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# Liquid Cell Transmission Electron Microscopy

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Annu. Rev. Phys. Chem. 2016. 67:719–47

The *Annual Review of Physical Chemistry* is online at [physchem.annualreviews.org](http://physchem.annualreviews.org)

This article's doi:  
10.1146/annurev-physchem-040215-112501

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## Keywords

liquid cell TEM, environmental TEM, materials transformation, solid-liquid interfaces, biological imaging, electron beam effects

## Abstract

Liquid cell transmission electron microscopy (TEM) has attracted significant interest in recent years. With nanofabricated liquid cells, it has been possible to image through liquids using TEM with subnanometer resolution, and many previously unseen materials dynamics have been revealed. Liquid cell TEM has been applied to many areas of research, ranging from chemistry to physics, materials science, and biology. So far, topics of study include nanoparticle growth and assembly, electrochemical deposition and lithiation for batteries, tracking and manipulation of nanoparticles, catalysis, and imaging of biological materials. In this article, we first review the development of liquid cell TEM and then highlight progress in various areas of research. In the study of nanoparticle growth, the electron beam can serve both as the illumination source for imaging and as the input energy for reactions. However, many other research topics require the control of electron beam effects to minimize electron beam damage. We discuss efforts to understand electron beam–liquid matter interactions. Finally, we provide a perspective on future challenges and opportunities in liquid cell TEM.

## 1. INTRODUCTION

Transmission electron microscopy (TEM) is a powerful and indispensable tool for the characterization of materials, and it provides critical structural and chemical information for them. In recent years, significant advances have been made in electron microscopy. Concurrent with aberration-corrected (scanning) TEM, which has made atomic imaging and spectroscopy a routine process (1–3), it has now been possible to image materials in liquid (including gas) environments at the subnanometer or atomic scale. Imaging through liquids with TEM can be traced back to 1934, the beginning of electron microscopy, when Marton (4) imaged biological samples sandwiched between two thin aluminum foils. However, in the next several decades, there were limited activities (5–11) in this area, likely resulting from the technical challenges in isolating the liquid sample from the high-vacuum environment of an electron microscope: A conventional transmission electron microscope requires high vacuum ( $10^{-6}$  torr or higher) within the microscope column to minimize electron scattering other than that from the sample.

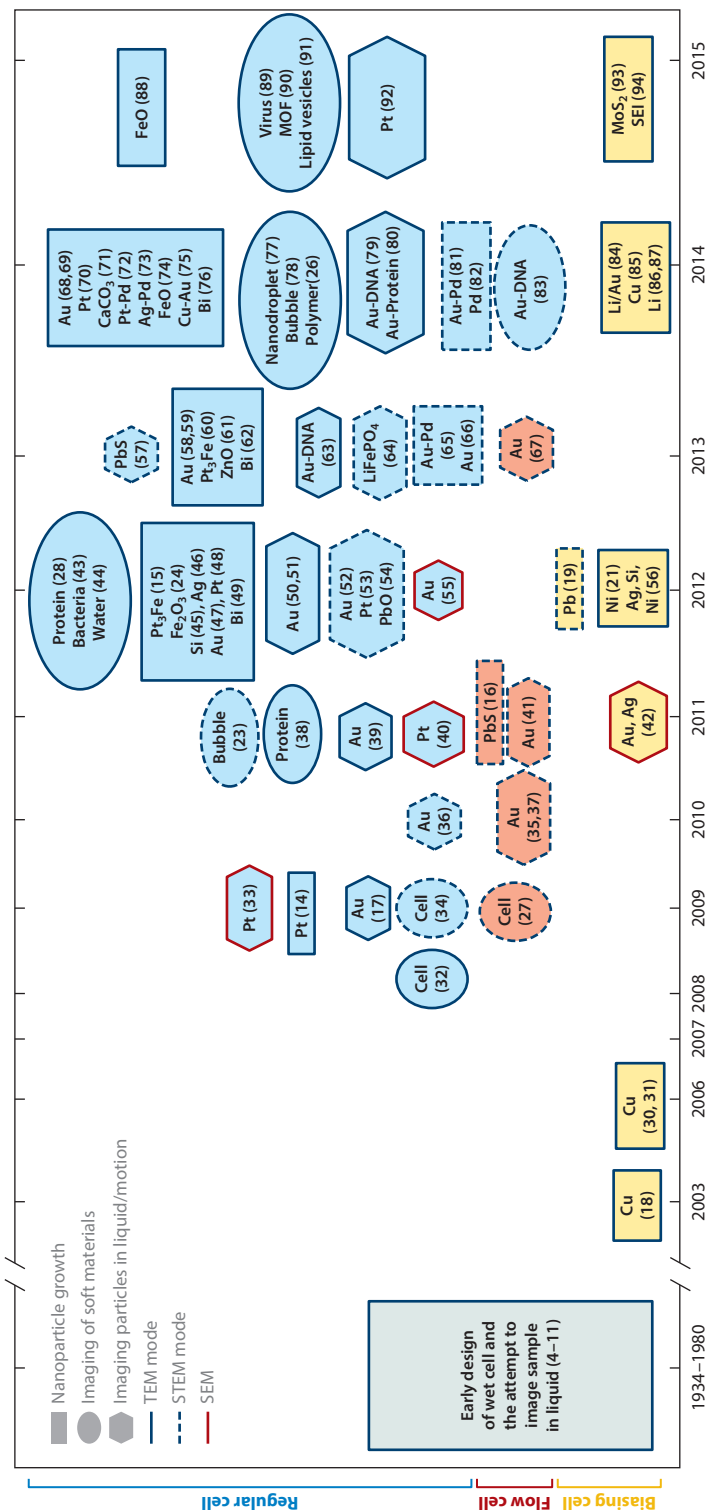
With technical advancements in liquid cell nanofabrication, imaging through liquids sandwiched between two ultrathin membranes with subnanometer resolution using TEM has only recently become possible. Liquid cell TEM is a fast-growing and fascinating area of research, which has drawn tremendous attention from various fields, ranging from materials science to chemistry, physics, and biology (12, 13). Many homemade liquid cells have been reported, and commercial liquid sample stages are available. Liquid cell TEM has been applied to the study of nanoparticle nucleation and growth (14–16); nanoparticle motion in solution (14–17); electrochemically driven reactions such as deposition, corrosion, and ion transportation (18–21); liquid nanodroplets and bubble formation (22, 23); biomineralization (24); organic materials (25, 26); and biological materials, such as proteins and whole cells in liquid water (27–29). **Figure 1** presents a statistic plot of published papers using the liquid cell TEM methodology over the years. It illustrates the drastic increase in publications in recent years (4–11, 14–19, 21, 23, 24, 26–28, 30–94). It is clear that liquid cell TEM plays an increasingly important role in a diverse set of scientific topics.

In this review, we first discuss the design and development of liquid cells and then review progress in different topics, including (*a*) the observation of nanoparticle formation, such as the mechanisms of nanoparticle growth and factors controlling nanoparticle morphology, including surfactants, neighboring particles, and precursor concentration; (*b*) tracking and manipulation of nanoparticles in a liquid cell; (*c*) the study of electrode-electrolyte interfaces using an electric biasing liquid cell; and (*d*) bioscience applications of liquid cell TEM. We also summarize the current understanding of electron beam–liquid matter interactions and our perspective on controlling electron beam effects. Finally, we provide an outlook of the future developments and applications of liquid cell TEM.

## 2. LIQUID CELL DEVELOPMENT

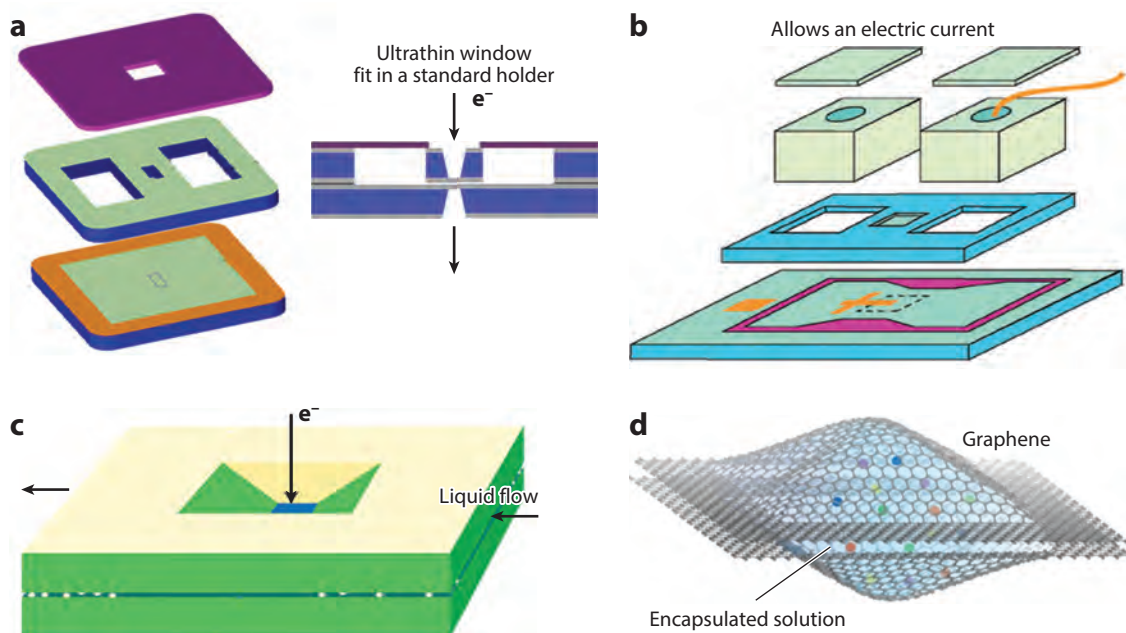
### 2.1. Design and Fabrication of Liquid Cells

Most liquids, including water and other organic solvents, have a high vapor pressure; thus, they are incompatible with the high-vacuum environment of a transmission electron microscope. A sealed liquid cell is required to separate water and other high-vapor pressure liquids from the vacuum environment. At the same time, the imaging window needs to be thin enough to allow the electron beam to go through and sufficiently strong to sustain the high vacuum. These general requirements and the concept of using a window-confined cell in TEM were discussed even in



**Figure 1**

A statistic plot of publications related to liquid cell electron microscopy since 1934. Abbreviations: MOF, metal organic framework; SEI, solid electrolyte interphase; SEM, scanning electron microscopy; STEM, scanning transmission electron microscopy; TEM, transmission electron microscopy.



**Figure 2**

Different types of liquid cells reported in recent years. (a) A self-contained liquid cell with an ultrathin SiN<sub>x</sub> membrane window. It can fit in a standard transmission electron microscopy sample holder. Panel a adapted from Reference 14 with permission. (b) An original electrochemical liquid cell with patterned electrodes inside the cell. Panel b adapted from Reference 18 with permission. (c) A flow cell allowing liquids to flow between two chips. Panel c adapted from Reference 27 with permission. (d) A graphene cell. Panel d adapted from Reference 96 with permission.

the earliest days of electron microscopy (reviewed in 95). From the early attempt of imaging wet samples using sandwiched thin aluminum foils (4) to the current functional thin SiN<sub>x</sub>/Si liquid cells (**Figure 2a–c**) and graphene liquid cells (**Figure 2d**), there was a several-decades gap, during which the standard TEM protocol of imaging dry samples *ex situ* by periodically stopping the reaction was applied. However, the dynamic processes of materials during reactions cannot be obtained using such an *ex situ* practice.

In 2003, Williamson et al. (18) reported the development of a liquid cell for TEM using silicon wafers with an electron transparent silicon nitride membrane window. Gold electrodes were deposited on the bottom chip, and it was glued together with the top chip with a glass spacer in between, forming an electrochemical liquid cell. Additional containers for liquid electrolyte were assembled in the electrochemical cell for electric biasing experiments (**Figure 2b**). The electrochemical deposition of copper clusters on the gold electrode was studied *in situ*. Because the electron beam has to penetrate a thick layer of mass (e.g., two silicon nitride membranes, each 100 nm, a 50-nm gold electrode, and over a 1-μm-thick liquid layer), limited resolution was achieved at that time (30, 31).

To study colloidal nanocrystal growth under TEM, Zheng et al. (14) reported in 2009 the development of self-contained liquid cells and achieved 1-nm resolution. Much thinner SiN<sub>x</sub> membranes (25 nm) were used for the liquid cell window, and a liquid layer of 100 nm was obtained using a sticky metal layer of indium as the spacer between the bottom and top chips. To make sure the thin membrane could survive the high vacuum, they used a much smaller rectangular window

of about a few micrometers by 50  $\mu\text{m}$  instead of the previous  $100 \times 100\text{-}\mu\text{m}$  window. Such thin silicon nitride liquid cells enabled the study of single platinum nanoparticle growth trajectories, and the unique growth mechanisms of colloidal nanoparticles through monomer attachment or coalesce were revealed (14). This work attracted much attention in the field of colloidal chemistry, and many studies on nanoparticle growth using liquid cell TEM have emerged (15, 60, 62, 70).

It is also possible to flow liquids between two silicon nitride membranes of a liquid cell using external tubing and a syringe pump (37). In 2009, de Jonge et al. (27) described the use of a flow cell to image whole cells in liquids (**Figure 2c**). The liquid flow capability is appealing to researchers interested in reactions involving mixing solvents instantaneously or injecting reactant agents into another type of liquid. Critical issues still need to be addressed, such as sample drift introduced by liquid flow, membrane rupture, and potential contamination. In many cases, a still liquid environment similar to that in a self-contained liquid cell is maintained during imaging.

In 2012, a graphene liquid cell for high-resolution imaging during platinum nanocrystal growth was reported (96). Small droplets of liquids are enclosed between two graphene sheets to fabricate a graphene liquid cell. As graphene is impermeable to liquids, and it is the thinnest material, the graphene liquid cell allows imaging with unprecedented high resolution. The development represents a significant advancement despite limitations on the kinds of experiments that can be performed using the cell.

Compared to graphene cells, silicon nitride liquid cells are still highly attractive as  $\text{SiN}_x$  is mechanically strong and relatively inert, and has low imaging contrast. Most importantly, an  $\text{SiN}_x/\text{Si}$  liquid cell provides an excellent developing platform for functional measurements, such as allowing experiments under an electric bias (18), heating (49, 62), and cooling (97). However, there are also issues associated with silicon nitride liquid cells. For instance, the pressure difference across the membranes can cause them to bow outward, inducing a thicker liquid layer. Efforts have been made to accurately measure the thickness of the imaging window and to limit the membrane bowing. Electron energy loss spectroscopy (EELS) has been used to estimate the window thickness (46, 57, 66, 95), and the results demonstrate that bowing can increase the liquid thickness by a factor of three in a typical liquid cell with a  $50 \times 50\text{-}\mu\text{m}$   $\text{SiN}_x$  membrane window (54). There are ways to minimize window bowing, such as thinning small areas within a thicker membrane to generate a patterned window (98) and reducing the total size of the membrane window (70).

In general, in a liquid cell experiment, the liquid solution is loaded into the cell, and the cell is placed on a conventional TEM sample holder or a commercial liquid stage. Then the liquid cell is tested to avoid leakage before it is loaded into the microscope. For studies of nanoparticle growth, the electron beam can be the energy source to drive the reaction. However, for studies of an electrochemical process or when imaging many other liquid samples, electron beam effects need to be controlled. In general, for real-world reactions, it is critical to understand electron beam–matter interactions and implement low-dose imaging techniques. Details on electron beam effects are discussed in Section 7.

In parallel to the development of a sealed liquid cell for liquid samples, an open cell with droplets of low-pressure liquids, particularly ionic liquids, has been reported. This open cell concept was initiated by Wang et al. (99) and Huang et al. (100) as the cell was developed to study battery electrode materials during lithiation and delithiation. We briefly discuss their work in Section 5.2. However, in this article, we focus on work using sealed liquid cells.

## 2.2. Information Available from Liquid Cell Transmission Electron Microscopy

With the ability to image through liquids with subnanometer resolution, liquid cell TEM has enabled, for example, the tracking of single nanoparticle growth trajectories, dynamic nanoparticle

movement in liquids, electrochemical deposition and lithiation of electrode materials, and the imaging of biological materials in liquid water. By combining other imaging and spectroscopy techniques, such as scanning transmission electron microscopy (STEM), energy dispersive X-ray spectroscopy, selected area electron diffraction, and EELS, researchers have provided rich information on the dynamic processes of materials (50, 64, 65).

For studies of materials transformations, there are many other *in situ* approaches, such as *in situ* optical spectroscopy (101), X-ray spectroscopic methods (102–106), atomic force microscopy (AFM), and scanning tunneling microscopy (STM) (107–109). Oezaslan et al. (110) reported *in situ* measurements of bimetallic platinum-copper alloy nanoparticles using high-temperature X-ray diffraction. Polte et al. (104) investigated the growth of nanoparticles from an average radius of 0.8 nm to 2 nm by time-resolved small-angle X-ray scattering with millisecond time resolution. Simm et al. (108) used *in situ* AFM to study the growth of cobalt nuclei on a boron-doped diamond electrode under potentiostatic control. The growth of the nuclei as a function of time was monitored under different deposition potentials. With these *in situ* methods, critical information on nucleation and growth has been achieved. However, these methods also have their limitations. For example, *in situ* spectroscopy methods lack the ability of direct visualization; AFM and STM techniques can be used only to image samples on a substrate; and the temporal resolution is also limited.

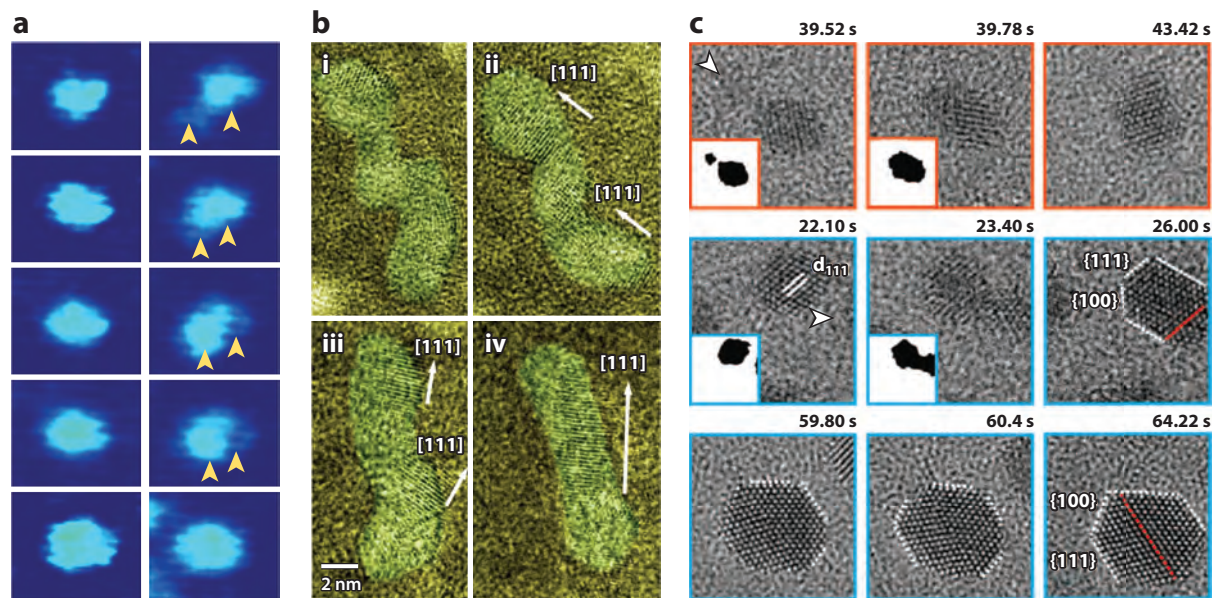
Liquid cell TEM has unique advantages in allowing the direct observation of the dynamics of materials transformation in liquids with high spatial and temporal resolution. It is also applicable to imaging of various organic materials and biological materials in a liquid phase. The major criticisms of the technique come from the damage caused by electron beam radiation and challenges in controlling the local temperature and reactant mixing, for example, during reactions. We discuss these issues in Section 7.

### 3. NANOPARTICLE GROWTH OBSERVED IN A LIQUID CELL

#### 3.1. Tracking Single Nanoparticle Growth Trajectories

Although colloidal nanoparticle synthesis has advanced significantly over the past 20 years, and nanoparticles with different size, shape, and architectures have been achieved, the prevalent approach to developing new nanomaterials is a trial-and-error process based on the resulting nanostructures. This is fundamentally limited in that the growth processes can be inferred only from the final synthetic structure. Such postmortem analysis cannot provide enough information on the synthesis process. Tracking single nanoparticle growth trajectories using a liquid cell provides an opportunity to develop a fundamental understanding of nanoparticle evolution and to elucidate nanoparticle growth mechanisms.

According to the classical theory of Ostwald ripening, nanoparticle growth proceeds by monomer attachment to an existing nucleus. It was assumed that growth by nanoparticle coalescence should be avoided to achieve monodisperse nanoparticles. By direct observation of platinum nanoparticle growth in a liquid cell, Zheng et al. (14) discovered that two types of growth, either by monomer attachment or by coalescence, lead to the same particle size. As shown in **Figure 3a**, the coalesced nanoparticles can eventually become a spherical nanoparticle, similar to that created by monomer attachment. Growth by nanoparticle attachment has also been demonstrated in Pt<sub>3</sub>Fe nanowire formation. Liao et al. (15) observed the growth of Pt<sub>3</sub>Fe nanowires by nanoparticles attached end to end (**Figure 3b**). Such nanoparticle chain formation was attributed to the dipolar interaction between nanoparticles. Using a graphene liquid cell, Yuk et al. (96) studied platinum nanoparticle growth with superior resolution. They found that coalescence is a site-selective,



**Figure 3**

Single nanoparticle growth trajectories studied using a liquid cell. (a) Sequential images showing platinum nanoparticle growth either by monomer attachment or by nanoparticle coalescence, leading to the same particle size. Yellow arrowheads represent the attaching of nanoparticles. Panel *a* adapted from Reference 14 with permission. (b) Sequential high-resolution transmission electron microscopy images showing both the crystal orientation and shape changes during the straightening of a twisted nanoparticle chain. Panel *b* adapted from Reference 15 with permission. (c) Platinum nanocrystal growth via coalescence and crystal-structure evolution observed with atomic resolution in a graphene liquid cell. White arrowheads denote incoming small nanocrystals, red dotted lines indicate the twin boundary, and the red and blue box outlines represent different sets of data. Panel *c* adapted from Reference 96 with permission.

specific facet, with the lowest surface energy or lowest ligand coverage ( $\{111\}$  for fcc) preferred during nanoparticle attachment. With atomic rearrangement after coalescence, a single crystal or a twinned nanoparticle is formed (Figure 3c).

Along with the above studies, there have been many reports on nanoparticle growth by monomer attachment or the coalescence of nanoparticles (including oriented attachment). We highlight a few selected from the literature below. These liquid cell TEM studies of nanoparticle growth provide useful information for our understanding of growth mechanisms of the selected nanoparticle system.

Liu et al. (61) reported ZnO nanoparticle precipitation for which they found that both Ostwald ripening and coalescence are the early stage growth mechanisms; however, nanoparticle aggregated growth is dominant at the later stage. Zhu et al. (82) showed that the growth of palladium dendrites can be achieved after nucleation of a cluster with the beam probe.

Woehl et al. (46) studied the relationship between the nanoparticle growth rate and electron beam dose rate. They reported that a low beam current facilitates reaction-limited growth, leading to faceted nanocrystals, whereas a higher beam current promotes diffusion-limited growth, introducing spherical nanocrystals. It was also demonstrated that lead sulfide nanoparticles grow by selectively decomposing a chemical precursor from a multicomponent solution (16).

Niu et al. (76) found that symmetric coalescence with two equal-size nanoparticles and asymmetric coalescence with two or more unequal-size nanoparticles are possible during the growth of bismuth nanoparticles. Both surface diffusion and grain boundary diffusion are mass transport

mechanisms during the relaxation period after coalescence. The relaxation time increases with the particle size. There is competition between coalescence and the collision time; the collision time is determined by factors such as nanoparticle concentration and the speed of nanoparticle movement, whereas the electron beam influences coalescence. Aabdin et al. (111) studied gold nanocrystal bonding in solution and found two pathways: (a) Coherent, defect-free bonding occurs when two nanocrystals attach with their lattices aligned within a critical angle, and (b) beyond this critical angle, defects form at the interfaces where the nanocrystals merge.

Interaction between nanoparticles is an important factor during nanoparticle growth, which may involve, for example, van der Waals forces, hydrophobic interaction, magnetic force, and charge interaction. Liu et al. (59) observed CTA-gold nanoparticle self-assembly to form nanoparticle chains. Anisotropic attractive interactions and size-dependent segregation have been reported, in agreement with Liao et al.'s (15) findings on the electrostatic dipolar interaction between Pt<sub>3</sub>Fe nanoparticles.

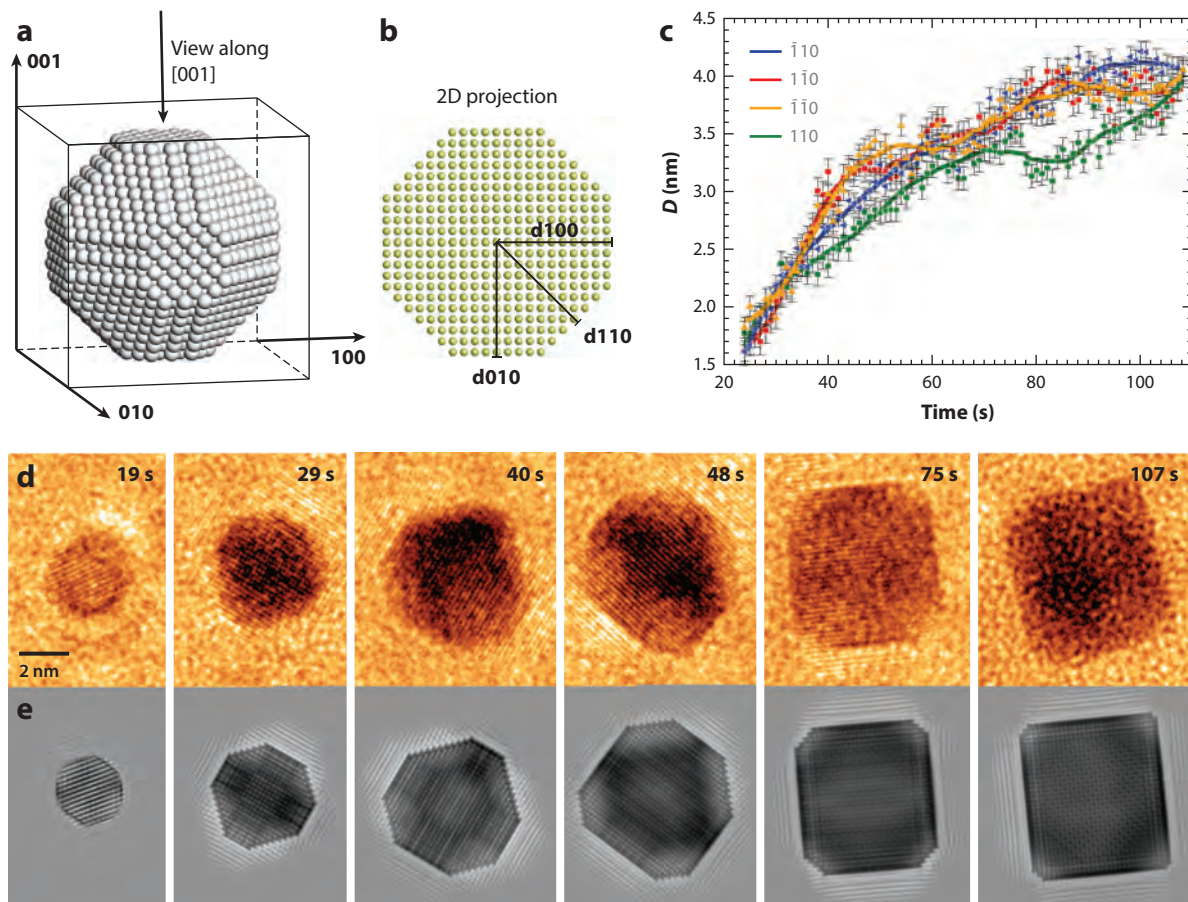
Woehl et al. (112) reported that the growth of silver nanoparticles is length-scale dependent, in which individual nanoparticles grow by monomer attachment and the ensemble large-scale growth is dominated by aggregation. Direct observations of aggregation revealed that growth follows a Smoluchowski model, and both the mean growth rate and particle size distribution were captured.

Li et al. (24) observed oriented attachment during iron oxide nanoparticle growth. Nanoparticles underwent continuous rotation and interaction before they found the perfect lattice match with the same orientation. Measured translational and rotational accelerations demonstrate that strong, highly direction-specific interactions drive crystal growth via oriented attachment.

### 3.2. Nanoparticle Shape Evolution

The shape of nanocrystals strongly influences their performance in catalysis, sensing, and many other surface-enhanced applications (113, 114). Nanoparticles with various shapes have been achieved, such as nanodots, one-dimensional (1D) nanowires and nanorods, faceted nanoparticles, and multipod nanostructures. However, the crystallization process is complex, involving the arrangement of thousands of atoms or molecules near the surface, and it is further complicated by interactions between atoms and influences from the surroundings. With environmental modifications, such as temperature, precursor, and surfactants, it is possible to control the reaction and growth to create nanocrystals with different shapes and structures. However, the shape-controlled mechanisms during colloidal synthesis are often not well understood or characterized. Liquid cell TEM has been proven to be a unique and effective method to study nanoparticle growth and to unravel the role of different factors in controlling the structure and morphology of nanoparticles.

Wulff construction (115, 116) has been used to predict the equilibrium shape of nanocrystals. It states that the length of a normal vector drawn from the crystal center to an external surface is proportional to the surface free energy. It is widely accepted that in nanocrystal growth, the high-energy facets grow at a higher rate than the low-energy facets; therefore, the fast-growing facets will eventually disappear, resulting in a nanocrystal terminated with low-energy facets (117, 118). It is assumed that the commonly used surfactants modify the energy of specific facets through preferential adsorption, influencing the relative growth rate of different facets and thus the shape of a nanocrystal (119, 120). However, the evolution of nanoparticle morphology is largely unknown, and the shape control mechanisms of nanocrystals need to be further explored. Recently, Liao et al. (70) imaged platinum nanocube growth using liquid cell TEM, showing that the surface energy minimization rules break down at the nanoscale. As shown in **Figure 4**, the growth rates of all low-index facets, {100}, {110}, and {111}, are similar until the {100} facets stop growing.



**Figure 4**

(a) The facet development of a platinum nanocube viewed along the  $[0\bar{1}1]$  axis. (b) The atomic model of a truncated platinum nanocube and its projection along the  $[0\bar{1}1]$  view zone axis. The distance from the crystal center to each of the  $(100)$ ,  $(011)$ , and  $(111)$  facets is highlighted. (c) The measured average distance from the crystal center to each facet as a function of time. (d) Sequential images showing the growth of the platinum nanocube. (e) Simulated transmission electron microscopy images of the platinum nanoparticle in panel d. Figure adapted from Reference 70 with permission.

The  $\{110\}$  facets continue to grow until they reach a limit, at which point they form an edge of a nanocube. The continued growth of  $\{111\}$  facets fills the corners of the cube. In combination with density functional theory calculation, such direct observation of atomic facet development in platinum nanocube growth reveals the selective facet-arrested shape control mechanisms. This work is an excellent example demonstrating that liquid cell TEM is highly useful in revealing hidden mechanisms of nanocrystal growth with high spatial and temporal resolution.

Besides modifying the growth rate of certain facets, surfactants can drastically influence the morphology of the final nanoparticles, inhibit nanoparticle aggregation, and prevent coalescence. Zheng et al. (14) found that, by decreasing surfactant within platinum nanoparticle growth, foil and dendrites could be obtained. Liao et al. (60) showed that it is essential to control oleylamine concentration to achieve platinum-iron nanoparticles with a desired shape. For instance, 20% oleylamine in the precursor solution led to an unstable nanoparticle chain that eventually broke into

nanoparticles; 30% oleylamine resulted in stable nanowires in the solution; and 50% oleylamine prevented nanoparticles from merging together, and the shapes were influenced by neighboring particles (**Supplemental Figure 1**; follow the **Supplemental Material link** from the Annual Reviews home page at <http://www.annualreviews.org>).

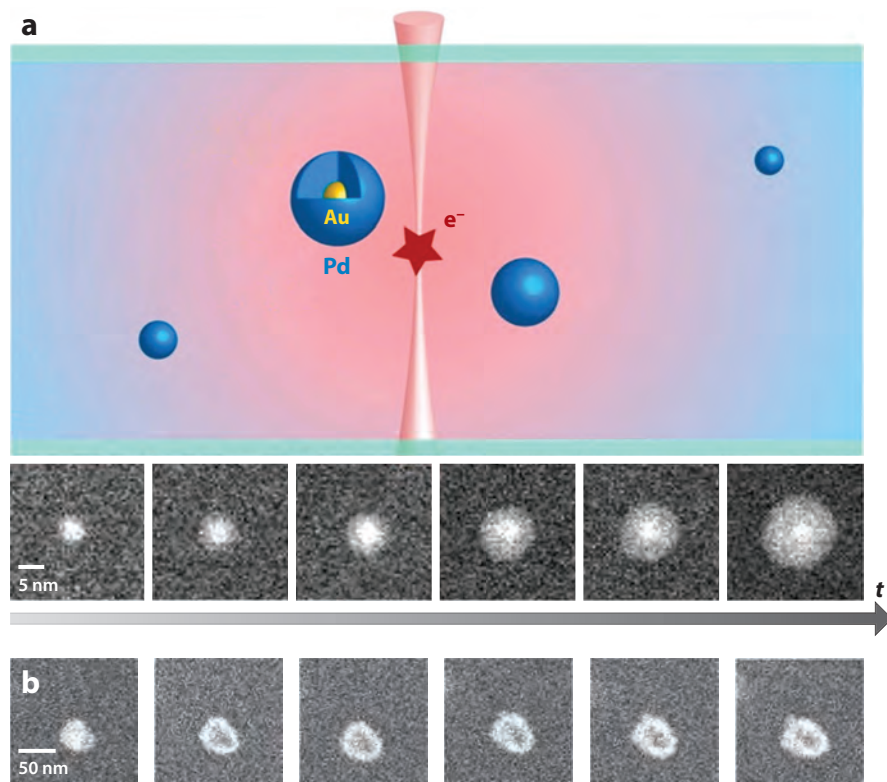
Growth with temperature control in a liquid cell has also been achieved. Xin & Zheng (49) reported the growth of bismuth nanoparticles in a TEM liquid cell at an elevated temperature using a commercial heating sample stage. The oscillatory growth dynamics of bismuth nanoparticles were observed when the liquid cell was heated to 180°C. Both individual and pairwise growth oscillations and collective fluctuations at global length scales were achieved. They also demonstrated that a depletion zone is present around a particle. This study suggests the possibility of counteracting the energetically favorable Ostwald ripening process to prevent nanoparticle coarsening, which is highly beneficial in the design of many industrial reactions, such as heterogeneous nanoparticle catalysis.

Solvent is another critical factor for morphology control. Among the three commonly used solvents in liquid cell TEM experiments (water, organic solvent, and ionic liquid), aqueous solution is most challenging to handle. Interactions between water molecules and the electron beam result in the ionization of water, from which different radicals can be generated. Organic solvent has also been widely used. Zheng's (14, 15, 60, 62, 70, 76, 121) research group used the organic solvent of pentadecane, dichlorobenzene, benzene ether for the growth of platinum nanospheres and nanocubes, Pt<sub>3</sub>Fe nanowires, bismuth nanospheres, etc. Yuk et al. (96) used a mixture of o-dichlorobenzene and oleylamine (9:1 in volume ratio) for platinum nanoparticle growth in a graphene liquid cell. As for ionic liquid, it can be used directly in the vacuum environment without evaporation issues or charging effects. For instance, using C<sub>9</sub>H<sub>13</sub>BrN<sub>2</sub> supported on a hole in a TEM grid by surface tension, Kimura et al. (122) studied NaClO<sub>3</sub> nucleation. The simultaneous formation and dissolution of prenucleation clusters and the formation of different phases were observed.

### 3.3. Growth of Heterostructured Nanoparticles

There have been many liquid cell TEM studies on the heterogeneous growth of nanoparticles using nanoparticle seeds. Nanostructures with complex shapes and architectures have also been achieved. Here we review some of these studies, which show diverse discoveries on different systems.

Using liquid cells, Sutter and colleagues (65, 73) investigated the heterogeneous growth of palladium on gold particle seeds. By using nanoparticle seeds in a precursor solution and taking advantage of radiolysis or galvanic replacement, they grew gold-palladium core-shell nanoparticles. They found that the size and shape of the gold seeds determined the morphology of the palladium shells. For small gold particles (5 nm), continuous and uniform shells were achieved by palladium monomer incorporation from the solution. In large particles (15 and 30 nm), nonuniform growth caused the palladium shell thickness to vary, and the slower depletion of palladium ions in the solution promoted competing growth process. They proposed that the hydrated electrons induced by the electron beam can reduce the chloropalladate complexes and influence the heterogeneous growth process. Heterogeneous growth is limited by the diffusion of hydrated electrons in the solution (65) (**Figure 5a**). Further analysis demonstrated that the as-grown palladium shell contains palladium-chloro complexes and that the redox reaction is first order with respect to the concentration of hydrated electrons. Sutter et al. (73) also investigated galvanic replacement reactions between a silver nanoparticle and aqueous palladium salt solution by using liquid cell TEM, transforming the silver particles into hollow silver-palladium nanostructures.



**Figure 5**

(a) Heterogeneous growth of palladium on gold seeds, forming a gold-palladium core-shell nanostructure. Panel *a* adapted from Reference 65 with permission. (b) Evolution of a silver particle in aqueous  $\text{PdCl}_2$  solution. Panel *b* adapted from Reference 73 with permission.

By comparison with ex situ experiments, the authors concluded that the electron beam strongly affects the galvanic-type process in the liquid cell (**Figure 5b**).

Wu et al. (123) recently studied the nucleation and growth of gold on platinum icosahedral nanoparticles. Quantitative analysis of growth kinetics was carried out based on real-time TEM observation. They showed that the growth process involves (a) the deposition of gold on corner sites of platinum icosahedral nanoparticles, (b) the diffusion of gold from corners to terraces and edges, and (c) the subsequent layer-by-layer growth of gold on gold surfaces to form platinum-gold core-shell nanoparticles. The in situ TEM results indicate that the diffusion of gold from corner islands to terraces and edges is kinetically controlled, as evidenced by measurements of diffusion coefficients for these growth processes.

Kraus & de Jonge (58) observed the growth of gold dendrites on gold nanoparticle seeds. They concluded that there is no correlation between the local seed morphology and the emerging dendrite morphology and that the dendrite growth is limited by diffusion. Zhang and colleagues (82) investigated the growth of 2D palladium dendrites in a liquid cell. They proposed that diffusion-limited aggregation and atomic deposition are responsible for the dendrite growth. Lewis et al. (75) investigated dynamic liquid-phase synthesis of core-shell nanostructures, in which they conducted

elemental mapping of nanostructures in solution to the compositional distribution for multiple elements within the resulting materials.

De Clercq et al. (72) reported the growth of platinum-palladium nanoparticles in a graphene oxide liquid cell. They found that the growth dynamics follow a power law with a growth exponent of 0.5, in agreement with the LSW (Lifshitz-Slyozov-Wagner) model in cases in which growth is limited by surface reaction. They proposed that surface reaction-limited growth mainly results from graphene oxide substrate effects, which pin the as-grown cluster and limit the coalescence of particles.

Liao et al. (68) studied the growth mechanism of fivefold twinned gold nanocrystals by imaging particle growth in an ionic liquid in situ. They identified the fivefold twinned nanocrystal growth pathways and proposed that nanoparticle sintering plays an important role in multi-twinned nanocrystal formation. Zhu et al. (82) studied the growth of 2D palladium dendritic nanostructures using in situ liquid cell TEM. Detailed in situ and ex situ high-resolution scanning TEM (S/TEM) characterization and fractal dimension analyses revealed that diffusion-limited aggregation and direct atomic deposition are responsible for the growth of palladium dendritic nanostructures.

### 3.4. Synthesis with a Template

Parent et al. (124) directly observed synthesis in a highly viscous lyotropic liquid crystal template at the nanoscale using fluid stage STEM. The nanoparticles nucleated and grew into 5-nm nanoparticles, at which point growth continued through the formation of connections with other nanoparticles around the micelles. Upon reaching a critical size ( $>10\text{--}15\text{ nm}$ ), the clusters became highly mobile in the template, displacing and trapping micelles within the growing structure to form spherical, porous nanoparticles. The final products matched those synthesized ex situ in the lab. This ability to directly observe synthesis at the nanoscale in rheological fluids, such as concentrated aqueous surfactants, provides an understanding of fundamental steps of nanomaterial growth. Parent et al. (125) also observed the growth of mesoporous palladium in a solvated block copolymer template under various synthesis conditions. The electron beam induced the nucleation of small particles in the aqueous phase around the micelles. The small particles flocculated and grew into denser structures that surrounded the micelles, forming an ordered mesoporous structure.

### 3.5. Etching and Corrosion

Oxidative etching prevails in the synthesis of nanocrystals. Jiang et al. (126) reported an in situ study of the oxidative etching of palladium cubic nanocrystals by liquid cell scanning TEM (**Supplemental Figure 2**). The etching was realized with oxidative radiation reactants from electron-water interaction in the presence of  $\text{Br}^-$  ions. Dissolution dynamics of monodispersed and aggregated nanocrystals were investigated and compared. Analyses on the dissolution kinetics of nanocrystals and the diffusion kinetics of the dissolved agents were carried out. The results provide quantitative information on the oxidative etching reaction.

The corrosion of metals or alloys is another branch of study that liquid cell TEM may impact. Developing an understanding of localized corrosion mechanisms remains a great challenge. Chee et al. (127) studied the localized corrosion of copper and aluminum thin films exposed to aqueous NaCl solutions using liquid cell TEM. They show the initiation of corrosion by applying an electric potential to an aluminum film, and the compositional changes can be used to modify corrosion susceptibility.

#### Supplemental Material

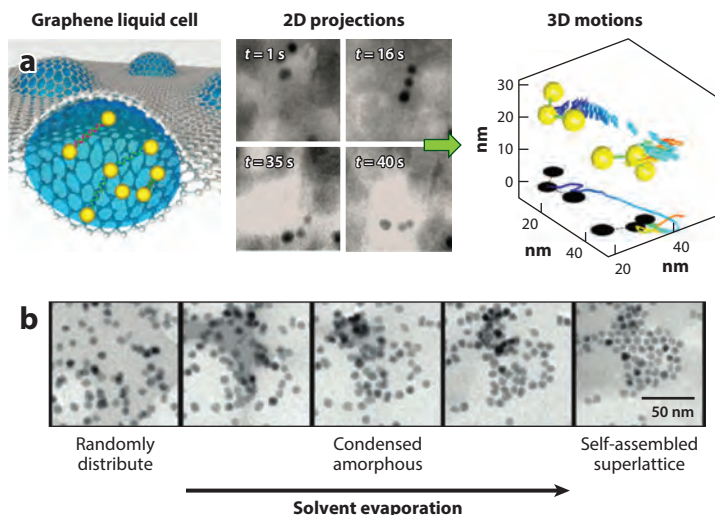
## 4. TRACKING AND MANIPULATION OF NANOPARTICLE MOVEMENT IN A LIQUID CELL

### 4.1. Tracking Single-Particle Motion

Nanoparticles move in solution. The motion of nanoparticles in a liquid cell may come from, for example, Brownian motion, chemical reaction-induced local environmental changes, liquid flow, and electron beam effects. It is important to develop an understanding of the physics and origin of nanoparticle motion. As the thickness of solution in a liquid cell approaches the nanometer scale, several factors influence particle motion, including solvent surface fluctuations and vapor-liquid or liquid-substrate interfaces, as well as intrinsic differences in relaxation and transport properties in an ultrathin liquid film compared to its bulk. In an ultrathin liquid film, the viscosity can be much higher than the bulk liquid, and the interaction between the solvent molecules and substrate surface can impact nanoparticle diffusion. The diffusion of nanoparticles in such thin liquid films is largely beyond the predictive capabilities of current theoretical computation.

So far, there have been many reports on nanoparticle motion imaged by liquid cell TEM in which both self-contained liquid cells (14) and flow cells (37, 50) were used. By taking advantage of the high spatial resolution of TEM, Zheng et al. (17) observed the microscopic details of nanoparticle motion during fluid evaporation. Tracking real-time diffusion of both spherical (5–15 nm) and rod-shaped ( $5 \times 10$  nm) gold nanocrystals in a thin film of water–15% glycerol revealed complex nanoparticle movements, such as rolling motions coupled to large-step movements and macroscopic violations of the Stokes-Einstein relation for diffusion. As drying patches form during the final stages of evaporation, particle motion is dominated by the nearby retracting liquid front.

Chen et al. (63) reported 3D motion of DNA-gold nanoconjugates in a graphene liquid cell (**Figure 6a**). The quantitative analysis of real-time nanocrystal trajectories shows that double-stranded DNA dictates the motion of linked nanocrystals throughout the imaging time of minutes. This sustained connecting ability of double-stranded DNA enabled continuous imaging under TEM, which is rarely achieved.



**Figure 6**

(a) Imaging of 3D motion of DNA-gold nanoconjugates (63). (b) In situ observation of superlattice formation by liquid cell transmission electron microscopy. Figure adapted from Reference 48 with permission.

Using STEM, de Jonge et al. (35) were able to image gold nanoparticles in water with a thickness of several micrometers. White et al. (23) studied charged platinum nanoparticle dynamics in water. Furthermore, Mueller et al. (67) captured the motion of gold nanorods in a flow cell.

Nanoparticle motion can also be utilized for the 3D reconstruction of nanoparticles. Park et al. (92) presented a hybrid method for reconstructing 3D structures of individual nanoparticles in solution. They used a graphene cell to image free rotating platinum nanoparticles in solution and derived the 3D structure at the near-atomic scale from images of individual nanoparticles, providing a way to understand the structure and stability of defects at the nanoscale (**Figure 7**).

## 4.2. Observation of Nanoparticle Assembly

The self-assembly of nanoparticles has attracted great attention. Assembled nanoparticles may show collective properties from different types of materials, with each kind of nanoparticles showing homogeneous and tunable properties with respect to their composition, size, and shape (128, 129). Nanoparticle assemblies are often formed empirically. An understanding of the fundamental mechanisms of assembly formation may help guide the creation of large-scale nanoparticle arrays suitable for effective device architectures. Liquid cell TEM provides a direct imaging platform to visualize the self-assembly of nanoscale objects. Although diffusion in a liquid nanofilm near the surface can vary from the real bulk liquid, nanoparticle self-assembly observed in a liquid cell provides useful information on the interaction between nanoparticles.

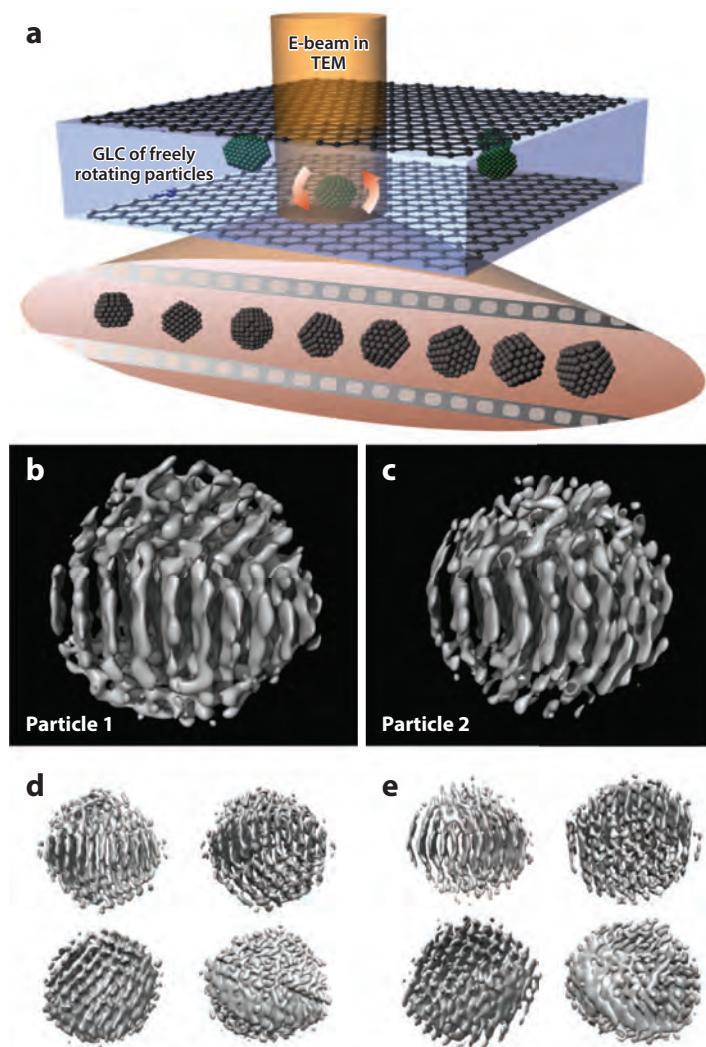
Park et al. (48) reported that an ordered nanoparticle superlattice can be formed from randomly distributed nanoparticles (**Figure 6b**), with both capillary forces and local solvent fluctuations by electron beam-induced local evaporation playing a role in the assembly process. Liao et al. (60) reported that nanoparticles can be self-assembled into a chain, ring, and 2D film during nanoparticle growth. Grogan et al. (39) observed the aggregation of gold nanoparticles using a custom-made liquid cell. The kinetics of movement and fractal dimension of the aggregates are consistent with 3D cluster-cluster diffusion-limited aggregation. Liu et al. (59) reported that a high-energy electron beam can induce the self-assembly of gold nanoparticles coated with positively charged CTA<sup>+</sup> and negatively charged citrate (CI<sup>-</sup>) ions in solution. Because of the different surface charges, gold nanoparticles behaved differently as they were illuminated with the electron beam. The self-assembly of positively charged gold nanoparticles into a chain was observed when the electron beam intensity exceeded a threshold of 5 pA/cm<sup>2</sup>, whereas negatively charged particles remained stationary regardless of the electron beam intensity.

## 4.3. Manipulation of Nanoparticles with Electron Beam

A highly focused electron beam can be used to manipulate nanoparticle movement (i.e., electron tweezers) and to probe the interaction forces between nanoparticles while observing dynamic nanoparticle motion. Oleshko & Howe (130) reported early work on electron tweezers. They showed that 20–300-nm solid aluminum particles inside a molten aluminum-silicon eutectic alloy can be trapped and steered using a focused electron beam inside a transmission electron microscope. Batson et al. (131, 132) reported the use of a swift electron beam in STEM to control the position of gold nanoparticles on an amorphous carbon film.

Zheng and colleagues (51, 133) reported the electron beam manipulation of gold nanoparticle movement in a liquid cell using TEM (**Supplemental Figure 3**). The degree of flexibility in nanoparticle manipulation was remarkable. Gold nanoparticles were trapped inside the beam, and their global movements followed the movement of the beam. The unique discovery in this work is that the trapping force of the electron beam was directly measured by the probability distribution of the gold nanoparticles, and it was calculated to be approximately 1 pN. Using an electron

### Supplemental Material



**Figure 7**

Illustration of in situ TEM imaging of platinum nanocrystals freely rotating in a graphene liquid cell and 3D electron microscopy density maps calculated from individual platinum nanoparticles in solution. (a) Scheme showing the experimental approach by collecting a movie of the single rotating platinum nanocrystal in a 2D projection. (b) Electron microscopy density map obtained from the 3D reconstruction of particle 1. The orientation of the particle is aligned to expose  $\{111\}$  planes of the core domain. Three distinct crystal domains can be identified. (c) Electron microscopy density map obtained from the 3D reconstruction of particle 2. (d) 3D electron microscopy density map of particle 1 with alternative viewing angles. (e) 3D electron microscopy density map of particle 2 with alternative viewing angles. Panels d and e present the two particles from the same angles and directions with respect to the orientations in panels b and c. Abbreviations: GLC, graphene liquid cell; TEM, transmission electron microscopy. Figure adapted from Reference 92 with permission.

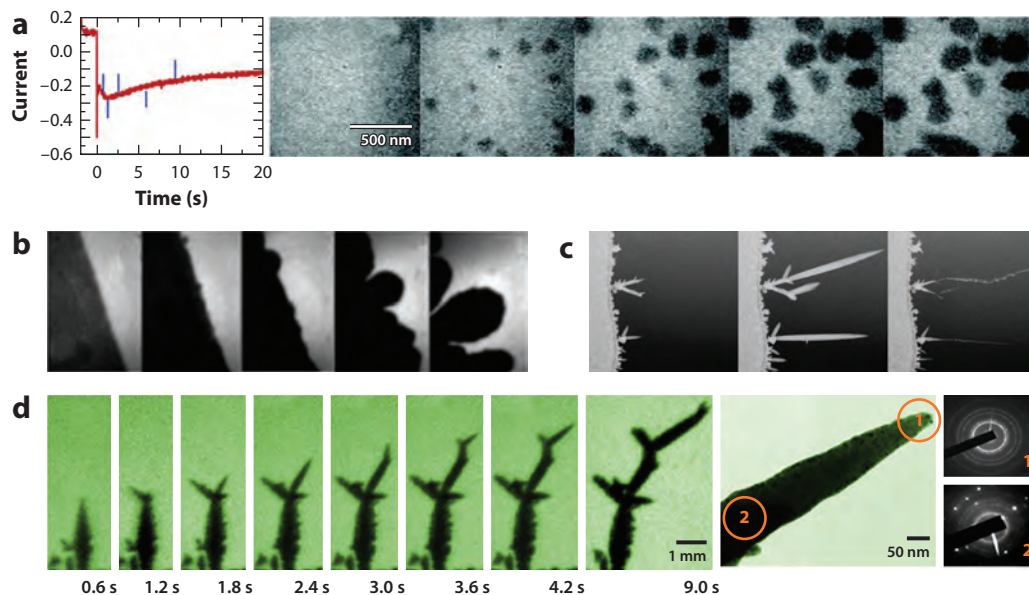
beam, they also showed the trapping of multiple nanoparticles in a liquid cell. Chen et al. (69) reported that nanoparticles can be attracted outside of the electron beam. The driving force for electron beam manipulation was attributed to electric charging effects, and it is a function of the particle-to-beam distance. Overall, the nature of nanoparticle–electron beam interaction needs to be further studied.

Whereas the electron beam tweezing of nanoparticles may bring useful applications, the study of nanoparticle diffusion and assembly using liquid cell TEM requires careful control of electron beam perturbation. In addition to reducing the electron beam dose, it is necessary to perform control experiments in which the electron beam is shut down periodically for comparison.

## 5. ELECTRIC BIASING IN A LIQUID CELL

### 5.1. Electrochemical Deposition

Electrochemical experiments can be carried out using a liquid cell by adding patterned electrodes inside the cell. A wide range of materials [i.e., gold (14, 134), titanium, platinum (135), carbon] can be used as the electrodes, although gold electrodes are most commonly reported. The design concept of an electrochemical liquid cell is similar to that in **Figure 2b** except that in most recent work, an extra container is not added as a reservoir and the electrode configuration varies. With an electrochemical liquid cell, the electrochemical deposition of metal can be studied in situ (see **Figure 8**). **Figure 8a** shows the electrodeposition of copper in a liquid cell (30, 31). Copper growth takes place on a polycrystalline gold electrode from an acidified copper sulfate



**Figure 8**

(a) Plot of current versus time recorded during the deposition of copper on polycrystalline gold at a potential of  $-0.07$  V. Panel *a* adapted from Reference 31 with permission. (b) Electrodeposition of copper onto polycrystalline platinum from the electrolyte in panel *a*. Panel *b* adapted from Reference 135 with permission. (c) Dendrite growth and collapse in  $1.5$  M  $\text{Pb}(\text{NO}_3)_2$  during application of square wave voltage pulses. Panel *c* adapted from Reference 19 with permission. (d) Sequential transmission electron microscopy images showing the electrochemical growth of lead dendrites. Panel *d* adapted from Reference 134 with permission.

electrolyte under an electric bias with constant voltage. The spatial distribution and growth kinetics of individual copper islands can be captured. The growth of copper clusters can be correlated with the applied electrochemical program. Pathways of copper diffusion and the island nucleation and growth mechanisms can be explored by comparing the growth rates measured from video of in situ experiments with that calculated from electrochemical models. Furthermore, scaling the island volumes and hence charge passed from the imaged area ( $2 \text{ } \mu\text{m}^2$ ) to the total electrode area ( $2,000 \text{ } \mu\text{m}^2$ ), and comparing with the measured current, suggests that all areas of the electrode are behaving uniformly, even those out of view. This type of calibration is important for the quantitative analysis of electrochemical processes.


Similar experiments examine the effects of additives and also of the electron beam (85). Instability occurs when the process is controlled by diffusion through the electrolyte so that areas projected further into the electrolyte can collect more ions and grow further. **Figure 8b** shows the development of an unstable copper growth front. The lateral growth of a uniform film can be achieved by controlling the growth and electrolyte chemistry. The lateral growth scenario provides an interesting model for the charging process in secondary batteries, such as those of zinc or lead batteries. In batteries, controlling growth front planarity is important, given that nonuniform deposition of metal onto the anode during charging can short the battery and cause damage or even a fire.

White et al. (19) reported lead electrodeposition in an electrochemical liquid cell (**Figure 8c**). With the applied electric potential program varied, lead dendrites either grew or were suppressed, with the results relevant to conventional lead-acid batteries. Sun et al. (134) investigated the growth mechanisms of lead dendrites as deposited on electrodes under an applied potential. They developed an electrochemical liquid cell by limiting the areas of electrode exposure to the electrolyte so that the observation under TEM represented the main stream of reaction inside the liquid cell and also avoided the possible issue of electrolyte completion in such nanodevices. The experiment provided detailed information on the development of lead dendrites by fast protrusion and tip splitting. With more in-depth characterization, the authors concluded that the tip of a branch comprises polycrystalline nanograins, which eventually develop into a single crystalline branch (**Figure 8d**). This study demonstrated the unique electrochemical growth of single crystal dendrites through nucleation, aggregation, alignment, and attachment of randomly oriented small grains. Additionally, it found that the lead concentration in the electrolyte drastically influences the morphology of dendritic formation.

## 5.2. Lithiation and Delithiation in a Liquid Cell Nanobattery

Tremendous progress has been made toward the direct observation of the structural and chemical evolution of electrodes for lithium ion batteries (LIBs). The first in situ TEM observation of the charge and discharge of LIBs was achieved with an open cell configuration by Wang et al. (99) and Huang et al. (100). The battery comprises a vacuum-compatible ionic liquid-based electrolyte, a single nanowire electrode, and bulk  $\text{LiCoO}_2$  as the counter electrode. A typical ionic liquid electrolyte consists of 10% lithium bis(trifluoromethane sulfonyl)imide ( $\text{LiTFSI}$ ) dissolved in a hydrophobic ionic liquid, 1-butyl-1-methylpyrrolidinium ( $\text{P}_{14}$ ) TFSI ( $\text{P}_{14}\text{TFSI}$ ). Wetting of the ionic liquid forms a thin layer of electrolyte around the nanowire. Therefore, this configuration to some extent mimics a real battery configuration, in that the liquid electrolyte forms a conformal coating around the active component in the electrode. The open cell configuration offers the possibility of atomic-level spatial resolution and the analytical capability to study the mechanisms of lithium ion insertion into electrode materials during the charge/discharge cycle (**Supplemental Figure 4**).

This open cell technique has helped reveal details of lithiation mechanisms and structural evolution in a range of materials, especially anode materials such as silicon (136), germanium

 Supplemental Material

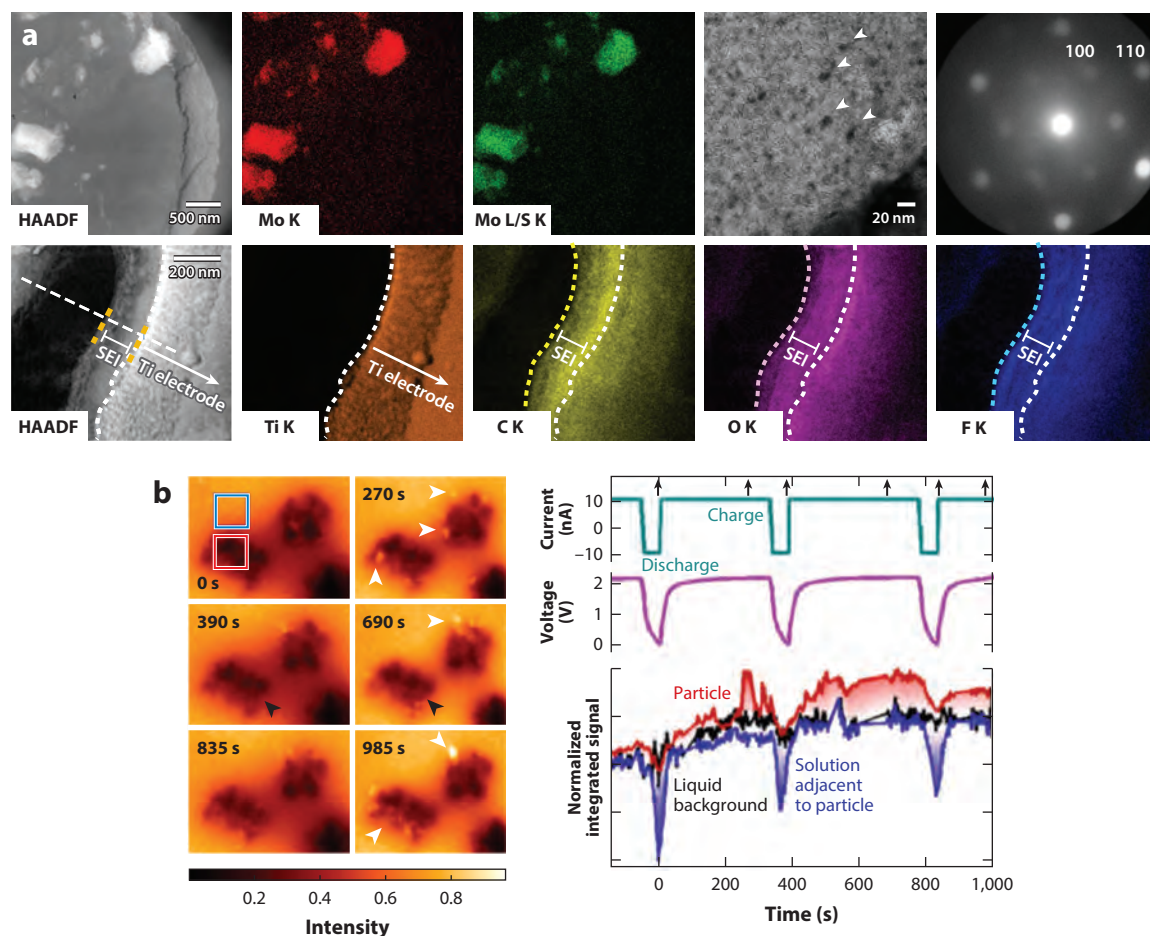
(137),  $\text{Al}_2\text{O}_3$  (138),  $\text{SnO}_2$  (100),  $\text{ZnO}$  (139), graphene (140), and carbon nanotubes (141). This method does have its drawbacks. First, the electrolyte is only in point contact with the electrode. This presumably modifies the diffusion pattern of lithium ions in the electrode, so the results are not necessarily representative of the real battery for which the electrode is fully immersed in the liquid electrolyte. Second, the open cell configuration forbids the use of carbon-based volatile electrolytes in commercial LIBs. Finally, the polymerization of the ionic liquid electrolyte occurs under the electron beam, and the cell can be cycled only a limited number of times, which cannot reveal the structural evolution of electrode materials in real batteries.

Using a sealed liquid cell, Gu et al. (20) studied the lithiation and delithiation of a silicon nanowire in a battery-relevant electrolyte, and similar devices have been demonstrated by other groups (20, 86, 87, 142, 143). The complex reactions occurring at the electrode-electrolyte interface lead to the formation of a passive layer, the solid electrolyte interphase (SEI), at the electrode surface (144). The SEI is fundamental to battery performance and lifetime because it controls the passivation, stability, and impedance of the electrode. The structure, chemistry, and evolution of the SEI with the cycling of the battery are therefore of key interest for liquid cell electron microscopy studies. Two very recent reports used closed liquid cells to examine several aspects of SEI formation. During electrochemical lithiation and delithiation of gold anodes in an  $\text{LiPF}_6/\text{EC}/\text{DEC}$  electrolyte, Zheng et al. (142) found that lithiation occurs inhomogeneously, with lithium metal dendritic growth, electrolyte decomposition, and SEI formation during cyclic voltammetry (**Figure 9**). The SEI layer was observed to develop uniformly on one gold electrode, concurrently with lithium dendrite growth on the other electrode. Similarly, in another observation using  $\text{LiPF}_6/\text{EC}/\text{DMC}$  (87), SEI formed in a dendritic rather than a uniform layer on a gold electrode. The SEI formed prior to the deposition of lithium and remained on the surface after lithium dissolution. Dendritic SEI formation prior to lithium deposition suggests that the electrolyte composition affects lithium deposition. Lithium deposition was also observed by other groups (94, 145), and the lithium-gold reaction was studied by Zeng et al. (84) in a commercial electrolyte.

Lithium ion transport in  $\text{LiFePO}_4 \leftrightarrow \text{FePO}_4$  serves as the prototypical example to address scientific questions related to ionic transport in cathode materials. It is known that removal and insertion of lithium ions in this system lead to a reversible phase transformation,  $\text{LiFePO}_4 \leftrightarrow \text{FePO}_4$ . Three models have been proposed to describe lithium ion transport: the shrinking-core (146), phase boundary migration (147), and solid solution (148) models. A systematic, quantitative understanding of the correlation of ionic transport with structure has yet to be established. With a closed liquid cell configuration, Holtz et al. (86) studied lithium ion transport kinetics and degradation mechanisms in  $\text{LiFePO}_4$  particles during charge/discharge cycles using energy-filtered TEM imaging. A valence energy loss peak at 5 eV was selected, which is unique for  $\text{FePO}_4$  but not for  $\text{LiFePO}_4$ . This allows the determination of the lithiation state of an  $\text{LiFePO}_4$  electrode and the surrounding aqueous electrolyte in real time with nanoscale resolution during electrochemical charge and discharge. Delithiation occurs particle by particle, with a slow nucleation and growth process within each particle starting at the edge and moving through the particle. The instantaneous enrichment/depletion of lithium captured during delithiation and lithiation of the particle highlights the advantages of nanoscale imaging under operando conditions.

## 6. BIOSCIENCE APPLICATIONS OF LIQUID CELL TRANSMISSION ELECTRON MICROSCOPY

Understanding cellular function at the molecular level requires techniques capable of imaging whole cells with a resolution that can image individual proteins in their native environment. Light microscopy has been used to image protein distributions via fluorescent labels in live cells in

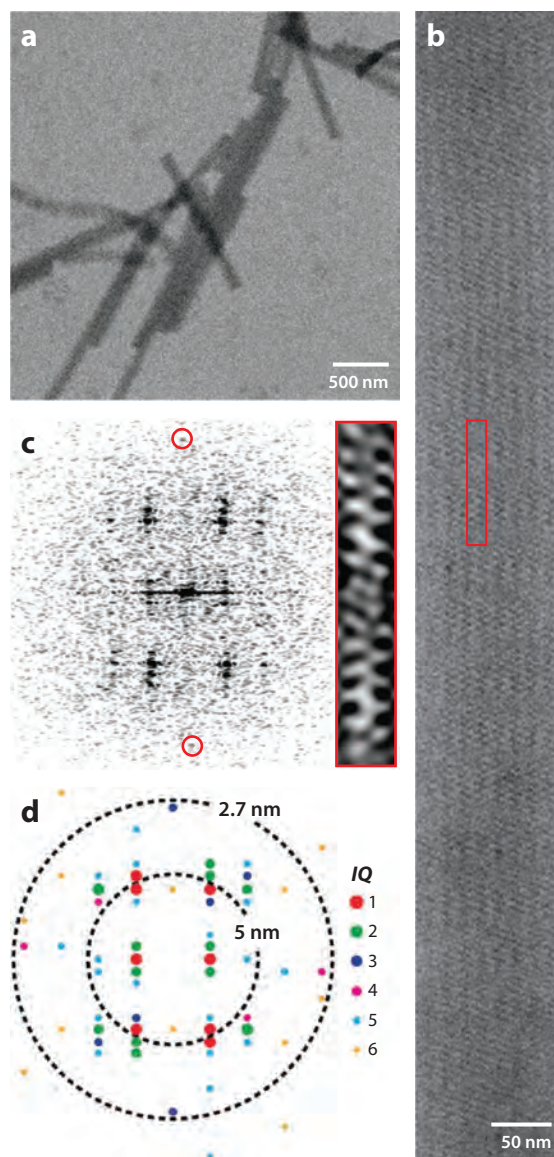


**Figure 9**

(a) In situ TEM observation of the MoS<sub>2</sub> reaction on a titanium electrode by using the electrochemical liquid cell and real-time electrode-electrolyte-interface formation in commercial LiPF<sub>6</sub>/EC/DEC electrolyte loaded in the liquid cell. Panel *a* adapted from Reference 93 with permission. (b, left) In situ energy-filtered TEM capturing the structural and chemical evolution of LiFePO<sub>4</sub> as a cathode and activated carbon counter electrode for a lithium ion battery. Regions of the particle are seen to light up and disappear, potentially owing to delithiating and fracturing off of the particle cluster. White arrowheads indicate bright charged particles and black arrowheads indicate dark discharged particles. (b, right) Integrated intensity over various regions, tracking with the voltage profile, from the regions shown at left by the boxes in red and blue. Panel *b* adapted from Reference 86 with permission. Abbreviations: SEI, solid electrolyte interphase; TEM, transmission electron microscopy.

liquid to investigate cellular function. Super-resolution techniques surpass the diffraction limit in optical microscopy but are still restricted to spatial resolutions of 10–20 nm. Electron microscopy is traditionally used to resolve the structures of individual proteins and to image protein distributions in cells. However, it demands sample preparation, such as protein crystals, stained thin sections, or frozen samples. The cells are thus not in their native liquid state. With the development of a liquid cell, it is possible to image cells and other biomaterials in their native environments. De Jonge and colleagues (34, 35) imaged cells in liquid with TEM by using a flow cell. The cells were placed in buffer solution in a liquid cell, and a spatial resolution of 4 nm and a pixel dwell

time of 20 ms were obtained. Huang et al. (43) described a self-aligned wet cell suitable for direct cell or bacteria incubation and observation in a wet environment inside a transmission electron microscope. Mirsaidov et al. (28) imaged acrosomal bundles in water in a self-contained liquid cell and determined the resolution to be at least 2.7 nm at doses of  $\sim 35 \text{ e}/\text{\AA}^2$ . (**Figure 10**). This




**Figure 10**

Imaging proteins in a liquid cell. (a) Low-magnification image of 80-nm-diameter acrosomal bundles in liquid. (b) An acrosomal bundle in h0l orientation. The unit cell is boxed in red. (c) Fourier transform pattern from a portion of the image of the acrosomal bundle in panel b. The meridional reflection at 2.7 nm is circled. The red box shows the unit cell reconstructed from reflections with a signal-to-noise ratio of  $>1.2$ . (d) IQ plot of the Fourier transform and the resolution shells at 5 and 2.7 nm. Figure adapted from Reference 28 with permission.

technique extends imaging of unstained and unlabeled macromolecular assemblies in water from the resolution of the light microscope to the nanometer resolution of the electron microscope.

Wang et al. (80) applied graphene liquid cells to other biological samples and examined them in their native state using aberration-corrected STEM. Atomic and electronic structures of hydrated ferritin were characterized using electron microscopy and spectroscopy through encapsulation in single-layer graphene in a biocompatible manner. It was demonstrated that graphene reduced the radiation damage to hydrogen bond breakage. The authors measured a reduction of the iron valence from 3+ to 2+ at nanometer resolution in ferritin, showing the initial stages of iron release by ferritin.

Park et al. (89) studied wet biological samples in a graphene liquid cell. The multilayer graphene sheets encapsulated and preserved biological samples in a liquid for TEM observation. They achieved nanometer-scale spatial resolution with high contrast using low-dose TEM at room temperature and used the graphene liquid cell to directly observe the structure of influenza viruses in their native buffer solution at room temperature. The graphene liquid cell was further extended to investigate whole cells in wet conditions with TEM (**Supplemental Figure 5**).

 **Supplemental Material**

## 7. ROLE OF THE ELECTRON BEAM AND ELECTRON BEAM DAMAGE CONTROL

In an in situ TEM experiment, one needs to understand how the imaging electrons modify the sample before drawing any conclusions about the mechanism of the process under study. For solid samples, the effect of a high-energy electron beam has been studied in detail both theoretically and experimentally (30, 31, 78, 85). The mechanisms of electron beam damage for imaging liquid samples can be different from those for solids, such as metals and semiconductors, given that various radicals, including secondary electrons, can be generated and these species can further participate in the reactions, which make the mechanism of radiation damage more complicated and system dependent.

According to Grogan et al. (135), high-energy electrons generate primary and secondary radiolysis products. These products rapidly (within seconds) reach equilibrium concentrations in the region irradiated by the electron beam. In the radiolysis of pure water, one product is hydrogen gas, which can produce bubbles if its steady-state concentration is above the solubility limit. Another product is hydrogen ions; thus, the electron beam can change the pH of a solution under study, which can alter the stability of other species in solution. A third, highly reactive product is the hydrated (or solvated) electron. It is thought to be responsible for the reduction of metallic cations in aqueous salt solutions, leading to the phenomena observed in experiments that measure the beam-induced growth of metallic nanoparticles (149, 150) and beam effects during electrochemical deposition (135). In more complex, nonaqueous solutions, such as the electrolytes for LIBs, the solvated electrons and other radical species can interact chemically with the salt and solvent. Identification and quantification of different species are needed for future study.

When liquid cell TEM is used to study nanoparticle growth, the electron beam is often used as the energy source to trigger the reaction. The high-energy electron beam can induce the decomposition of the liquid or precursor. Nanoparticle growth under the electron beam often occurs above a certain dose threshold. Although the electron beam can initiate nanoparticle growth, it can also induce side reactions. For example, with a sufficiently high dose rate, gaseous products, such as bubbles, can be generated in an aqueous solution (78).

**Supplemental Figure 6** summarizes a possible reaction pathway of nanoparticle growth in a liquid cell under an electron beam. The nucleation and growth of nanoparticles start from the supersaturation in the solution. There are different ways to initiate nanoparticle formation, such as

heat, chemical reduction, radiation, and the electron beam. As reported in many previous studies, nanoparticle growth under an electron beam shares many similarities with those of flask synthesis. A liquid cell TEM study of nanoparticle growth under thermal heating has also been reported, in which a commercial heating sample stage and a liquid cell compatible to the sample stage were used (49, 62).

The electron beam can also be utilized in a liquid cell to create beam-induced patterning at the nanoscale. Den Heijer et al. (85) patterned metal clusters using electrochemical deposition under the electron beam. By operating an electrochemical cell in a transmission electron microscope, they deposited copper on gold under potentiostatic conditions. When chloride ions were added into the liquid precursor, nucleation occurred only in areas irradiated by the electron beam under a range of applied potentials. By scanning the beam, patterns of deposited copper were generated. The process is analogous to laser-induced plating, but the high-energy electron beam can provide finer patterns, which can be useful for certain applications. Chen et al. (151) fabricated SiC<sub>x</sub> nanodots and nanowires with sizes from 60 nm to approximately 2  $\mu$ m using liquid cell TEM.

In general, to minimize the electron beam damage, one can consider reducing the accelerating voltage or lowering the electron dose. Depending on the specific system and the role of various factors, such as solvated electrons, bond cleavage, and local heating, there are different strategies to limit electron beam damage. According to Grogan et al. (78), during interactions of high-energy electrons with water, radiolysis plays an important role, but heating is typically insignificant. However, more vigorous study of the mechanisms of electron beam damage is highly sought. As all electron beam effects are dose dependent, low-dose imaging can be an effective way to reduce electron beam damage in all system. Techniques developed for biological imaging in cryo-electron microscopy can be very helpful in the future of imaging liquid samples.

## 8. OUTLOOK

Liquid cell TEM provides unique capabilities for the study of materials transformations in liquids with high spatial and temporal resolution. It has provided tremendous opportunities to observe colloidal nanoparticle nucleation and growth and many other materials and materials processes in liquid environments, such as the self-assembly of nanomaterials, electrochemical processes relevant to batteries, and biological imaging. Publications on liquid cell TEM have increased rapidly in the past several years. However, given the short time development, there is still much room for improvement.

In the future, more effort is needed and breakthroughs are expected in liquid cell TEM. For example, although atomic-scale resolution imaging has been achieved by incorporating ultrathin silicon nitride membranes or graphene in a liquid cell, improving the spatial resolution in liquid cell TEM is necessary for many studies. So far, the study of electrochemical processes in a liquid cell has been limited to low-resolution imaging, partly constrained by electron beam damage. Along with other approaches to control the damage, a highly sensitive detector is crucial for future developments. Moreover, improving the temporal resolution is important to study the transformation dynamics of materials, such as molecular dynamics in liquids. With the newly developed fast direct electron detection camera, imaging with a frame rate of 1,600 frames per second has been achieved. However, ultrafast imaging and spectroscopy (i.e., in a picosecond or femtosecond regime) is needed to understand certain scientific problems, and this area is under active research. Additionally, more capabilities need to be incorporated into liquid cell TEM. For instance, integrated highly sensitive and fast chemical detection and mapping are desired to study many reactions. Finally, we need to advance the liquid cell design or liquid cell TEM setup. Liquids with high vapor pressure (i.e., water and other low-boiling point organic solvents) are hard

to handle because they can easily dry out during sample loading or vanish under the electron beam, creating challenges for experiments and limiting the application of liquid cell TEM techniques. In addition, liquid cells with a well-calibrated environment, precursor mixing, and a controlled applied stimulus, for example, are often required to study certain controlled reactions. Advancing the liquid cell apparatus is an ongoing task.

We envision that as the technology matures, liquid cell TEM will experience revolutionary growth in the near future. It can become possible to reveal single molecules or individual atoms in liquids during reactions. Liquid cells allowing the mixing of different liquids in situ, fast detection, and mapping of different chemical species, a controlled local environment, can be achieved. Liquid cell TEM will continue to impact and advance broad interest in materials science, chemistry, physics, and biology.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

## ACKNOWLEDGMENTS

The authors thank Xiaowei Zhang for help with editing the references. We also thank the DOE Early Career Research Program for funding support.

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## Errata

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