Up close and personal to atoms

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The latest microscopes provide a new level of sophistication not only in imaging but also for interacting with matter at the atomic scale.

Microscopes have been pivotal in opening new frontiers in science. The optical microscope revolutionized biology by allowing scientists to image the living cell, and the advent of electron microscopy has shaped much of our understanding of the structure of cells and inorganic materials. The invention and development of scanning probe microscopy has taken the ability to image matter to the atomic scale and opened fresh perspectives on everything from semiconductors to biomolecules. But researchers are not just passive observers; they are devising methods to modify and measure the microscopic landscape and so explore its physical, chemical and biological features.

The scanning revolution

The invention of the scanning tunnelling microscope (STM) by Binnig and Rohrer in the early 1980s — marked by the award of a Nobel prize in 1986 — was the catalyst of this technological revolution[1]. In the STM, a sharp metallic tip (ideally terminating in a single atom) is positioned within a few atom-widths of a conducting surface. Such precise spatial control is achieved using piezoelectric ceramics, which change size ever so slightly in response to an electric field. When placed near the sample, electrons quantum mechanically 'tunnel' between the tip and the surface of the sample. This tunnelling process is sensitive to any overlap between the electronic wavefunctions of the tip and sample, and depends exponentially on their separation. The STM makes use of this extreme sensitivity to distance. In practice, the tip is scanned across the surface, while a feedback circuit continuously adjusts the height of the tip above the sample to keep a constant tunnelling current (typically 10^9 electrons s^{-1}, comparable to the rate of tunnelling between atoms in a metal of about 10^{13} electrons s^{-1}). The recorded trajectory of the tip creates an image that maps the electronic wavefunctions at the surface, revealing the atomic landscape in fine detail.

On semiconductor and metallic surfaces, the STM can easily resolve single atoms, and probe the structural and electronic properties of these surfaces (Fig. 1). From the outset, STM imaging has been used to resolve long-standing questions about how atoms arrange themselves differently at the surface of a material compared to the way they do in the interior. These differences are crucial to understanding technologically important processes such as surface-induced catalysis, growth of thin films and microfabrication techniques used in the semiconductor industry.

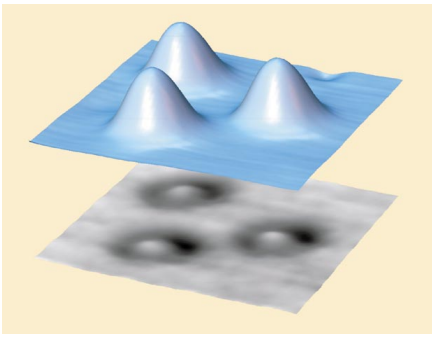


Figure 1 **The dimension beyond the images. Spectroscopy of three magnetic atoms on the surface of a superconductor. Top, the STM topograph; bottom, an image constructed from spatially resolved spectroscopy showing dark patches where superconductivity is suppressed near the magnetic atoms[6].**

The STM works best in the stringent conditions of an ultrahigh vacuum, in which clean conducting surfaces can be prepared. Over the past decade, STM has led to other nanometre-scale imaging techniques that do not rely on vacuum tunnelling, but still map the interaction of a pointed probe with the sample. Collectively these new instruments are called scanning probe microscopes (SPMs). The most widely used SPM, which can operate in air and liquids, is the atomic force microscope (AFM), an instrument that maps the forces between the tip and the sample. In this microscope, a tip is mounted at the end of a soft cantilever that bends when the sample exerts a force on the tip. By optically monitoring the cantilever motion it is possible to detect tiny chemical, electrostatic or magnetic forces, which are only a fraction of those required to break a single chemical bond or to change the direction of magnetization of a small magnetic grain. Applications of the versatile AFM include *in vitro* imaging of biological processes[2].

Imaging with SPMs has brought us up close and personal to single atoms, molecules and molecular assemblies, and techniques are advancing to include more interactive experiments by using these instruments as nanoscopic tools rather than microscopes. Precise measurements of the local interactions between SPM probes and materials — so-called spectroscopic measurements — give a new dimension of information about physical, chemical and biological processes on the nanometre scale. Such data are obscured or lost in conventional 'macroscopically averaged' measurements. The strong interaction between the probe tip and the sample has also been used to move atoms around on the surface, allowing the construction of nanostructures. Such techniques are at the heart of new explorations of physics on scales comparable to an electron's wavelength, as well as chemistry and biology on the scale of single molecules.

High-resolution spectroscopy

Binnig and Rohrer's original motivation was to develop a spatially resolved spectroscopic tool for studying surfaces[1], rather than to build a microscope. Tunnelling spectroscopy has been an important technique in solid-state physics since the 1960s, when studies of planar metal-oxide tunnel junctions helped confirm the theory of superconductivity in metals. But whereas planar tunnelling, like other spectroscopic techniques, gives only spatially averaged information, the STM can directly read spatial variation in electronic phenomena. In practice, spectra are measured with a metallic tip held at a fixed height above the sample, which monitors the tunnelling current as the voltage difference between the tip and the sample is varied. Tunnelling spectra are typically determined by the local density of electronic states in the sample and can be used to examine their energy and spatial dependence.

High-resolution spectroscopy was a goal of STM from the start, but its progress was limited because the requirements for vibrational stability and low electrical noise are far higher than for imaging. In fact, the first success with STM spectroscopy was in studying the voltage- and current-dependence of STM images of semiconductor surfaces[3,4]. Since then, the energy resolution of STM spectroscopy at low temperatures has reached microelectronvolts — comparable to the best spatially averaged techniques. And as Binnig and Rohrer hoped, high-resolution spectroscopy is possible over length scales of a few tenths of a nanometre. Now STM is being used to investigate spatial variation in electronic phenomena, such as superconductivity and magnetism, which up to now have been mostly studied using macroscopically averaged techniques.

One of the first uses of high-resolution STM spectroscopy at low temperatures was to image the individual magnetic vortices threading a superconductor[5]. The instrument was used to map electronic states near isolated vortices and to show unpaired electrons bound to their cores (superconducting electrons usually travel in pairs). This work inspired further studies of superconductivity near isolated defects, as well as studies of the competition between magnetism and superconductivity on the atomic scale, where magnetic impurities can induce localized, unpaired electronic states analogous to those found at vortex cores[6] (Fig. 1). Similar STM experiments have been carried out on metallic surfaces to examine the physics of electron scattering from magnetic atoms. Such studies detected the screening of magnetic atoms by conduction electrons — the so-called Kondo effect, which dominates the conductivity of metals doped with magnetic impurities at low temperatures[7,8]. Advances in the use of ferromagnetic tips (such as iron) have led to spin-selective spectroscopy, which will make it possible for magnetism to be probed even more closely[9]. Such high-precision studies are, in turn, driving new theories about the local behaviour of electronic states and the spatial variation of electronic phenomena — previously thought impossible to measure directly.

Probing nanostructures

In the realm of the very small, nothing beats the STM for studying nanometre structures and the electrons confined within them. Work on semiconductors has established the importance of electron energy levels and conductance quantization for future miniaturization of electronics. Imaging and spectroscopy with the STM are powerful ways to study these electronic effects in the next generation of small structures. One example, and an icon of STM experiments, is the quantum corral[10]. Here, assemblies of atoms are used to confine surface electrons, so that they display wave-interference phenomena and occupy quantized energy levels. Similar phenomena occur in chemically fabricated nanostructures, such as carbon nanotubes or semiconductor nanocrystals, and STM provides a new way to study them. For example, in isolated nanotubes, STM experiments have been used to probe the one-dimensional electronic states of these tubes, which may one day act as 'quantum wires'[11,12] (Fig. 2). In even smaller structures, researchers are using STM as a local electrode to investigate the effects of adding electrons to these structures and to extend our understanding of charging effects and conductance quantization at the single-molecule and atom limit[13,14]. At these extreme limits, tunnelling spectroscopy is also being used to examine the electronic and vibrational states of individual atoms and molecules at surfaces (Box 1).

Structures made up of just a few atoms or molecules have quantized energy levels, through which electrons can move, and these may one day form the basis of nanometre-sized electronic devices. The STM will be vital in this work — for example, STM studies of carbon nanotubes have linked the structure of the tubes with their conducting or insulating behaviour[11,12]. Such data are almost impossible to obtain from a macroscopic measurement of a collection of nanotubes, because nanotube fabrication naturally yields a distribution of tubes with different structures, sizes and defect densities.

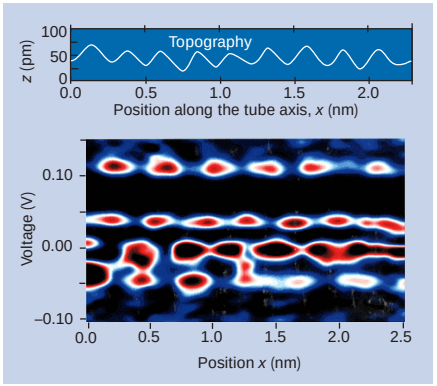


Figure 2 **In carbon nanotubes, STM images both the atomic corrugation (topography, top) and the quantized electronic standing waves (spectroscopy, bottom). The periodicity in the spectroscopic image is determined from the square amplitude of the electrons' wavefunctions at discrete energies (voltage)[35].**

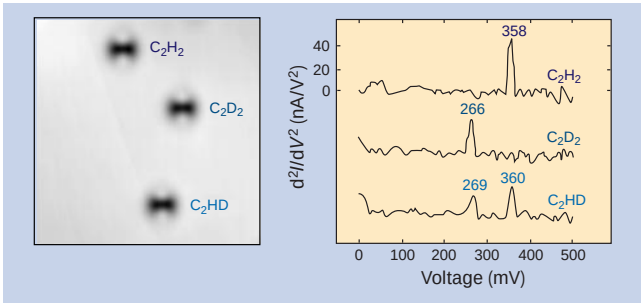
Forces in chemistry and biology

The size and range of intermolecular forces determines many critical processes in biology and chemistry, from general membrane assembly to specific binding and recognition. One of the most powerful tools for studying these processes is AFM, which has a unique ability to measure small forces with

Box 1: Fingerprinting individual molecules

The atoms in a molecule vibrate against each other at characteristic frequencies determined by the strength of their chemical bonds. Different vibration modes and their frequencies make up a 'fingerprint', which identifies molecules and pinpoints changes in their bonding owing to chemical reactions. For example, when a molecule is absorbed at a surface, depending on the location or orientation of its absorption site, its vibrational modes may shift in frequency or be suppressed. Knowing these changes is critical to understanding a variety of surface phenomena, such as absorption and release processes, heterogeneous catalysis and epitaxial growth.

Since its invention, the scanning tunnelling microscope (STM) has had the potential to perform site-selective measurements of vibrational spectra of single molecules[32]. This approach was motivated by the success of much earlier experiments in planar metal-oxide tunnel junctions, when the tunnelling conductance was shown to make characteristic jumps at energies corresponding to the characteristic vibrational frequencies of molecules adsorbed at the metal-oxide interfaces in these devices. The underlying principle is that when the energy of the tunnelling electron exceeds that required for exciting a molecular vibrational mode, electrons can tunnel inelastically as well as tunnelling between states of the same energy. This means that they lose energy by causing a molecule near the tunnel junction to vibrate. Sharp steps in the measured conductance at different energies correspond to the onset of inelastic tunnelling processes and provide the fingerprint of the molecular vibrational modes.



A group at Cornell University, using an STM operating at low temperatures and in ultrahigh vacuum, has succeeded in reproducibly measuring the vibrational spectra of individual molecules[28]. Most impressively, they have used inelastic tunnelling spectroscopy to identify individual molecules by their characteristic vibrational energies[33]. The STM image and inelastic spectra of three similar molecules, C_2H_2, C_2D_2 and C_2HD are shown here. Although STM imaging cannot distinguish between the three molecules, the inelastic tunnelling spectra measured with the tip can reveal their vibrational fingerprints and identify them. The peaks correspond to incremental increases of conductance associated with exciting the C–H and C–D bonds. **A. Y.**

high spatial resolution. Usually, AFM is used to record the surface topography of a sample by recording the vertical motion of the probe tip as it is scanned over the sample. With a customized probe tip, however, specific interactions between the tip and sample surface can be measured. For example, the self-assembly of organic monolayers on AFM tips has been used to explore the surfaces of organic and polymer materials[15]. Such 'chemical force microscopy' can record differences in the intermolecular forces between the tip and different sample regions, and thereby map chemically distinct regions. Spectroscopy can potentially provide a new dimension of information (Box 2), and, with AFM, it is force spectroscopy — the measurement of force against separation — that researchers have been developing. Force spectroscopy with customized probes can measure how strongly things stick together, which is essential if you are planning to build nanostructures.

The way things stick together is especially critical in biology, defining, for example, ligand–receptor interactions and protein folding. Force spectroscopy can probe these processes at the single-molecule level. In a typical experiment, the ligand is attached to an AFM tip, receptors are linked to the substrate, and then the two are brought together and separated again. To be sure that only a single ligand–receptor interaction is measured, the active species are attached at a low density to the tip (which is much bigger than most biological molecules). Notably, measurements of force against separation for the protein receptor avidin and its ligand biotin have shown a clear signature for the unbinding of single biotin molecules from the protein, demonstrating that single ligand–receptor events can be investigated[16] (Fig. 3, overleaf). This approach, or simply adsorbing much larger molecules onto AFM probes, has been used in force spectroscopy experiments to investigate the unfolding of multidomain proteins and structural changes of carbohydrate polymers[17–19].

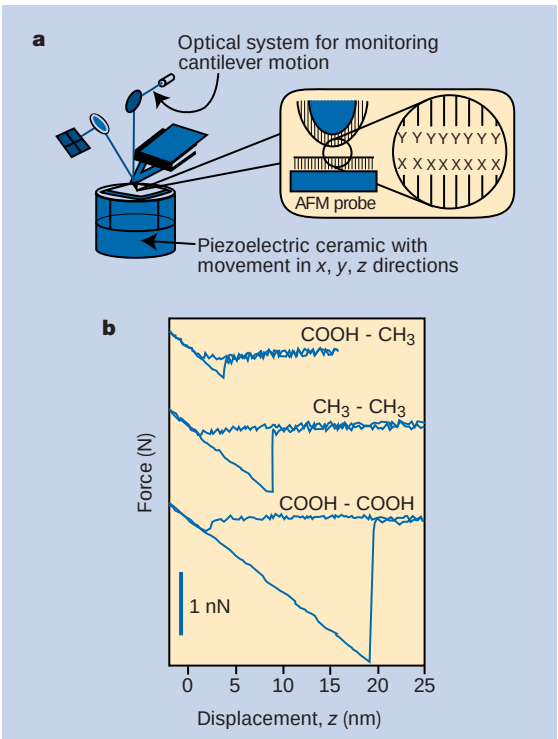
One of the attractions of these single-molecule force spectroscopy experiments is that they allow a quantitative dialogue with theory that benefits both[19]. But these experiments have their limits and there is competition from other techniques. For example, optical tweezers, which work by trapping micrometre-sized beads at the focal point of a laser beam, have considerably better force resolution than AFM, although they must be used with biological structures larger than the beads. The AFM should excel in the investigation of individual proteins, polymers and submicrometre assemblies, and such studies could be particularly fruitful because microscopic changes, for example of single nucleotides or amino acids, can be made using standard chemical and biological techniques. But it will be necessary to define exactly where an 'active' ligand is attached relative to the probe surface, something that has not been possible using conventional AFM tips. Tips made from carbon nanotubes — modified to measure single ligand–receptor unbinding — can overcome this limitation, and may help us image biological interactions with molecular precision[20].

Making atoms move

Almost 40 years ago, Richard Feynman[21], speculated that "in the great future — we can arrange the atoms the way we want; the very atoms, all the way down!". Now SPMs, with their capacity to cause controllable changes on the nanometre scale, give us this power[22,23]. The idea behind SPM lithography is to exploit the forces between probe and sample (which are always present in these microscopes but usually kept to a minimum). For example, during imaging, the tip of an STM is held sufficiently high above the sample to reduce the chemical interaction between probe and sample. When it is much closer, the tip can exert enough force to move individual atoms or molecules and to modify the atomic landscape. The interaction between the tip and atoms or molecules bound to the surface (adsorbates) can be repulsive or attractive, allowing the tip to push or pull individual adsorbates on the surface. These techniques have been used to construct impressive nanostructures, such as the 'quantum corral' (by moving single atoms)[10] and the 'molecular abacus' (by moving individual C_{60} molecules)[24].

The SPM can also be used to modify a

Box 2: Fingerprinting chemical bonds



In atomic force microscopy (AFM), molecular groups, such as carboxylic acids (–COOH) can be added to the tip. Separating the tip and sample deflects the cantilever-tip assembly until the restoring force exceeds the bonding interaction — at this point there is a mechanical instability and the tip and sample jump apart. The magnitude of the cantilever deflection immediately before the onset of this instability can be used to calculate the intermolecular bonding interaction: $F_{bind} = k_{cant}\Delta x$, where F_{bind} is the binding force, k_{cant} is the spring constant of the cantilever-tip assembly and Δx is the displacement. This approach has been used to distinguish different types of non-covalent bonding[15] (shown here) and different ligand–receptor interactions, and to investigate the breaking of single covalent Si–C bonds[34].

The figure shows a customized tip (**a**) and force spectroscopy data (**b**) that can distinguish between different bonding interactions. In **a**, a tip modified with a monolayer terminating in the functional group Y is shown probing a sample that terminates in the functional group X (where X and Y can be either COOH or CH_3 groups). Force spectroscopy data in **b** show clear differences in breaking COOH–COOH, CH_3–CH_3 and COOH–CH_3 non-covalent bonds.

Such experiments are technically impressive and promise to expose the details of interactions at the single-bond level. But some thorny issues have to be addressed first. For example, the detailed orientation of the CH_3–CH_3 bond in the above experiment, which defines the reaction coordinate — that is, the direction along the potential energy surface describing the interaction between the groups — was not known because of the large curvature of the tip and other modifications. Knowledge of the reaction coordinate is necessary for a detailed and meaningful comparison of experiment with theory. A solution to this vexing problem may come from customized carbon-nanotube tips, which are now enabling researchers to localize single molecules in a precisely defined orientation at the end of a molecular-sized probe[20]. **C. M. L.**

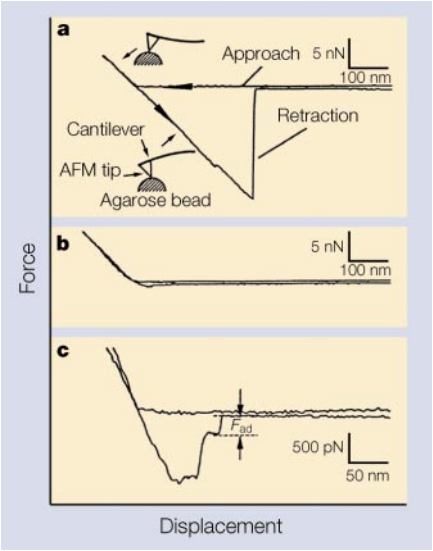


Figure 3 **Biological forces. The adhesion force between an AFM tip terminating in avidin and agarose beads coated with biotin is measured by recording the deflection of the AFM cantilever on approaching and retracting from the bead[16]. The strong interaction recorded in** a **can be blocked by adding an excess of free avidin to the solution** (b)**. When the biotin is only partially blocked by avidin, unbinding occurs in discrete steps** (c)**, corresponding to an adhesion force, F_{ad}, of 160 ± 20 pN.**

sample indirectly by applying large electric fields or injecting energetic electrons[22,23]. An intense local electric field can change the energy of chemical bonds at the sample surface and reduce the barriers that hinder the motion of atoms and molecules. Local injection of energetic electrons can be used to excite the electronic or vibrational modes of molecules, which can result in breaking of individual bonds. In this way, STM experiments have demonstrated translation[22], rotation[25], desorption[26] (or release of adsorbates) and dissociation[27] of individual molecules at the surface.

Quantitative measurements of the interaction of SPM probes with adsorbates and surfaces provide new insights into the physical mechanisms of molecular motion. A step towards detailed understanding of STM-induced modifications has been the development of inelastic tunnelling spectroscopy with the STM[28] (Box 1). This is a quantitative way of directly measuring the frequency of vibrational modes of individual adsorbates, providing a link between vibrational excitation and atomic motion on the surface.

Precision lithography

Progress in exploring SPM-induced modification of materials points to an exciting future for SPMs as an alternative high-precision lithographic tool for making nanometre-sized electronic devices. Functional devices, such as single-electron transistors, have already been created[29] using the STM and AFM to apply intense electric fields to conducting films, oxidizing them in a pattern that defines the device structures. Of course, plenty of hurdles will have to be overcome to compete with conventional methods of lithography, which can create three million transistors in a single chip. One problem is the serial nature of SPM lithography, which is associated with relatively slow throughput, but it can be addressed using arrays of SPM probes to perform imaging and lithography simultaneously (Fig. 4)[30]. Work is underway to make even larger arrays, perhaps with ten thousand probes; the engineering challenge lies in developing circuits for controlling the probes in parallel and for real-time processing of the large-scale images they produce.

Another problem with using SPMs for lithography is the task of making probes that can withstand the forces exerted on them during the lithographic process. These forces can lead to uncontrolled modification of the AFM or STM tips, making them unreliable tools. Fortunately, carbon nanotubes appear to have all the properties required of an ideal tip; they are chemically inert, mechanically resilient and can be electrically conducting. Such tubes have been used as robust tips for both imaging and lithography[31].

Continuing evolution

The SPM has evolved from a passive imaging tool into a sophisticated probe of the nanometre scale. These advances point to exciting opportunities in many areas of physics and biology, where SPMs can complement macroscopically averaged measurement techniques and enable more direct investigations. More importantly, these tools should inspire new approaches to experiments in which controlled measurements of individual molecules, molecular assemblies and nanostructures are possible. The future will also be shaped by the relevance of these probes to technology, such as their possible use as electronic or magnetic memory devices or for advanced lithography. Indeed, the rapidly growing number of versatile scanning probes, besides the STM and AFM discussed here, although remaining primarily research tools, will strongly influence the development of nanometre-sized electronic devices and biological sensors. ■

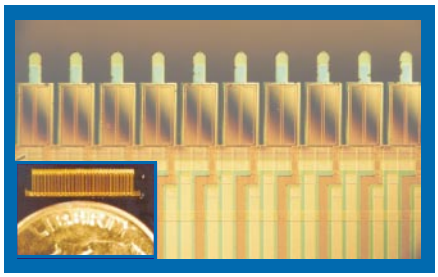


Figure 4 **Thousands of tiny tools. A 1-cm linear array of 50 high-speed scanning probes with integrated sensors and actuators fabricated using micro-machining techniques. The spacing between the tips is 200 μm. The inset shows the entire array next to a US dime, whereas the full image shows a magnified view of ten probes.**

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