Pertinent Experience and Past Performance related to NanoParticles

Overview

Dr. Donald Chernoff is one of the pioneers in the field of Atomic Force Microscopy(AFM) and related Scanning Probe Microscopy(SPM) technique, including Scanning Tunneling Microscopy(STM). In 1986, he started the STM lab at the Standard Oil (Ohio) Research Center. When the first commercial AFM became available in 1990, this expanded the range of material surfaces that could be examined from electrically conductive surfaces to nearly any surface you can touch. He founded Advanced Surface Microscopy, Inc. (ASM) to provide analytical testing and research services using Atomic Force Microscopy(AFM) and related Scanning Probe Microscopy techniques. In 1994, he was the first person to recognize that AFM phase imaging provides contrast between different materials on surfaces, with sensitivity to a single molecular layer. This very important technique is now a standard feature in virtually all AFMs.

We have gained a broad perspective on AFM applications. Since 1990, ASM has performed more than 1500 analytical projects for more than 270 different customers on more than 140 different kinds of materials and devices. About half of our work has been on polymers and nanoparticles. The other half has been on materials from A to Z (e.g. from Aluminum beverage cans to Zirconium alloy parts for nuclear reactors). Industries served include: Aerospace, Automotive, Chemicals, Data Storage, Electronics, Energy, New Materials, Optics, Paper, Semicon, Telecom, and Pharmaceuticals/Biomedical (including therapeutics, diagnostics, and implants). We give back to the scientific community through publications, presentations and service in voluntary standards-setting organizations, such as ASTM's Committee E42 on Surface Analysis, Subcommittee E42.14 on STM/AFM. Dr. Chernoff helped write the ASTM E 2382–04 "Guide to Scanner and Tip Related Artifacts in Scanning Tunneling Microscopy and Atomic Force Microscopy". By understanding the artifacts and limitations of a technique, one can avoid misinterpretation of results and one can find ways to improve the technique.

The strengths of our laboratory include:
-a singular focus on AFM technology and applications;
-a dedication to excellence in calibration and measurement that has resulted in 2 US Patents and many publications; and
-an international reputation within the AFM community.

Accurate measurements at nanoscale

Dr. Chernoff invented and patented procedures for making high accuracy measurements of the size, shape and position of regular arrays of marks using general purpose, affordable AFM's. This led to a test method and software sold worldwide. It was one of the many innovations that enabled the optical disc industry to increase data density 40-fold as it progressed from compact discs (CDs) to DVDs and Blu-Ray discs. This method supports more than half the world's production of these discs. ASM has collaborated with several of the national metrology labs around the world that are responsible for accurate nanometer-scale length measurements. In one study with NIST (National Institute of Standards and Technology) and the Singapore counterpart of NIST, ASM and the other two labs each independently measured the same 70-nm pitch standard, with the objective of determining the average pitch, traceable to the international meter. Our results all agreed within +/-0.025 nm (< 4 parts in 10,000). This is a testament to the care with which we do our work.

Nanoparticles

ASM's experience with nanoparticles and nanomedicine began in the early 1990's, with experiments using gold nanoparticles and biopolymers. We investigated the feasibility of depositing few-nm diameter gold clusters on AFM tips to create a sharper tip and the deposition of the gold clusters on a flat substrate for use as tip characterizers. We performed some of the first AFM studies of collagen. We prepared AFM specimens of collagen 'monomers' (a rod-like protein about 280 nm long x 1.5 nm diameter) and of collagen fibrils assembled spontaneously from the monomers. "Collagen in solution", a medical product, is a suspension consisting primarily of collagen monomers. Whereas chromatography provides an indication of the molecular weight distribution, AFM visualizes and measures individual molecules. We assessed several attributes: the lengths of the monomers (which indicates the molecular weight of each particle), the occurrence of fragments (greatly shortened monomers), and the occurrence and form of dimers, trimers and higher aggregates. Later, we imaged DNA molecules in various forms. We imaged conformational features of plasmid DNA. In 2006, we imaged "mop-head" DNA, a complex of DNA and peptide LL-37. This complex is a key molecular species in the inflammatory process causing psoriasis. ASM was responsible for the design and execution of the AFM work, including sample preparation, image capture, image interpretation, reporting and visual rendering. This work was published in Nature. [Nature 449, 564-569(2007) doi:10.1038/nature06116. "Plasmacytoid dendritic cells sense self-DNA coupled with antimicrobial peptide" R. Lande et al. ASM's contribution is acknowledged in the main article and described in detail in the supplementary material.]

In 2008, NIST introduced gold nanoparticle reference materials (RM8011, RM8012 and RM8013), with nominal diameters of 10, 30 and 60 nm. These materials are not "standard reference materials" because the size is not traceable. Working with ASTM and other parties, NIST helped organize a large interlaboratory study of these materials. Although the primary objective was to characterize the performance of Dynamic light scattering (DLS) instruments in measuring particle size, the study also included measurements by AFM, SEM (scanning electron microscopy), and TEM (transmission electron microscopy). 26 labs participated in the study. ASM was one of 8 labs that contributed AFM results. One of the important findings was that different techniques produced similar, but somewhat different numerical results. This is not surprising, since each technique interacts with the nanoparticles in a different way.

Iron carbohydrate

We have been measuring iron carbohydrate nanoparticles using AFM since 2008. This work was **inspired** by the pioneering work of Kudasheva et al (, "Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations", J. Inorg. Biochem. 98 (2004) 1757–1769) and **motivated** by various versions of FDA's "Draft guidance on Iron Sucrose", which have explicitly or implicitly suggested that AFM can be used to characterize the particle morphology and the iron core size.

Performing proprietary research sponsored by more than two companies and by FDA, we have measured Venofer®(iron sucrose), Ferrlecit® (iron gluconate) and other formulations. In more than 10 studies, involving more than 120 samples, we have imaged and measured more than 40,000 particles. Based on our general knowledge of AFM, our experience with other nanoparticle materials, and the specific experience gained through these studies, we have refined the sample preparation, image capture and data analysis procedures.