Introduction: Principles of Electron Tomography

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1. WHAT IS ELECTRON TOMOGRAPHY?

Tomography is a method for reconstructing the interior of an object from its projections. The word *tomography* literally means the visualization of slices, and is applicable, in the strict sense of the word, only in the narrow context of the single-axis tilt geometry: for instance, in medical computerized axial tomography (CAT-scan imaging), the detector–source arrangement is tilted relative to the patient around a single axis (Fig. 1a). In electron microscopy, where the beam direction is fixed, the specimen holder is tilted around a single axis (Fig. 1b). However, the usage of this term has recently become more liberal, encompassing arbitrary geometries, *provided that the specimen is actively tilted into multiple angles*. In line with this relaxed convention, we will use the term *electron tomography* for any technique that employs the transmission electron microscope to collect projections of an object that is tilted in multiple directions and uses these projections to reconstruct the object in its entirety. Excluded from this definition are 'single-particle' techniques that make use of multiple occurrences of the

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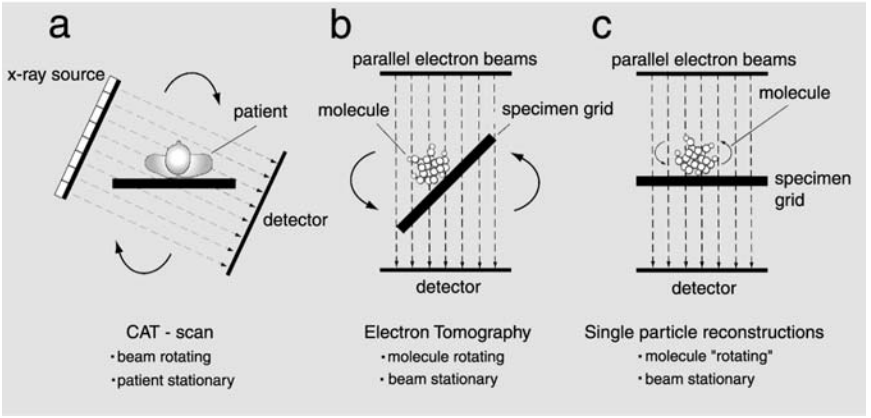

FIGURE 1. Three popular data collection geometries in 3D construction. (a) CAT-scan geometry, with the patient being stationary and a rigid source–detector arrangement tilted by equal increments; (b) equivalent single-axis tilt geometry in the transmission electron microscope, with the source–detector arrangement being stationary and the specimen tilted by equal increments; (c) as (b), but tilting replaced by the multiple incidence of molecules found in different random orientations.

object in different orientations, with or without the additional aid of symmetry (Fig. 1c). These techniques are covered elsewhere (non-symmetric: Frank, 1996, 2006; symmetric: Glaeser *et al*., 2007).

The terms '3D *imaging*' and '3D *electron microscopy*' have come into use as general terms to denote the capabilities of the instrument combined with the necessary computational tools to obtain a 3D image of an object's interior. For instance, a new series of Gordon Conferences was started in 1985 under the title 'Three-dimensional Electron Microscopy of Macromolecules', with the intention of providing a forum for scientists approaching the study of biological structure with both crystallographic and non-crystallographic techniques. (The term 3D *electron microscopy* may actually sound misleading since it conjectures an instrument with true 3D imaging performance. Such an instrument was actually conceived (Hoppe, 1972; Typke *et al*., 1976) but never advanced beyond the blueprint stage.)

2. A HISTORICAL PERSPECTIVE

3D imaging techniques are now commonplace in many areas of science, and it is difficult to recall that they have emerged only within the past 30 years; before that time, computers were simply too slow to be useful in processing 3D data on a routine basis, although much of the mathematical theory was well developed.

We may consider Plato's simile of the cave as a precursor to the reconstruction problem: here our ignorance of the essence of reality is depicted