Cryo-transmission electron microscopy (TEM) based molecular and cellular sciences

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UNIVERSITY OF MARYLAND

DEPARTMENT OF CHEMISTRY & BIOCHEMISTRY

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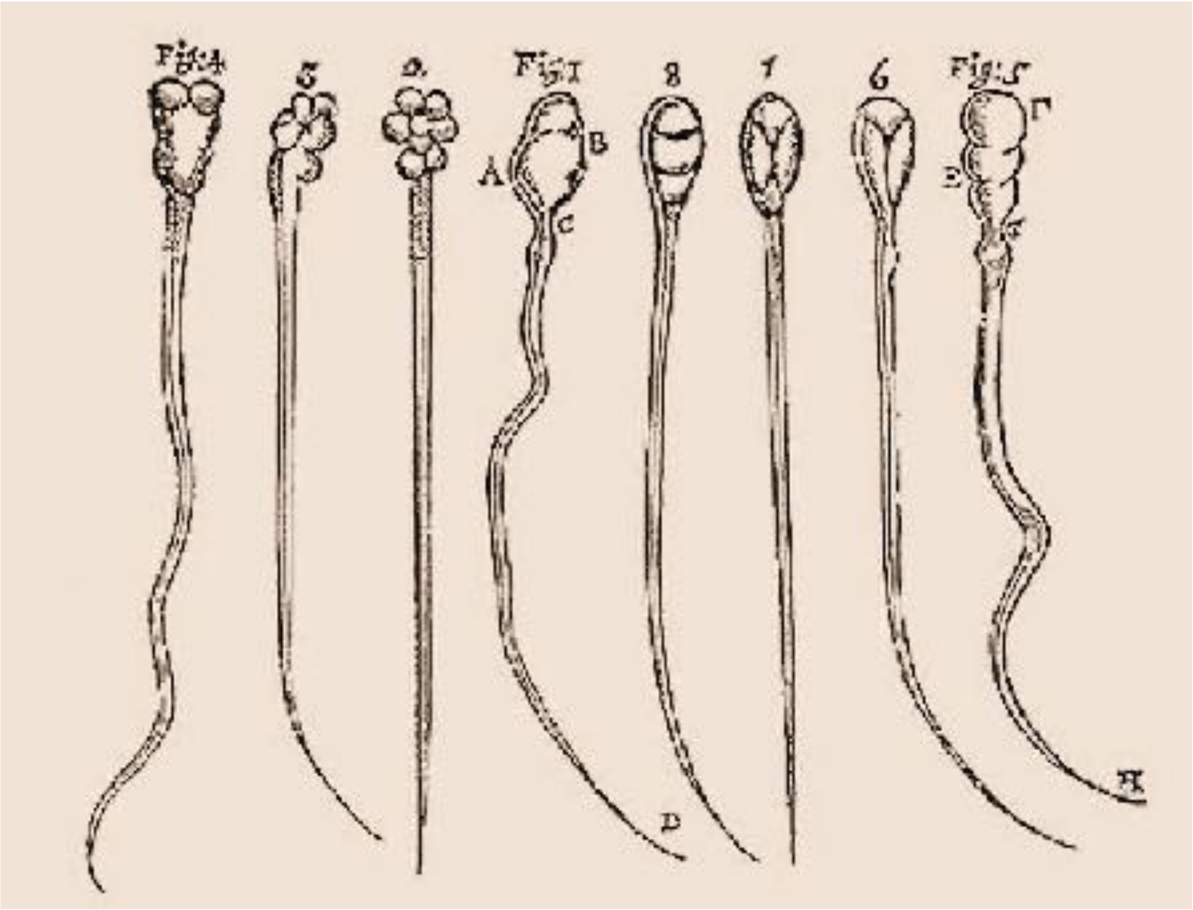
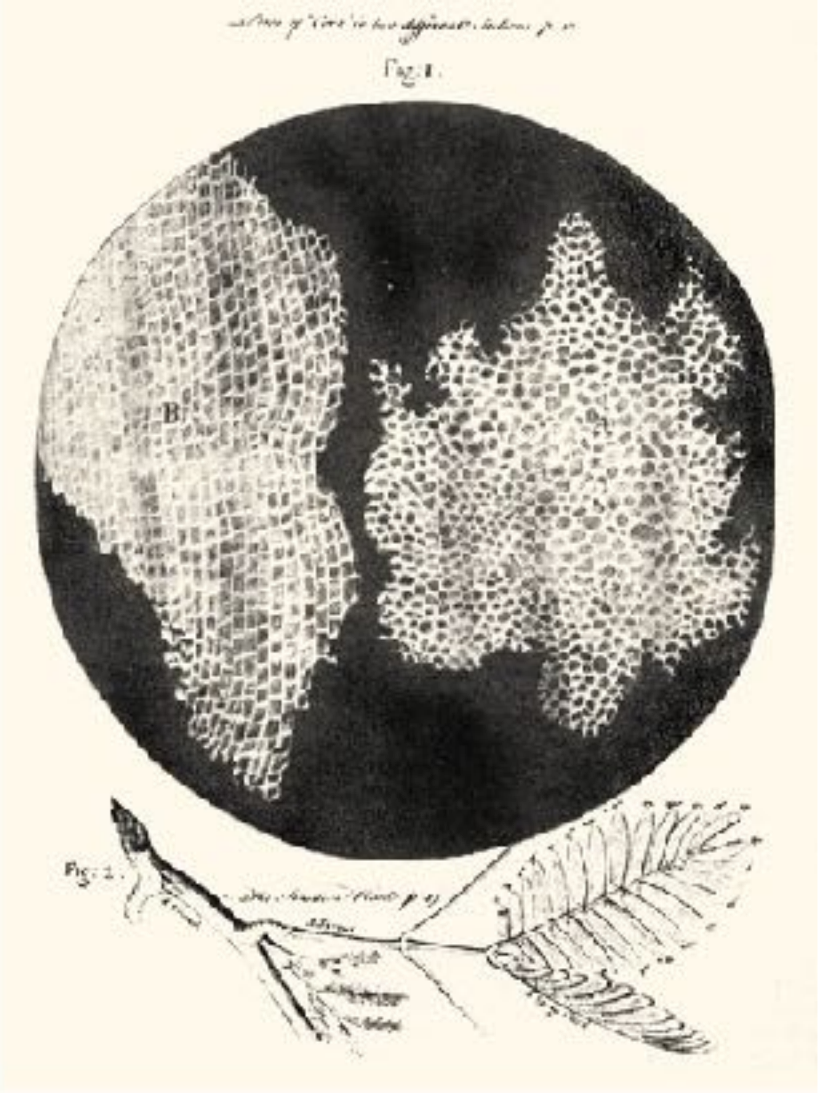
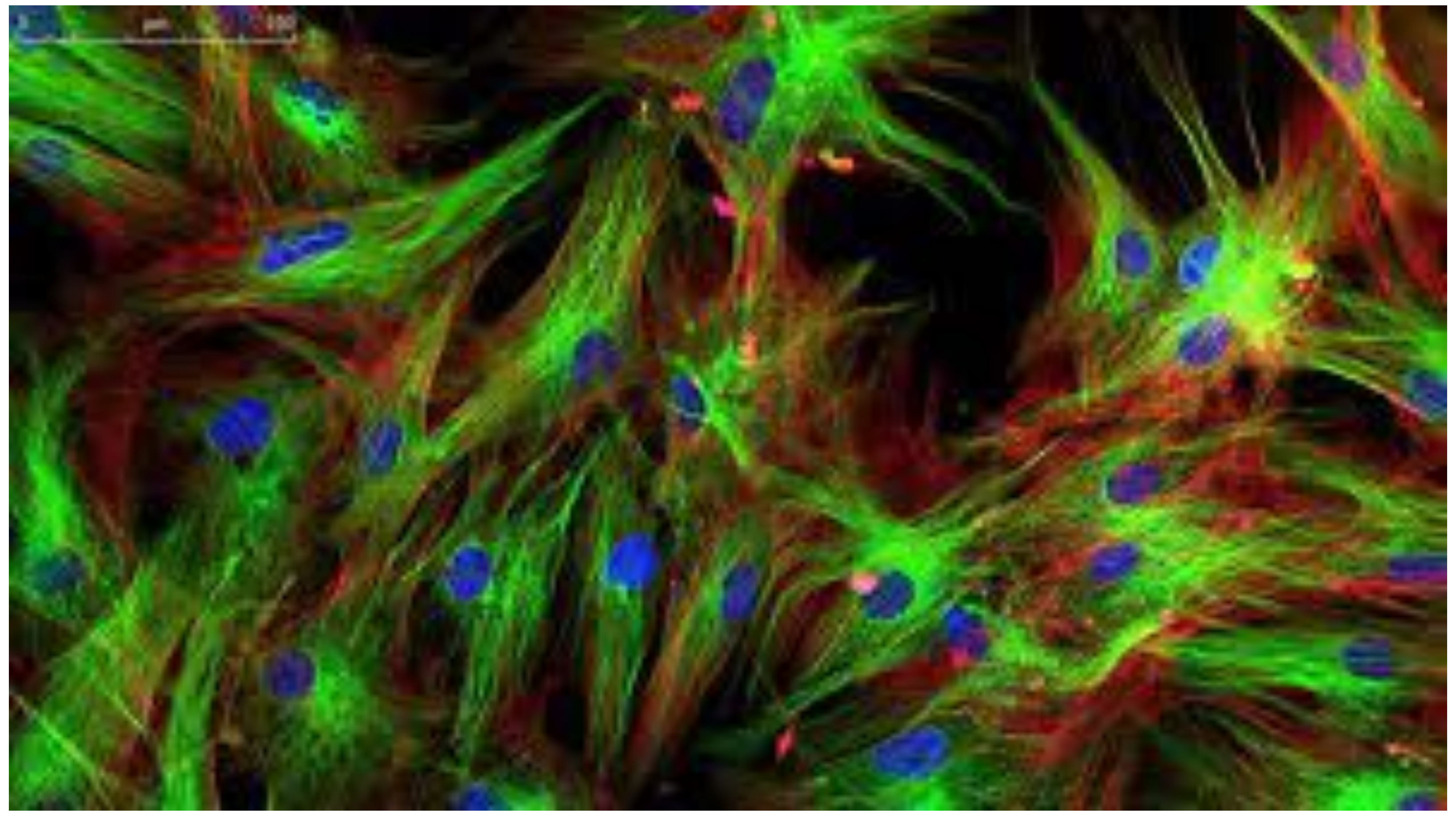
Light microscopy

Antonie van Leeuwenhoek (1632-1723)

Robert Hooke (1635-1703)

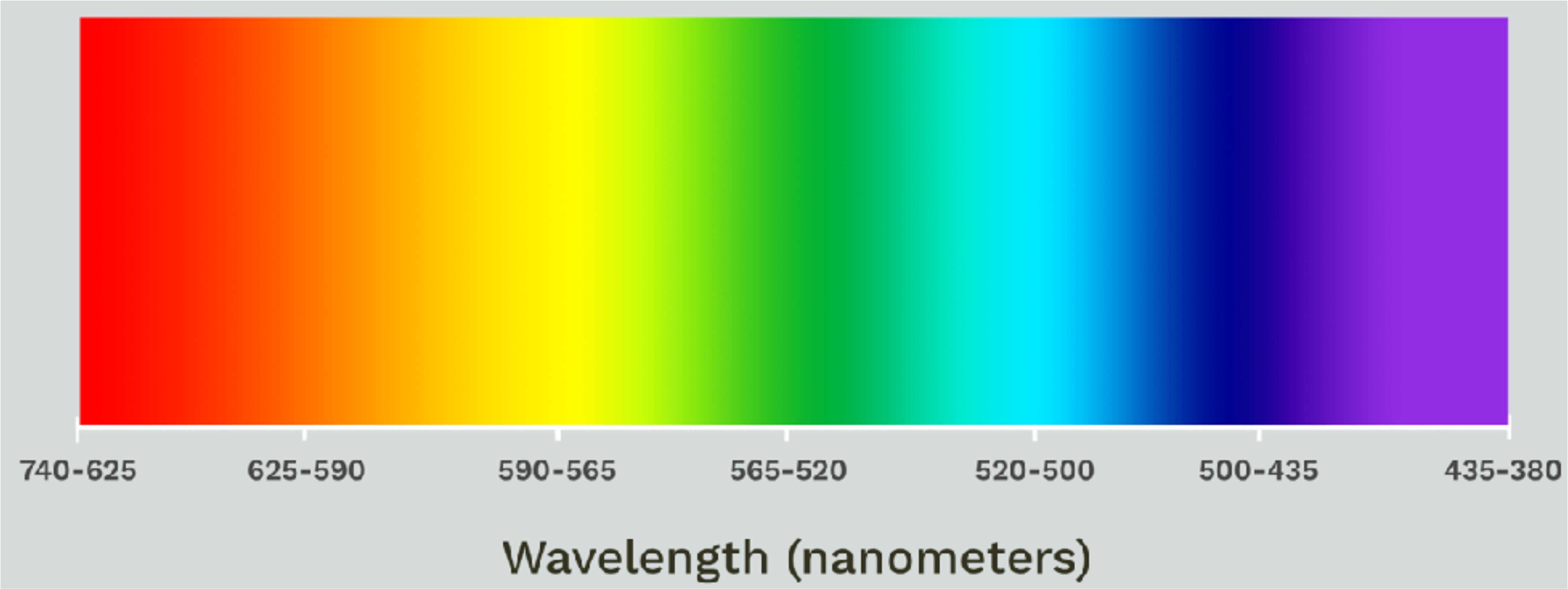






Why electron?

Visible light:



Electron:

De Broglie Wavelength:
$\lambda = h/mv$

Electron mass:
$m_e = 9.1 \times 10^{-31}$ kg

Energy conversion:
1 keV = 1.6×10^{-16} J

Energy conservation:
$E = mv^2/2 = eV$

Voltage:
V=200kV

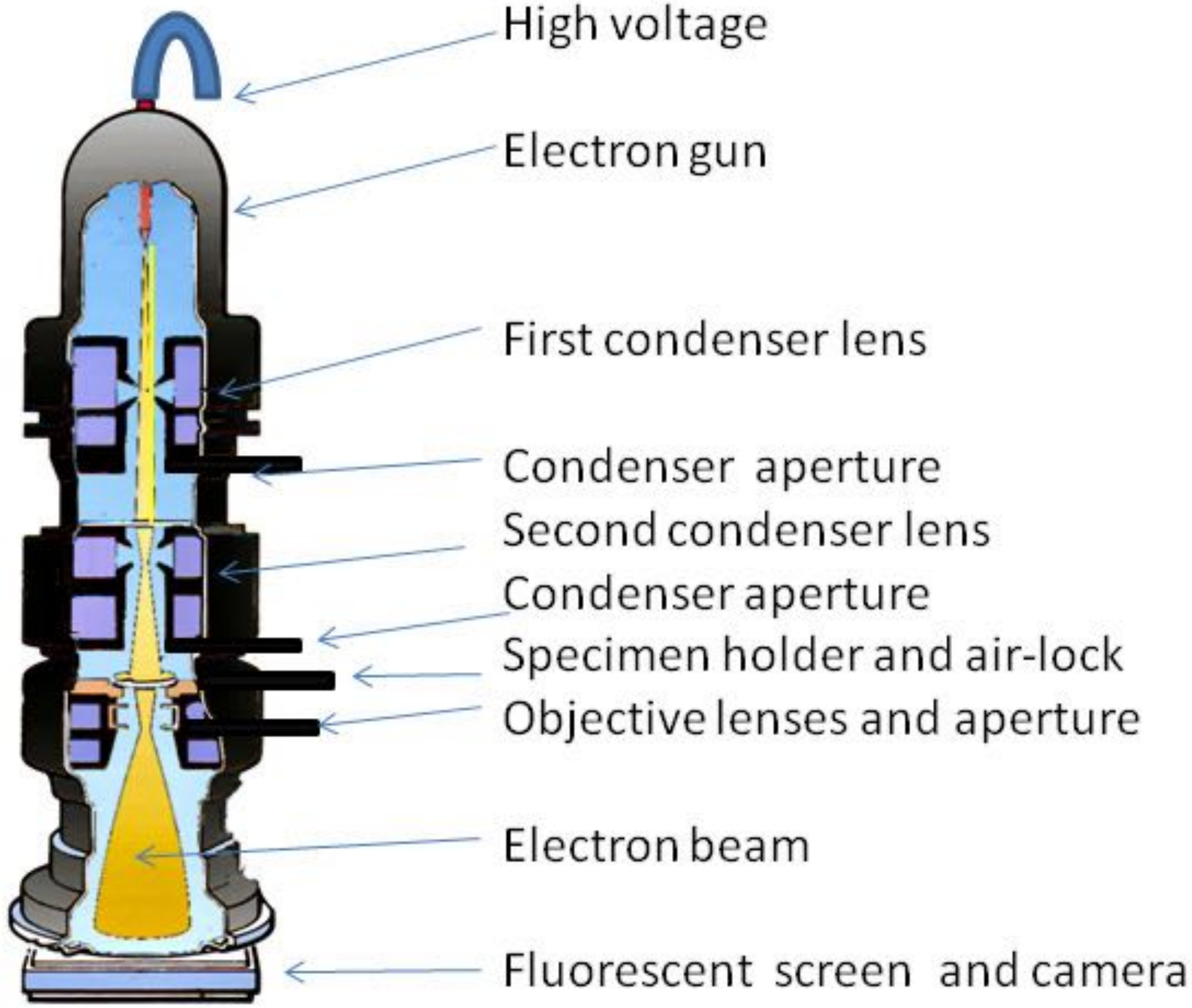
Planck Constant:
$h = 6.63 \times 10^{-34}$ J/Hz

Electron speed:
v ~ 70% speed of light

Electron wavelength:
λ ~ picometer (10^{-12} m)

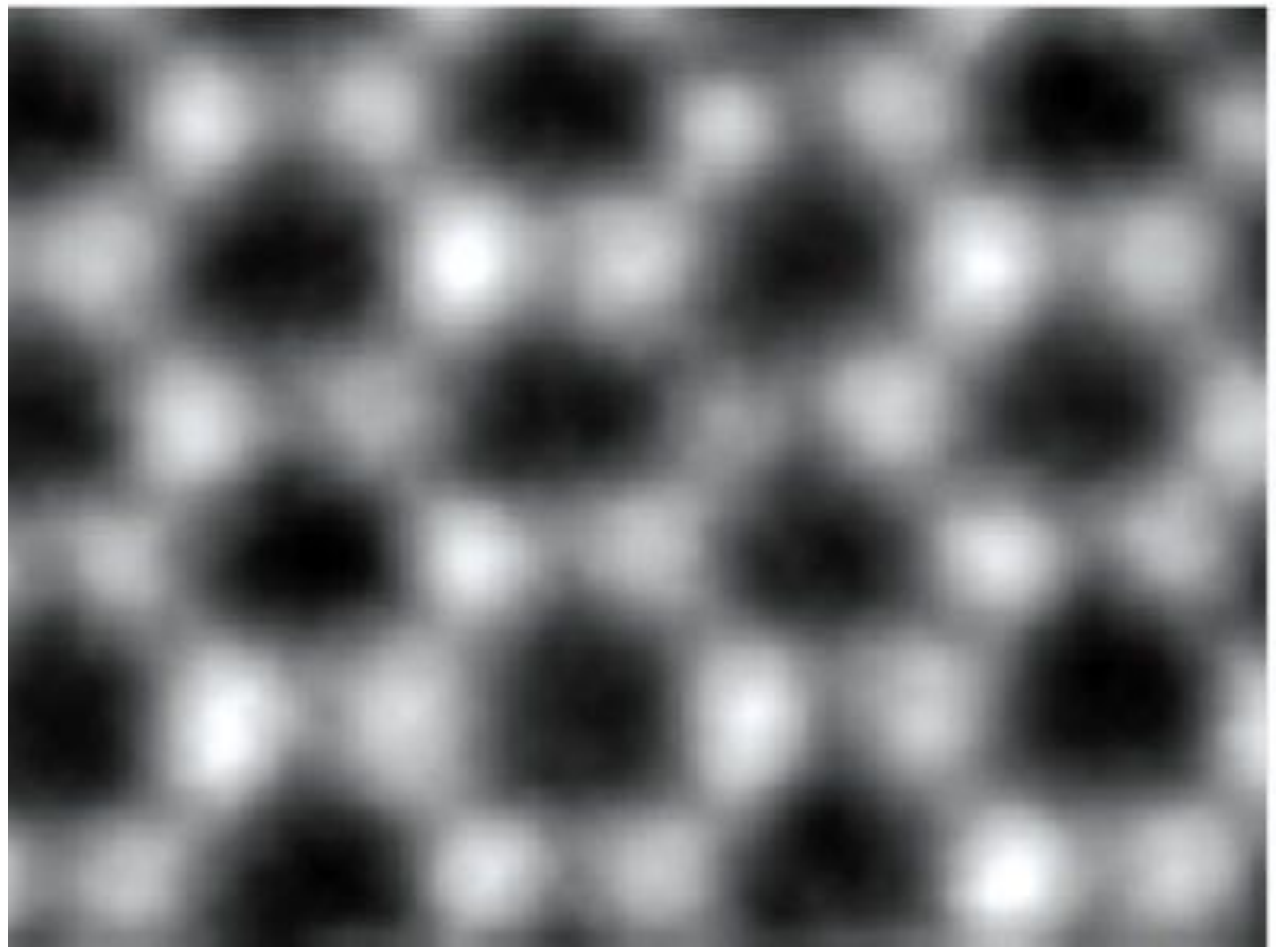
Electron microscopy

Ernst Ruska 1933



Challenge in using electron microscopy for biology

Material Science



MoS_2 at 0.39 Å

De Broglie Wavelength:
$\lambda = h/mv$

Energy conservation:
$E = mv^2/2 = eV$

Electron speed:
v ~ 70~80% speed of light

Limitation:
Radiation Damage

Cryo-electron microscopy (Cryo-EM)

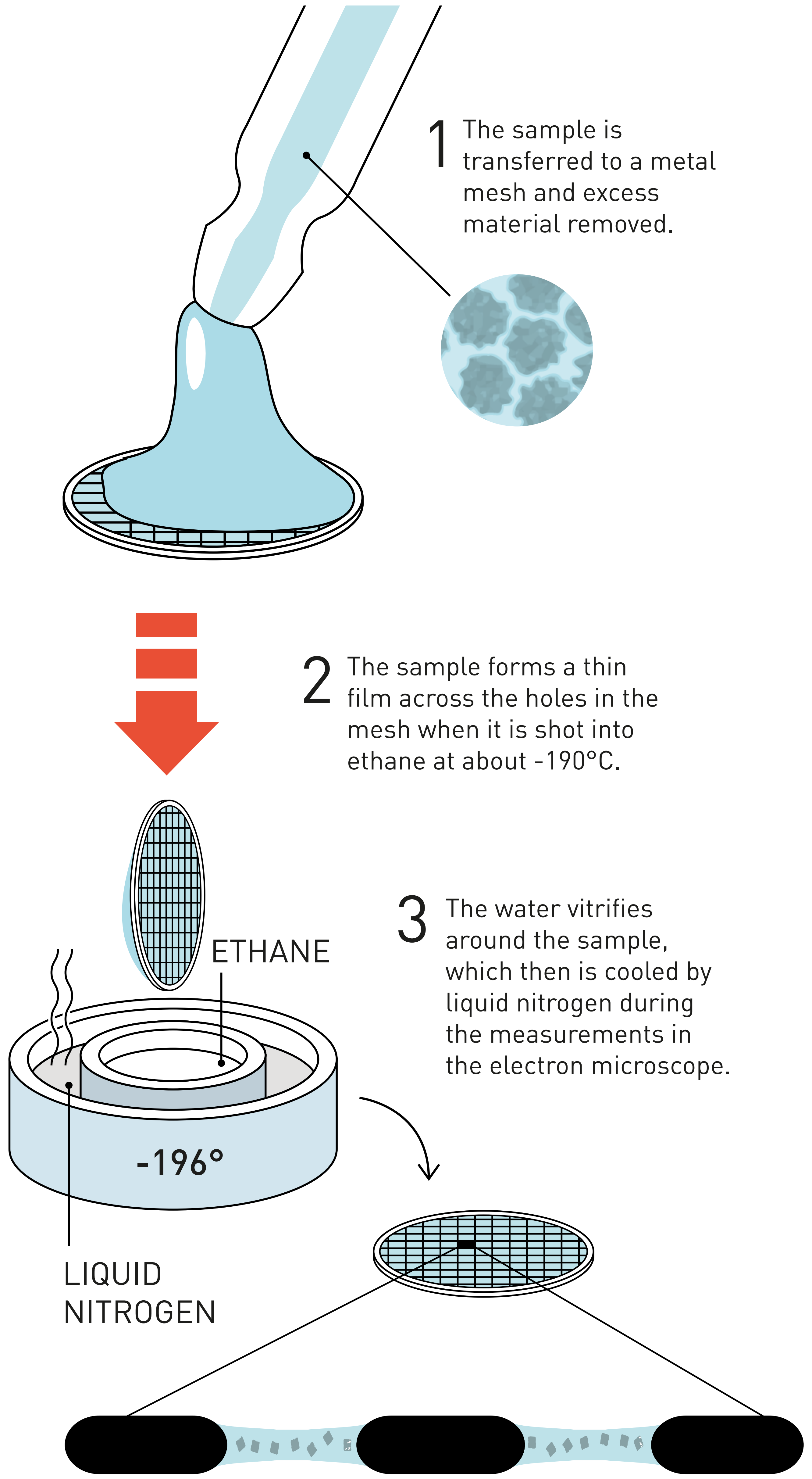
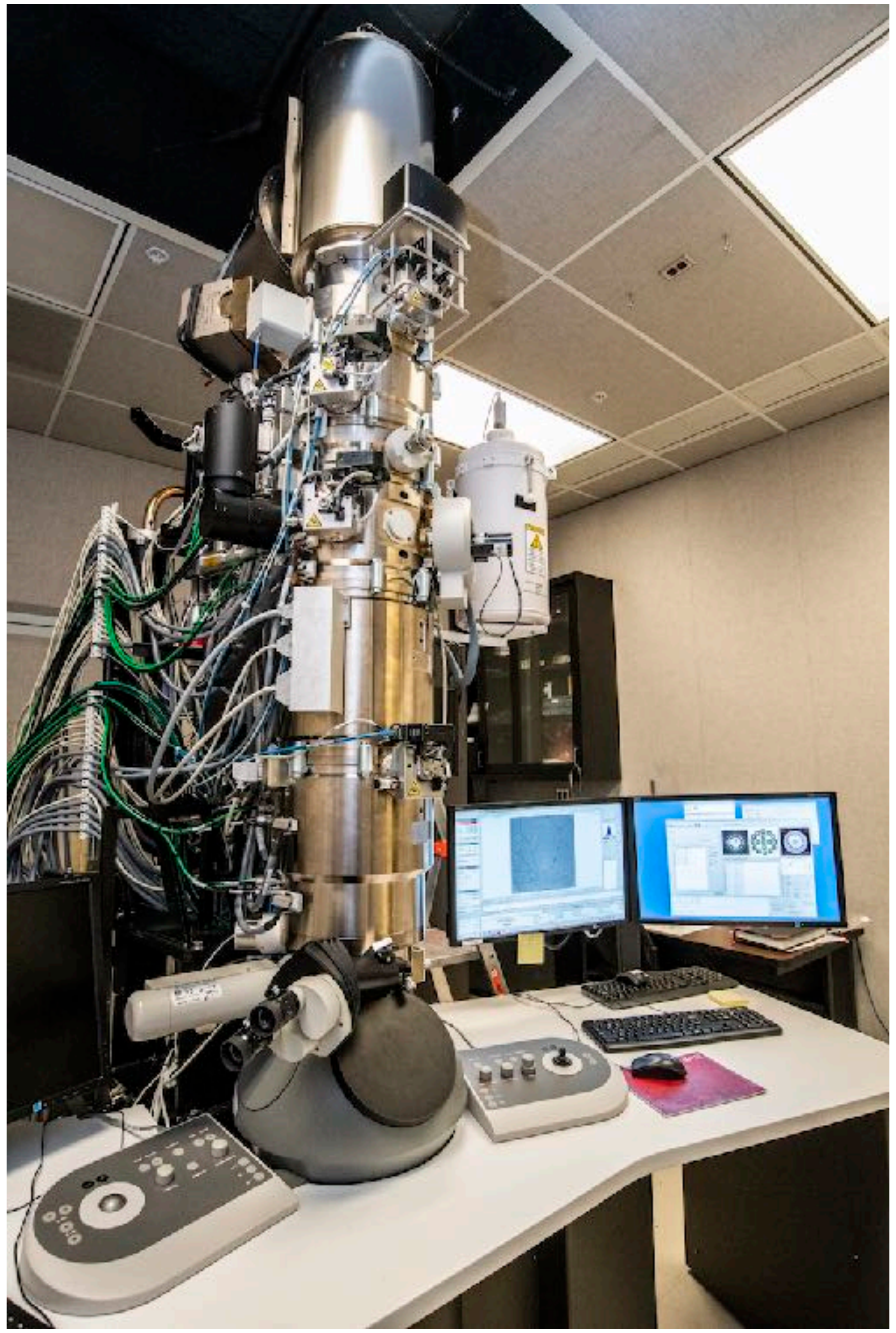


Illustration: ©Johan Jarnestad/The Royal Swedish Academy of Sciences

Cryogenic electron microscopy (Cryo-EM)



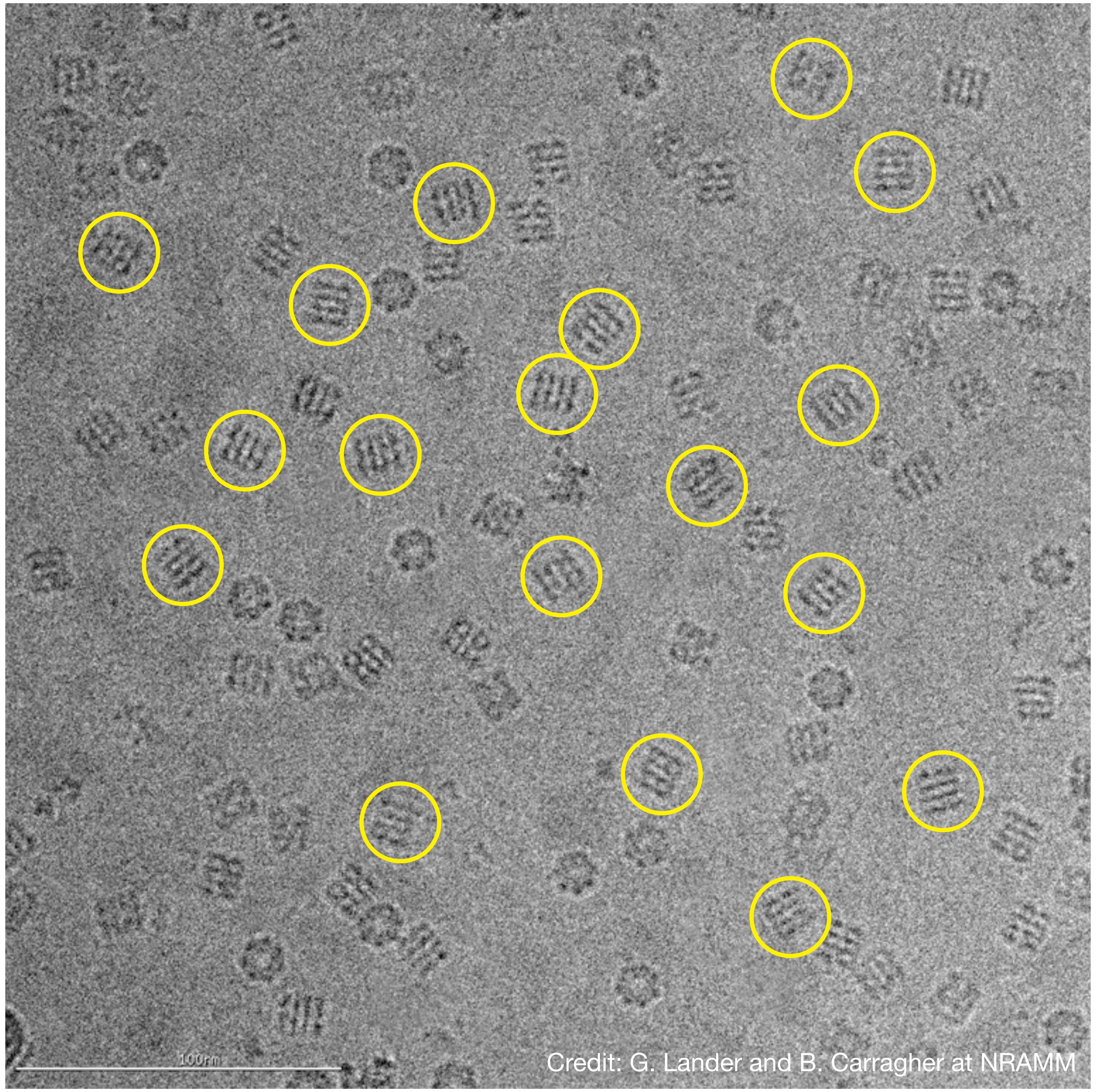
Why electron?

Better resolution!

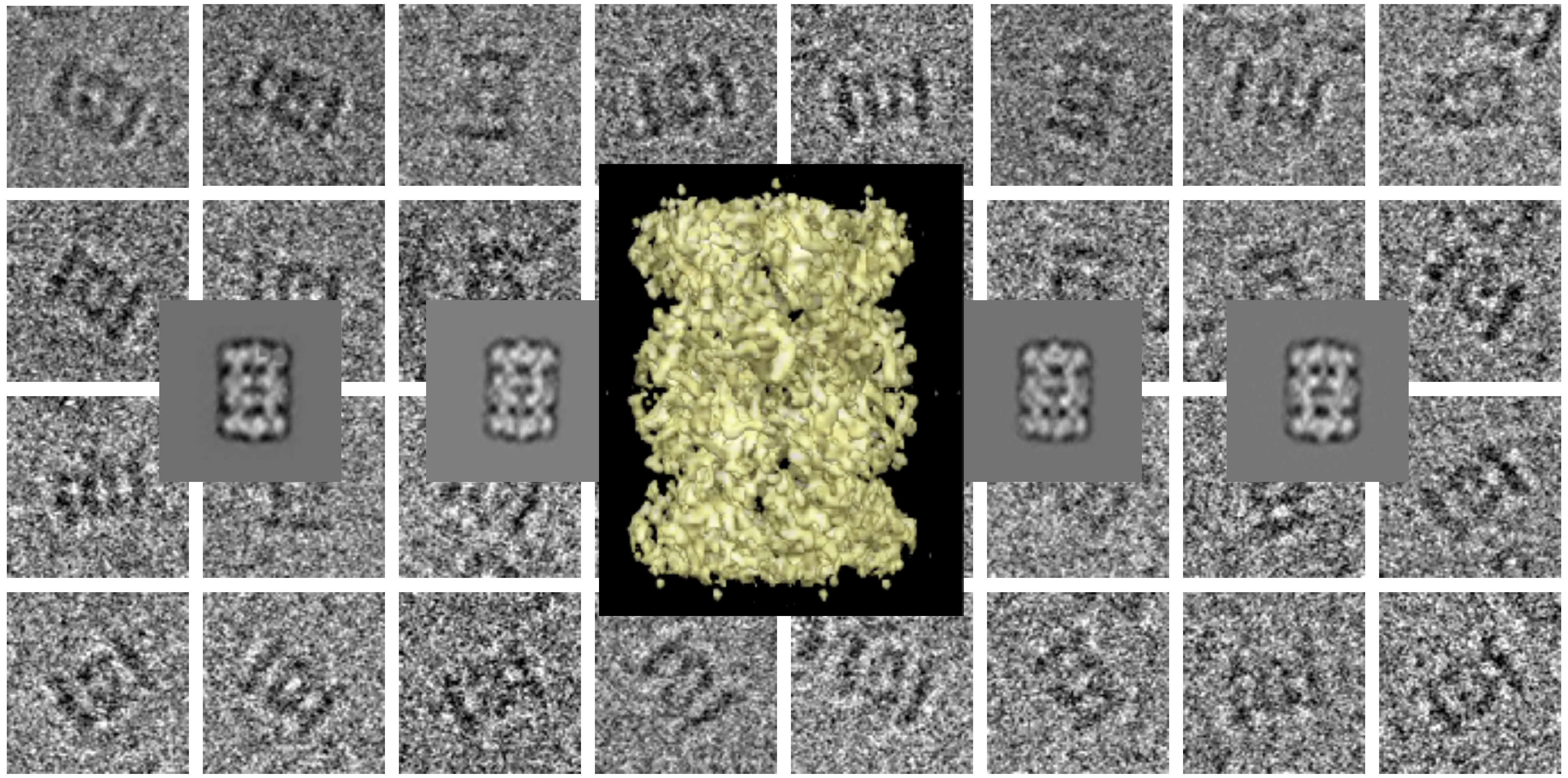
Why cryogenic?

Protect biological sample!

Single particle cryo-EM



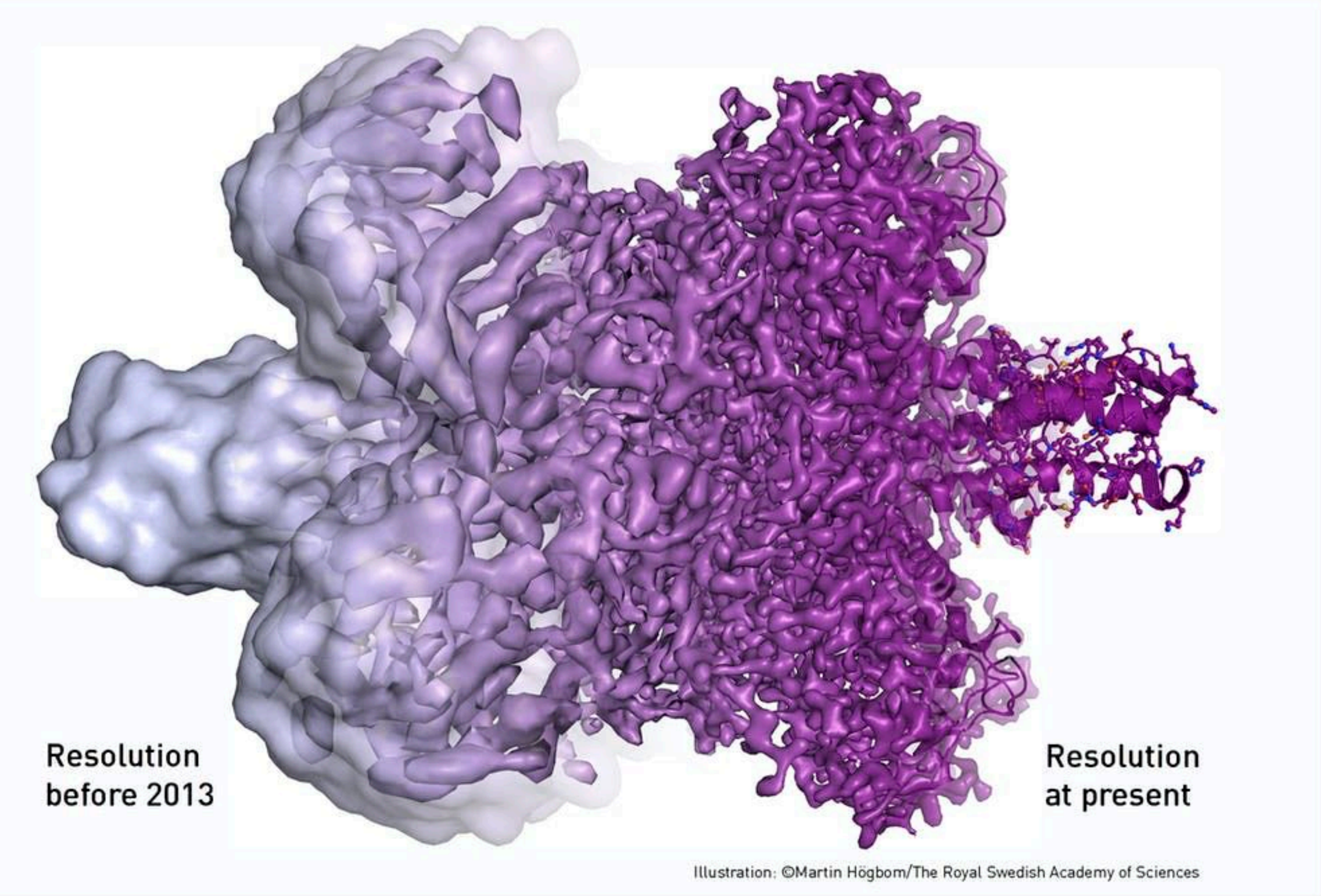
Single particle cryo-EM



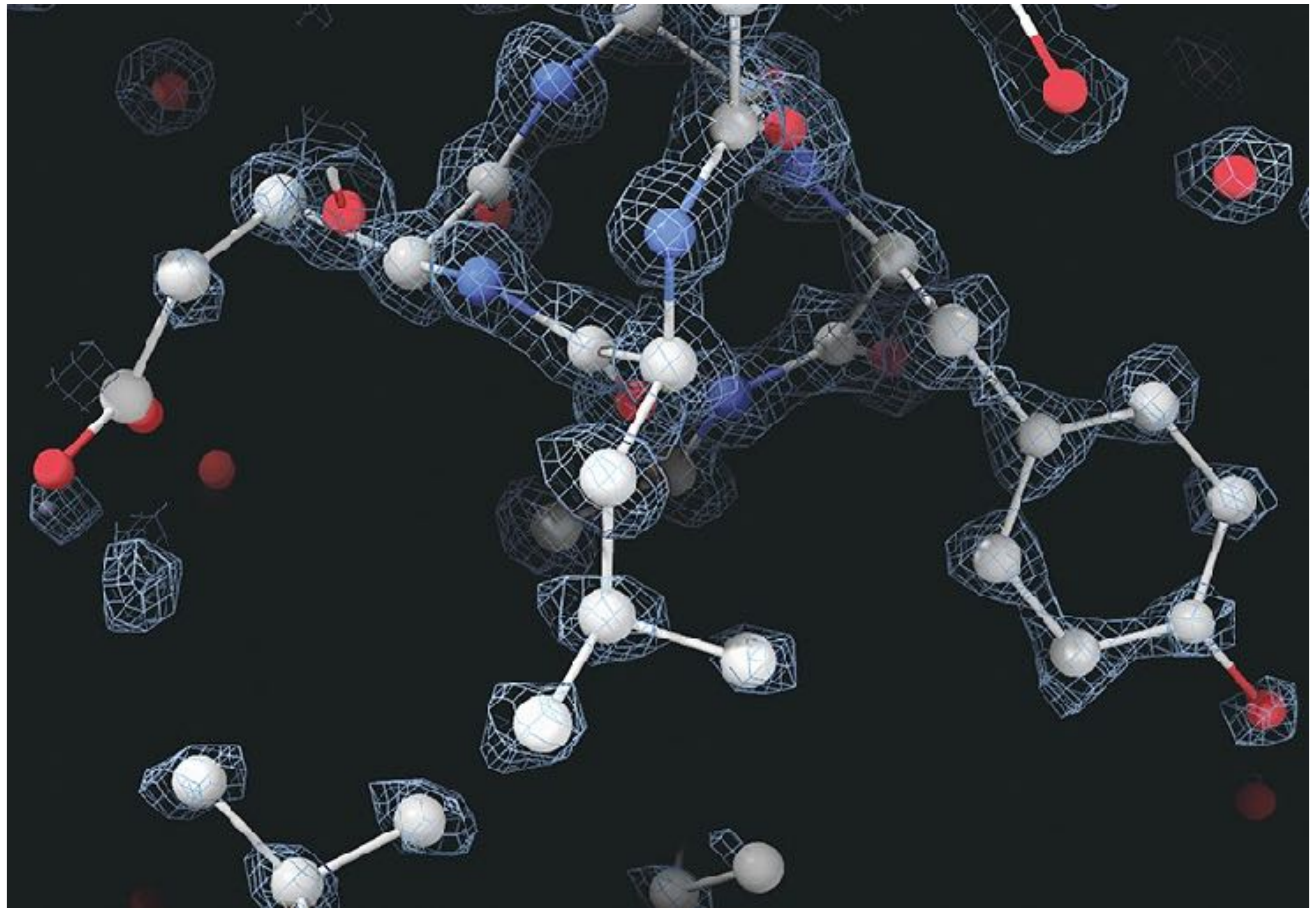
Box out [illegible] images

Credit: G. Lander and B. Carragher at NRAMM

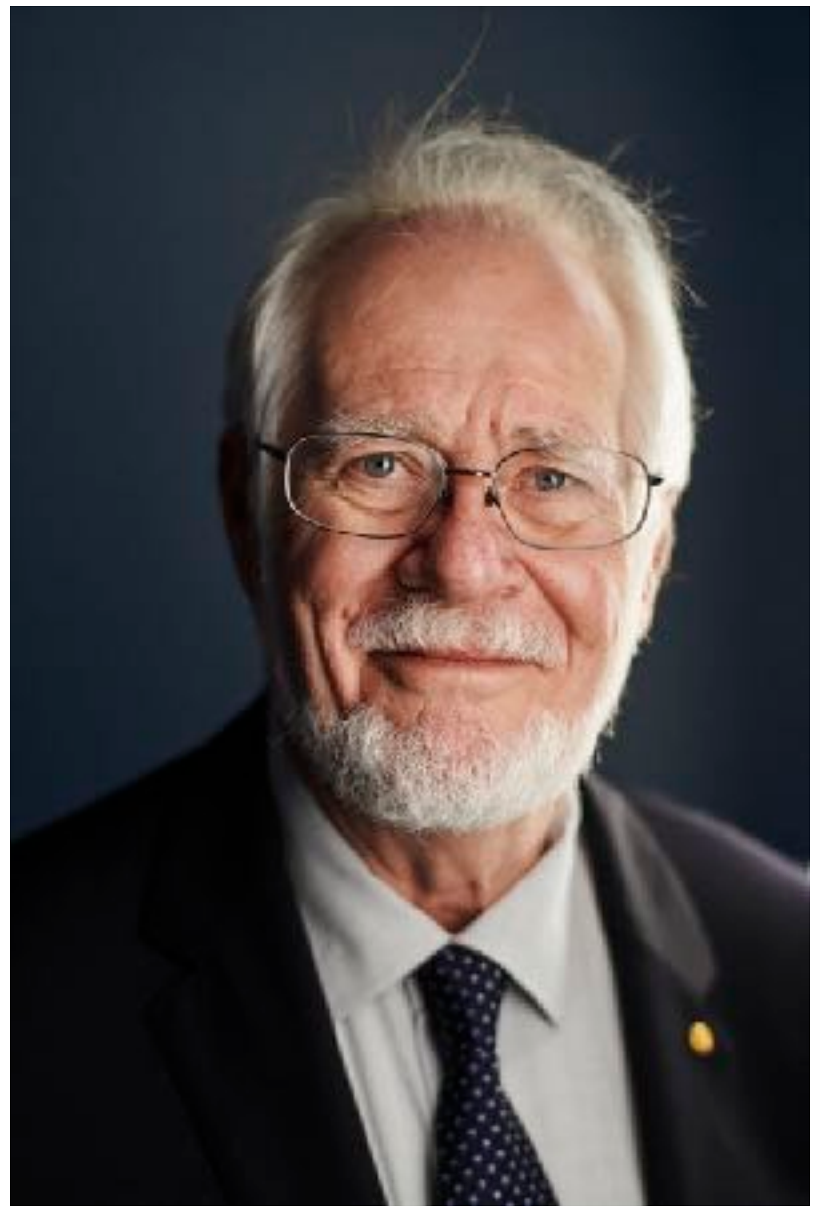
Resolution revolution in cryo-EM



1.2 Å cryo-EM map



Yip, K. M. et al. 2020
Nakane, T. et al. 2020

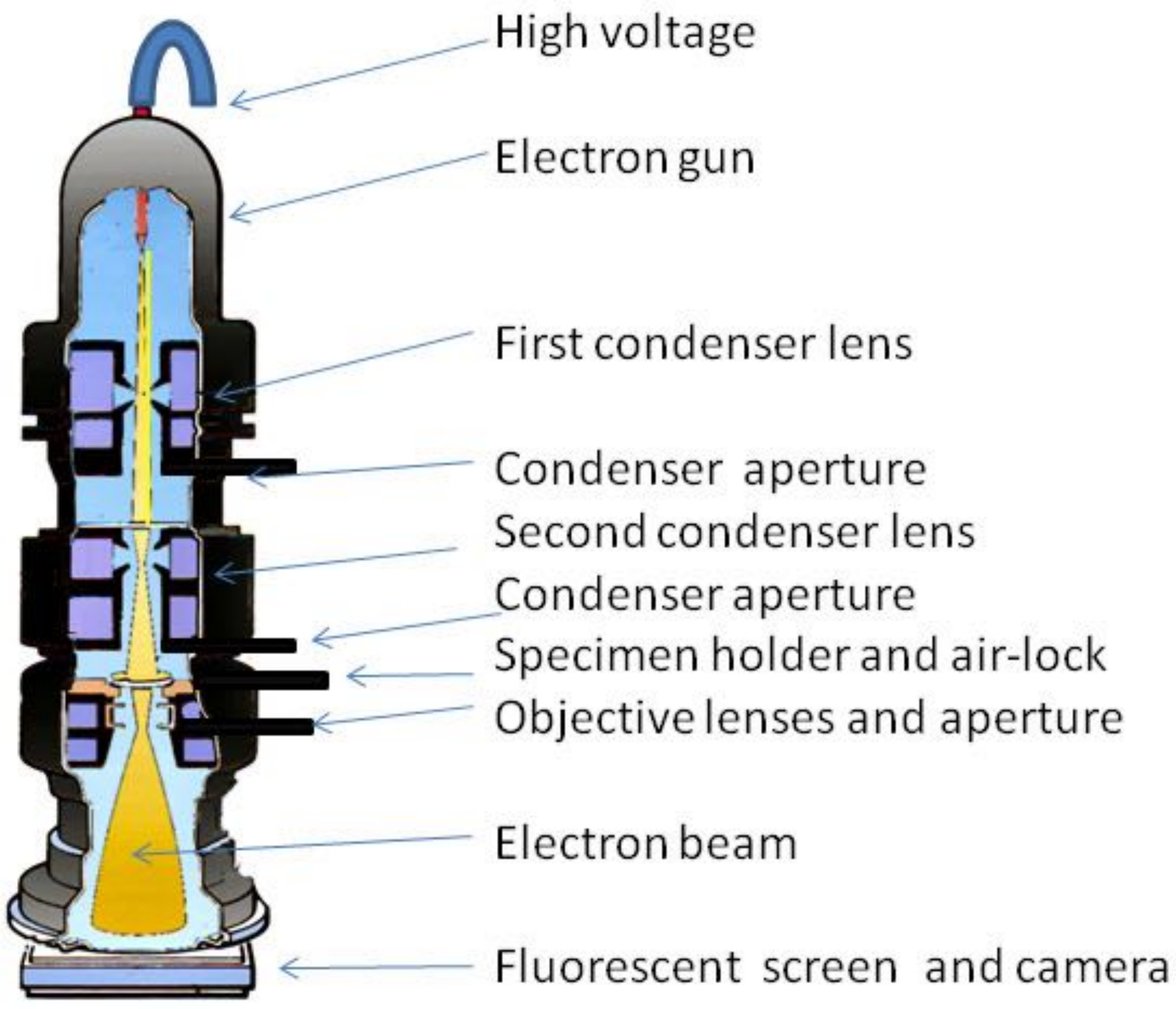


Jacques Dubochet **Joachim Frank** **Richard Henderson**

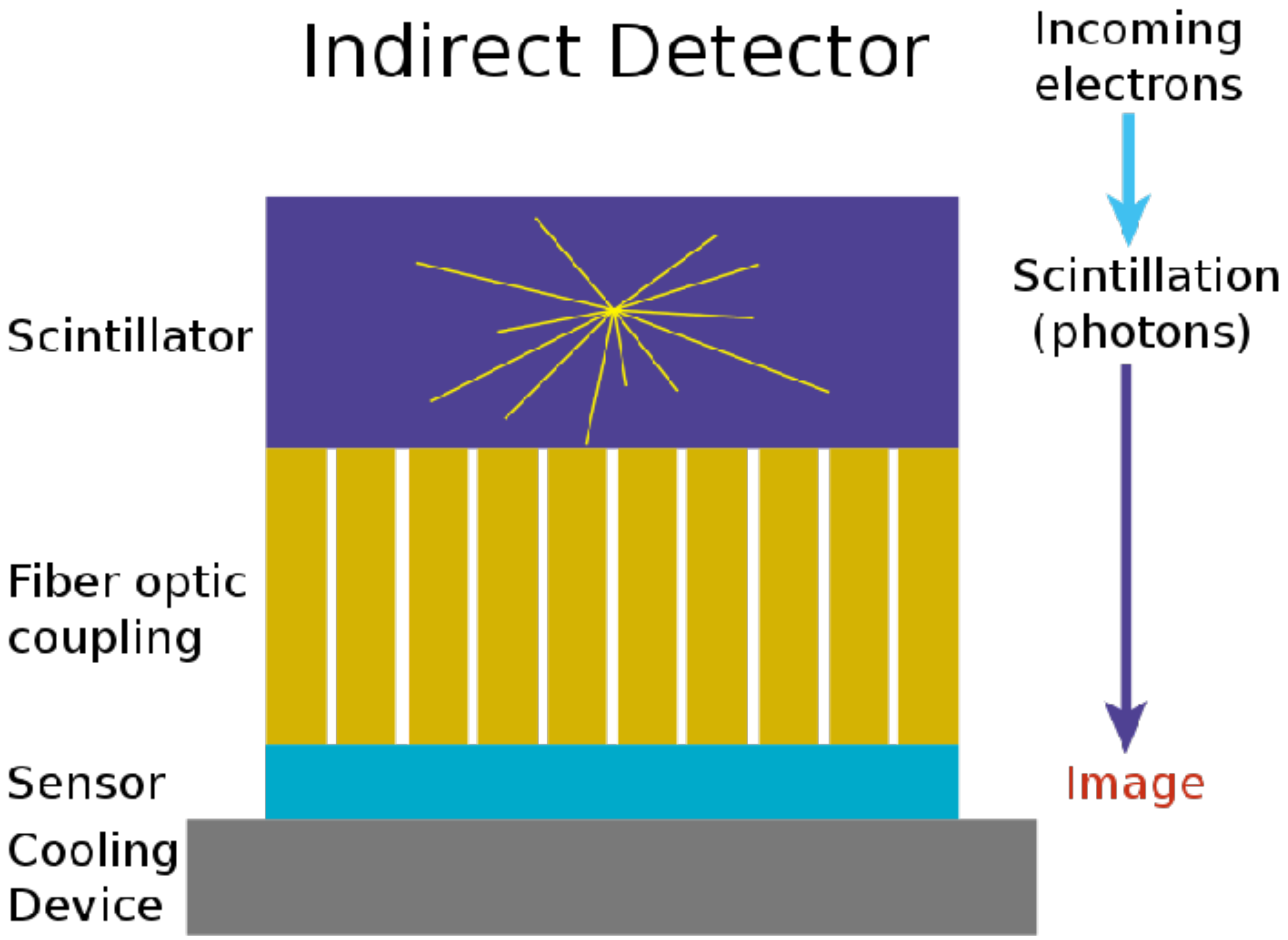
The Nobel Prize in Chemistry 2017

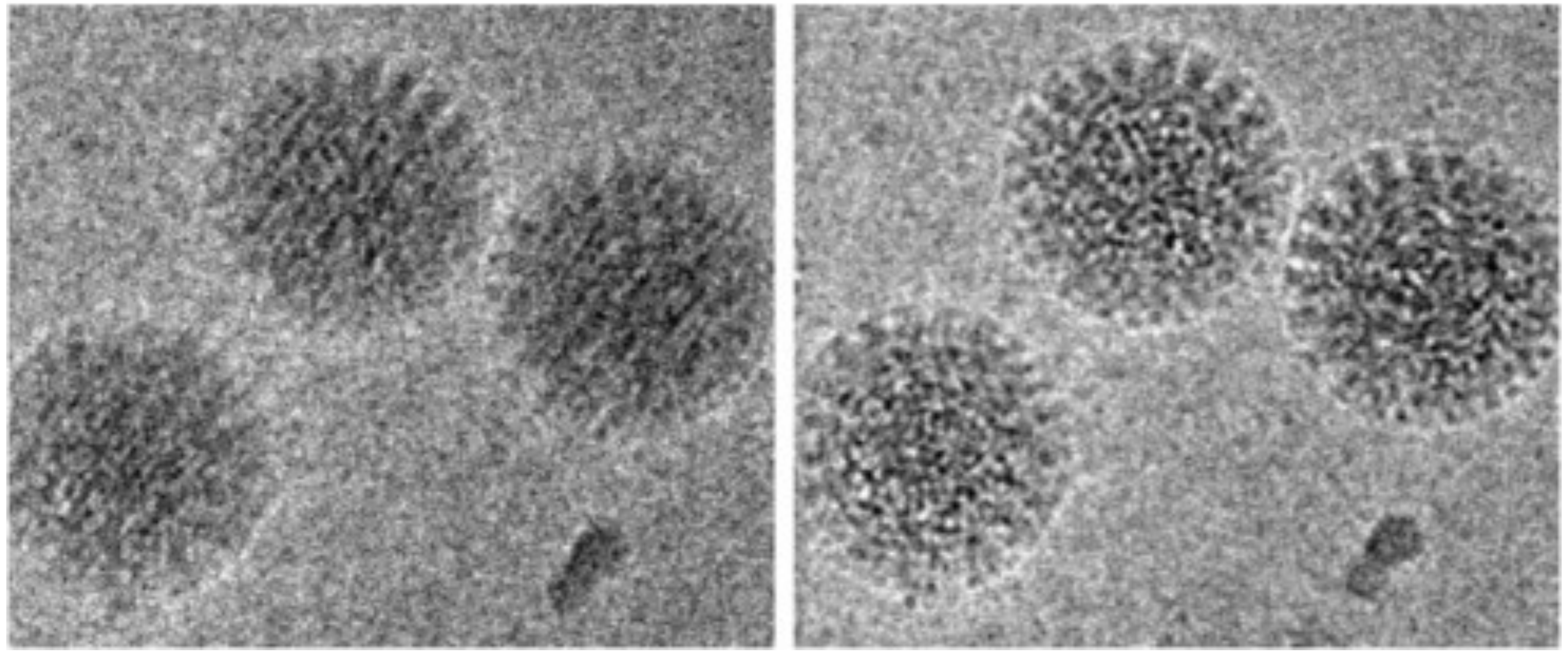
“for developing cryo-electron microscopy for the high-resolution structure determination of biomolecules in solution”

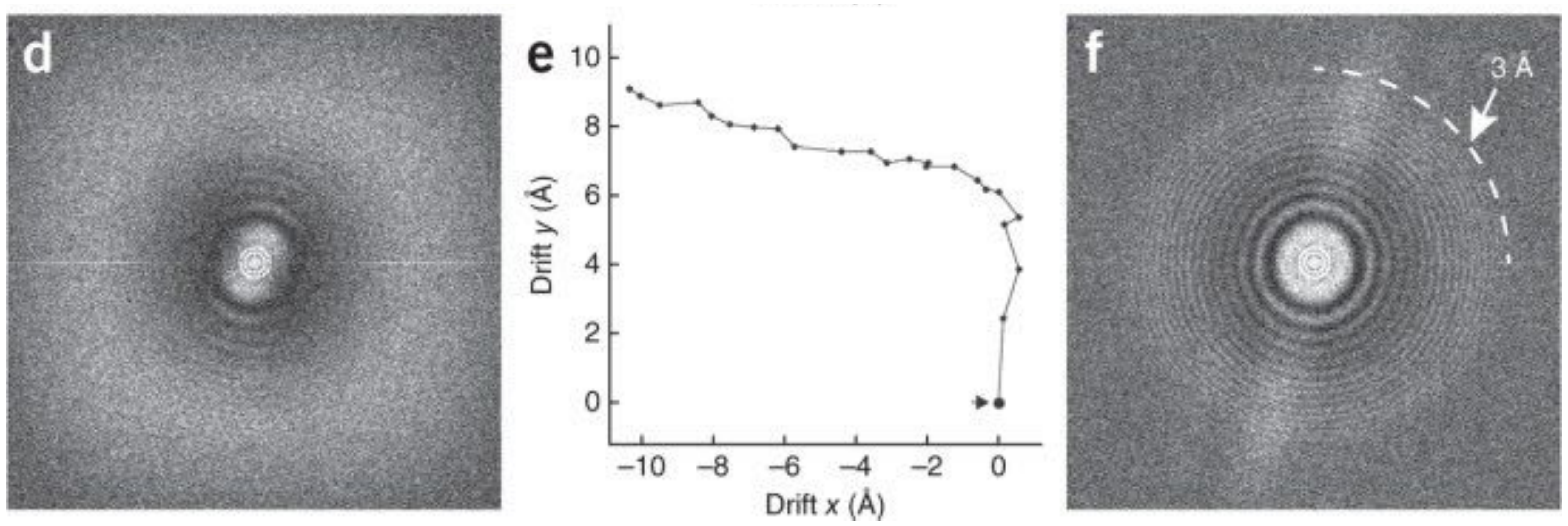
What enabled the resolution revolution in cryo-EM: better microscope



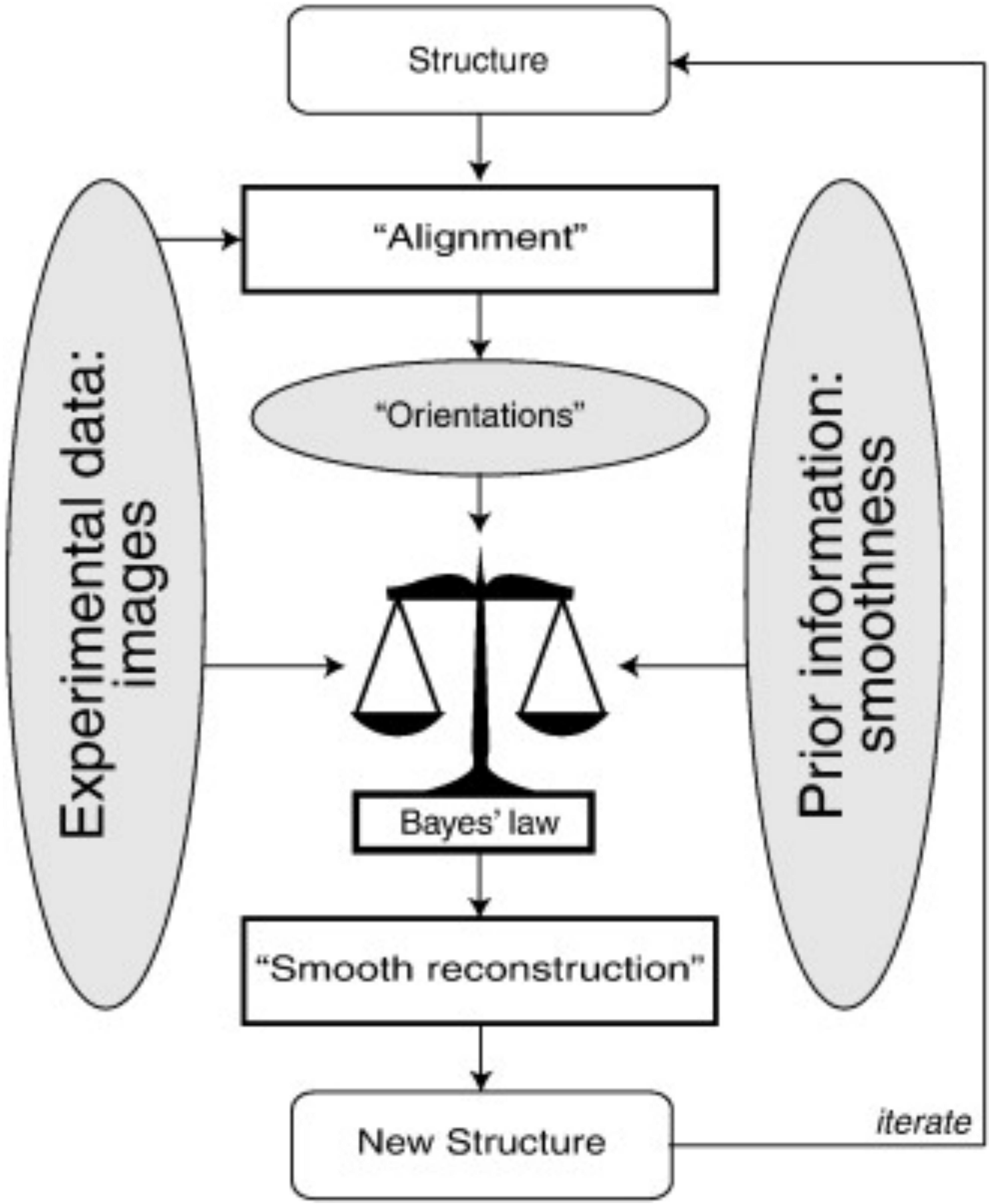
What enabled the resolution revolution in cryo-EM: better camera







What enabled the resolution revolution in cryo-EM: better algorithm



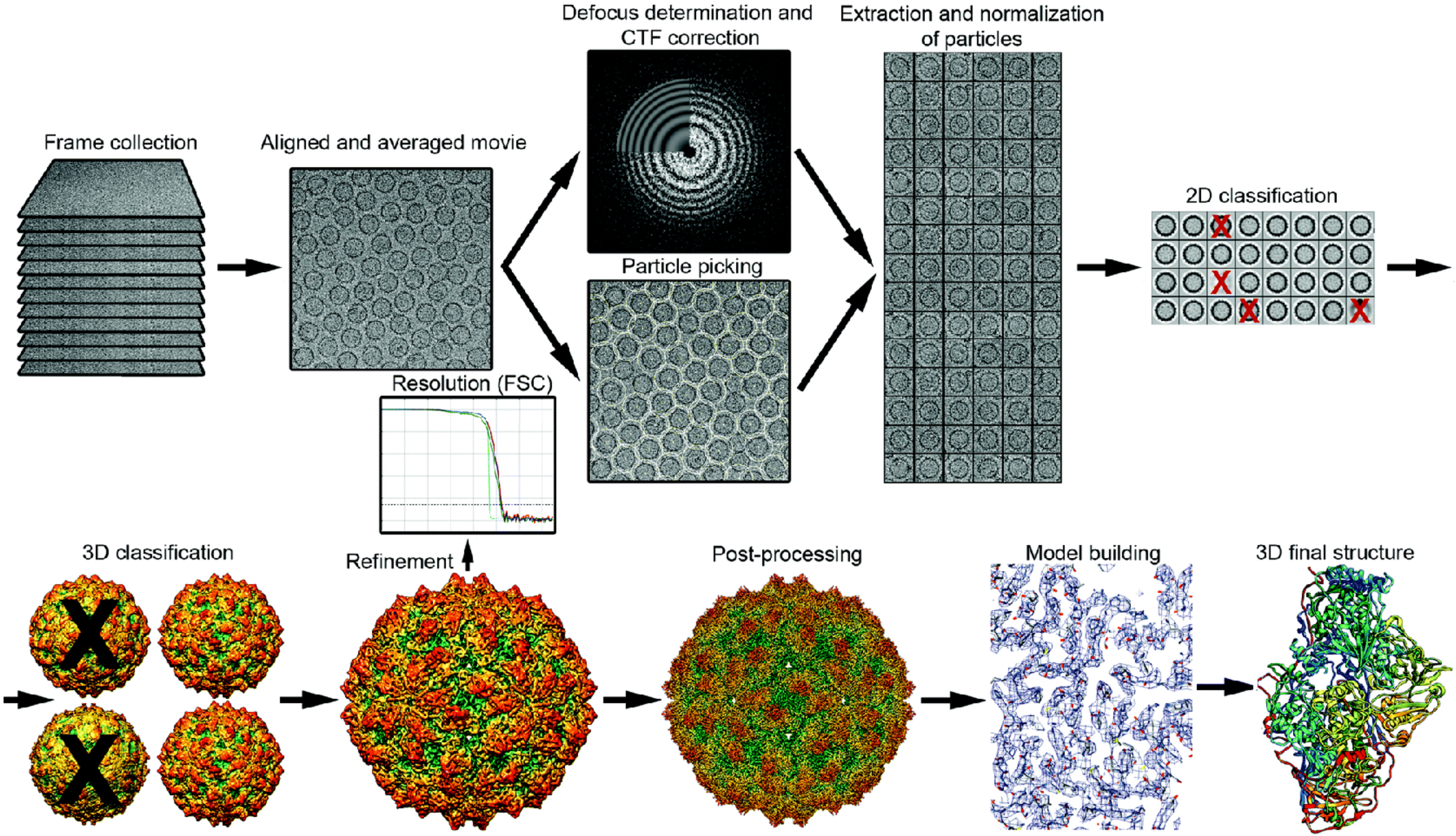
Bayesian statistics

$$Posterior = \frac{Likelihood\ x\ Prior}{Evidence}$$

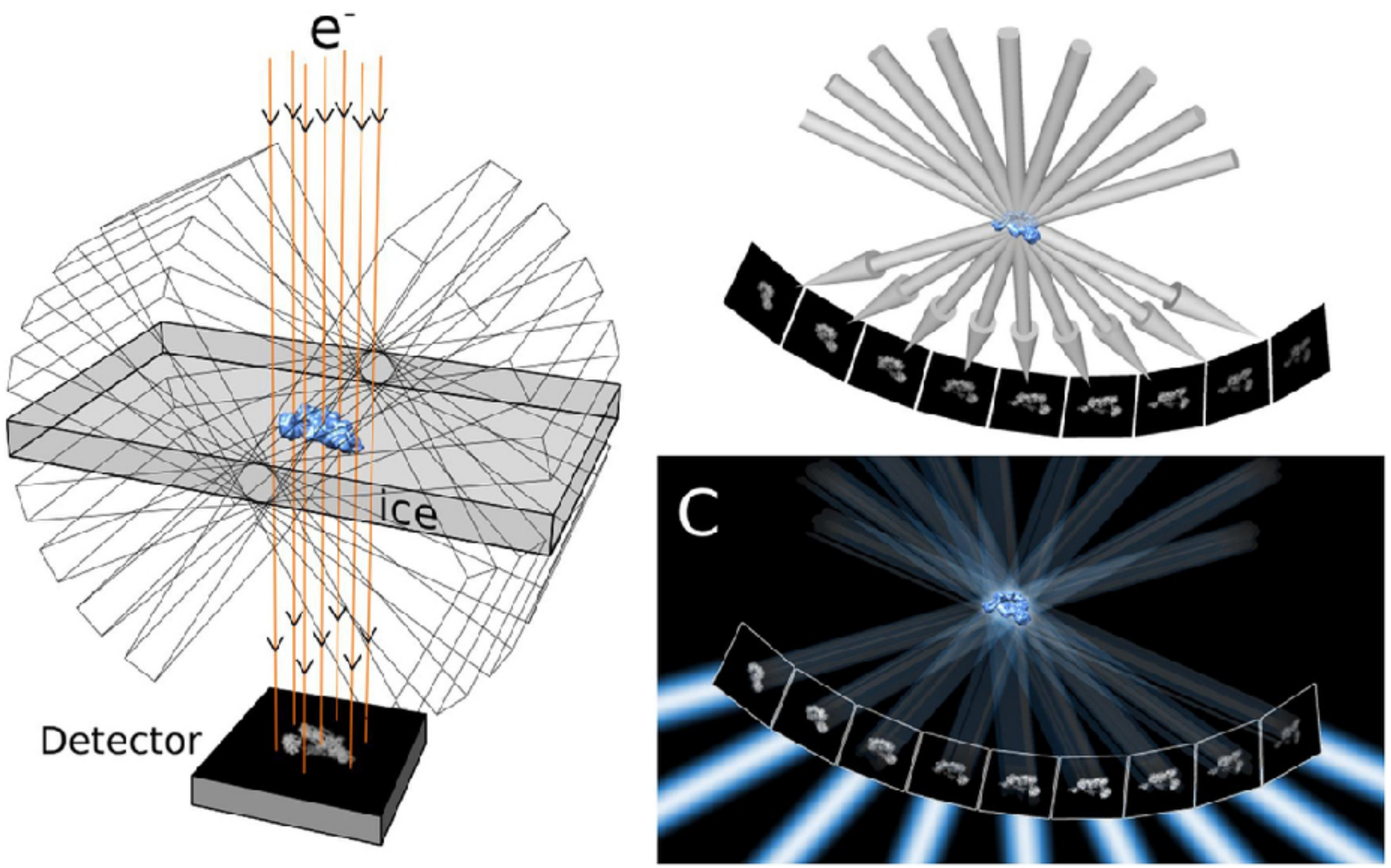
$$P(A\,|\,B) = \frac{P(B\,|\,A)P(A)}{P(B)}$$

$$P(C\,|\,+) = \frac{P(+\,|\,C)P(C)}{P(+)}$$

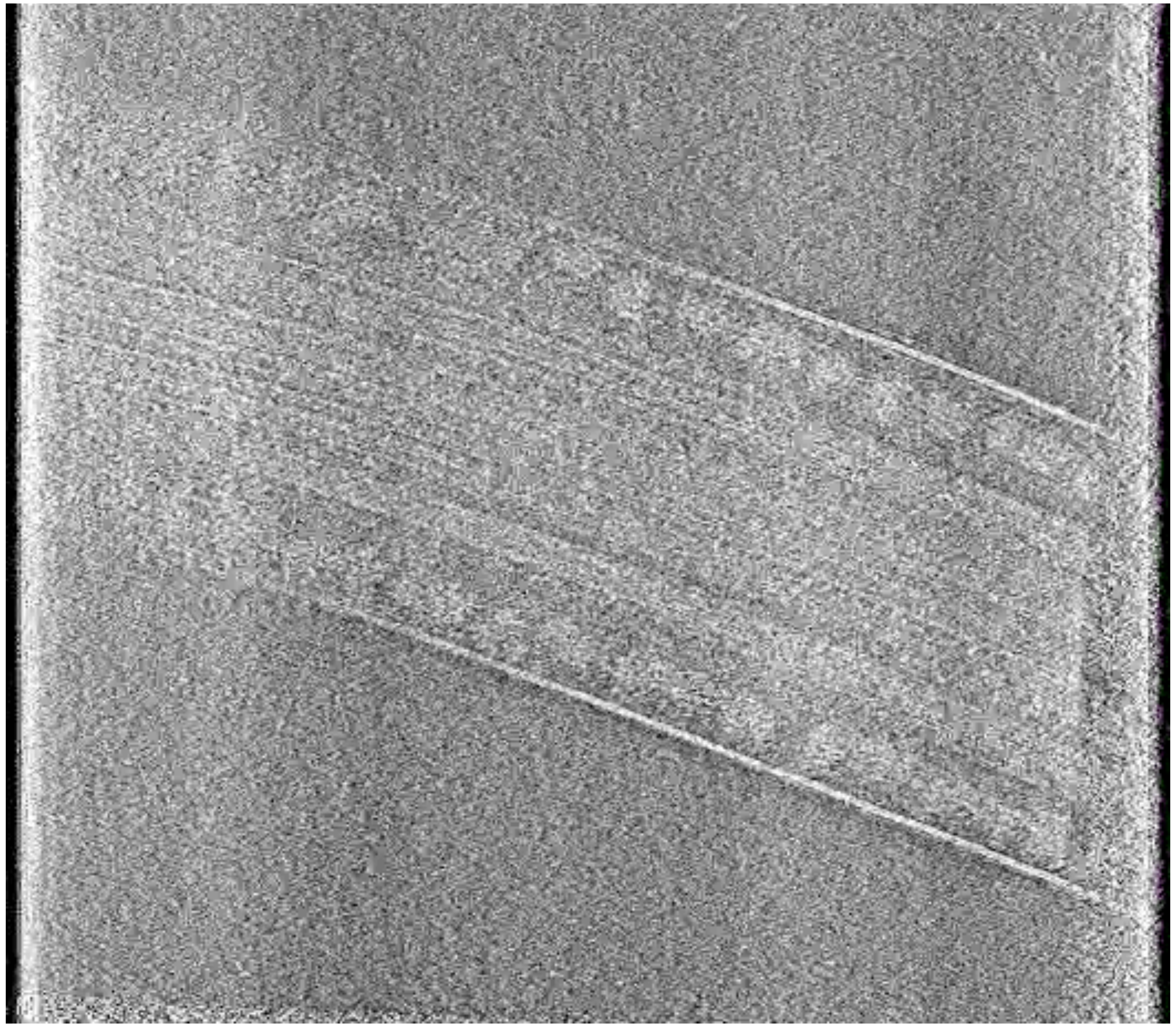
NEW cryo-EM workflow



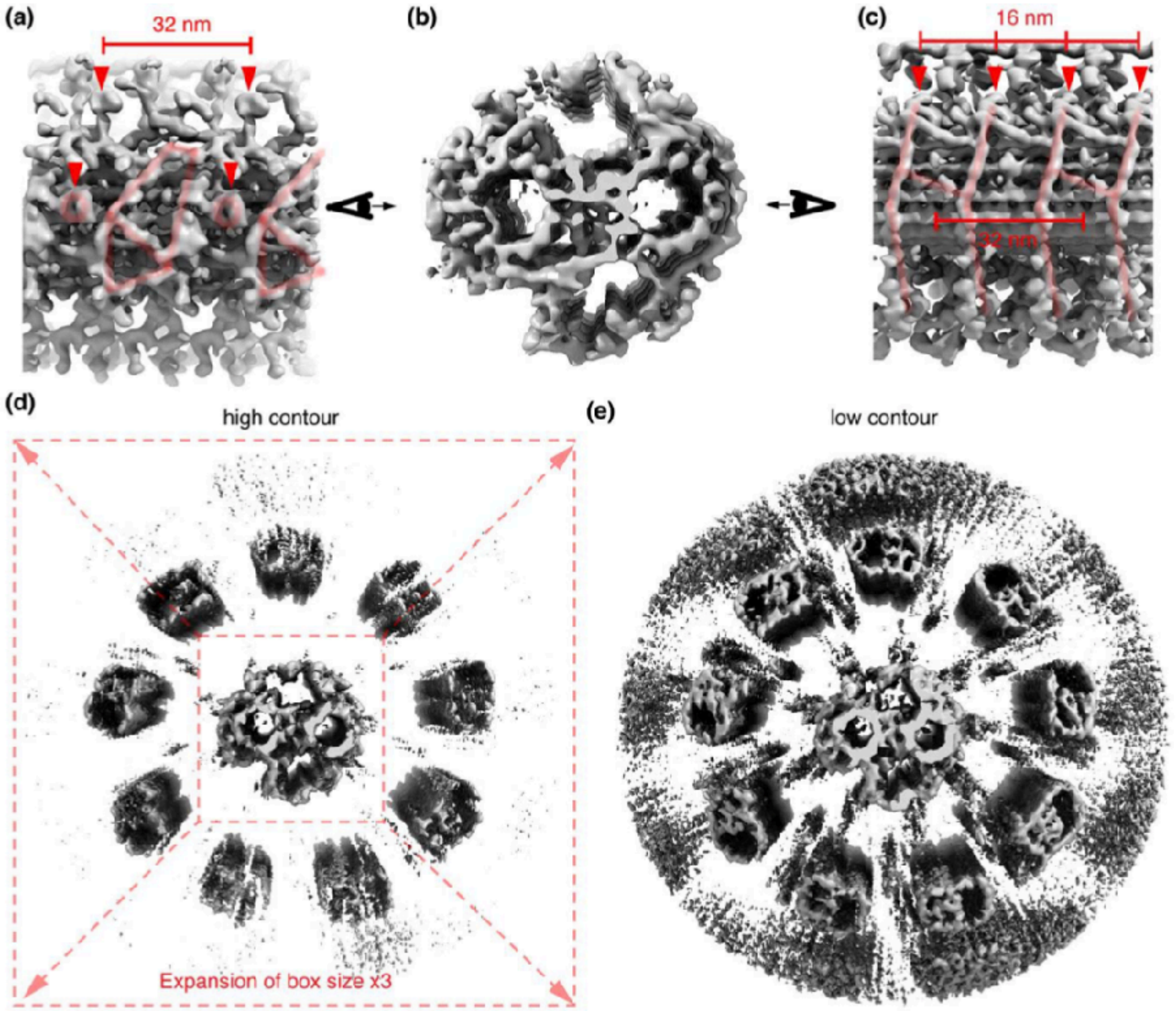
Cryo-electron tomography



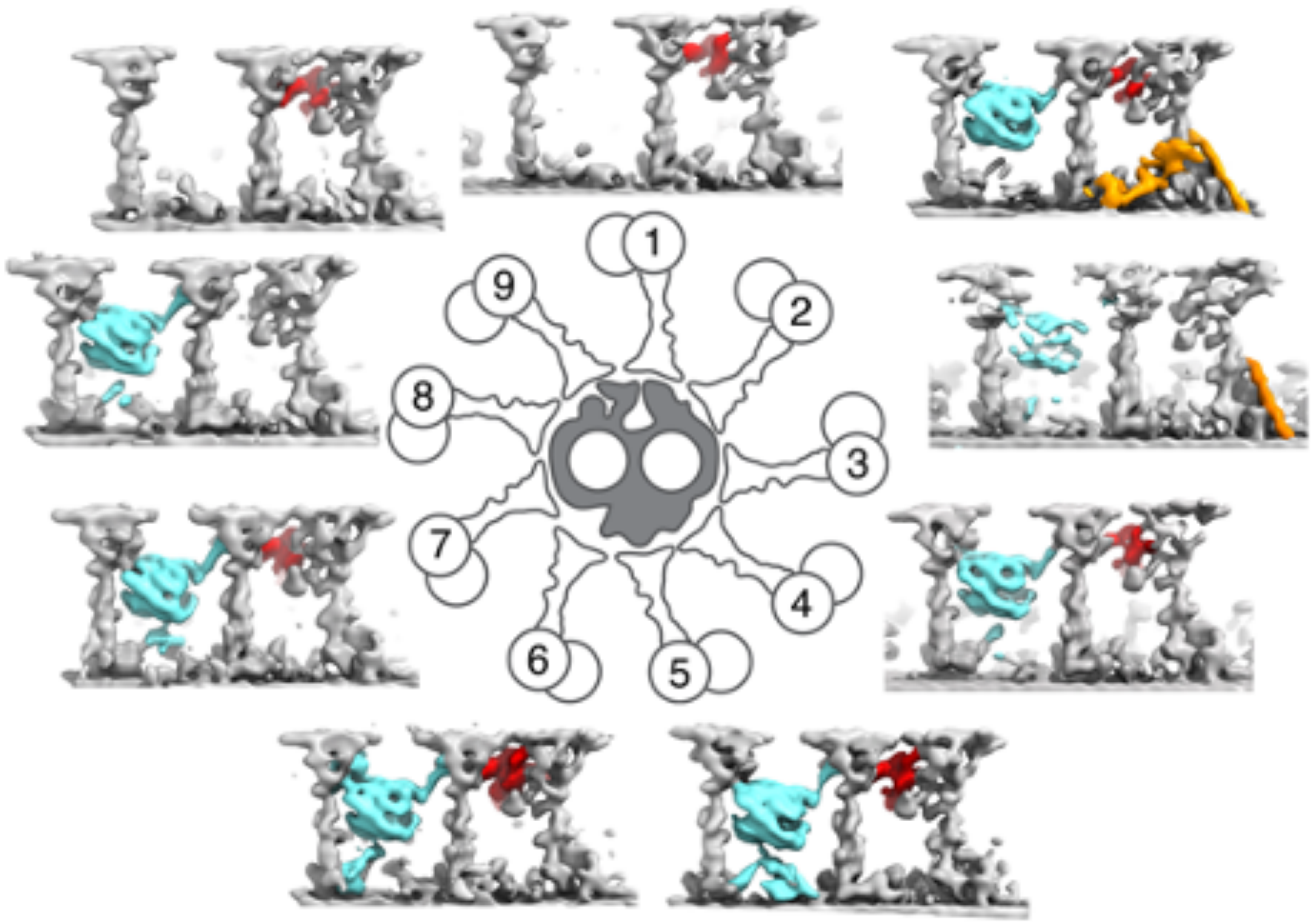
Challenges in cryo-electron tomography



3D reconstruction of sperm tail



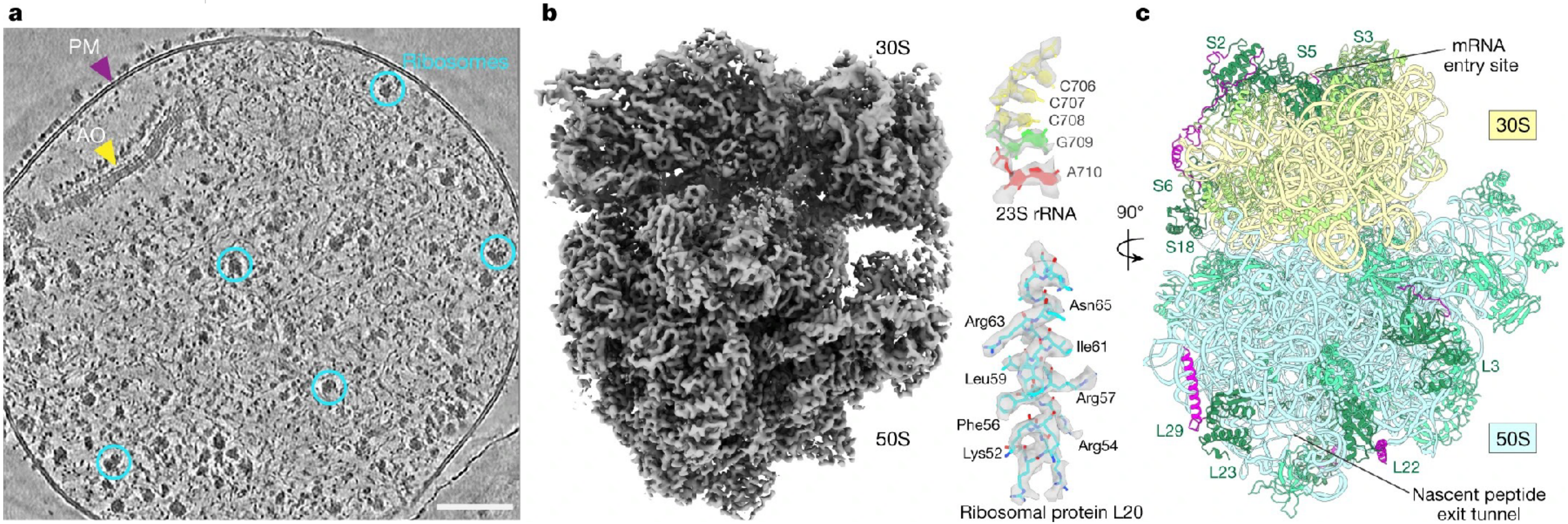
Asymmetric distribution of novel non-motor protein complexes (Radial Spokes)



In situ atomic resolution cryo-electron tomography

Article

Visualizing translation dynamics at atomic detail inside a bacterial cell



SRF as electron source for Cryo-EM: Opportunities

	FEG	SRF	Benefit
Brightness	~10^{11} A sr^{-1} m^{-2}	>10^{13} A sr^{-1} m^{-2}	Sharper, higher SNR Images
Enenrgy	200-300 keV	MeV	Thicker sample
Energy Spread	0.3-0.7 eV	<0.1 eV	Less chromatic aberration
Temporal coherence	ns–μs	fs–ps	time-resolved cryo-EM
Stability	Hours	Days	Automation

tungsten/LaB6 guns (thermionic) → Schottky FEGs → cold FEGs → SRF

SRF as electron source for Cryo-EM: Challenges

- **Radiation damages: Low dose, fast data collections, better detector**
- **Size & complexity: cryogenic infrastructure and vacuum systems**
- **Energy mismatch: compact and tunable cavities**
- **Integration with TEM optics**
- **Cost: Synchrotron vs tabletop instruments**

Thank you!