Visualization and Natural Control Systems for Microscopy
Submitted to Visualization Handbook, Christopher Johnson and Charles Hansen editors

Authors:

Russell M. Taylor II (1,2,3), David Borland (1), Frederick P. Brooks, Jr. (1), Mike Falvo (3), Martin Guthold (4), Tom Hudson (5), Kevin Jeffay (1), Gail Jones (6), David Marshburn (1), Stergios J. Papadakis (2), Lu-Chang Qin (2,3), Adam Seeger (1), F. Donalson Smith (1), Dianne Sonnenwald (7), Richard Superfine (2,3), Sean Washburn (3,2), Chris Weigle (1), Mary Whitton (1), Phillip Williams (8), Leandra Vicci (1), Warren Robinett (9).

1: University of North Carolina at Chapel Hill department of Computer Science.

2. University of North Carolina at Chapel Hill department of Physics & Astronomy.

3. University of North Carolina at Chapel Hill Curriculum on Applied and Materials Science.

4. Wake Forest University department of Physics.

5. University of North Carolina at Wilmington department of Computer Science.

6. University of North Carolina at Chapel Hill school of Education.

7. University of North Carolina at Chapel Hill school of Information and Library Science.

8. NASA Langley.

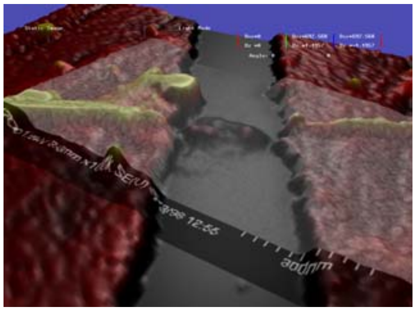
9. Robinett.com.

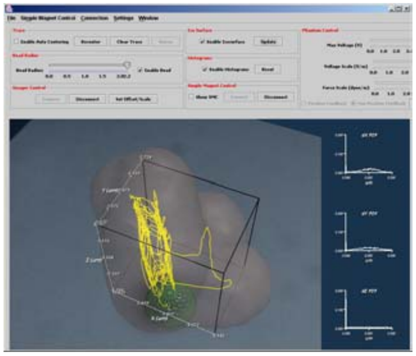
Overview

The world now stands at the threshold of the age of nanotechnology, which biologists have been exploring for years. Imagination has already leapt ahead to the day when it will be possible to touch proteins within living cells, to tug on DNA as it is transcribed and to manipulate molecules one atom at a time. To reach these goals, scientists need *instruments* and *interfaces* that extend their eyes and hands into this new nanoscale world. This chapter is about the construction of such interfaces.

For ten years, the growing Nanoscale Science Research Group (NSRG) at the University of North Carolina at Chapel Hill has been building visualization systems that intuitively map the additional sensing made available by various microscopes into the human senses, and control systems that project human actions directly into this world. The NSRG is composed of teams of computer scientists, physicists, materials scientists, information scientists, and educators. Three systems have been developed to the point where they have been used in physical science experiments:

- The *nanoManipulator* (nM) provides an interactive 3D graphics and force-feedback (haptic) interface to atomic force microscopes (AFMs) to enable scientists to naturally control experiments as if they could directly see, touch, and manipulate nanometer-scale objects on surfaces. Begun in 1991, this system has been used to perform a wide variety of experiments on viruses, [12] carbon nanotubes, [11, 14, 15, 45, 46] fibrin (the fiber that forms blood clots), [28] and DNA. [25]
- The *Nanometer Imaging and Manipulation System* (NIMS) augments the nM with a scanning electron microscope (SEM), using projective texture mapping and manual alignment of SEM and AFM data sets to enable viewing during direct manipulation of samples inside the SEM. The goal is to use visualization hardware and software to combine the two microscopes into one virtual microscope that combines the capabilities of each and mitigates their limitations. Begun in 1998, this system has been used to perform experiments on carbon nanotubes and their use in actuating devices (from MEMS to NEMS). [67-69]
- The *3-Dimensional Force Microscope* (3DFM) provides an interactive 3D graphics and haptic interface to a custom 3D optically-tracked, magnetically-driven force microscope (3DFM) that can track and control sub-micron beads on and near living cells. A recently-completed prototype of this system is being used to study viscosity and force in lung cell cultures to investigate the causes and mechanisms of cystic fibrosis.



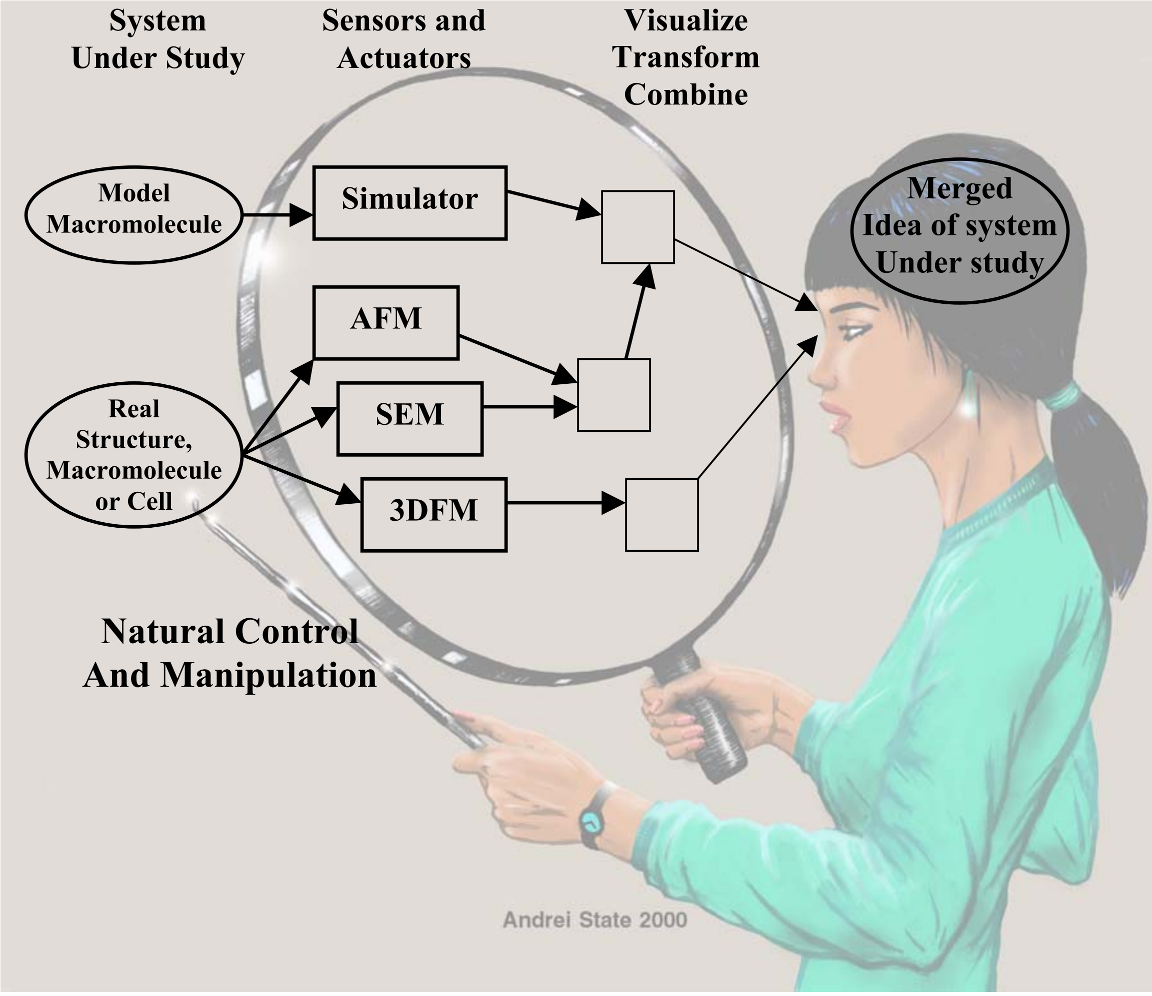


The NSRG has also begun to design and develop interfaces for a new microscopy system:

- The Keck *Atomic Imaging and Manipulation System* (AIMS) will add atomic-scale manipulation capabilities to a transmission electron microscope (TEM) that is capable of near-atomic-resolution imaging of carbon nanotubes and other small structures. This system will be used to study the details of atomic lattice deformations for nanotube structures under stress.

This chapter presents these microscope systems, along with brief descriptions of the science experiments driving the development of each system. Beginning with a discussion of the philosophy that has driven the NSRG and the methods used, it describes the lessons learned during system development, including both useful directions and blind alleys. It also describes techniques to enable telemicroscopy in the context of remote experiments and outreach.

NSRG Philosophy and Methods



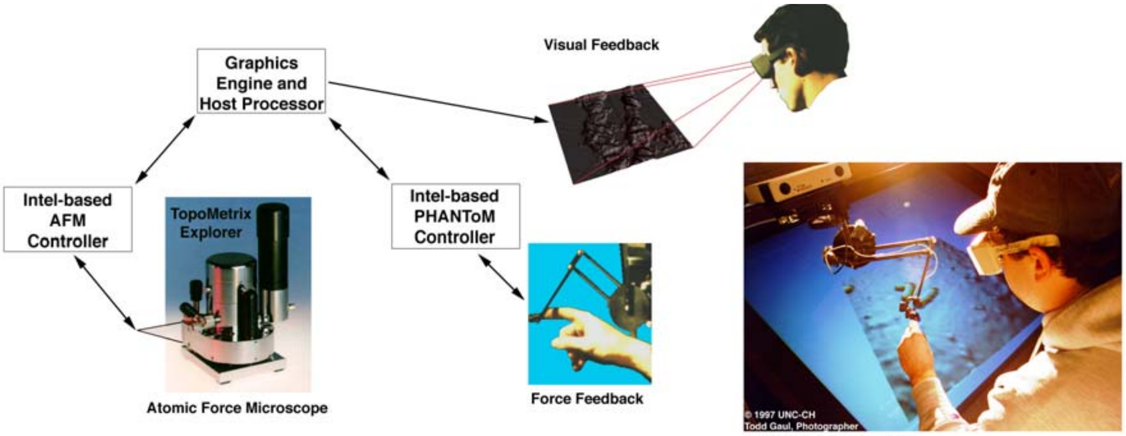
The NSRG aims to provide tools that are, like a lens, transparent and easy to use, yet as powerful and versatile as contemporary computing technology can make them – tools that enable direct viewing of, and interaction with, real and simulated molecules, viruses, and cells. Virtual filters enable the transformation and overlay of multiple data sets in order to map them from the raw instrument data formats onto more natural and useful views. Haptic (force-feedback) display coupled to the microscope's probe enables real-time exploration of the properties of real, touching and moving them to feel how they respond. The goal is to enable the scientist to pay great attention to the experiment and little to the tools, rapidly and easily chasing down "what if" scenarios as they present themselves.

Fred Brooks put forward the two major philosophies that have guided this research. [7, 8] The first is the "driving problem" method of doing computer science research. This posits that excellent computer science research arises from tackling a real-world problem and addressing it on its own terms, as a total system problem, and aiming to satisfy not just computer scientists but professional practitioners in the problem domain. This requires facing all aspects of a problem, not merely the tractable or publishable aspects.

The second major research philosophy is that human-machine systems can address more difficult problems than can machines alone, an idea that can be cast as “Intelligence Amplification is better than Artificial Intelligence.” This posits that at any given level of technological advancement a person plus a machine can beat a machine-only system. This suggests building human-computer shared-work systems, where the human provides creativity, pattern matching, and decision making in the presence of incomplete information and the computer provides precise recollection from large databases and performs the tedious transformations from instrumentation space to the 3D world.

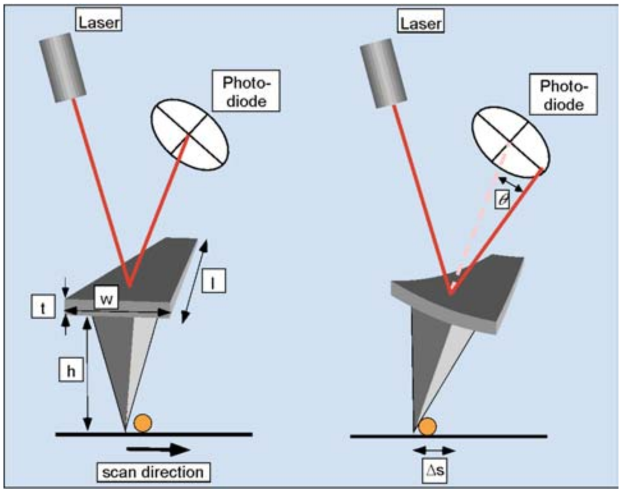
NanoManipulator

How do you examine an unfamiliar object? You look at it. When possible, you pick it up, hold it at arm’s length, and turn it around. You may squeeze or prod to determine its stiffness; a fingernail feels for grooves or surface texture. If the object is on a surface, you may use a fingertip or pen to roll it around.



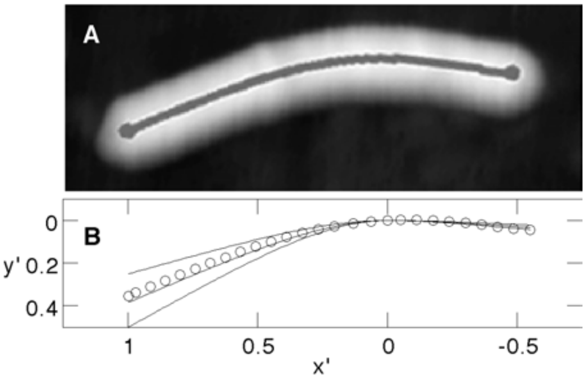
UNC Nanomanipulator

The nanoManipulator System (nM) shown above provides a scientist with the ability to perform these actions on objects as small as single molecules while at the same time quantitatively measuring both the surface shape and forces applied. The nM uses the ultra-sharp tip of a atomic-force microscope (AFM) as tool both to scan and to modify samples. It uses advanced computer graphics to display the scanned surface to the user. A force-feedback haptic device (like a robot arm, but used to present forces to the user) enables the user to feel and modify the surface. [10, 17, 26, 57, 58] It is basically a teleoperation system that operates at a scale difference of about 100,000 to 1.



The diagram on the right shows the basic operation of the AFM, which uses a fine tip at the end of a cantilever to scan and push objects on a surface. The cantilever bends when it comes into contact with the surface or objects on it, causing deflection of a laser beam that bounces off the cantilever. The deflection is detected by a quadrant photodiode, which is able to measure both the normal and lateral forces applied by the tip to the surface. The cantilever is very sensitive: sub-nanoNewton forces can be measured. For imaging, the tip is scanned across the surface in a raster pattern. Feedback moves the sample up and down maintain a constant (very small) applied force. The resulting trajectory yields the topography of the surface. The user can also direct the tip with the robot arm, feeling around on the surface. To modify the surface, the force applied by the tip is increased. The user's hand motions are scaled down by a factor of up to a million, enabling sub-nanometer control over the position of the AFM tip.

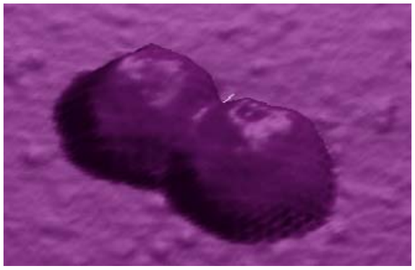
Driving Problems



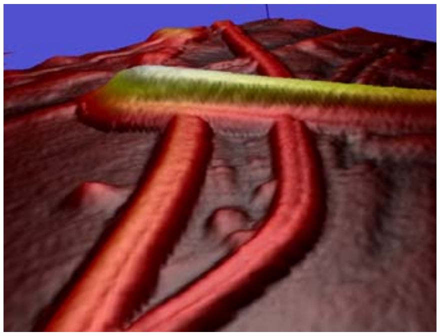
Virus Particles: One of the earliest biological applications was the study of tobacco mosaic virus (TMV). The nM was used to probe the mechanical properties of the virus. Figure A shows an AFM image of a TMV that has been dragged across a graphite substrate with the AFM tip. The resulting bent shape is the balance between the bending rigidity of the virus and the friction between the TMV and the substrate. In the image, brightness corresponds to surface height. The darker gray line drawn along the central axis of the TMV was found by the medial-axis location software developed by the UNC MIDAG group. [18]

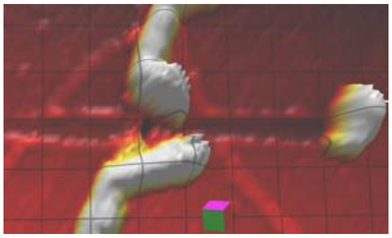
Figure B shows where the mechanical equations for beam bending for a beam under uniformly distributed force are fit to the shape of the TMV found with the medial-axis software. This fit yields the ratio of distributed frictional force to the bending rigidity of the TMV.

Another series of investigations has explored the physical properties and surface interactions of adenovirus. Adenovirus is an icosahedral virus that is being used by the UNC Gene Therapy Center as a vector for gene therapy. The elastic properties of the virus in air and in liquid were studied by placing the AFM probe on top of an individual virus using haptic feedback. A semi-automatic position vs. force measurement tool was then used to map the response of the virus to increasing force. [43] The nM is also being used to push adenovirus across different surfaces to investigate the adhesion between the virus and each surface and to determine whether the viruses slide or roll. The image to the right shows two adenovirus particles, one of which has been dimpled at the top using the nM.



Carbon Nanotubes: Carbon nanotubes are of interest both because of their mechanical properties (they are the strongest known material) and because of their electrical properties (they are insulating or conducting depending on the details of their construction). They are also interesting because they are atomically-precise constructions with atomic spacing exactly matching that of graphite. The nM system has been used to probe all of these characteristics. It was used to probe the bending and buckling behavior of the tubes by manipulating them by hand on various surfaces. [11, 13] It revealed that the atoms in the tube lock in like gear teeth at the appropriate orientation on graphite, causing them to roll or slide depending on orientation. [9, 15, 16] Adding electrical measurements to the manipulation ability revealed that the electrical resistance through the tubes to a graphite surface is an order of magnitude smaller when they are in alignment than when they are not [46]. The effects of strain on conductance were also explored. [45] Each of these experiments required carefully controlled manipulation of tubes. The image to the right shows a configuration where one tube was pushed end-on to slide over another pair of tubes; the AFM probe was then carefully inserted by feel between the first two tubes to peel them apart – leaving the third tube suspended between them.





Blood Clotting Disorders: Blood clots are composed of blood cells trapped in a matrix of fibrin fibers. While the fibrin from normal, "wild type" clots prevents excess bleeding, mutant versions found in clotting disorders either form clots too easily (leading to stroke) or too poorly (causing excess bleeding). Although the bulk properties of the clots found in these disorders have been measured and the specific gene defects for many of these variants are known, the mechanisms by which the defects cause large-scale change to the properties are not. The strength, thickness, and stickiness of fibrin variants are being studied to help bridge this knowledge gap. Wild-type and mutant fibers are formed and deposited on a surface. Their height is measured using an AFM, which is then employed to cut the fibers. During cutting, measured force profiles reveal the strength of adhesion between the fiber and surface, the springiness of the fibers, and their rupture strength. Imaging after manipulation reveals whether the fibers undergo elastic or plastic deformation. The image to the right shows a fibrin fiber after being cut using an AFM (which tore out the portion seen on the right side of the image). [28]

System Description

Achieving a working system required overcoming the computer-science challenges of:

- real-time rendering of a large and dynamically-updated surface model,
- integration of haptics, teleoperation, and a virtual-reality system,
- real-time, low-latency, distributed heterogeneous computing, and
- network-aware real-time AFM control system.

The **dynamic, large-model rendering challenge** was initially tackled using the world's fastest graphics computer (Pixel-Planes 5, developed at UNC under DARPA funding). [19] This machine was fast enough to render the number of triangles needed for the scanned surfaces, but its graphics pipeline was unable to handle the required dynamic update of the surface as the microscope scanned. This was addressed by reprogramming Pixel-Planes' parallel array of geometry processors and developed a more efficient protocol for sending updates from the host processor to the graphics subsystem. [58] The rendering challenge has been solved over time by advances in rendering technology to the point where the nM now runs effectively on a laptop with an Nvidia GeForce2Go graphics processor.

The **haptics subsystem** was initially implemented using the Argonne III Remote Manipulator (ARM) developed for use by Ming Ouh-Young in an earlier UNC project – his Docker program that simulated the docking of drugs within protein receptor sites. [6] This used *Armlib,* a UNC-developed network-aware ARM server. When the higher-performance Phantom haptic display from SensAble Devices became available, the nM was ported to it. Since there was no haptic control software library available for the device, the Armlib software was modified to also control the Phantom. [42] The nM currently runs on top of the manufacturer-supplied *GHOST* software toolkit, using the UNC-developed public-domain *Virtual Reality Peripheral Network* (VRPN) library as the network layer that enables remote graphics machines to control the device. [60, 61] The physical separation of microscope and haptic display pushed the development of novel *intermediate representations* to enable both the microscope feedback and haptic display feedback to proceed at their required rates of 100kHz and 1kHz while updates between them occur over the network at only 30 Hz. The resulting techniques were published in [42].

The **real-time, low-latency, distributed heterogeneous computing** challenges were first addressed by adopting the techniques that had been developed to enable the Docker program to do its parallel computation on a MasPar computing array connected to a Vax, its haptic display on a Sparcstation connected to the Argonne ARM, and its graphics display on an SGI or Evans & Sutherland display console. This required careful control over network link settings (using TCP_NODELAY for one-way streams and limiting the attempted packet transmission rate to that sustainable by the network); common numerical encodings (using the *htonl()* functions for integer conversion, and hand-tuned binary conversions between

IEEE and Vax floating point because binary-to-ASCII routines were too slow in this extreme-low-latency environment); careful management of relative loop rates, buffering and pipelining to enable data to be ready when needed without introducing unacceptable delays; and the development of robust, operating-system-independent remote process creation/destruction to enable rapid startup and to avoid leaving behind cycle-burning processes that occupied resources when the system was shut down. These techniques have been formalized and documented over time, and make up the core of the public-domain VRPN library and described in [61].

The **network-aware real-time AFM control system** developed in four steps.

- The first implementation controlled a user-built scanning tunneling microscope (STM) sent from Stan William's group at UCLA; it ran on Microsoft's *DOS* operating system and coordinated network activity using Sun's *PC-NFS* network stack, a finite-state machine to implement the control interface, digital-to-analog control using Data Translation boards, and external Hewlett-Packard pulse generators for tip voltage bias and modification by voltage pulses. A nonlinear analog feedback control system for the STM was designed and built to improve the instrument's performance. [57, 58]
- The second implementation was for a Digital Instruments (DI) brand Atomic Force Microscope. DI kept its interfaces proprietary, requiring extreme measures to achieve external program control over the instrument. This made it necessary to use a second, auxiliary control computer that drove the DI's signals by replacing analog multiplexer chips on the control system board and effecting changes in the digital control by transmitting characters through a serial port to the keyboard buffer on the main control computer.
- The third implementation was done in software on top of the TopoMetrix (since then the company has merged into ThermoMicroscopes and now Veeco) control software under Microsoft *Windows*. Topometrix provided the source code to their control system as part of an equipment donation to the project. The current version uses a custom VRPN object type [56] as the network transport layer.

Lessons Learned

Several system features have proven very useful by enabling new types of experiments or revealing previously unseen phenomena. These features are listed in detail in [59], along with the particular insights revealed by each. A summary of the highlights:

- **Graphics.** Augmenting the standard real-time 2-D view with user-controlled, real-time, publication-quality 3-D views enables the scientist to gain insight during experimentation that otherwise would be missed. Subtleties of shape and interactions between 3D objects become clearer when viewed in their natural 3-D context and from changing viewpoints. ("The map is not the terrain.")
- **Haptics.** Touch enables the scientist to find the correct location to measure or start an experiment, even in the presence of drift and positioner nonlinearities. During manipulation, the probe is busy, so no new scanned images can be produced: the user works blind. However, forces are continually measured. When these forces are displayed, this feedback during manipulation enables understanding and controlling the path of delicate modification ("pushing bags of Jell-O across a table in the dark with a screwdriver without breaking them"). Slow, deliberate feeling can find the location of objects that scanning would knock aside ("haptic imaging").
- **Virtual tips.** Switching between an oscillating mode for imaging and contact mode for modification enables imaging fragile samples, which are then modified with known force. A sewing-machine mode enables finer lines to be formed in thin films without tearing. A virtual whisk-broom enables extended structures (such as TMV) to be moved as units.

- **Replay.** Storing the entire experiment and enabling replay lets the scientist see things missed the first time around, as well as enabling the application of new analysis techniques to old experiments. ("Flight data recorder.") Data is exported in a variety of formats to existing image-analysis tools (Kaleidagraph, SPIP, ThermoMicroscopes) and standard file formats (TIFF, PPM, ASCII).

Design in machine independence and replay: Because the microscope control computer and the graphics computer for the nM system were of different architectures and communicated across a network, the system had to be designed to use a machine-independent wire protocol to communicate between them. This has borne much fruit: it simplified the storage and replay of experiments, it simplified the porting of parts of the system to different architectures with time, and it enabled remote access. One specific design decision that enables replay is to make the application rely only on responses from the microscope to determine the system state (whether it is in modify mode or touch mode, the actual size of a region that is selected, etc.). This also made the system robust to instrument limitations: if asked to do something beyond its capabilities, a particular microscope would either not respond or reply with a clipped version of the request. This required a few specialized state-indicating messages to be added to the network interface: "Tell me I think I'm in modify mode now," and "Tell me I think I'm in touch mode now." These messages preserve the user's intent, which cannot be inferred from other nM system parameters.

Design for more than one instrument: When scientists perform an experiment, it is often the case that they use more than one instrument. For some nanotube experiments, a computer-controlled voltage source and current monitor were used to explore changes in conductance while the AFM was used to apply strain to the tubes. The control and measurement for all instruments needed to be time-aligned within the tolerances of the experiment design and ideally be controlled from within a single framework. This is true both during the experiment and during replay. This becomes even clearer in some of the later systems that explicitly combine two or more instruments.

Give them the data: Whenever a scientist thinks that they have obtained a new insight into a problem, they seek to verify the insight by comparing its predictions with the data at hand. This requires access to the data from the experiments, not just derived visualizations of the data. It is tempting to design a new user interface for display and analysis of raw data values, a process which may takes weeks or months. Often, the data in a very raw ASCII format that can be imported into spreadsheets or other analysis tools is really what is needed. Providing the data in this format makes it available to the scientist sooner and involves spending less time designing tools that mimics those that already exist.

There was no one "best" immersive interface for this system: different people preferred different interfaces. Washburn preferred wearing a head-mounted display (HMD) when doing experiments because of its stereo display and the ease of navigating using motions of head and hand. Falvo preferred operating using a non-head-tracked stereo projection display because of its higher resolution compared to the HMD. Stan Williams preferred to direct by watching a non-stereo projected display while Taylor was driving the experiment from inside the HMD interface. One trend has emerged as experiment lengths stretched to hours: for this application, scientists found the additional headwear and eyestrain required for stereo head-tracking not to be worth the benefit using the technologies available.

Exact calibration may not be worth the effort: The goal of constructing the nanoWorkbench system displayed in the nM system diagram was to align the graphics and haptics display within 1mm (1 display pixel) of the virtual model to enable direct and precise interaction with the model. After years spent chasing this goal, the scientists asked that the force display be offset from the visual display by several centimeters so that the end-effector would not visually obscure the point of contact. A task-level analysis should have been done before pursuing the technology-driven of exact alignment. Alignment was both more difficult and less useful than expected.

nM Summary

The nM system has been in continuous use exploring and modifying surfaces since 1993 and biological samples since 1995. It is the longest running of the systems described here, and is in the most advanced state of development. The nM system currently has 101 hierarchically grouped functions, each asked for by a user to address a particular challenge in an experiment. It has been ported from its initial configuration using a custom-built haptic display device, a custom-built SPM controller, and a custom-built graphics supercomputer to a configuration running entirely on commercially available equipment (PC-based graphics, the Phantom haptic display and TopoMetrix-derived AFMs). It was developed into the commercial *NanoManipulator™ DP-100* by Aron Helser at 3rdTech and has been sold to NASA and a number of University departments. [30]

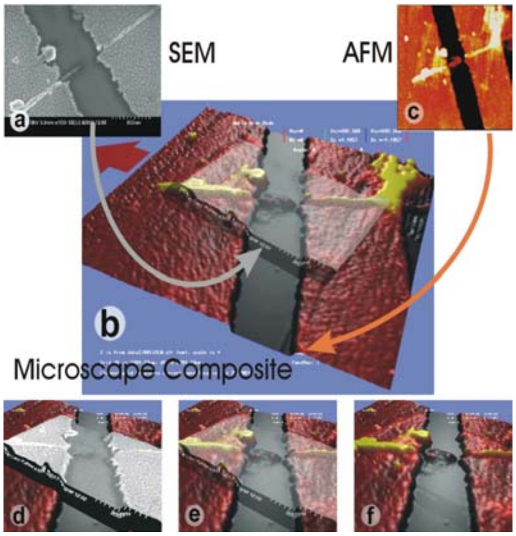
The nM brings advanced visualization, analysis and modification tools to bear *as experiments are happening*, providing immediate feedback that can be used to select the most promising step forward at each stage of an experiment. It forms the base software for expansion into the NIMS. It also forms the base for the telemicroscopy efforts. Despite the system's long tenure, new capabilities are continually being added to support new experimental needs.

What Makes This Possible

Current Project Personnel: *Computer Science Toolbuilders:* Russ Taylor, Mary Whitton, Leandra Vicci, Steve Pizer, Paul Morris, David Marshburn, Aron Helser, Tom Hudson, Yonatan Fridman, Jameson Miller. *Physical Scientist Collaborators:* Richard Superfine, Sean Washburn, Mike Falvo, Stergios Papadakis, Garrett Matthews, Michael Stadermann, Adam Hall, Rohit Prakash, Dorothy Erie. *Information Science Collaborators:* Diane Sonnenwald, Kelly Maglaughlin. *Education Collaborators:* Gail Jones, Dennis Kubasko, Michele Kloda, Tom Trettor, Atsuko Negishi.

Project Funding and Support: NIH NCRR program, grant number 5-P41-RR02170 has supported the development and application to biology throughout. NSF's HPCC program supported advanced visualization, scalability, and network access through grant number ASC-9527192. NSF's ARI program, grant number DMR-9512431 supported installation of the first nanoManipulator in the scientists' laboratory. Initial support for bringing the system from UCLA to UNC was provided by NSF's SGER program, grant number IIS-9202424.

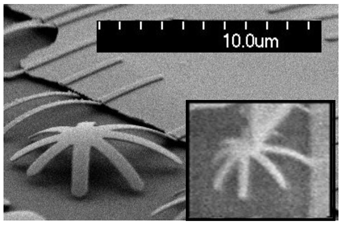
NIMS: nM+SEM



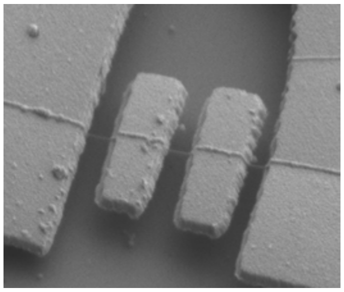
Although the nM enables both precise manipulation and imaging, they are separate functions. Since there is only one probe in the AFM, at one time it can be used for either imaging or manipulation. The scientist can feel the force on the probe at the point of contact, but cannot watch the probe and sample deformation during manipulation. The end configuration of objects on the surface is imaged after manipulations by a subsequent raster scan of the sample. The *Nanoscale Imaging and Manipulation System* (NIMS) incorporates the AFM into a Hitachi S4700 scanning electron microscope (SEM), a 1.5 nm resolution instrument that enables electron microscope imaging during AFM manipulation. This effectively "turns the lights on" for the user while they are manipulating samples.

The image to the right shows the overview of AFM and SEM scans of the same area, a carbon nanotube that was draped between two raised electrodes and then broken. The simplest combination of the two data sets is shown here: the data sets were aligned by hand and the SEM laid over the underlying AFM topography using projective texture mapping. The user can adjust the relative mixture of the two data sets.

Driving Problems



Thermally-Actuated Mobile Structures (TAMS): Bimetallic multi-armed structures with smallest dimensions under a micron are being formed with the intention of driving their motion using differential heating. An eight-legged version seen to the right is one of the prototype designs. The inset shows the AFM probe in the NIMS pressing on one from above to measure its stiffness and see its response.



Carbon Nanotubes (CNT): Building on the fabrication and analysis described in the nM section, NSRG scientists are designing and characterizing nanoscale mechanisms such as the torsion oscillator seen in the image to the right. The structure is composed of two metallic paddles fabricated on a suspended CNT between two metallic leads. [69]

Problems: How to measure shape deformation from one or more SEM views? How to determine Z position of AFM tip within SEM projection view to enable rapid and safe manipulation?

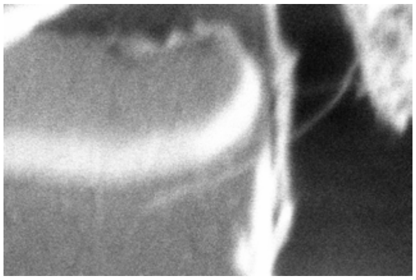
System Description

New interaction modes were added to those of the standalone nM to support experiments on fragile structures. One enabled control of the AFM probe in 3 dimensions, rather than keeping it always touching the surface. Another provided the ability to drop down onto the surface from above and measure the position offset of an object as the force was uniformly increased and then decreased.

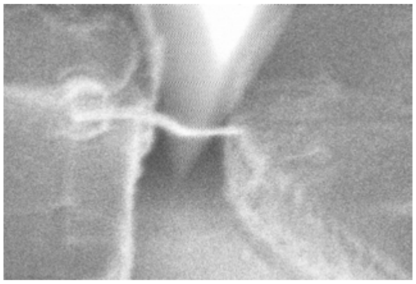
A method of calibration between SEM and AFM images has been developed that enables the system to show the AFM probe in its proper 3D location compared to the AFM scan. The method uses manually selected corresponding points in the AFM and SEM images to solve for the transformation between the images. This has been extended to include calibration between the AFM probe position, the SEM image, and a geometric model of the surface being studied to enable manipulation experiments on fragile samples without requiring a complete AFM scan of the sample.

Projective texture mapping is used to display AFM scan, SEM image, surface model, and AFM probe position within the same image to provide an optimal understanding of the sample to enable planning of intricate manipulations and electron beam lithography.

Results



The images to the right show two steps in an experiment that shows the NIMS being used as a combined tool, employing the capabilities of the SEM and the AFM together. The top image shows a carbon nanotube draped over a gap between the tip of an AFM probe (upper right corner) and one half of a MEMS test structure. Direct 3D control of the AFM probe is being used to touch one end of the tube to the surface at the correct location. Once there, the AFM probe is locked into place and the electron beam is switched from scanning mode to focusing its energy at the point of contact between the tube and the surface. This causes carbon atoms in the "vacuum" to accrete, effectively welding one end of the tube down.



The lower image shows the case after each end of the tube has been "welded" down on opposite sides of the test structure. The SEM beam has returned to scanning, and the AFM is being used to test the tube's strength (the tip is blurred because it is in motion). In the final portion of the experiment (not shown here), the AFM probe was used to move one arm of the test structure. This caused flexion of the tube and then broke the connection between the tube and one end of the structure – the weld failed before the tube ruptured.

Lessons Learned

Look to add-ons when the manufacturer doesn't supply a programmable interface: The software interface provided by a standard SEM add-on controller from EDAX was used to provide scanning and directed-beam modification control within the SEM. This enabled the NIMS system to control beam parameters and scanning, without which the combined instrument would have been impossible to build. The EDAX control is performed through attachments that have become standard in the SEM industry. It exports a library of functions intended for scripting that was used in the NIMS system to integrate the SEM with the rest of the system.

Advancing science and computer science: Sometimes, the most acceleration of an experiment comes from applying pedestrian computer science to the most time-consuming part of an experiment. Spending time developing tools of this type helps cement the usefulness of the computer science and can make colleagues willing to spend time in system development. It can also result in science publications co-authored by computer science students.

What Makes This Possible

Current Project Personnel: *Computer Science Toolbuilders:* Russ Taylor, Leandra Vicci, Steve Pizer, Paul Morris, David Marshburn, Adam Seeger, David Borland, Yonatan Fridman. *Physical Science Collaborators:* Richard Superfine, Sean Washburn, Mike Falvo, Stefan Seelecke, Stergios Papadakis, Michael Stadermann, Onejae Sul, Hakan Deniz, Adam Hall, Aarish Patel, Rohit Prakash.

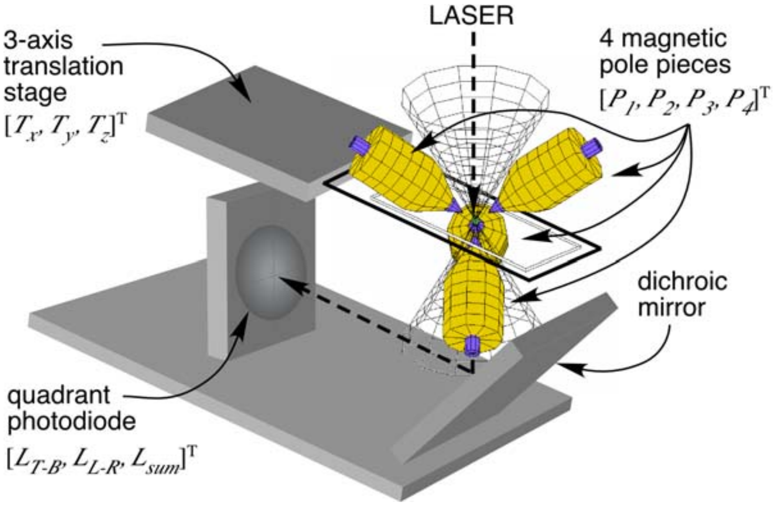
Project Funding and Support: ARO funded the equipment purchased for this system through two successive DURIP awards in 1998 and 1999. The research and tool development for use in carbon nanotubes has been supported by ONR through the MURI program.

3DFM

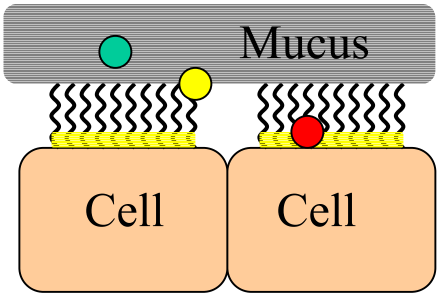
The AFM has two major drawbacks for biological imaging. First, the measuring probe is attached to a cantilever for position control and force sensing. It cannot probe beneath objects, but only the tops of surface-bound objects. Second, it cannot go inside living cells because the cantilever would have to penetrate the cell membrane.

Freeing the tip of the probe from the cantilever alleviates both of these problems. This requires new methods for tracking the tip and for applying forces to it. This has been done using an optical beam in a laser tweezers configuration [21], where a focused laser beam is used both to apply forces and to track the particle position. Whereas this technique has made possible experiments in single molecule dynamics [55], the optical beam can generate only relatively small forces, normally up to several tens of picoNewtons. [44] This is insufficient to break covalent bonds, or to measure the full mechanical properties of biological fibers such as microtubules. Also, the method of applying the force is nonspecific, causing the beam to accumulate extraneous material.

The NSRG physical science team has invented a 3D free-particle force microscope (3DFM) that uses magnetic beads to apply forces using techniques similar to those found in [4, 5]. The particle is tracked using optical light scattering as in laser tweezers. [2, 22, 23]. The diagram to the right shows the components of the integrated system, including a 3-axis translation stage that is used to move the sample so that the bead remains centered in the laser beam.

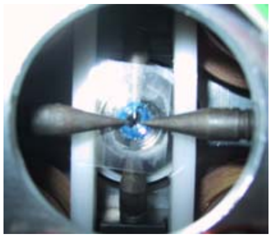


Driving Problem



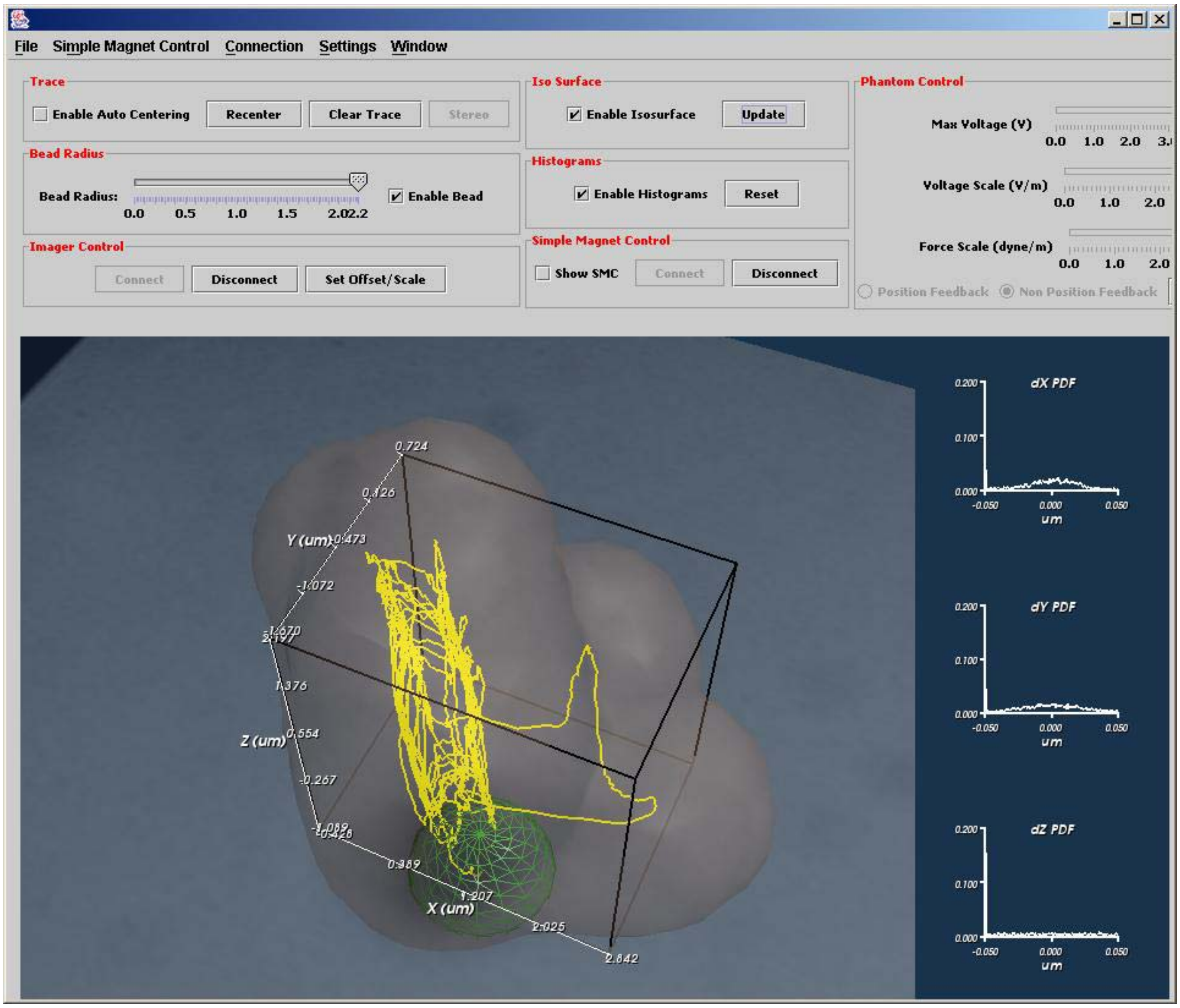
Cystic Fibrosis: The UNC Cystic Fibrosis (CF) Center is investigating the mechanisms by which CF affects its victims. They hope to place sub-micron fluorescent beads in the viscous mucus layer to study its viscosity and motion, attached to the cilia that beat to move the mucus, and attached to cell surfaces. The beads will be viewed using either 2D widefield optical or 3D confocal microscopy. Tracking bead diffusion in the mucus enables calculation of viscosity of different fluid layers. Applying forces to the beads on the cilia will help determine system reactions to force and stall force of cilia. Applying forces to cell surfaces will enable determination of mechanical deformations and system responses. ***Problems:*** How to control the positions and forces to enable applying forces using the beads and measuring the system response to those forces? How to display volumetric viscosity information, lines and volumes of bead travel, and surfaces of cells without confusing the user?

System Description



The tracking and position-control portions of the system are not described here because they function essentially as black boxes from the visualization and user-interface point of view. The magnet control system, on the other hand, has a feature that is exposed to the UI designer. Because the four magnetic poles in the system (seen to the right) can only generate forces towards each pole, forces in arbitrary directions must be broken down into time-sequential tugs towards each of the poles. This design enables the poles to be very close to the sample (thus applying more force), but it requires that the system map the force commands from the user to sequences of forces to be applied by the magnets.

A prototype user interface for the 3DFM built using the visualization toolkit (VTK) [65] and Java Swing is shown below. It includes a 2D section for control over visualization and microscope parameters and connections to the bead tracker, video stream, magnet controls, and haptic device.



☐ Enable Auto Centering
☑ Enable Bead
☑ Enable Isosurface
☑ Enable Histograms
☐ Show SMC
○ Position Feedback
● Non Position Feedback

The 3D section (shown here in a monoscopic view but also displayable in stereo) displays the current location of a tracked bead as a wireframe sphere. This sphere is centered in the live video display (the gray plane with dark spot surrounding the sphere in the image). This plane of video moves with the bead through the volume. The sphere leaves a yellow line as a trail, showing where the bead has moved during an experiment. A transparent shell can also be drawn around the volume that has been "carved out" by the bead as it has moved along the trace; it shows the boundary of the explored region. To the right are three histograms of the bead's motion in X, Y, and Z.

Results

The 3DFM has been used to estimate the viscosity of corn-syrup test samples by tracking the Brownian motion of included beads, and to apply force to estimate the viscosity by observing bead velocity. It has also been used to track the motion of a bead attached to a group of cilia on a lung cell culture, and to apply forces to the cilia through the bead.

Lessons Learned

Displaying intent while recording details: An attempt to provide the most faithful force representation to the users by driving the force display with the same alternating force sequence used to drive the magnet cores resulted in force display that was uninformative and difficult to control. Displaying the average force to the user was more satisfactory; the actual sequence of forces is recorded to the experiment log so that analysis can be done using the detailed force information.

Build in annotation support: The experiment-data logging system for the 3DFM is being augmented with a mechanism to enable scientists to record text comments that are time-aligned with the experiment data. These comments can be added either during the experiment or during replay of a previous experiment. This is being added by request of the scientists, so that they can record significant events as well as interesting locations in the experiment.

What Makes This Possible

Current project personnel: *Computer Science Toolbuilders:* Russ Taylor, Mary Whitton, Leandra Vicci, Gary Bishop, Greg Welch, Prasun Dewan, Paul Morris, David Marshburn, Kurtis Keller, Chris Weigle, Haris Fretzagias, Jonathan Robbins, Tatsuhiro Segi, Ben Wilde, Rajeev Dassani. *Physical Science Toolbuilders:* Richard Superfine, Tim O'Brien, Stefan Seelecke (NCSU), Kalpit Desai, Jay Fisher, Jeremy Cribb, Debbie Sill. *Physical Science Collaborators:* Garrett Matthews, C. William Davis, Lisa Cameron.

Project Funding and Support: NIH NCRR program, grant number 5-P41-RR02170 has supported the development throughout. NIH NIBIB has provided five years of support for development of a beyond-prototype system including a confocal microscope. The Cystic Fibrosis Center at UNC has provided support for equipment and personnel.

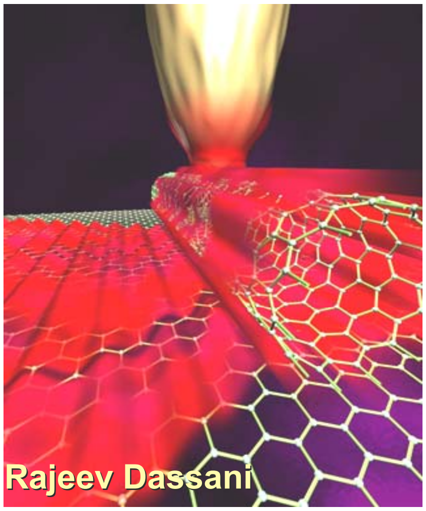
AIMS: TEM + MEMS

The NIMS provides a resolution of about 2 nanometers, which is too coarse to resolve the individual layers in a carbon nanotube or the fine details of other molecular systems. The Atomic Imaging and Manipulation System (AIMS) will address this limitation by combining a 200kV field emission transmission electron microscope (TEM) with MEMS-based manipulation and electrical measurement. The TEM provides better than 0.2 nm resolution for imaging the atomic sidewalls of carbon structures and the atomic positions within nanoparticles. AIMS is being developed as a unified scientific exploration system that will be capable of simultaneous manipulation, measurement and atomic-scale imaging.

Driving Problems

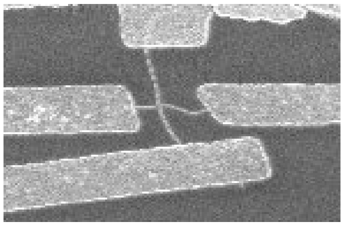
There are two broad classes of experiments driving AIMS development: mechanical contact and electrical transport in nanoscale junctions.

Nanoscale Mechanical Contact: NSRG researchers seek to explore the configuration of the atoms in the contact region between carbon nanotubes. This study will include the distortion of atomic arrangements and the re-bonding of atoms across the interface, energy loss, and electron transport. It is predicted that distortion of the contacting surfaces (right figure) occurs because of the strong attractive forces that bind materials together, but no one has imaged these interfaces in contact for moving nanoscale devices. It has been predicted that the local distortion can dramatically change the properties of the interface, increasing energy loss during motion and enhancing electron transport.



While a TEM by itself can image contact regions, manipulation capabilities are essential for creating particular arrangements of interest (tee junctions, sliding rails, etc.), and for creating motion. AIMS will be used to explore: atomic-scale distortion during motion, interfacial wear at the atomic scale during the sliding of lattices, and the atomic origins of friction and energy flow.

Nanoscale Electrical Junctions: The AIMS will also be used to move nanomaterials into atomic contact. Experiments target both nanotube-nanotube junctions and nanotube-nanoparticle junctions. For the former, new carbon structures with positive and negative curvature have been proposed to form integrated tee junctions. In this case, the nanotubes are not simply lying on top of one another, but are intimately connected like the tee junction of a water pipe. The figure at the right is an SEM image of a crossed-nanotube device created in the NSRG laboratory (the nanotubes, about 2 nm in diameter, are the very thin crossing connections).



Problems: How to provide an atomic scale view of these devices, and enable creation of the proposed integrated tee junctions? How to move nanotubes into atomic contact and then induce re-bonding of the carbon lattices through heating or electron bombardment? How to provide *in situ* electronic characterization to monitor the atomic bonding?

System Planning

The AIMS project presents difficult challenges in the integration of atomic scale motion control, force sensing and in-situ electrical characterization within the extremely tight confines of the sample stage of a TEM. This integration within the tight confines of the TEM sample volume will initially be implemented using MicroElectroMechanical Systems (MEMS). MEMS technology applies processing techniques common to silicon electronic device fabrication to create actuating and sensing systems integrated onto silicon chips.

The user interface paradigms employed to build the NIMS system will be re-used in the AIMS system. Although there are no AFM scans in AIMS, the models and projective texture alignment techniques will be similar. The first step has been preparing prototype applications using different visualization display libraries to select the most effective existing toolkit for this application.

Lessons Learned

Include software interface criteria in the instrument purchase decision: During the TEM selection process, the availability of real-time digital access to the control and imaging systems of the TEM were requirements. This disqualified one manufacturer whose image quality was slightly better than that of the system that was purchased.

Talk with others who have interfaced to each instrument: Talking with experts in other groups who have attempted to digitally control a particular instrument can reveal pitfalls and suggest required system components: sending a student to Mark Ellisman's NCRR helped determine which camera to use.

What Makes This Possible

Current Project Personnel: *Computer Science Toolbuilders:* Russ Taylor, Leandra Vicci, Steve Pizer, Paul Morris, Kurtis Keller, David Borland, Yonatan Fridman. *Physical Science Toolbuilders and Collaborators:* Richard Superfine, Sean Washburn, Mike Falvo, Lu-Chang Qin, Stefan Seelecke (NCSU), Stergios Papadakis.

Project Funding and Support: The W. M. Keck foundation provided the TEM. UNC Chapel Hill has provided engineering and graduate-student support.

TeleMicroscopy

Remote use of AFM, SEM, and TEM systems to view samples is becoming widespread: The nM software has been used by the IN-VSEE group at Arizona State as a base to provide remote web-based access to AFMs. [3, 53]. Mark Ellisman's NIH Resource at UCSD routinely uses a TEM from Japan remotely [29, 47]. The MAGIC group at CSU Hayward has remote access tools for SEM, SPM, and confocal microscopes. [49] Oak Ridge National Laboratory has a web-based interface to its electron microscopes and is developing remote manipulation techniques. [20] The Bugscope project at the Beckman Institute has a complete educational system built around remote access to an SEM. [48] CERN is developing an *OpenLab for Nanotechnology* that will interface with live instruments on the Grid. [24] There are other groups as well. The manufacturer JEOL has even provided a web-based interface to its SEM systems. [70]

Low-latency Remote Microscope Control

Remote control of microscope viewing parameters and viewing the resulting images requires high-bandwidth connections to support interactive use. Manipulation experiments impose the additional challenge of providing remote haptic interaction for touching and manipulating the sample.

Effective deployment of such networked virtual-environment systems requires paying special attention to network latency, jitter, and loss. [32, 36] Graphical and VE applications have particularly stringent latency requirements because their interfaces are interactive: users directly manipulate parameters controlling the images they see using continuous input devices such as mice. The usability of interactive interfaces degrades significantly when visual feedback is not essentially immediate. [33]

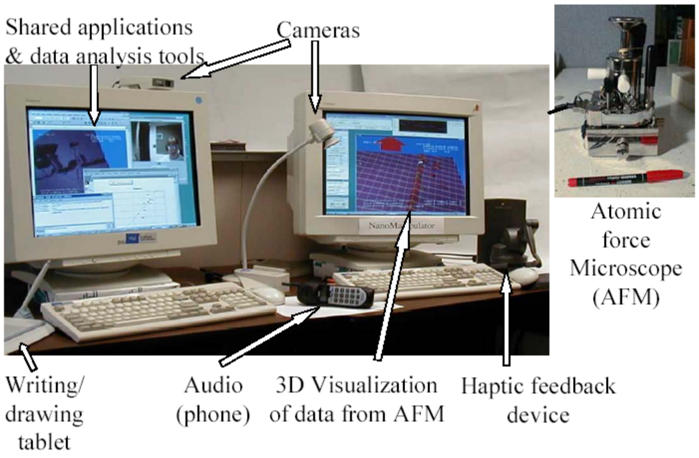
Providing stable and accurate force-feedback control during remote experiments is even more challenging, falling into the domain of remote teleoperation. When force feedback is being used simultaneously, or user input is driving a control loop, response time becomes even more critical: 50 ms of latency in flight simulators reduces performance, and only a little more is needed to cause system instability. [66]

The nM system operates over a network by default, so it might seem that operating it over wide-area networks would be straightforward. Indeed, there have been several instances of successful operation over distance: Internet2 network engineers provided a dedicated, low-latency link from an AFM at UNC to a graphics and haptics user interface located in Washington D.C. for the 1999 Internet2 conference. [35] A similar Internet2/T1 connection from Ohio was used during the BioMEMS and Biomedical Nanotechnology World 2000 conference. [31] (A video showing this in operation is available at [27].) For Orange County High School, McDougle Middle School, and Stanback Middle School (all near UNC) the round-trip network latency is acceptable to enable remote experiments.

There have also been unsuccessful attempts: An Internet2-based link to Microsoft Research in Washington was created in 2001, over which the latency was too high to provide reliable manipulation in the absence of application adaptations. Internet-based connections through a network reflector at Louisiana State University had unacceptably high loss.

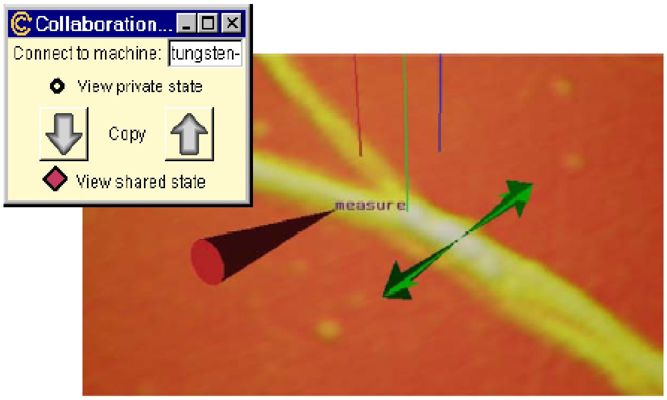
Hudson has developed network-level and application-specific adaptations to minimize, hide, or enable the user to deal with higher latency and jitter. [33, 34, 36] Networking adaptations within the transport protocol are used to reduce jitter and latency and application-level adaptations deal with the latency and jitter that remains. Providing the appropriate intermediate representation [1] was critical to achieving stable and responsive haptic display in this virtual-environment application, especially when operating over a wide-area network. [33, 42]

Remote Microscope-Based Distributed Collaboration



A *collaboratory* has been defined as “a center without walls, in which researchers can perform their research without regard to physical location – interacting with colleagues, accessing instrumentation, sharing data and computational resources, and accessing information in digital libraries.” [XXX ref Wulf] As a step towards this goal, a collaborative version of the nM system has been developed with which two users who are remote from each other and the AFM can share microscope control and visualization. [50, 51] As seen in the figure, each user has their own nM display and control interface (which can be either shared or private) as well as a second computer to support shared work. This shared-work computer runs Microsoft Netmeeting to provide video conferencing between the two ends and enables sharing of word processor and analysis packages. Two video cameras (only one or the other sending data at any time) are located at each end, one stationary and providing a head and shoulders view of the user for conversations, and one on a gooseneck that can be positioned as desired to share views of hand drawings and other things in the room. Hands-free telephones were used for audio.

The collaboratory system allows scientists to dynamically switch between working together in shared mode and working independently in private mode (see image to the right). In shared mode, remote, i.e., non-collocated, collaborators view and analyze the same (scientific) data. Mutual awareness is supported via multiple pointers, each showing the focus of attention and interaction state for one collaborator. Optimistic concurrency techniques are used in shared mode [52], eliminating explicit floor control and enabling collaborators to perform visualization operations synchronously. Because of the risk of damage to an AFM, control of the microscope tip is explicitly passed between collaborators. In private mode, each collaborator can independently analyze the same or different data from stored experiments previously generated or from a live microscope. When switching back to private from shared mode, collaborators return to the exact data and setting they were using.



A report on a repeated-measures, controlled experiment evaluating the collaborative nanoManipulator is in [52]. Twenty pairs of upper-level undergraduate science majors participated in two lab sessions, one session face-to-face using the standard nanoManipulator and the other session using the Collaborative nanoManipulator. As expected, participants reported disadvantages to collaborating remotely. When working remotely, interaction was less personal, individuals received fewer cues from their partner, and some tasks, such as sharing math formulas, were more difficult. However, participants also reported that some of these disadvantages are not significant in scientific work contexts, and that coping strategies, or work-arounds, can reduce the impact of other disadvantages.

Participants reported that remote collaboration also provided several advantages compared with face-to-face collaboration, including the ability to more easily explore the system and their ideas independently and increased productivity with the ability to work simultaneously on the data visualization. While the statistical analysis of graded lab reports produced a null result, i.e. the scores in the collaborative condition were not significantly lower than those in the face-to-face condition, considering both the quantitative and qualitative data, the NSRG collaboration team concludes that there is positive promise for effective remote scientific collaboration.

The study participants were asked what they like and didn't like about the system in post-experiment interviews. Many participants reported that they liked the ability to simultaneously adjust visualization-Model parameters when in shared mode and found that using the explicit floor control in shared applications running in NetMeeting hindered their work.

Remote Microscopy for K-12 Science Classes: Visualization for Education

For six years, a team of educators, physicists, material and computer scientists have taken "reverse field trips" to local middle and high school classes to enable students to participate in multidisciplinary science. Students were able to control the microscope and experiment with viruses using the nM interface over the Internet to control an AFM at UNC. Studies were done on the educational impacts of designed learning experiences on students' knowledge of viruses, nanoscale science, scale, and the nature of science. [37]

This remote microscopy enabled students to experience the interdisciplinary nature of cutting-edge science first-hand. [38-41, 54, 64] Student response to the visits was overwhelmingly positive. Formal questionnaires showed strong positive shifts in attitudes towards science and the process of science, particularly for girls. [39] Students' written evaluations of the project were also very compelling:

> "In the course of a week, I have learned so much. Coming into this experiment we knew so little about viruses, and now we can describe their size, some of their characteristics, and how viruses infect you and make you sick. The visiting scientists have inspired me and so many others to join a field in science. They have lit a flame that cannot be put out." – Female high school student, 1999.

Data showed that students were highly motivated and interested in learning about nanoscience and learned more about viruses, scale, science processes, and scientists. [38, 39]

These reverse field trips continue to press the limits of the available network. Although the schools each have fractional T1 lines to points of presence very near UNC's, providing responsive control required that Internet use in other classrooms be curtailed during the remote microscope operation. Firewalls and network address translation prevent the use of UDP, thus imposing TCP congestion control on all streams to and from the AFM. As the field trips continue to schools with networks that are further (in terms of packet hops) from UNC, or with more loss, new techniques will be needed to maintain responsive control.

Lessons Learned

Network latency is the critical parameter for remote haptics: Providing haptic feedback requires different networking characteristics than remote control of viewing parameters. Whereas high bandwidth is required to send microscope images and video across the network, latency and jitter are the critical parameters for remote haptic display.

Shared and private spaces: Shared and private spaces are important to enable each scientist to explore visualizations and hypotheses independently.

Design primarily for collaborative science rather than social interaction: For this system, designing to support collaborative science enabled remote use that was as effective and as satisfying as sharing a single local system. Some preferred the local system, and some preferred the remote system. Another local researcher (David Stotts) has also found that sometimes people prefer working remotely for pair programming because it reduced the amount of time spent socializing during the work.

Optimistic concurrency control was needed to make collaboration work with acceptable latency in this application. Compared to Netmeeting, which was operating over the same network using explicit token passing, the latency was much lower.

Asynchronous remote procedure calls (RPC), where the calling process does not wait for the return before continuing to process other events, enabled the decoupling of system responsiveness from network latency; the user interface continues with the latest available data and callbacks are used to update the display as requested data arrives.

Providing the appropriate intermediate representation [1] is critical to achieving stable and responsive haptic display in this virtual-environment application, especially when operating over a wide-area network. [33, 42]

Use telephone for remote audio: Compared to the audio included in remote conferencing systems, telephone audio had lower latency, better quality, and was easier to use.

What Makes This Possible

Current Project Personnel: *Computer Science Toolbuilders:* Mary Whitton, David Marshburn, Tom Hudson, Jameson Miller, Kent Rosenkoetter. *Information Science Toolbuilders:* Diane Sonnenwald, Kelly Maglaughlin. *Physical Science Collaborators:* Martin Guthold (Wake Forrest), Roger Cubicciotti (NanoMedica). *Education Toolbuilders and Collaborators:* Gail Jones, Dennis Kubasko, Michele Kloda, Tom Trettor, Atsuko Negishi.

Project Funding and Support: A supplement to the NIH NCRR program, grant number 5-P41-RR02170 has supported the development throughout. NSF's HPCC program supported network access through grant number ASC-9527192. NSF's ROLE program EDU-0087389 has supported studying the educational impact of bringing the system to K-12 schools. The UNC Chapel Hill Chancellor's office provided seed funding for the K-12 outreach.

Conclusions and Other Lessons Learned

Several lessons learned during the development of these microscope sessions are listed here. These are more general lessons not specific to one system.

Begin software development at least as soon as hardware development: It was possible to obtain the software interface before the TEM was delivered. This has enabled software development to commence before system integration. The development of the other microscope systems showed us repeatedly that software development should be begun as early as possible. Some manufacturers provide simulators for their instruments; these can be very useful for debugging.

Partner with experts in required technologies: The MEMS designs for the AIMS system were advanced by collaborating with Mike Sinclair at Microsoft Research, who has done dozens of preliminary designs. Design and manufacturing are also proceeding with the help of Shuo-Hung Chang's nanotechnology center at the National Taiwan University.

Stefan Seelecke's group at North Carolina State University is working with the NSRG on the development of shape-memory alloy actuators and advanced control systems for magnetic and piezo-ceramic actuators for several of the microscopes described here. These systems serve as driving problems for Seelecke's own research.

Jean-Marc Brequet and his students within the nanorobotics group at the EPFL in Lausanne, Switzerland have completed two design iterations on compact piezoceramic-based 2-axis translators for use in the

3DFM system. The second design is also being incorporated into the NIMS system to enable larger range on the AFM.

Partnering with outside experts in required technology can enable a group to concentrate on its strengths and leave other research parts of the system to others.

Build on existing visualization toolkits: Whereas the nM interface was based on custom rendering and interaction codes [10, 17, 57, 59], the 3DFM prototype is based on the Visualization ToolKit. [62, 63, 65] This has enabled rapid implementation and testing of different visualization techniques during interface development. There have been cases during development where a bug deep inside the various toolkits caused several weeks of searching. These weeks-long chases also happened during the development of the nM system, but when they were fixed in the 3DFM the rest of the toolkits were still available for application development.

Effective before cost-effective: The NSRG attempts to use the best available computer technology to develop *effective* systems for use by the physical science team, which then become *cost-effective* and can be deployed on widely-available hardware as technology marches on.

Acknowledgements

Warren Robinett and R. Stanley Williams had the initial idea to hook up a scanning tunneling microscope to a virtual-reality interface; the nanoManipulator was born, which led to all of the work described here. The following individuals participated in the development one or more of the above systems: Benito Valencia Avila, Ron Bergquist, Gary Bishop, Alexandra Bokinsky, David Borland, Brian Boyd, Don Brenner, Fred Brooks, Stephen Brumback, Lisa Cameron, Anthony Canning, Chun-Fa Chang, Jun Chen, Zhi (James) Chen, Jason Clark, Michelle Clark, Greg Clary, Nathan Conrad, Jeremy Cribb, Lin Cui, Jeremy Cummings, Elan Dassani, Rajeev Dassani, C. William Davis, Kalpit Desai, Chris Dwyer, Stephen Ehmann, Dorothy Erie, Mike Falvo, Mark Finch, Jay Fisher, Joseph Fletcher III, Mark Foskey, Darlene Freedman, Charlampos (Haris) Fretzagias, Yoni Fridman, Jacob Furst, Ashes Ganguly, Jai Glasgow, David Glick, Brian Grant, Xiaohu Guan, Martin Guthold, Adam Hall, Jonathan Halper, Gregory Hamamgian, Jing Hao, David Harrison, Bil Hays, Chris Healey, Aron Helser, Amy Henderson, Youn-Joo Heo, Andrea Hilchey, Mark Hollins, Phil Holman, Mave Houston, Tom Hudson, David Jack, Kevin Jeffay, Ja-Yeon Jeong, Gail Jones, Jeff Juliano, Kurtis Keller, Jake Kitchener, Sang-Uok Kum, Eileen Kupstas-Soo, Tom Lassanske, Bin Li, Alena Lieto, Ming Lin, Qiang Liu, Shawn Liu, Noel Llopis-Artime, Tanner Lovelace, Claudia Low, Kelly Maglaughlin, Jim Mahaney, Renee Maheshwari, David Marshburn, Chuck Mason, Garrett Matthews, Roberto Melo, Jameson Miller, Paul Morris, Atsuko Negishi, Shoji Okimoto, Timothy O’Brien, Shayne O'Neill, Lu-Chang Qin, Sherry Palmer, Stergios Papadakis, Ramkumar Parameswaran, Kimberly Passarella-Jones, Aarish Patel, Scott Paulson, Steve Pizer, Daniel Plaisted, Leila Plummer, Latita Pratt, Sharif Razzaque, Daniel Rohrer, Kent Rosenkoetter, Stefan Sain, Adam Seeger, Stefan Seelecke, Tatsuhura Segi, Woojin Seok, Deborah Sill, Kwan Skinner, Don Smith, Neal Snider, Eric Snyder, Diane Sonnenwald, Michael Stadermann, Anthony Steed, Josh Steele, Onejae Sul, Rich Superfine, Russ Taylor, Pichet Thiansathaporn, John Thomas, Kelly van Busum, Gokul Varadhan, Leandra Vicci, Frederic Voegele, Hong Wang, Sean Washburn, Chris Weigle, Mary Whitton, Ben Wilde, Phillip Williams, Bill Wright, Dongxiang Wu, Joe Yandle, and Christine Yao.

Due to the number of years and people included in the above list and the frailty of human memory, it is almost certain that someone important to the development of at least one of the projects was not included. The authors apologize for any such oversight.

References Cited

1. Adachi, Y., T. Kumano, and K. Ogino. *Intermediate Representation for Stiff Virtual Objects*. in *Proc. IEEE Virtual Reality Annual International Symposium (VRAIS'95)*. 1995. Research Triangle Park, NC. p. 203-210.

2. Allersma, M.W., F. Gittes, M.J. deCastro, R.J. Stewart, and C.F. Schmidt, *Two-dimensional particle tracking of ncd motility by back focal plane interferometry.* Biophys. J., 1998. **74**: p. 1074-1085.

3. Anshuman Razdan, N.K.B., Ashish Amresh, B.L. Ramakrishna, Ed Ong, Junyi Sun, *Remote Control and Visualization of Scanning Probe Microscopes via the Web.* Webnet Journal, 2001. **January-March 2001**: p. 20-26.

4. Bausch, A., F. Ziemann, A.A. Boulbitch, K. Jacobson, and E. Sackmann, *Local measurements of viscoelastic parameters of adherent cell surfaces by magnetic bead microrheometry.* Biohpys. J., 1998. **75**: p. 2038-2049.

5. Bausch, A.R., W. Möller, and E. Sackmann, *Measurement fo local viscosity and forces in living cells by magnetic tweezers.* Biophys. J., 1999. **76**: p. 573-579.

6. Brooks, F.P., Jr., M. Ouh-Young, J.J. Batter, and P.J. Kilpatrick. *Project GROPE - Haptic displays for scientific visualization*. in *Computer Graphics: Proceedings of SIGGRAPH '90*. 1990. Dallas, Texas. p. 177-185.

7. Brooks, J., F. P. *The Computer 'Scientist' as Toolsmith: Studies in Interactive Computer Graphics*. in *Invited paper, Proc. International Federation of Information Processing Congress '77*. 1977. Toronto, Canada: Amsterdam: North-Holland. p. 625-634.

8. Brooks, J., F.P. *The Computer Scientist as Toolsmith II*. in *Keynote/Newell Award address at SIGGRAPH 94: Computer Graphics*. 1996. Orlando. p. 281-287.

9. Falvo, "Nanometer scale tribology of carbon nanotubes", presented at *Centennial Meeting of the American Physical Society* in Atlanta, GA (1999).

10. Falvo, M., M. Finch, V. Chi, S. Washburn, R.M. Taylor II, F.P. Brooks Jr., and R. Superfine. *The Nanomanipulator: A Teleoperator for Manipulating Materials at the Nanometer Scale*. in *Proceedings of the 5th International Symposium on the Science and Engineering of Atomically Engineered Materials*. 1996. Richmond, VA: World Scientific Publishing. p. 579-586.

11. Falvo, M.R., G.J. Clary, R.M.I. Taylor, V. Chi, F.P.J. Brooks, S. Washburn, and R. Superfine, *Bending and buckling of carbon nanotubes under large strain.* Nature, 1997. **389**(October 9): p. 582-584.

12. Falvo, M.R., S. Washburn, R. Superfine, M. Finch, F.P.J. Brooks, V. Chi, and R.M.I. Taylor, *Manipulation of individual viruses: friction and mechanical properties.* Biophys. J., 1997. **72**(March): p. 1396-1403.

13. Falvo, M.R., G. Clary, A. Helser, S. Paulson, R.M. Taylor II, V. Chi, F.P. Brooks Jr., S. Washburn, and R. Superfine, *Nanomanipulation experiments exploring frictional and mechanical properties of carbon nanotubes.* Microscopy and Microanalysis, 1999. **4**: p. 504-512.

14. Falvo, M.R., R.M. Taylor, A. Helser, V. Chi, F.P. Brooks, S. Washburn, and R. Superfine, *Nanometre-scale rolling and sliding of carbon nanotubes.* Nature, 1999. **397**(6716): p. 236-239.

15. Falvo, M.R., J. Steele, R.M.T. II, and R. Superfine, *Gearlike rolling motion mediated by commensurate contact: Carbon nanotubes on HOPG.* Phys. Rev. B, 2000. **62**(October 15): p. 10665-10667.

16. Falvo, M.R., J. Steele, R.M.T. II, and R. Superfine, *Evidence of commensurate contact and rolling motion: AFM manipulation studies of carbon nanotubes on HOPG.* Tribology Letters, 2000. **9**: p. 73-76.

17. Finch, M., V. Chi, R.M. Taylor II, M. Falvo, S. Washburn, and R. Superfine. *Surface Modification Tools in a Virtual Environment Interface to a Scanning Probe Microscope*. in *Computer Graphics: Proceedings of the ACM Symposium on Interactive 3D Graphics*. 1995. Monterey, CA: ACM-SIGGRAPH. p. 13-18.

18. Fritsch, D.S., D. Eberly, S.M. Pizer, and M.J. McAuliffe, *Stimulated Cores and their Applications in Medical Imaging.* Information Processing in Medical Imaging, 1994. **1995**: p. 365-368.

19. Fuchs, H., J. Poulton, J. Eyles, T. Greer, J. Goldfeather, D. Ellsworth, S. Molnar, G. Turk, B. Tebbs, and L. Israel. *Pixel-Planes 5: A heterogeneous multiprocessor graphics system using processor-enhanced memories*. in *SIGGRAPH '89*. 1989: ACM SIGGRAPH

20. Geist, A., *Remote Control of Scientific Instruments: Electron Microscope Project*, (Web page): http://wikihip.cern.ch/twiki/bin/view/Openlab/OpenLab. (1996).

21. Ghislain, L.P. and W.W. Webb, *Scanning force microscope based on an optical trap.* Opt. Lett., 1993. **18**: p. 1678-1680.

22. Gittes, F. and C.F. Schmidt, *Thermal noise limitations on micromechanical experiments.* Eur. Biophys. J., 1998. **27**: p. 75-81.

23. Gittes, F. and C.F. Schmidt, *Interference model for back focal plane displacement detection in optical tweezers.* Optics Lett., 1998.

24. Grey, F., *OpenLab for Nanotechnology*, (Web page): http://wikihip.cern.ch/twiki/bin/view/Openlab/OpenLab. (2002).

25. Guthold, M., M. Falvo, W.G. Matthews, S. Paulson, A. Negishi, S. Washburn, R. Superfine, F.P. Brooks, and R.M. Taylor, *Investigation and Modification of Molecular Structures with the NanoManipulator.* Journal Molecular Graphics & Modeling, 1999. **17**(3): p. 187-197.

26. Guthold, M., M.R. Falvo, W.G. Matthews, S. Paulson, S. Washburn, D. Erie, R. Superfine, F.P. Brooks, and R.M. Taylor, *Controlled Manipulation of Molecular Samples with the nanoManipulator.* IEEE/ASME Transactions on Mechatronics, 2000. **5**(2): p. 189-198.

27. Guthold, M. and A. Helser, *Remote AFM Manipulation of Fibrin Fibers Over Internet2*, (Quicktime movie): http://www.cs.unc.edu/Research/nano/documentarchive/demonstrations/2000_Guthold_BioMEMS_movie.mov. (2000).

28. Guthold, M., J. Mullin, S. Lord, D. Erie, R. Superfine, and R. Taylor, *Controlled Manipulation of Individual Fibrin Molecules.* Biophys. J., 2000. **78**: p. A53.

29. Hadida, M., Kadobayashi, Y., Lamont, S., Braun, H.W., Fink, B., Hutton, T., Kamrath, A., Mori, H., Ellisman, M.H. *Advanced Networking for Telemicroscopy*. in *Proceedings of the 10th Annual Internet Society Conference (INET2000)*. 2000. Yokohama, Japan

30. Helser, A., *NanoManipulator*, (Web page): http://www.nanomanipulator.com/NanoManipulator.htm. (2000).

31. Helser, A. and M. Guthold, "Remote AFM Manipulation of Fibrin Fibers Over Internet2", presented at *BioMEMs & Biomedical Nanotechnology WORLD 2000* in Columbus, OH (2000).

32. Hudson, T., D. Sonnenwald, K. Maglaughlin, M. Whitton, and R. Bergquist, *Enabling Distributed Collaborative Science: The Collaborative nanoManipulator*, in *Video Proceedings of ACM Conference on Computer Supported Collaborative Work 2000*. 2000.

33. Hudson, T., A. Helser, D.H. Sonnenwald, and M.C. Whitton. *Managing Collaboration in the Distributed nanoManipulator*. in *IEEE Virtual Reality 2003*. 2003. Los Angeles, CA

34. Hudson, T.C., M.C. Weigle, K. Jeffay, and R.M. Taylor II, *Experiments in Best-Effort Multimedia Networking for a Distributed Virtual Environment.* Proceedings of Multimedia Computing and Networking, 2001(January): p. 88-98.

35. Jeffay, K. and R. Taylor, "Network Support for Distributed Virtual Environments: The Tele-NanoManipulator", presented at *Internet2 Conference* in Washington, D.C. (1999).

36. Jeffay, K., T. Hudson, and M. Parris. *Beyond Audio and Video: Multimedia Networking Support for Distributed, Immersive Virtual Environment*. in *27th EUROMICRO Conference*. 2001. Warsaw, Poland. p. 300-307.

37. Jones, G., *Nanoscale Science Education*, (Web Page): http://www.cs.unc.edu/Research/nano/ed/. (2001).

38. Jones, G.M., R. Superfine, and R.M.T. II, *Virtual Viruses.* Science Teacher, 1999. **66**(7): p. 48-50.

39. Jones, M., Andre, T, Superfine, R, Taylor, R, *Learning at the nanoscale: The impact of students' use of remote microscopy on concepts of viruses, scale, and microscopy.* Journal of Research in Science Teaching, in press. **40**(3).

40. Jones, M., Bokinsky, A, Andre, T, Kubasko, D, Negishi, A, Taylor, R, Superfine, R. *NanoManipulator applications in educaton: The impact of haptic experiences on students' attitudes and concepts*. in *IEEE Computer Science Haptics 2002 Symposium*. 2002. Orlando, FL: IEEE Computer Society. p. 295-298.

41. Jones, M., Bokinsky, A, Tretter, T, Negishi, A, Kubasko, D, Superfine, R, Taylor, R, *Atomic force microscopy with touch: Educational applications*, in *Science, technology and education of microscopy*, A. Mendez-Vilas, Editor. 2002, Formatex: Madrid.

42. Mark, W., S. Randolph, M. Finch, J.V. Verth, and R.M.T. II. *Adding Force Feedback to Graphics Systems: Issues and Solutions*. in *Computer Graphics: Proceedings of SIGGRAPH '96*. 1996. p. 447-452.

43. Matthews, W.G., A. Negishi, A. Seeger, R. Taylor, D.M. McCarty, R.J. Samulski, and R. Superfine, *Elasticity and binding of adenovirus in air and in liquid.* Biophysical Society 43rd annual meeting, Feb. 13-17, 1999, Baltimore, MD; Biophys. J., 1999. **A27**.

44. Mehta, A., J.T. Finer, and J.A. Spudich, *Reflections of a lucid dreamer: optical trap design considerations*, in *Methods in Cell Biology*. 1998, Academic Press: New York. p. 47-69.

45. Paulson, S., M.R. Falvo, N. Snider, A. Helser, T. Hudson, A. Seeger, R.M. Taylor, R. Superfine, and S. Washburn, *In Situ Resistance Measurements of Strained Carbon Nanotubes.* Applied Physics Letters, 1999. **75**(19): p. 2936-2938.

46. Paulson, S., A. Helser, M.B. Nardelli, R.M.T. II, M. Falvo, R. Superfine, and S. Washburn, *Tunable resistance of a carbon nanotube-graphite interface.* Science, 2000. **290**(December): p. 1742-1744.

47. Peltier, S., Hadida, M., Levy, D., Crum, J., Wong, M., Lamont, S., Ellisman, M.H., *Web-based Telemicroscopy with the JEM-4000EX*, in *JeolNews, Special Edition for Microscopy and Microanalysis*. 2000.

48. Potter, C.S., B. Carragher, M. Ceperley, C. Conway, B. Grosser, J. Hanlon, C. Hoyer, N. Kisseberth, S. Robinson, J. Sapp, P. Soskin, D. Stone, U. Thakkar, D. Weber. *Bugscope: A sustainable web-based telemicroscopy project for K-12 Classrooms*. in *Proceedings Microscopy and Microanalysis 99,*. 1999. p. 514-515.

49. Smith, N., *Microscope And Graphic Imaging Center: Remote Control of Instrumentation*, (Web page): http://www.csuhayward.edu/SCI/sem/remote.html. (1997).

50. Sonnenwald, D.H., E. Kupstas Soo, and R. Superfine *A Multi-Dimensional Evaluation of the nanoManipulator, a Scientific Collaboration System.* ACM SIGGROUP Bulletin, 1999. **20**(2): p. 46-50.

51. Sonnenwald, D.H., R. E. Bergquist, K. L. Maglaughlin, E. Kupstas-Soo, and M.C. Whitton, *Designing to support collaborative scientific research across distances: The nanoManipulator environment*, in *Collaborative Virtual Environments*, E. Churchill, D. Snowdon, and A. Munro, Editors. 2001, Springer Verlag: London. p. 202-224.

52. Sonnenwald, D.H., M. Whitton, and K. Maglaughlin, *Evaluating a Scientific Collaboratory: Results of a Controlled Experiment.* ACM Transactions on Computer Human Interaction, 2003. **In press.**

53. Sun, J. and A. Razdan. *Remote Control And Visualization of Scanning Probe Microscope via Web*. in *IEEE Second Workshop on Multimedia Tools and Applications*. 1999. p. 209-214.

54. Superfine, R., Jones, MG, Taylor, R. *Touching viruses in a networked microscopy outreach project*. in *K-12 Outreach from University Science Departments*. 2000. Raleigh, NC: North Carolina State University. p. 151-153.

55. Svoboda, K. and S.M. Block, *Biological applications of optical forces.* Annu. Rev. Biophys. Biomol. Struct., 1994. **23**: p. 247-295.

56. Taylor, "VRPN: A Device-Independent, Network-Transparent VR Peripheral System", presented at *Virtual Environment Research Talk series* in (2001).

57. Taylor II, R.M., W. Robinett, V.L. Chi, J. Frederic P. Brooks, W.V. Wright, R.S. Williams, and E.J. Snyder. *The Nanomanipulator: A Virtual-Reality Interface for a Scanning Tunneling Microscope*. in *SIGGRAPH 93*. 1993. Anaheim, California: ACM SIGGRAPH. p. 127-134.

58. Taylor II, R.M., *The Nanomanipulator: A Virtual-Reality Interface to a Scanning Tunneling Microscope*, in *Computer Science*. 1994, University of North Carolina: Chapel Hill. p. 139.

59. Taylor II, R.M., J. Chen, S. Okimoto, N. Llopis-Artime, V.L. Chi, J. Frederick P. Brooks, M. Falvo, S. Paulson, P. Thiansathaporn, D. Glick, S. Washburn, and R. Superfine. *Pearls Found on the way to the Ideal Interface for Scanned-probe Microscopes*. in *Proceedings of IEEE Visualization '97*. 1997. Phoenix, AZ: IEEE Computer Society Press. p. 467-470.

60. Taylor II, R.M. *Network Access to a PHANToM Through VRPN*. in *PHANToM User's Group Workshop*. 1998. Dedham, MA. p. 4 pages.

61. Taylor II, R.M., T.C. Hudson, A. Seeger, H. Weber, J. Juliano, and A.T. Helser. *VRPN: A Device-Independent, Network-Transparent VR Peripheral System*. in *ACM Symposium on Virtual Reality Software & Technology 2001*. 2001. Banff Centre, Canada

62. Taylor II, R.M., "A 3D Force Microscope: Manipulation/Measurement in Cellular Systems", presented at *CISMM External Advisory Board Meeting* in Chapel Hill (2002).

63. Taylor, R.M., "Nanoscale Computer Science", presented at *CSIT visualization lecture series* in Tallahassee, FL (2002).

64. Tretter, T., Jones, MG, *Different worlds: The Importance of size.* Science Teacher, in press.

65. vtk.org, *VTK Home Page*, (Web Page): www.vtk.org.

66. Wickens, C.D. and P. Baker, *Cognitive Issues in Virtual Reality*, in *Virtual Environments and Advanced Interface Design*, W. Barfield, I. Furness, and T. A, Editors. 1995, Oxford University Press: New York. p. 514 - 541.

67. Williams, P.A., S.J. Papadakis, M.R. Falvo, A.M. Patel, M. Sinclair, A. Seeger, A. Helser, R.M. Taylor II, S. Washburn, and R. Superfine, *Controlled placement of an individual carbon nanotube onto a microelectromechanical structure.* Applied Physics Letters, 2002. **80**(14): p. 2574-2576.

68. Williams, P.A., S.J. Papadakis, N.E. Snider, H. Deniz, M.R. Falvo, S. Washburn, R. Superfine , and R.M. Taylor II, "Progress on Field Emission Studies of Individual, Cantilevered Multi-walled Carbon Nanotubes", presented at *American Physical Society March Meeting 2002* in Indianapolis (2002).

69. Williams, P.A., S. J. Papadakis, A. M. Patel, M. R. Falvo, S. Washburn, and R. Superfine, *Torsional Response and Stiffening of Individual Multiwalled Carbon Nanotubes.* Physical Review Letters, 2002. **89**(25): p. 25502-1 - 25502-4.

70. Yamada, A., *The Remote Control Scanning Microscope with Web Operation Interface (Web SEM)*, (Web page): http://www.jeoleuro.com/news/jeolnews/NEWSHOME/News%20home/25/. (2001).