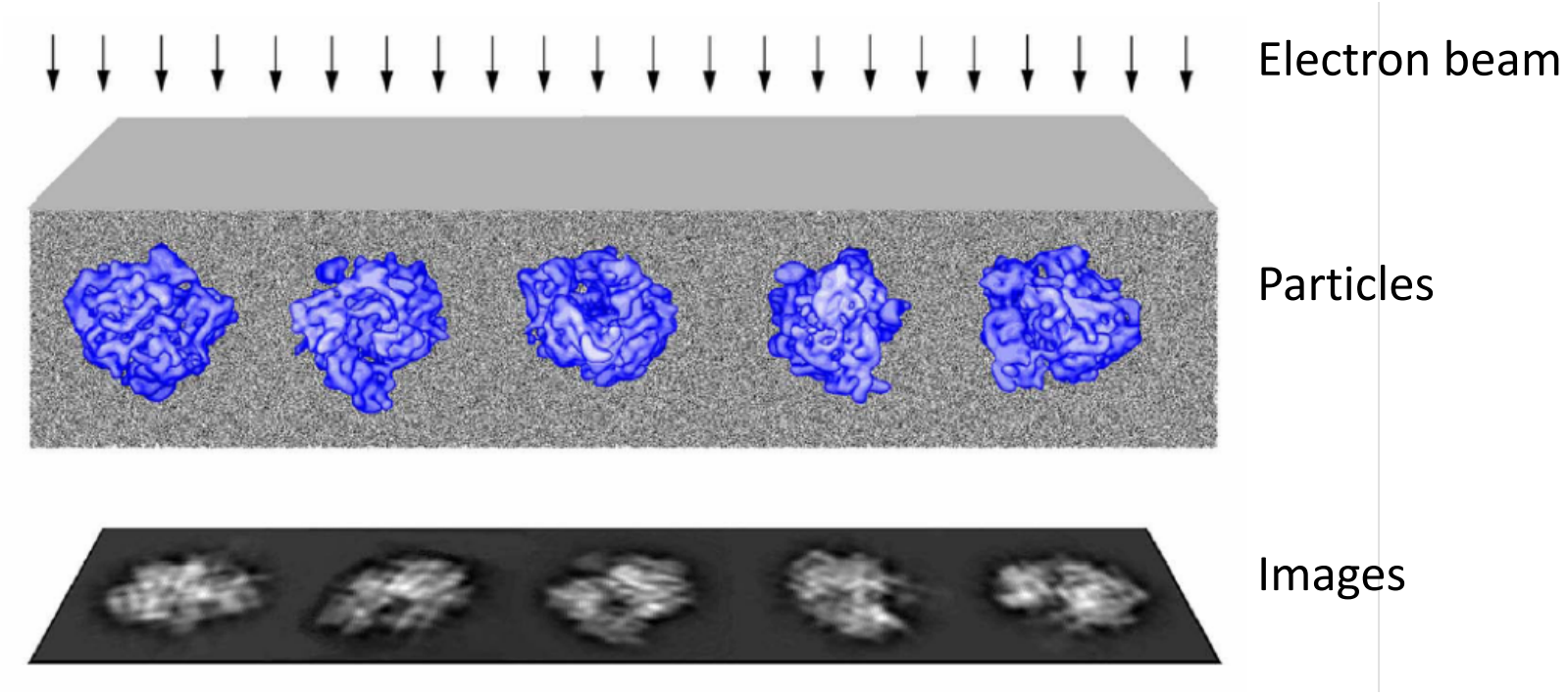


Image from Joachim Frank
http://biomachina.org/courses/structures/091.pdf

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

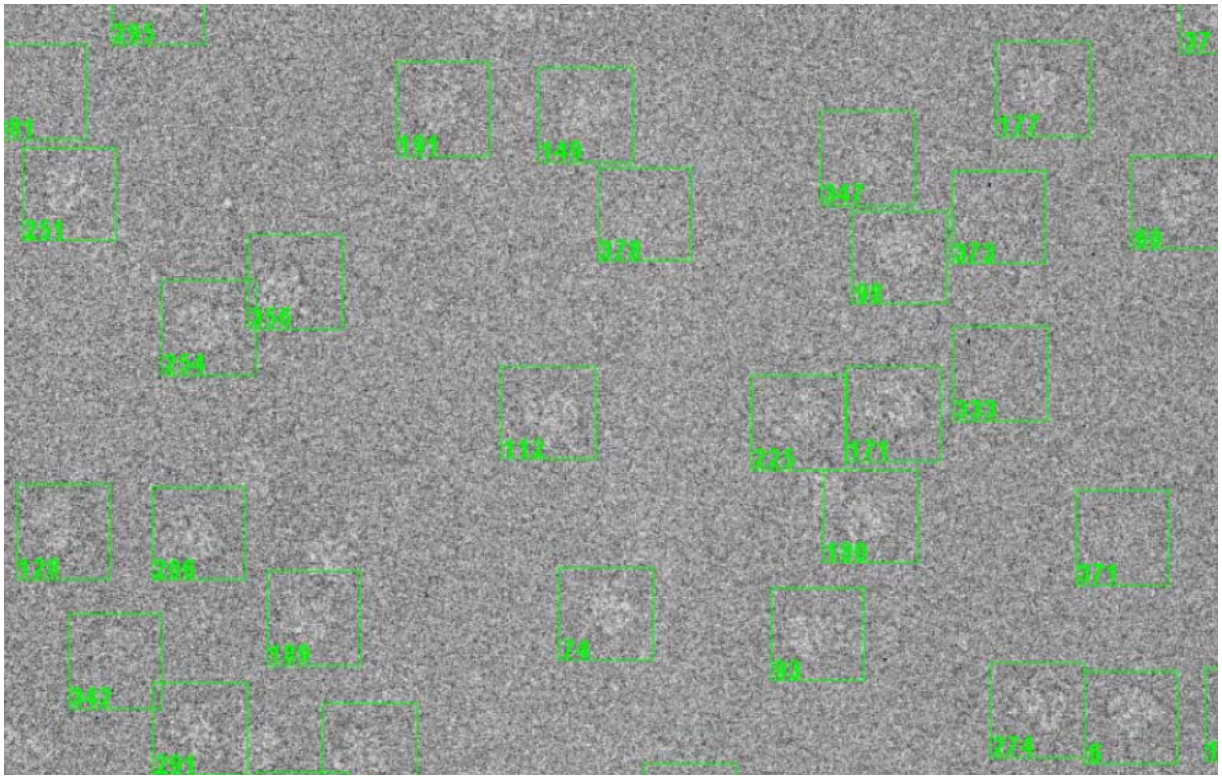


Image from Joachim Frank
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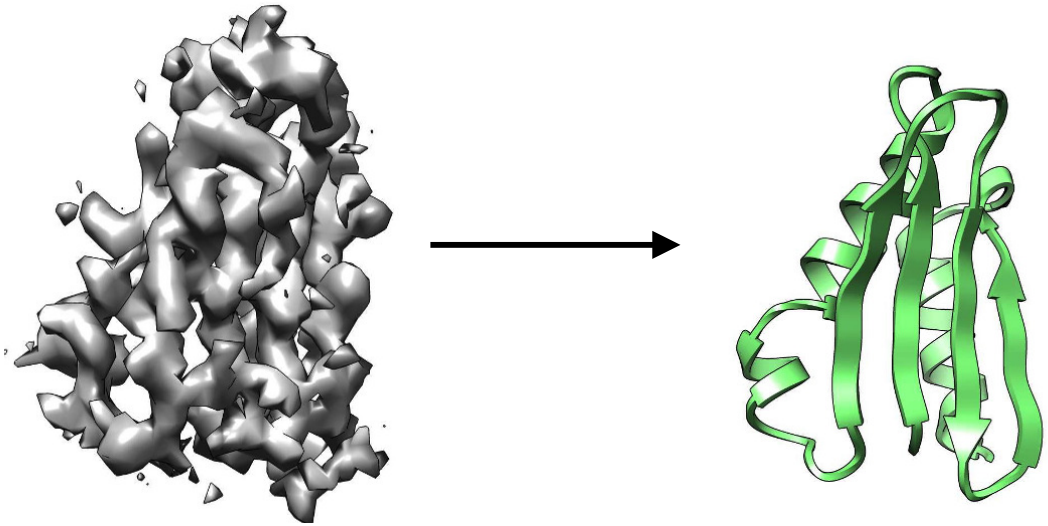
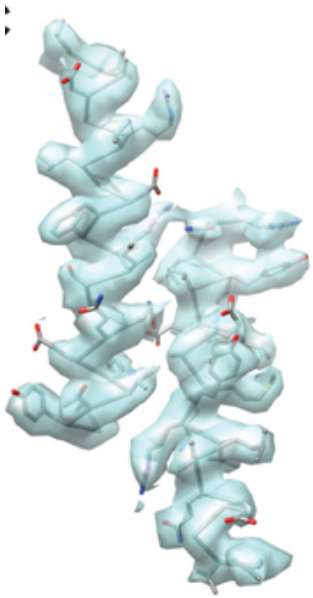
Automated structure refinement

- Once one has the molecule shape (a “density map”), one can model in the actual atoms
  - This is usually done manually, and it’s tricky
  - One of next week’s paper presents an automated method for improving (refinement) manual models



Wang et al., eLife 5:e17219 (2016)



Li et al., Nature Methods 10:584 (2013)

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 next week's papers aims to recover a full ensemble (that is, the full range of conformations — essentially a "movie")
  - Uses manifold embedding methods

Background information

- My slides on single-particle electron microscopy from CS/CME/Biophys/BMI 279:
  - http://web.stanford.edu/class/cs279/lectures/lecture15.pdf
- My slides on Fourier transforms and convolution from CS/CME/Biophys/BMI 279:
  - http://web.stanford.edu/class/cs279/lectures/lecture9.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 next Thursday)