

GSK LECTURE

# Nanotechnology in the real world

The GlaxoSmithKline International Achievement award for 2003 was presented to Professor Martyn Davies and colleagues from the biophysics and surface analysis group at the University of Nottingham and Molecular Profiles Ltd on 16 September. Christine Clark reports on the group's work

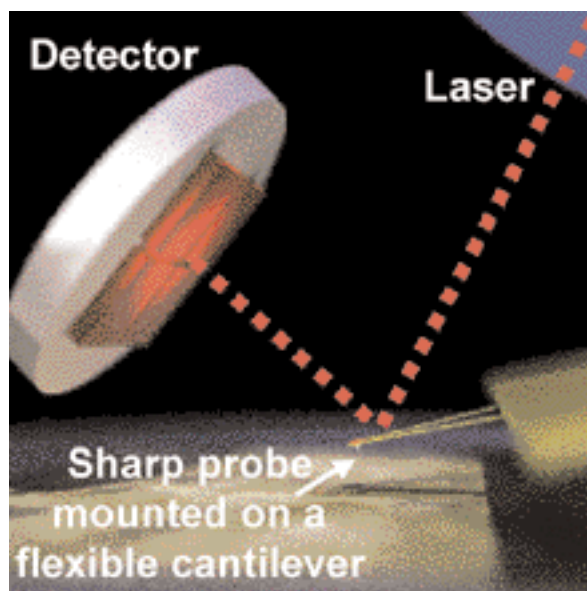


Figure 1: How scanning probe microscopes work



Figure 2: A crystal of aspirin dissolving along the line marked

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Nanotechnology is a catch-all description of activities at the level of atoms and molecules that have applications in the real world, Professor Martyn Davies said. The study of biology at the nano-level is likely to lead to the development of better ways of giving drugs, the design of new sensors and the development of new materials. "Far from being a remote theoretical science, nanotechnology is inherent in everything that we do," he explained.

Scanning probe microscopes (SPMs) are used to examine materials at the nano-level. These have a sharp probe that scans across the surface of the material that is being examined. The microscope is designed to detect one of a number of signals, such as force (as in the atomic force microscope, AFM), light, magnetism or heat.

The sharp tip or probe is positioned at the end of a soft spring (cantilever). As the tip moves across a sample the cantilever moves up and down. A beam of laser light is directed at the back of the cantilever and the reflected light is detected by a suitable instrument and an image is created (see Figure 1). This approach allows the visualisation of single molecules. It can be used in a range of environments, such as in air or, preferably, in water.

Professor Davies said that one of the first biological applications of AFM within the Nottingham group was the examination of DNA and, in particular, the action of drugs on DNA. One experiment concerned the addition of ethidium bromide to DNA. As the concentration of ethidium bromide increased the conformation of the DNA

changed from a relaxed form, at first, then to the super-coiled toroidal form and finally to plectonemic (coiled around another molecule) forms. "These changes are important because they affect the mechanical properties of DNA", Professor Davies said.

The behaviour of individual DNA molecules can be clearly visualised using AFM. For example, his team has shown that a single enzyme can degrade DNA producing dramatic structural changes as the molecule becomes uncoiled and, for practical purposes, destroyed.

During imaging, the tip of the AFM probe has an interaction with the surface or product that is being scanned and this feature can be exploited. For example, the tip could be coated with a biological material and the surface of the sample could be mapped for characteristics such as adhesion or hydrophobicity.

"A mechanical fingerprint of a single DNA molecule can be constructed by picking up a single DNA molecule with the probe and stretching it. This produces a characteristic fingerprint and it is possible to show that the fingerprint changes when DNA binds to drugs — each drug-DNA combination producing a unique fingerprint." This might offer a possibility for screening of future drugs, suggested Professor Davies.

Another application for AFM lies in the understanding of physiological processes at the molecular level. For example, the properties of titin, a substance integrated into muscle cells that functions as a biological, molecular spring, have been examined. The relationships between force and velocity of

unfolding of individual titin molecules have been studied and the effects of alterations in the amino acid sequence have been investigated. "The real forces of nature are down at this level," he said. This method has made it possible to show the mechanical properties of the titin molecule, which have subsequently been published in *Nature*.

The application of SPM-based approaches to particle analysis in pharmaceutical formulation has been particularly useful. For example, it is possible to map two polymorphic forms of a substance in a sample to show how they are distributed. Chemically functionalised probes have been used to examine different planes in crystals and examine their surface chemistry. For example, one plane of the aspirin crystal is dominated by phenyl and methyl groups and is strongly hydrophobic; another plane comprises mainly oxygen and methyl groups. The AFM tip can sense their different properties and detect the differences between the crystal faces.

AFM can be also used to observe dissolution or formation of crystals at molecular level in different conditions — for example, steps on the surface of an aspirin crystal that are each one molecule high (see Figure 2).

"Finally, AFM enables the examination of surfaces for potential biomedical applications. It is possible to construct images of isolated biomolecules using sensitive probes and, as the technology improves, it should be possible to look at substructural elements. AFM can also be used to look at the packing of molecules on surfaces of importance in biotechnology, tissue engineering and sensors," Professor Davies concluded.