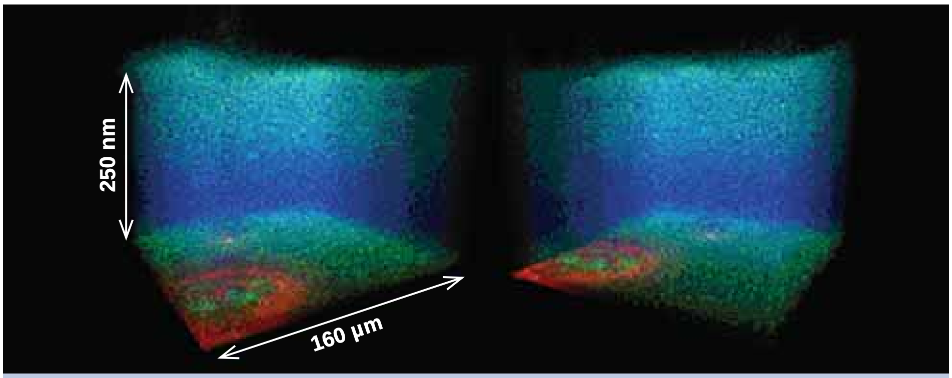
NPL
National Physical Laboratory

Health *Matters*

A National Measurement Newsletter

Winter 2007 | Issue 3



Two views of a three-dimensional reconstruction of a defective drug-loaded polymer film. Sodium contamination is red, intact drug molecules are green and the polymer is blue. Defects are associated with sodium contamination on the underlying substrate and the drug has segregated to the top and bottom of the film.

Inside:

Organic films designed for controlled release of drugs

The NPL NanoAnalysis group has constructed layered organic films, which now make it possible for its analysts to develop a deep understanding of controlled drug release systems.

Controlled drug release systems commonly comprise of a therapeutic agent (a drug) dispersed in a biodegradable polymer. The distribution of the drug determines the release rate, and this must be maintained above a minimal therapeutic level, but below toxic levels, for an extended period. For example, drug eluting stents release therapeutic agents designed to inhibit cell proliferation and reduce the occurrence of in-stent restenosis, which is a major cause of failure in coronary angioplasty. By using a surface sensitive and chemically specific spectroscopy, such as secondary ion mass spectrometry (SIMS), it is possible to record signals from individual organic components as a function of depth, obtaining a 'depth profile' through the material. This enables designers to confirm that the predicted distributions have been achieved, or to determine the cause of poor function or failure.

To obtain a better understanding of organic depth profiling, NPL has constructed novel, layered organic films. Experiments on these NPL 'organic delta layers' have provided a wealth of understanding of the depth profiling process, making possible the interpretation of results from samples of technological importance. The image shows example results from a drug delivery material. Similar measurements have been taken on commercial drug eluting stents. SIMS can be used as an imaging spectroscopy, making three-dimensional reconstructions possible, as shown. Processing, visualising and understanding such an experiment is extremely challenging. The NanoAnalysis group at NPL is actively providing analysts with the necessary tools for this task.

For further information please contact Alex Shard on 020 8943 6193 or e-mail alex.shard@npl.co.uk

Department for **Innovation, Universities** & **Skills**

Surgical skills on display

The NPL displays group is working with surgeons at St Mary's hospital to measure the effects of stereoscopic displays on task performance and visual comfort.

Minimally invasive surgery uses remote controlled instruments inserted into the body through a small incision or through an anatomical opening. Although the operating time can often be longer compared with open surgery, the hospitalisation time can be cut dramatically because the healing time for smaller incisions is much faster. Advances in imaging technology mean that today an estimated 2000 major medical procedures involve some form of display.

Displays that present a three-dimensional image to an observer offer considerable advantages over two-dimensional displays, but in practice the applications are limited by the level of comfort experienced by the viewer. Some systems require the observer to wear headgear, while autostereoscopic systems are free of viewing aids. The latter are generally considered more practical, and work by encoding the viewing zone such that the observer sees stereoscopic pairs of images that are combined to give the impression of a 3D image. A common cause of viewing discomfort is image cross-talk, which is leakage of the optical signal from the channel corresponding to the right eye, to the channel corresponding to the left eye or vice versa.

To enable measurement of the effects of cross-talk, NPL have built a stereoscopic system that is inherently free of cross-talk. Controlled amounts of cross-talk can be introduced electronically. Members of NPL undertook a series of tasks, designed to be representative of real applications, viewed via a pair of identical cameras, with due consideration for illumination and the ergonomic requirements of the user. The techniques used to measure the effects of introducing cross-talk included Galvanic Skin Resistance (which monitors the user's workload), measuring error in the alignment, and subjective questionnaires.

By understanding the effects of viewing artificial 3D, and the extent of those effects, the NPL 'displays' group aim to be able to provide useful feedback to both manufacturers and end users.

For further information please contact Sunil Pala on 020 8943 6812 or e-mail sunil.pala@npl.co.uk

Biopharmaceutical summer school

NPL has teamed up with the National Institute of Biological Standards and Control to improve the measurement of the structure and function of biopharmaceuticals

Biopharmaceuticals are an increasingly important class of products in the global pharmaceutical industry, where biological processes are applied in the development and production of new drugs. The drugs are often large, highly complex structures produced by living cells as a result of recombinant DNA technology, and include proteins, vaccines, hormones and gene therapy products. They are considerably more difficult to analyse than traditional chemical drugs.

The biological activity of biopharmaceutical products depends on the primary, secondary, tertiary and quaternary structure of the molecule, its post-translational modifications and levels of aggregates. For most biological products, there is a regulatory requirement that the structure and potency of individual batches are tested upon release of the batch. Establishing relationships between data from different analytical techniques supports the selection of a suitable set of tests for the characterisation of individual biopharmaceutical preparations.

A project that addressed this topic was recently completed in the 2004-2007 Measurements for Biotechnology programme, and data generated was presented at a Biopharmaceutical Summer School in Fitzwilliam College, Cambridge. Dr Jane Robinson, Principal Scientist in the Division of Immunology and Endocrinology, gave a talk on 'Exploring the basics of biological assay development and validation' which was summarised in the delegate pack at the workshop. The workshop is designed for those who are new to the biopharmaceutical industry and wish to broaden their knowledge or develop their careers in the field. The presentation served as a useful forum for highlighting the importance of sound measurement practice in the highly regulated biopharmaceutical arena.

For further details please contact Anna Hills on 0208 943 6334 or e-mail anna.hills@npl.co.uk

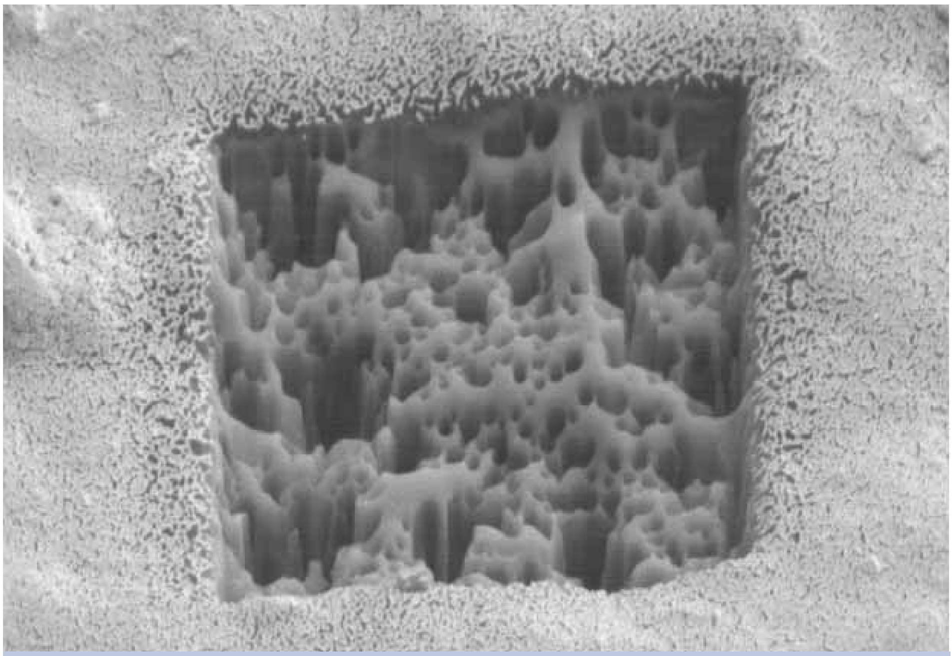
3D imaging techniques show character

In the past 20 years, a series of true 3D internal imaging techniques have emerged and are finding applications in a broad range of materials. NPL has conducted a feasibility study to investigate 3D internal imaging and characterisation of a wide range of materials, including bio- and nano-materials.

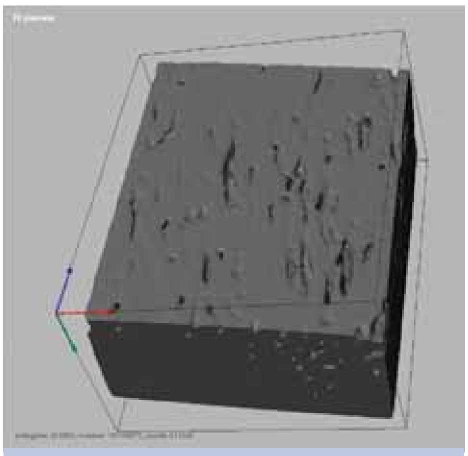
Industrial needs for understanding and optimising behaviour of complex material artefacts are increasing rapidly. 3D imaging techniques are becoming powerful metrology tools that not only offer high-resolution visualisation, but can also characterise the internal structures of a wide range of materials, from traditional to emerging nano- and bio-materials. Specific examples are in evaluating tissue scaffolds, bone and bone cements, developing dental restorative and soft materials, manufacturing metal and polymer foams, and characterising nano-composites. Beyond the conventional uses of 3D images in the medical fields, the performance of intricate material architectures, at the macro level, can be determined from 3D internal imaging studies of their complex internal structures and imperfections at micro- or nano- levels.

The importance of internal organic or inorganic structures in dictating the final properties of materials is well documented. For example, understanding 3D morphology, distribution, interconnectivity and crystallography of non-biological solids containing two or more phases and/or cellular solids is critical in characterising material performance precisely. Until recently, three-dimensional structures were derived from 2D observations from optical, SEM (scanning electron microscopy) and TEM (transmission electron microscopy) studies. Over the last 20 years, however, a series of novel and innovative true 3D internal imaging techniques have emerged, which although used successfully in medical science to this day, are gradually finding new applications in a much broader materials arena.

The current status of 3D internal imaging and characterisation methods was recently investigated in an NPL feasibility study that covered a wide range of materials (including bio- and nano-) at macro-, micro- and nano- resolution levels. The findings were included in two user reference databases. The principal focus was on understanding industrial drivers, barriers and scope of 3D imaging methods, with inputs obtained from key players in the UK. The study has also explored the new opportunities, applications and developments in 3D metrology in the novel and traditional materials fields. Techniques are classified in eight generic groups based on their energy sources (i.e. Magnetic, Nuclear, X-ray, Gamma-ray, Acoustics, Optical, Electron, Thermal), and are listed as per their strengths, limitations and applications.



SEM/FIB image showing milled 3D internal structure of lamb bone from a rib joint.



Representation of 3D image data of the cortical bone, which has been processed by ScanIP software (courtesy: Simpleware Ltd.).

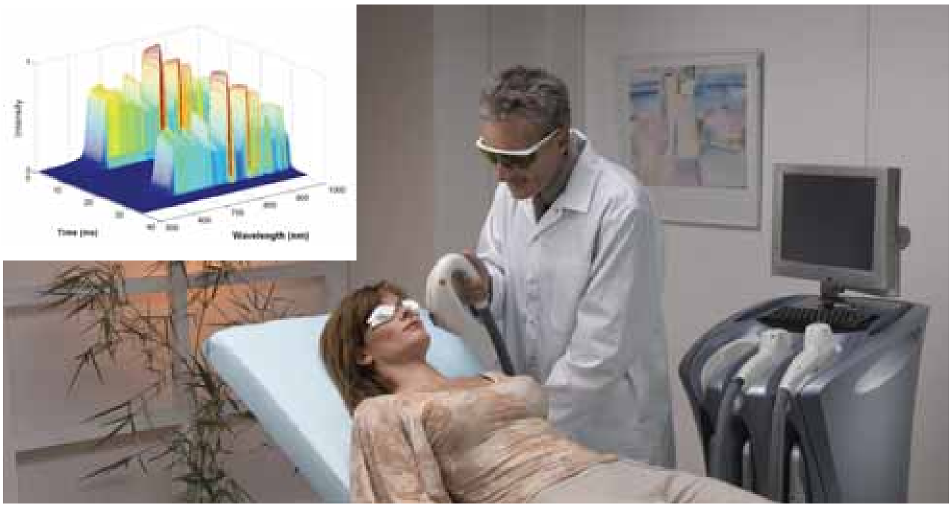
The study concludes with a list of recommendations, and provides user-guidance on selecting and sourcing suitable 3D metrology tools for a vast range of end products economically and effectively based on the latest technology and knowledge based options. The three most promising techniques are considered to be: X-ray Micro-focus CT, SEM/STEM + FIB and Ultrasound CT, which could find their diversified applications and rapid industrial uptake within the next 5 years on a variety of complex organic and inorganic end products.

NPL is currently formulating a new project to investigate the metrology and modelling of complex anisotropic materials behaviour from 3D internal images. The collaboration of industrial and academic partners, from UK and abroad, are welcome.

For further information please contact Sekhar Chakravorty on 020 8943 6919 or e-mail sekhar.chakravorty@npl.co.uk

Safe & effective use of Intense Pulsed Light sources

NPL has developed a traceable measurement system for Intense Pulsed Light systems, which are used for the treatment of cosmetic conditions by increasing numbers of people, and is contributing to the development of regulatory standards.



Intense Pulsed Light (IPL) systems are used mainly for the treatment of cosmetic conditions such as hair removal, vascular problems and photorejuvenation. They emit high intensity, non-coherent broadband radiation in the range of 400 nm to 1200 nm. Since the first commercial IPL system was developed in 1994, the technology has advanced rapidly to take advantage of profitable opportunities and a lack of clear regulatory standards. Safety and efficacy are of increasing concern as a growing population are exposed to IPL. There is a need for in-depth independent measurement of IPL systems to aid the regulators and reduce the risk to both patient and practitioner.

The Optical Technologies and Scientific Computing (OTSC) team at NPL have been working in collaboration with University of Dundee / Ninewells Photobiology Unit to determine the dosimetry needs for IPL devices, and then to develop suitable measurement systems based on these needs.

Key measurement parameters for the determination of safety and efficacy are time-resolved spectral irradiance, pulse length and shape, and pulse-to-pulse repeatability.

A traceable measurement system has been developed at NPL, and this has been used to measure IPL devices provided by UK manufacturers. The ability to assess the efficacy of treatment will be of clear advantage to the manufacturer, but also to the clinical user and to the customer or patient receiving treatment.

NPL and Ninewells inform the Health Protection Agency on these safety assessments of IPLs. NPL and Ninewells aim to provide recommendations of a measurement procedure and measurement techniques; these will be input into the developing IEC Safety of Intense Light Source Equipment standards.

For further information please contact Paul Miller on 020 8943 6757 or e-mail paul.miller@npl.co.uk

Wound measurement instrument sales achieved and new applications established

MAVIS (Measurement of Area and Volume Instrument System) is a novel instrument that promises to assist in the monitoring and healing of wounds, such as leg ulcers. Previously described in Health Matters issue 1 (Spring 2006), MAVIS measures wound dimensions and monitors wound colour. After being made traceable to national standards at NPL the first sales of this instrument have been achieved, and new applications have recently been found.

MAVIS was developed by Isotec Imaging Ltd, a company that grew out of research at the University of Glamorgan, and was the subject of a project funded for 12 months through the DIUS Measurement for Innovators programme. Working with Isotec Imaging and the Royal National Hospital for Rheumatic Diseases (RNHRD) at Bath, the National Physical Laboratory developed measurement artefacts and techniques to ensure the dimensional and colour measurements were traceable to national standards. The colour of a wound gives important information to clinicians about the state of the healing process. Because MAVIS uses commercially available cameras, it is essential that calibration is carried out to correct for production variations between units.

Isotec Ltd has now changed its name to Photometrix Imaging Ltd, and the instrument is being engineered into a stand-alone solution, using two 5-megapixel camera heads on a single processing platform. Additionally, a new quad-photogrammetry system

Bioprocessing community gets set for MSET

Measurement and Standards for Emerging Technologies (MSET) forum launches on the bioProcessingUK KTN website.

A new resource of measurement and standards information will launch January 2008 on the bioProcessUK Knowledge Transfer Network website. The Measurement and Standards for Emerging Technologies (MSET) forum aims to give researchers and developers of biopharmaceuticals and advanced cell therapy technologies easy access to relevant and up to date information that will help them in their business or research activities.

The bioProcessUK MSET forum outlines how measurement concepts such as uncertainty and traceability apply in a biological setting, and provides a coherent overview of all the various standards organisations operating in the bioprocessing and health sectors. It also shows how the UK bioprocessing community can direct and benefit from the UK's National Measurement System (NMS) research programmes.

The MSET concept has been designed to help users quickly find information on the qualifying measurement science needed to underpin new and emerging technologies. In addition to being an information resource, the forum has an interactive element and uses Interwise software to run online meetings.

The forum is moderated by Anna Hills, a senior research scientist at the National Physical Laboratory with 10 years experience of working in the pharmaceutical industry. "It's a great opportunity to collate and communicate all the relevant research outputs and standards impacting upon the sector," she says of the MSET forum; "We've worked with the bioProcessUK KTN and our NMS colleagues at LGC to produce a valuable tool which can help the UK's competitiveness in this area. I'm looking forward to interacting with the bioprocessing community to develop it further".

The bioProcessUK MSET is the latest in a number of MSET forums that have been developed as part of collaborations with a spectrum of KTNs and a DIUS-funded project lead by the National Physical Laboratory. Prior to the launch on the bioProcessUK KTN site, the MSET forum can also be viewed at www.mset.org.uk/bioprocessuk

For further information, please contact Anna Hills on 020 8943 6334 or e-mail anna.hills@npl.co.uk

has been developed and patented, to improve robustness and the precision of computations. The first sales of the instrument have been achieved, and the application has been widened to include scar tissue measurements. Other applications have been found in cosmetics and other non-medical sectors.

The outlook for sales of MAVIS looks positive, as awareness and confidence in the instrument builds. The colour analysis work for MAVIS was reported in a paper given to the BMVA symposium on Colour in Vision Analysis in London, and has been written up in an NPL report. Carl Jones from the University of Glamorgan exhibited a poster, and the measurement system, at the Royal Society for Medicine in London, and on the NPL stand at the Inaugural Health Technology Devices Conference in Warwickshire.

Photometrix Imaging Ltd is currently seeking distributors for MAVIS.

MAVIS calibration artefact.

Trials of MAVIS were carried out at Diving Diseases Research Centre, Plymouth (with Dr. Phil Bryson), Royal National Hospital for Rheumatic Diseases, Bath (with Dr. Jacqueline Shipley), Dept. of Dermatology, University of Kiel, Germany, (with Prof. Ulrich Mrowietz) and Dept. of Orthopaedics, Case Western Reserve University, Cleveland, USA (with Dr. Kath Bogie).

For further information please contact Richard Stevens on 020 8943 6484 or e-mail richard.stevens@npl.co.uk

Measurements of skin made more reliable

Measuring the rate of water loss through skin can give early warning of skin damage. An NPL collaborative project has developed a way to increase the accuracy of these measurements.

Trans-Epidermal Water Loss (TEWL) is the loss of water through skin. It is considered a reliable measure of barrier function – a sign of whether the skin is functioning properly. It is used to identify skin damage before it becomes visible to the eye, and to monitor the rate at which skin heals or recovers from trauma.

TEWL sensors actually measure water vapour flux, or evaporation, from skin (or other surfaces). Typical healthy skin loses water at between 10 g m^{-2} h^{-1} and 50 g m^{-2} h^{-1}.

The measurements have various applications. In the workplace, TEWL is measured in occupational monitoring for factory workers exposed to industrial solvents, while developers of toiletries and cosmetics measure TEWL to gauge the impact of products on skin. TEWL is also a powerful tool for clinical dermatology research.

All of these users rely on TEWL measurement devices to give correct readings, but past methods of calibration did not ensure consistency between instruments from different suppliers.

A collaboration of TEWL instrument users and suppliers, together with NPL, approached the problem with a new calibration technology.

The prototype uses calibration ‘wells’ which produce a known rate of evaporation when primed with a measured droplet of water. Using several of these ‘wells’, each giving a different rate of evaporation, the team can take readings with TEWL devices. A calibration correction can then be determined and applied.

In future TEWL instrument users will be able to benefit from calibrations that are reliable, consistent, and traceable to national measurement standards. NPL plans to launch a calibration service for TEWL instruments within the next 18 months.

For further information please contact Stephanie Bell on 020 8943 6402 or e-mail stephanie.bell@npl.co.uk

Progress in the development of an IEC standard for testing advanced digital hearing aids

Modern digital hearing aids use advanced digital signal processing techniques to enhance speech and reduce unwanted noise. Currently there are no standard measures to allow hearing aid users and distributors to compare the realistic performance of such devices – many of the advanced features have to be bypassed to run the tests described in the current IEC (International Electrotechnical Commission) and ANSI (American National Standards Institute) standards.

In September 2004 the acoustics group at NPL held a discussion with UK stakeholders to gather opinions on the subject. Since the meeting, the hearing aid working group (WG13) of the IEC Technical Committee 29, which includes a representative from NPL, have made some progress towards the introduction of a new measurement method that will form the basis of a new part (Part 15) in the IEC 60118 series of standards.

Part 15 will contain tests that are relevant to users and suppliers of hearing aids. While there is potential to extend the scope to incorporate other measures such as noise reduction and speech quality, the current focus is on a single 'speech gain' measurement. Part 7 will contain the traditional pure tone measurements used by manufacturers. Once these are in place, parts 0, 1, 2 and 6 will become obsolete and will be withdrawn.

EHIMA (the European Hearing Instrument Manufacturers Association), as part of the ISMADHA project (International Standards for Measuring Advanced Digital Hearing Aids), have produced a proposal for the speech gain test procedure. The hearing aid is pre-programmed for one of a set of standard audiograms and stimulated with a speech-like test signal. The input and output signals are time aligned and segmented into overlapped rectangular windows, then the speech gain in each window is calculated in 1/3-octave bands. The results are presented as the 99th percentile (peak) gain, the 30th percentile (minima) gain and the average band (LTASS) gain.

A new speech-like test signal was specially developed for the purpose by Hörtech of Germany, according to a refined version of the requirements described in ITU-T P.50 (1999) 'Artificial Voices'. The prototype signal consists of concatenated female speech in eight different languages including Mandarin, English, Spanish and Arabic. As no single subject could speak all eight languages, a number of female speakers were recorded and the F0 (pitch) of all were harmonised.

Round Robin testing of the method has taken place, with several manufacturers, plus DELTA in Denmark taking part. WG 13 aims to complete the research and development needed to underpin the new part 15 by 2008, leading to a new draft standard for international circulation and formal review. The standard will describe the measurement method, the presentation of results, and the new speech-like test signal. It is likely that the test method will also be adopted as an ANSI standard once the IEC version has been published. NPL will be involved as a member of the Working Group.

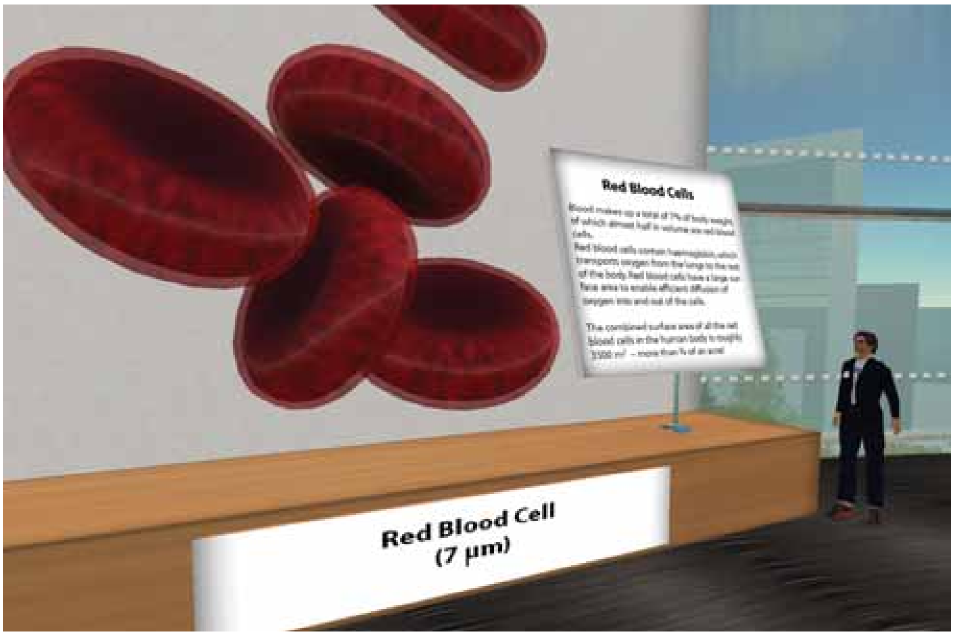
For further information please contact Jill Barrie on 020 8943 7188 or e-mail jill.barrie@npl.co.uk

If you would like further information on any aspect of **Health Matters,** *please contact:*
Tel: 020 8943 6880 | **Fax:** 020 8943 7160 | **E-mail:** health@npl.co.uk

Quality of Life Division
National Physical Laboratory | Teddington | Middlesex | United Kingdom | TW11 0LW
Helpline: 020 8943 6880 | **Fax:** 020 8614 0446 | **E-mail:** enquiry@npl.co.uk

Nano and virtual worlds converge

Nanoscience and virtual reality - two frontiers of technology - are coming together in an exciting development which will change the way the scientific community exchanges information and ideas.



Nanotechnology is already reaching into all areas of our lives, from computers to cars, from skin creams to environmental monitoring. It is impacting on medical research, clinical medicine, health and safety, and medical imaging. Now nanotechnology is stepping from the real world into the virtual world. NPL has launched NanoLands in the 3D virtual world of Second Life, establishing a real-time, interactive environment where the global nanotechnology community can come together and discuss key ideas and research.

NanoLands is unique within Second Life; based in the multi-disciplinary archipelago called SciLands, NanoLands offers regular events and opportunities for people to network, encouraging them to play a role in envisioning and defining the future of nanotechnology. NanoLands can also provide resources and mentoring to help nanotechnology-related researchers and businesses to get started in Second Life.

The NanoLands Challenge

In support of NanoLands, NPL is running a global competition offering funding assistance to help people build or develop exhibits for displaying on the NanoLands. The competition has the aims of demystifying perceptions of nanotechnology amongst the general public, fostering new relationships between scientists, engineers, policymakers and regulators, and promoting the use of Second Life as a powerful communications medium. NPL will provide technical help through the in-world mentoring system unique to NanoLands.

To find out more about the possibilities of NanoLands and the NanoLands Challenge, visit http://nanolands.org and follow the links to the competition application form.

For further information contact Gordon Clark on 020 8943 6839 or e-mail gordon.clark@npl.co.uk

Forthcoming events

www.npl.co.uk/events

Tip Enhanced Raman and Fluorescence Spectroscopy – Challenges and Opportunities
24 – 25 January 2008
NPL, Teddington
www.npl.co.uk/mnt/meetings/terfs

2008 Practical Course in Reference Dosimetry
28 – 31 January 2008
NPL, Teddington
http://www.npl.co.uk/ionrad/training/pcrd/

Developing Advanced Scientific Engineering Spreadsheet Applications
14 – 15 May 2008
NPL, Teddington
http://www.npl.co.uk/server.php?show=ConWebDoc.2032

7159/SEA/1k/1207