Abstract:

Single-particle cryogenic electron microscopy (SP cryo-EM) has transformed the way we can study biological molecules as it enables us to determine structure of molecules freely suspended in solution (as “single particles”), and to gauge the way they

change their shape as they interact with one another in the cell. Freezing, by plunging the sample into a cryogen at liquid nitrogen temperature, is necessary to trap the molecules in a fixed position during imaging and to reduce the damage inflicted by the electrons in the process. Tens or hundreds of thousand projection images are captured in the electron microscope and computationally analyzed, resulting in sharp 3D images of the biomolecules.

Following the introduction of novel cameras for detecting single electrons in 2012, near-atomic resolution has been achieved for many molecules and molecular machines of biomedical relevance, including membrane-spanning ion channels and receptors, and atomic models can be built. Compared to the long-established method of structure research by X-ray crystallography, cryo-EM has the advantage that (i) it requires no crystals and that (ii) the results obtained reflect the actual range and variability of structures found in the cell.

For these reasons, SP cryo-EM is now contributing increasingly to the growing publicly available knowledge base of protein and RNA structures, and to the development of drugs in molecular medicine. For instance, most recently single-particle SP cryo-EM has contributed in major ways to the development of vaccines and cures for COVID-19. The list of diseases with cures benefiting from structure research by SP cryo-EM is impressive and growing: among these are COVID-19, heart diseases implicating mutations of RyR, cancer, cystic fibrosis, diabetes, and Alzheimer’s.

In view of prevalent confusion in the public about the possible role of AI, it must be noted that experiments are, and continue to be, the corner stone of science. AI predictions are based on mining the results from decades of painstaking experimental research; they are useful in some contexts but can in no way replace empirical research.