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Advances in Cryo-Electron Microscopy: Techniques, Applications, and Future Directions

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Abstract: ***This abstract highlights the principles, applications, and impact of Cryo-EM on our understanding of biology and disease. Cryo-Electron Microscopy (Cryo-EM) is a revolutionary imaging technique that has transformed the field of structural biology. By rapidly freezing biological samples in a vitreous ice state, Cryo-EM enables the visualization of macromolecules, cells, and tissues at near-atomic resolution. This technique has overcome traditional limitations in electron microscopy, allowing for the study of biological specimens in their native, hydrated state. Cryo-EM has revealed intricate details of protein structures, elucidated mechanisms of cellular processes, and enabled the development of novel therapeutics. With its ability to image a wide range of biological samples, Cryo-EM has become an indispensable tool for researchers seeking to understand the intricacies of life at the molecular level. Cryo-Electron Microscopy (Cryo-EM) has revolutionized the field of structural biology, enabling researchers to visualize biological macromolecules, cells, and tissues at unprecedented resolution. By combining advanced cryogenic techniques, high-vacuum environments, and sophisticated electron optics, Cryo-EM has overcome traditional limitations in electron microscopy.***

I. INTRODUCTION

In Structural biology, Cryogenic-Electron Microscopy (cryo-EM) has become a potent tool that can provide high-resolution density maps of macromolecular structures. Now that resolutions close to 1.5 A are achievable, maps in the 1-4 A range provide highly reliable information for building atomistic models. A surge in interest in using cryo-EM has resulted from researchers' new ability to detect macromolecular structures at high resolution and without the necessity for crystallogenesis. On 3-mm-diameter TEM support grids coated with a carbon sheet with a consistent pattern of holes, protein suspensions are frozen. The grids are constructed of a conductive substance (such as Cu or Au). The diameter is 1-2 μm. rost accumulation on the grid is caused by water vapor. These ice crystals appear on the grid surface beneath the TEM as massive rocks that totally obstruct the electron beam. For this reason, grids are kept as submerged in liquid nitrogen as possible to reduce frost contamination In1968, physicist George Gamow and microbiologist Martynas Ycas released a popular scientific book. Up until a few years ago, scientists could only dream of being able to examine cells and organelles in greater depth using an electron microscope in order to learn more about the atomic minutiae of the biomolecules that support their structure and function. Recently, a number of significant advancements made it feasible to fully benefit from the groundbreaking discoveries and advancements made by Jacques Dubochet , Joachim Frank, and Richard Henderson, turning this ideal into a reality. These developments now enable single-particle1 cryo-electron microscopy (EM) to be used for the high-resolution structural analysis of non-crystalline biomolecules in solution. (Jacques Dubochet, 4 oct, 2017) Research on biomacromolecules and related complexes has been conducted using electron microscopy. The study of biomacromolecule structure has been facilitated by the development of electron microscopy through experience and increased comprehension. (C-C, 2018) The fundamental idea behind cryo-EM is to project protein molecules in all directions by imaging biological macromolecules that have been frozen and preserved in glassy ice. After that, a computer is utilized to process and compute.[3,4] microscope to study small-scale structures. Imaging biological material at cryogenic temperatures—typically liquid nitrogen temperatures, or around -196°C—is known as cryo-electron microscopy, or cryo-EM. With the aid of this method, scientists can examine the composition and arrangement of biological components, tissues, and cells in their original, hydrated states. This is a definition of the term: - Cryo-: denotes the preservation of the sample by application of cryogenic temperatures. - Electron: denotes the use of an electron beam rather than a light source to photograph the sample. - Microscopy: refer to the use of a microscope to study small scale structure.

II. PRINCIPLE

Cryo-electron microscopy (cryo-EM) uses a beam of electrons to image biological samples at cryogenic temperatures. The electrons interact with the sample, producing a 2D image that can be reconstructed into a 3D structure using computational methods.

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Samples used in cryo-EM are usually:

1) Vitrified: quickly frozen to stop the development of ice crystals and maintain the original structure.
2) Mounted: in a sample container or on a cryo-EM grid.
3) Imaged: at cryogenic temperatures using a transmission electron microscope (TEM).
4) Processed: 2D or 3D pictures of the sample are reconstructed using computational techniques.

While the cryo-EM technique was first developed in the 1970s, its widespread attention has been drawn in the last ten years due to the attainment of near-atomic resolution (<4 A).[5]

Since airborne molecules deflect electrons, electron microscopes need to be run in extremely high vacuums. Studying biological samples presents an issue because the majority of them naturally occur in watery environments. In addition, biological structures are vulnerable to radiation harm.[6] Three electrons will deposit energy in the sample for every electron that aids in the creation of an image. Chemical bonds break as a result of this energy, and the target structures are finally destroyed.Cryo-electron microscopy, or cryo-EM, preserves samples in a high vacuum and offers them some defense against radiation damage by maintaining them at cryogenic temperatures.[7] A computer analyzing the 2D projection images can still be used to calculate the relative orientations of individual particles a posterior. [8]a method called single-particle analysis.

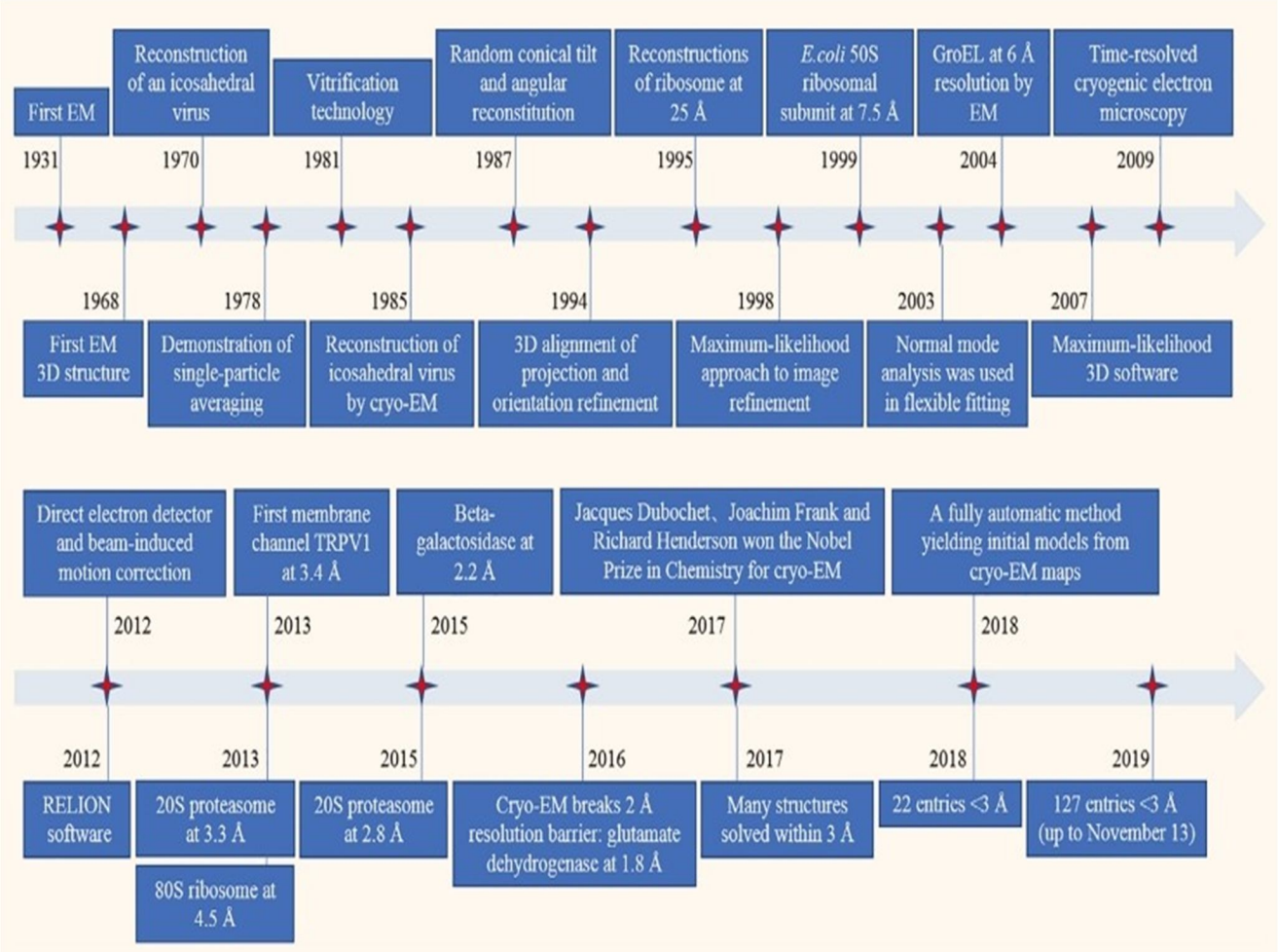
III. HISTORY AND DEVELOPMENT

The past: The first transmission electron microscope was created in 1931 by German scientist Max Knoll and his pupil Ernst Ruska. In 1933, they achieved the first breakthrough beyond the optical microscope's limitations, enabling the observation of even smaller particles. The imaging process of electron microscopy requires a high vacuum, and biological samples are highly vulnerable to electron radiation damage. As a result, in the decades that followed, scientists could only use heavy metal salt staining to scan biological samples.The two issues of radiation damage and high vacuum were resolved as a result. The vitrification process not only preserves the sample's natural state but also shields it against dehydration.[9]De Rosier and Klug described the 3D structure of the T4 phagetail in 1968 and developed and established the overall concept and method of 3D reconstruction.[10] The first structure seen under an electron microscope. Taylor and Glaeser (1974) advocated the use of cryo-EM to lessen the radiation damage produced by high-energy electrons.[11]The historical development wheel is turning forward! Alasdair McDowall, Jacques Dubochet's colleague, and they achieved a breakthrough in electron microscopy technology in 1981. They developed the fast freezing technique, [12,13]Computer software does 3D reconstruction after acquiring 2D photos at various angles in order to examine the 3D structure of biomolecules. The resolution of the Escherichia coli ribosome's 50S large subunit was enhanced to 7.5 Å by 1999 about 2000, the number of electron microscope structuresbegan to increase year by year, but the resolution was nothigh. However, after 2013, the number of structures analyzed by electron microscopy began to improve rapidly and the resolution also increased to near atomic level.The structure of β-galactosidase reported in 2015 had aresolution of 2.2 Å [14] the resolution of the 20 Sproteasome[15] the 70S-EF-Tu complex[16] Cryo-EM has advanced significantly in computer image processing over the last few years, including the creation of user-friendly software[17].Glutamate dehydrogenase's (334 kDa) 3D structure was revealed in 2016, with a resolution of 1.8 Å.[18]The expansion of cryo-EM-based structural analysis applications is a result of these technologies' progress. The PDB database now has 3,874 total electron microscope structures as of October 17, 2019, and it is anticipated that this number will continue to rise at a faster rate in the future. Direct electron detector device (DDD) cameras have been instrumental in the extraordinary advancement of single-particle cryo-EM over the past two years.Superior detective quantum efficiency (DQE), which gauges an imaging system's overall performance in terms of both signal and noise, is exhibited by DDD cameras.[19] As of 2010, the quality of accessible cryo-EM protein structures was not consistent with radiation damage theories, which postulated that protein complexes with molecular weights as low as 100 kDa should be able to determine their structures to atomic resolution[20]. The ineffective electron detection may contribute to the discrepancy. Photographic film was used to record images initially, but in the early 2000s, digital charge-coupled devices (CCDs) were developed into cameras, which allowed for higher throughput and automated data collecting [21]. Only roughly one-third of the incoming electrons are detected by photographic film. Nevertheless, CCDs are even less effective since an additional electron-to-photon conversion results in a detection rate that is less than one-fifth of the entering electrons overall[22]. By 2012, three businesses had manufactured digital electron detector prototypes. The novel chips' high level of radiation resistance allowed for the direct detection of electrons, increasing detection efficiency to around half of the incoming electrons[23].2013 saw the commercial release of digital electron detectors, which set the cryo-EM field up for revolutionary change. These detectors produced images of previously unheard-of quality, which made orientation assignments more precise. Also, there was an improvement in the capacity to isolate particles from different structural states.

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This era was marked by structures such as the coenzyme F420-reducing hydrogenase[24]. The current achievement was made possible by the introduction of new electron detectors in electron microscopes, which are the latest technological breakthroughs. The Monolithic Active Pixel Sensors used in the construction of these detectors are based on Complementary Metal Oxide Semiconductors, or CMOS technology. Around the middle of the 2000s, preliminary reports on the usage of these sensors for electron detection were published[25, 26]. But these detectors had already been used as a tool in studies of charged particles in other research fields, such as astronomy Silica-based charge-coupled devices (CCD) had been used earlier; however, for technical reasons these detectors were not used to monitor electrons directly. Instead, the electron flux was first converted into light, which introduced noise to the signal. As a result, in many cases, film was a preferred choice when analysing high-resolution data.65/125 Words. The capacity to detect high-energy electrons at low intensities with less noise than film was improved by the new Direct Electron Detectors. The speed at which these cameras function is another benefit.[27] The ability to record a "movie" is frequently employed to offset specimen motion brought on by temperature fluctuations and electron irradiation. Additionally, electron counting is now feasible[28,29].The signal-to-noise ratio and spatial resolution dramatically increased as a result of these advances in detector technology taken together[30-33]. The more recent advancements were also greatly aided by other technological advancements, such as reliable cold stages and Albert Crewe's field emission cannon, or electron source. The present advancements have also been made possible by recent and continuing advancements in computer software and image processing techniques. In electron microscopy, for instance, maximum likelihood algorithms[34,35]were especially crucial after improved resolution was attained with the new electron detector.

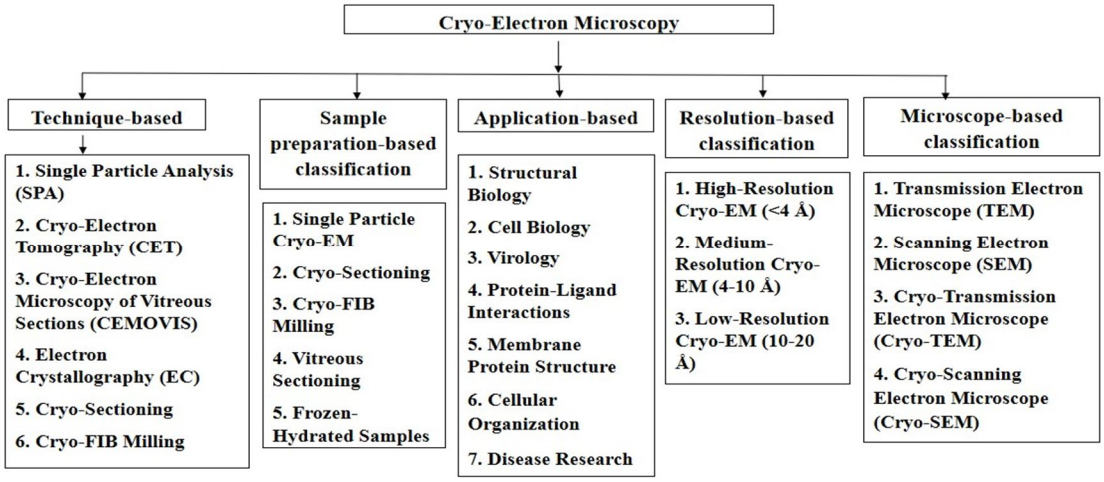
There are some key events during development of cryo- electron microscopy given as follows:



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IV. CLASSIFICATION



A. Technique-based Classification

1) Single Particle Analysis (SPA): Single Particle Analysis (SPA) is a technique used in cryo-electron microscopy (cryo-EM) to reconstruct the three-dimensional (3D) structure of a biological macromolecule, such as a protein or a virus, from a large number of two-dimensional (2D) images of individual particles.

2) Cryo-Electron Tomography (CET): Cryo-electron tomography (cryo-ET) is a technique used to reconstruct the three-dimensional (3D) structure of a biological sample at the nano-scale. It combines cryo-electron microscopy (cryo-EM) with tomography, which involves imaging the sample from multiple angles.

3) Cryo-Electron Microscopy of Vitreous Sections (CEMOVIS): Cryo-Electron Microscopy of Vitreous Sections (CEMOVIS) is a cutting-edge method that combines cryo-electron microscopy (cryo-EM) with vitreous sectioning to study the structure of biological samples at the nanoscale.

4) Electron Crystallography (EC): Electron Crystallography (EC) is a method that combines cryo-electron microscopy (cryo-EM) with crystallography to determine the three-dimensional (3D) structure of biological macromolecules.

5) Cryo-Sectioning: Cryo-Sectioning is a method used to prepare thin sections of biological samples for cryo-electron microscopy (cryo-EM) imaging. It involves cutting the sample into thin slices while it is in a frozen, vitreous state.

6) Cryo-FIB Milling: Cryo-FIB (Focused Ion Beam) Milling is a method used to prepare biological samples for cryo-electron microscopy (cryo-EM) imaging. It involves using a focused beam of ions to mill and shape the sample into a thin lamella, suitable for cryo-EM imaging. (Focused Ion Beam) Milling is a method used to prepare biological samples for cryo-electron microscopy (cryo-EM) imaging. It involves using a focused beam of ions to mill and shape the sample into a thin lamella, suitable for cryo-EM imaging.

B. Microscope-based classification

1) Scanning Electron Microscopy (SEM): Scanning Electron Microscopy (SEM) is a powerful method for the investigation of surface structures of mollicutes. This technique provides a large depth of field, which means, the area of the sample that can be viewed in focus at the same time is actually quite large [36]. SEM has also the advantage that the range of magnification is relatively wide allowing the investigator to easily focus in on an area of interest on a specimen that was initially scanned at a lower magnification.

2) Transmission Electron Microscope (TEM): Transmission Electron Microscopy (TEM) has the advantage over SEM that cellular structures of the specimen can be viewed at very high magnifications. However, TEM sample preparation for mollicutes is longer and more difficult than that for SEM and includes additional steps such as postfixation, the embedding of mollicutes in a resin, the sectioning of samples, and the staining of semithin and ultrathin sections. Bozzola and Russell pointed out that perhaps the least forgiving of all the steps in TEM is the sample processing that occurs prior to sectioning.

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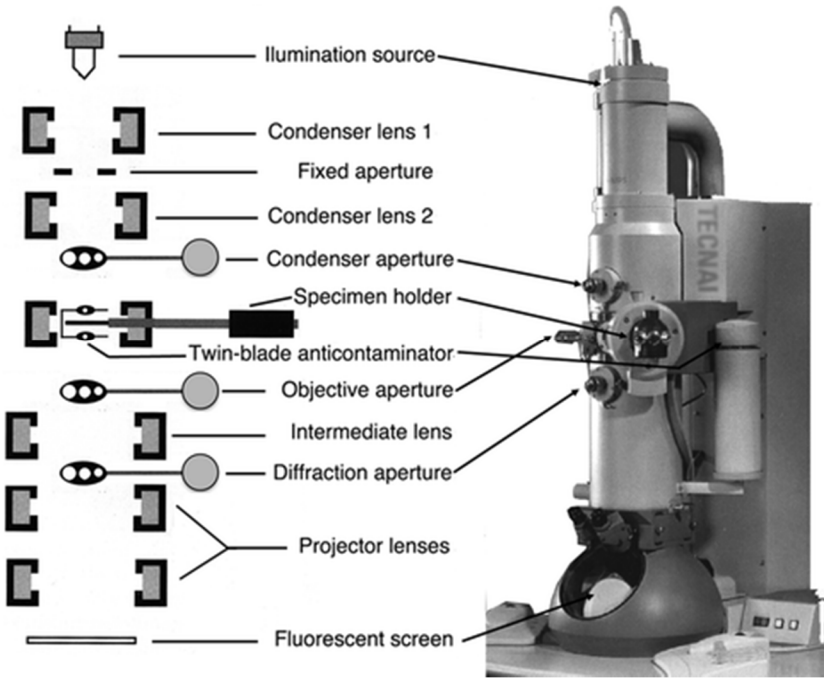
3) Cryogenic transmission electron microscopy (Cryo-TEM): Cryogenic transmission electron microscopy (Cryo-TEM) Specimen preparation took place in a home-made controlled environment vitrification system (CEVS) [37]. Specimens were prepared at a constant temperature of 25 or 37uC. To prevent solvent evaporation and changes in solvent concentration, the specimens were prepared in a chamber at 100% relative humidity [38].

4) Cryo-Scanning Electron Microscope (Cryo-SEM): Cryo-Scanning Electron Microscopy (Cryo-SEM) is a powerful tool for imaging and analyzing the surface morphology of samples at cryogenic temperatures. Here are some key points about Cryo-SEM and cryo electron microscopy:

V. CRYO ELECTRON MICROSCOPY

Cryo-Electron Microscopy (Cryo-EM) is a potent imaging method that visualizes biological materials at the molecular level using a transmission electron microscope (TEM). It is quickly freezing biological materials in a vitreous ice condition so that their original structure is preserved, and then using a TEM to image them. Many advances in the domains of structural biology, cell biology, and neurology have been made possible by the growing use of cryo-EM as a potent tool for understanding biological systems.

A. Structure



B. Construction

The construction of Cryo-EM requires precise engineering and manufacturing to ensure optimal performance and image quality. The components work together to maintain a high-vacuum environment, cryogenic temperatures, and precise control over the electron beam, enabling high-resolution imaging of biological samples.

The construction of Cryo-Electron Microscopy (Cryo-EM) consists of the following components:

1) Transmission Electron Microscope (TEM)

a) Electron Gun: In cryo-EM, an electron gun is a device that produces a beam of electrons to image frozen biological samples. It's essentially an electron source that generates a high-energy beam, which is then focused onto the sample. That produces a beam of electrons.

b) Electron Optics: Electron optics refers to the use of magnetic or electrostatic lenses to manipulate and focus the electron beam in cryo-EM. These lenses control the beam's trajectory, size, and shape, enabling high-resolution imaging. That focuses and controls the electron beam

c) Vacuum System: The vacuum system is a critical component in cryo-electron microscopy (cryo-EM). Maintains a high-vacuum environment.
d) Column: The column is a critical component in cryo-electron microscopy (cryo-EM). Houses the electron optics and sample stage.

2) *Cryo-Stage*
a) Cryo-Transfer System: The Cryo-Transfer System is a specialized system designed to transfer cryogenically frozen samples from the cryo-preparation equipment to the cryo-EM microscope while maintaining their frozen state. Transfers samples from the freezer to the TEM
b) Sample Holder: The Sample Holder, also known as the cryo-stage or specimen holder, is a specialized device that holds the frozen sample in place within the cryo-EM microscope. Holds the sample in place.
c) Cryogenic Cooling System: The Cryogenic Cooling System is a specialized system designed to maintain extremely low temperatures (<-150°C) within the cryo-EM microscope, ensuring the preservation of frozen biological samples. Maintains the sample at cryogenic temperatures (typically liquid nitrogen)

3) *Detector*
a) CCD Camera: A CCD Camera is a type of detector used to capture high-resolution images of frozen biological samples in cryo-EM. Captures the transmitted electrons and converts them into an image
b) Direct Electron Detector: A Direct Electron Detector is a type of detector that directly detects electrons scattered by the sample in cryo-EM, without the need for a scintillator or phosphor screen. Captures high-resolution images with improved contrast

4) *Cryo-Transfer System*
a) Cryo-Transfer Rod: A Cryo-Transfer Rod is a specialized rod used to transfer cryogenically frozen samples from the cryo-preparation equipment to the cryo-EM microscope while maintaining their frozen state. Transfers samples from the freezer to the TEM
b) Cryo-Transfer Station: A Cryo-Transfer Station is a specialized vacuum chamber that connects the cryo-preparation equipment to the cryo-EM microscope, allowing for the transfer of cryogenically frozen samples while maintaining their frozen state. Loads and unloads samples from the cryo-transfer rod

5) *Vacuum System*
a) Pumping System: A Pumping System is a combination of vacuum pumps and control systems that maintain the ultra-high vacuum (UHV) environment required for cryo-EM. Maintains high vacuum in the TEM column
b) Vacuum Gauges: Vacuum Gauges measure the pressure in the cryo-EM microscope's vacuum chamber, ensuring optimal conditions for high-resolution imaging. Monitors the vacuum pressure

6) *Control and Imaging System*
a) Computer: Controls the TEM and processes images
b) Software: Acquires, processes, and analyzes images

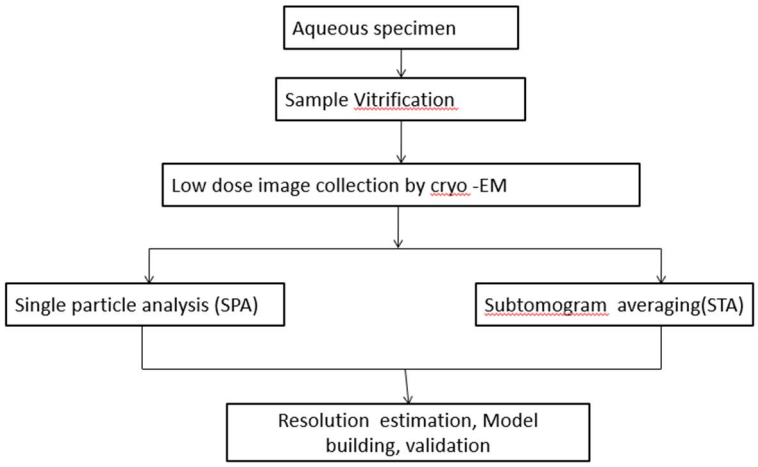
7) *Cryogen Storage*
a) Liquid Nitrogen Dewar: A Liquid Nitrogen Dewar is a specialized container used to store and transport liquid nitrogen (LN2) in cryo-EM. Stores liquid nitrogen for cryogenic cooling
b) Liquid Ethane Dewar: A Liquid Ethane Dewar is a specialized container used to store and transport liquid ethane (LE) in cryo-EM. Stores liquid ethane for vitrification

C. Working

Cryo-electron microscopy (cryo-EM) is a powerful imaging technique used to study the structure and function of biological macromolecules, cells, and tissues at the nanoscale.

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Working Process:



D. Sample Preparation

1) Sample Selection: Biological samples are prepared and frozen in a vitreous ice state using cryogens like liquid nitrogen or ethane.

2) Cryo-Transfer: Cryo-transfer refers to the transfer of a cryogenically frozen sample from one location to another, such as from a cryo-storage dewar to a cryo-EM microscope, while maintaining its frozen state. The frozen sample is transferred to the TEM using a cryo-transfer system.

3) Cryo-Stage: A Cryo-Stage is a specialized stage in a cryo-EM microscope that maintains the cryogenically frozen sample at extremely low temperatures, typically below -150°C. The sample is placed on the cryo-stage, which maintains the sample at cryogenic temperatures.

4) Electron Beam: An Electron Beam is a stream of electrons used to image the sample in cryo-EM. The electron gun produces a beam of electrons, which is focused onto the sample using electron optics.

5) Image Formation: Image Formation is the process by which the electron beam interacts with the sample to produce an image. The transmitted electrons are captured by the detector, forming an image.

6) Image Processing: Image Processing is the use of computational methods to enhance, correct, and analyze cryo-EM images. The raw image is processed to enhance contrast, remove noise, and reconstruct 3D structures.

VI. ADVANTAGE

1) High Resolution: Cryo-EM has the capability to offer a resolution ranging between 3-4Å, which provides coherent knowledge of the structure of biological macro molecules.[39]

2) Native State: Cryo-EM maintains a sample in its physiological state and no dehydration is required as done in cryo-SEM.[40]

3) Flexibility: Cryo-EM is highly versatile when it comes to the type and size of samples that can be analyzed, including proteins and protein complexes of various sizes and cells.[41]

4) Minimal Sample Preparation: Cryo-EM poses minimal sample preparation which limits the alteration of the sample's structure.[42]

5) No Staining or Fixation: Organic structures of the sample do not need to be stained or fixed commonly in cryo-EM, unlike in other microscopy techniques.[43]

6) High Contrast: light images are provided and hence, excellent contrast images of biological macromolecules can readily be obtained.[44]

7) Rapid Structure Determination: Cryo-EM allows for the rapid determination of structures which would be useful in countering new threats in biology.[45]

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VII. APPLICATION

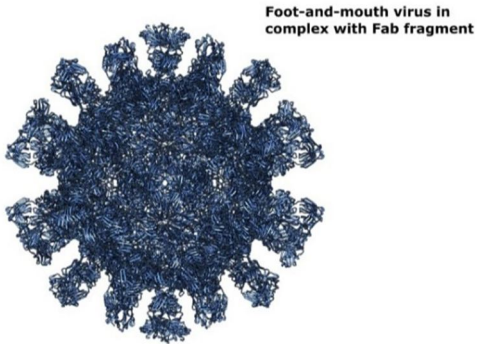
A. Cryo-EM in Virology

1) Virus structure determination: Cryo-EM provides the architecture of viruses for deciphering their assembly, entry, and replication processes [46].

2) Virus-receptor interactions: With the help of Cryo-EM, it is possible to identify interactions of viruses with receptors of host cells and design new vaccines and antiviral drugs [47].

3) Viral protein structure and function: Cryo-EM resolves structures of viral proteins to analyze their functions in viral replication and disease progress [48].

4) Virus-host cell interactions: Cryo-EM provides views on how the viruses interact with the host cells, how the viruses enter the cells and replicate themselves, as well as how they block the host's immune response [49].

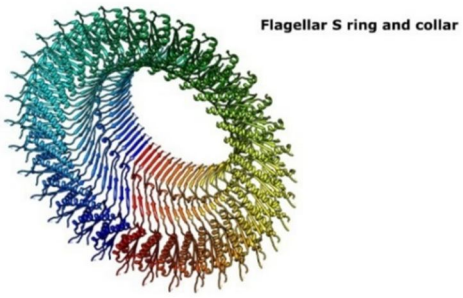


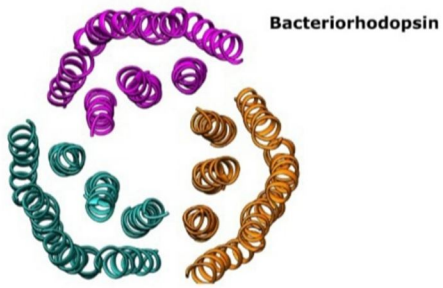
B. Cryo-EM in Immunology:

1) Structural analysis of immune complexes: Cryo-EM reconstructs the three-dimensional structure of immune complexes, including antibodies, antigens, and so on [50].

2) Vaccine development: Cryo-EM is used in the design of the vaccines because it reveals the structures of the surface of the viruses and bacteria [51].

3) Immunotherapy development: Cryo-EM enables the design of immunotherapies like CAR-T cell therapy because the structure of the interacting immune cells may be visualized [52].





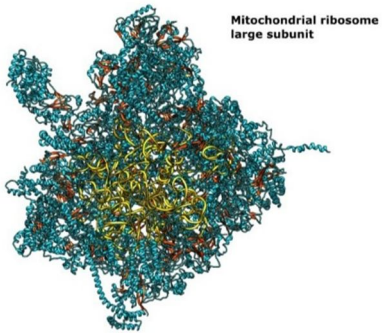
C. Cryo-EM in cell biology

1) Cell & organelles structural analysis: The 3D structure of cells, organelles, and cellular components is determined through Cryo-EM [53].

2) Cellular dynamics and transport: Protein transport and membrane trafficking are two salient processes studied in terms of their dynamics using Cryo-EM [54].

3) Viral structure and replication: The structure of viruses and their replication mechanisms are revealed by Cryo-EM [55].

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D. Cryo-EM in Cancer Research

1) Structural analysis of cancer proteins: Cryo-EM locates the formations of cancer-associated protein such as p53 and BRCA1; [56].

2) Cancer cell signaling pathways: Cryo-EM facilitates the analysis of the structure of proteins that are part of the signaling pathways in cancer cells [57].

3) Tumor micro environment analysis: Cryo-EM examines the shape of tumor microenvironment with blood vessels and immune cells [58].

4) Cancer stem cell research: The function of cancer stem cells and their micro environment are also examined through cryo-EM [59]

VIII. CONCLUSION

Therefore, Cryo-Electron Microscopy (Cryo-EM) has become an indispensable tool in structural biology for visualizing life's structural complexity at the molecular and cellular level. Families of post-reconstruction applications Benefits of Cryo-EM In traditional electron microscopy, the directions of the microscopes used are limited in order to make room for the electron beam to pass through; this kind of confinement has only been eliminated by Cryo-EM through the application of state-of-art cryogenic methods, high vacation technologies, and electron optics. This harmonious integration of progressive methods has enabled scientists to depict intricate biological structures with even greater clarity and add deeper understanding to the functional basis of life, which has led to further progression of various studies in modern science, including medicine, biotechnology, and many more. Future trend show that Cryo-EM is likely to expand our ways to look at the biological world, leading to various more unexplored scientific discoveries and advancements.

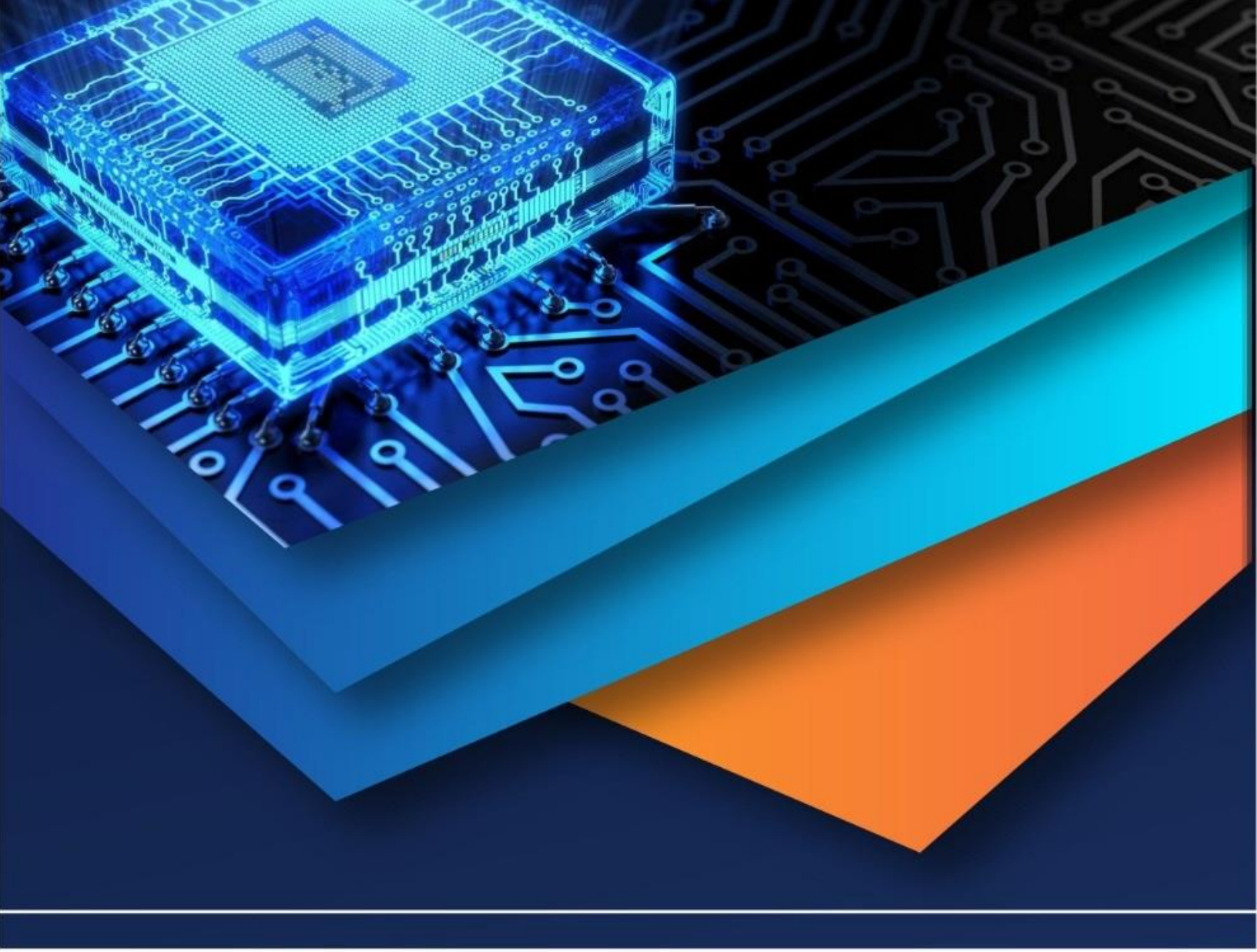
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