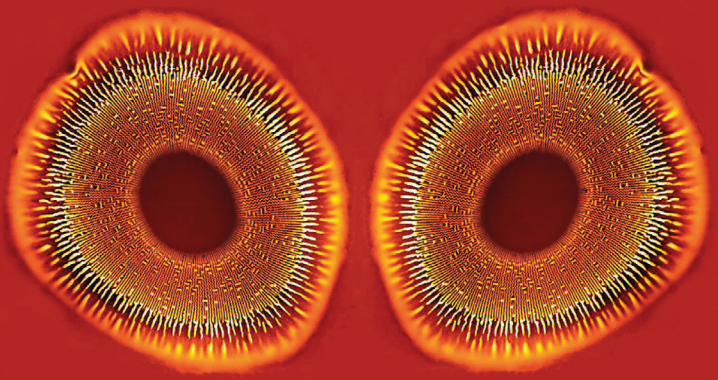
NPL
National Physical Laboratory

Commercial services from NPL - Surface, Nano and Biophysical characterisation



Delivering product development support to Healthcare, Agrichemicals, Advanced Material Manufacturing, Speciality Chemicals and Nanoparticles companies

Contact us to discuss your measurement challenges

surfacebio_enquiries@npl.co.uk

www.npl.co.uk/nanoanalysis **www.npl.co.uk/biotechnology**

Confidence in measurement with independence, integrity and impartiality

Our expertise and innovation eases the pressure on specialist in-house resources to increase capacity, reduce technical risk, and deliver cost and time savings for complex technical challenges.

We deliver solutions in world-class research facilities, with a range of state-of-the-art techniques and unique, beyond state-of-the-art capabilities for surface analysis under vacuum, ambient or liquid environment. This allows us to obtain key quantitative information on physical properties and chemical composition with nanometre resolution.

Our customers range from government departments, start-ups to large global multi-national corporations and have access to over 500 multi-disciplinary scientists along with an extensive national and international network of partners. Our independence and reputation give absolute confidence that we will translate our science excellence in to current and future real world requirements of our customers.

Examples of how NPL services can support you

Healthcare and Agrichemical

- Drug disposition in tissue and cells
- 3D imaging of control release coatings of drug on stents, to measure the drug distribution and migration
- Medical devices and drug delivery systems
- Investigating how conditioners stick to hair using SIMS imaging, and correlating with other physical properties such as friction
- Pharmaceutical manufacturing tablet composition and degradation
- Personal care products - measuring the change in nanoscale mechanical properties (modulus and friction) of hair, teeth and skin
- Drug permeation through skin and nanoparticle distribution in tissues
- High sensitivity, low cost, real time, label free measurement and quantification of unlabelled adsorbates (proteins /biomolecules /polymers) on surfaces
- Optical and label free chemical analysis of formulations

Advanced Materials Manufacturing and Speciality Chemicals

- Characterisation of graphene and other 2D-materials.
- Improving the performance of organic LED displays and solar cells including identifying contamination and work function of organic electronics
- Silicon dioxide on silicon thickness for the semiconductor industry
- QC wafers and microelectronics
- Identification of counterfeit products and packaging support
- Catalysis and corrosion studies
- Topography and nanomechanical properties of coatings including paints, polymers, ceramics, glasses and wool fibres
- On-line monitoring of chemical processes
- Investigation of organic nanostructures, thin films, inorganic nanostructures

Nanoparticles

- Sizing including separation of aggregations
- Particle surface chemistry and coating thickness, for example core-shell and core-shell-coating nanoparticles
- Charge measurements
- Mechanical properties of individual nanoparticles
- Micro and nano bubbles
- Nanoparticle distribution in tissues

Biophysical support

- Custom peptide synthesis
- Super-resolution light microscopy for cellular and macromolecular imaging
- Molecular and Membrane Biophysics Suite
- Biomolecular binding and kinetics
- Biomolecular chemistry and molecular biology
- Protein aggregation studies
- Mammalian and Microbial Cell Culture facilities
- Aspergillus fumigatus bioaerosol monitoring service
- Lateral flow immunoassay development service

Table of contents and list of services

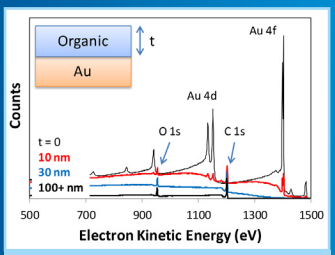
X-ray Photoelectron Spectroscopy (XPS)

- quantitative surface chemistry and binding state

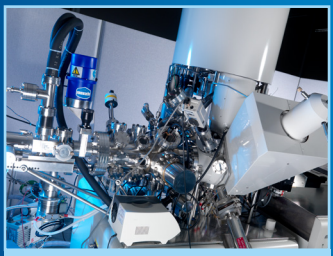
- Elemental identification excluding hydrogen and helium
- Chemical state identification (e.g. oxidation state)
- Compatible with most materials including organics
- Information depth of up to 10 nm
- Non-destructive depth profiling with <0.1 nm precision
- Sputter depth profiling for elemental depth distributions
- Highly quantitative
- Limited sensitivity and spatial resolution. X-ray exposure may damage some materials

Example applications

- Identification and measurement of surface contamination and organic overlayers, eg to solve problems of adhesion of coatings on substrates
- Chemical analysis and layer thickness of nanoparticles
- Silicon dioxide on silicon thickness measurement for the semiconductor industry
- Identification of counterfeit products, Catalysis and corrosion studies, paints, polymers, ceramics and glasses
- Characterisation of graphene
- Ultraviolet photoelectron spectroscopy for measurement of work function of organic electronics



XPS spectra of an organic layer with varying thickness on a gold substrate



NPL X-ray Photoelectron Spectrometer

Attribute	Value	Unit
X-Y resolution	3 (imaging), 15 (spectroscopy)	µm
Z depth resolution	< 1	nm
Sensitivity	about 0.1	atom %
Analytical information	Elemental and some chemical state	
Types of material	Solids	
Sample preparation	None usually	
Quantitative	Yes	

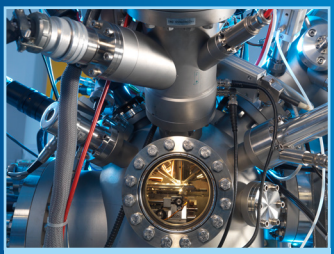
Secondary Ion Mass Spectrometry (SIMS)
– surface and interface chemistry, trace organics

- Identification of trace elements, organic molecules and polymers on surfaces and interfaces, with better than 1 ppm sensitivity for some molecules and ppb sensitivity for some elements
- Surface chemical imaging with better than 200 nm resolution
- Extremely surface sensitive information from top 1 nm of sample
- 3D chemical imaging of inorganics and organics with better than 5 nm depth resolution

Example applications

- Drug disposition in tissue and cells
- Analysis of complex molecules and organics, including wool fibres, medical devices, tablets, and drug delivery systems
- Improving the performance of organic LED displays and solar cells, by characterising surface and interfacial chemistry of organic layers and identifying contamination
- 3D imaging of controlled release coatings of drug on stents, to measure the drug distribution and migration
- Investigating how conditioners stick to hair using SIMS imaging, and correlating with other physical properties such as friction
- Pharmaceutical manufacturing tablet composition and degradation

3D SIMS image of one pixel in an OLED display



NPL secondary ion mass spectrometer

Attribute	Value	Unit
X-Y resolution	<1	µm
Z depth resolution	5	nm
Sensitivity	<1	ppm
Time resolved	No	
Analytical information	Molecular composition and imaging	
Types of material	Versatile	
Sample preparation	Vacuum compatible	
Quantitative	Semi-quantitative	

Ambient mass spectrometry
- analysis and imaging of molecules in complex samples

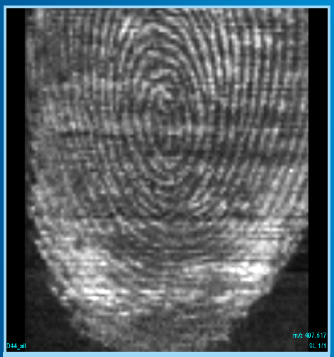
- Applications in formulation, cell biology, forensics, plant sciences, pharmaceuticals
- Direct analyses of surfaces under ambient conditions in real time
- Two main techniques:

Desorption Electrospray Ionisation (DESI)

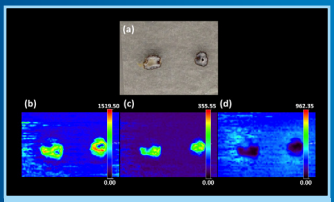
- Uses electrospray source of highly charged aqueous spray droplets to gently desorb and ionise molecules from a sample surface
- Spot mode or imaging possible - typical spatial resolution is approximately 100 µm - 200 µm
- Soft ionisation process, very little fragmentation
- Can be coupled to any mass spectrometer allowing for identification and MS/MS studies
- In principle, no sample pre-treatment required

Plasma Assisted Desorption Ionisation (PADI)

- RF generated, atmospheric helium plasma used to desorb and ionise molecules from the surface
- PADI can analyse polymers and molecules, at ambient pressure with minimal sample preparation, enabling high-throughput of samples and quick analysis times
- Most suited to volatile materials although low vapour pressure molecules can be analysed with thermal assistance



DESI MS imaging of a fingerprint



(a) Cardamom seeds imaged with microplasma source. Variation in intensity of the ions at m/z (b) 81, (c) 95 and (d) 151

Attribute	Value	Unit
X-Y resolution	100 - 200	µm
Z depth resolution	N/A	
Sensitivity	Femtomolar and lower, depending on sample	
Time resolved	Possible for reaction monitoring	
Analytical information	Molecular composition and imaging	
Types of material	Various	
Sample preparation	In principle, not required	
Quantitative	Semi-quantitative, with standards	

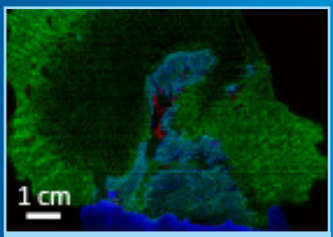
Matrix Assisted Laser Desorption Ionisation (MALDI)

- analysis and imaging of small and large molecules

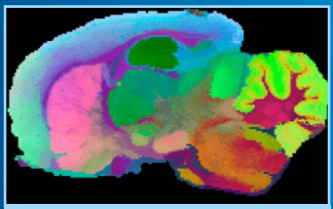
- MALDI mass spectrometry imaging can be used to identify and image small and large molecules, e.g. proteins, peptides, lipids, drugs and metabolites
- A matrix compound, usually a small organic acid, is applied to the sample surface. Ionisation of analytes occurs when the dried matrix is irradiated with a focused laser beam. A mass spectrum of the ions is then recorded
- Experiments can be performed in vacuum or at atmospheric pressure
- In imaging experiments typical spatial resolution is approximately 10-200 µm

Example applications

- Disease state profiling
- Microbiology
- Forensics
- Plant science
- Analysis of pharmaceuticals, e.g. tissue imaging in preclinical studies



MALDI MS images of small molecules in porcine kidney



Hyperspectral image of biomolecules from a rat brain tissue section

Attribute	Value	Unit
X-Y resolution	~10-200	µm
Z depth resolution	N/A - 'surface' analysis of extracted compounds in thin sections	
Sensitivity	Analyte dependent - femto-molar for selected species	
Time resolved	No	
Analytical information	Molecular composition and distribution	
Types of material	Typically thin tissues sections, frozen, freeze dried or fixed	
Sample preparation	Matrix application required	
Quantitative	Semi-quantitative	

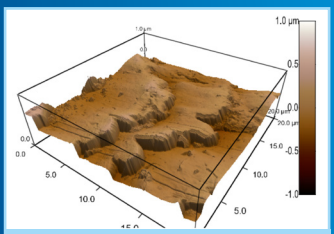
Atomic Force Microscopy (AFM)

- highest resolution surface topography/ roughness with additional information (mechanical, chemical, etc)

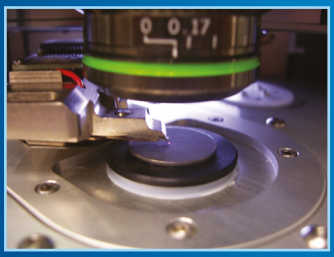
- Uses an ultra sharp tip to build up a topographic image of the surface at nanoscale resolution, operating in imaging or spectroscopic modes
- Operates in air or liquid, looks at time dependent or temperature dependent properties at high resolution
- Surface roughness
- Image sizes - ~100 nm up to 80 µm
- Combines topography with material physical information (adhesion, modulus, stiffness, friction), chemical information (via imaging/ spectroscopy for specific functionalisation/ binding and phase differences)
- Electrical, magnetic and thermal information

Example applications

- Inorganics, polymers, coatings and bio-samples
- Personal care products - measuring the change in nanoscale mechanical properties (modulus and friction) of hair, teeth and skin
- Nanoparticles, fibres, nano-capsules, micro-bubbles
- Topography and nanomechanical properties of coatings
- Characterisation of graphene and other two-dimensional materials



AFM topography image of hair cuticle



Attribute	Value	Unit
X-Y resolution	1	nm
Z depth resolution	1	nm
Sensitivity	Single binding event upwards	
Time resolved	Yes	
Analytical information	Topography with some physical and chemical information	
Types of material	All (very soft to hard)	
Sample preparation	None	
Quantitative	Yes for dimensional and force, semi for chemical	

Raman techniques
– chemical mapping

Spontaneous Raman Spectroscopy

- Uses visible or near-infrared laser to obtain molecular specific information from complex environments
- The technique utilises intrinsic molecular vibration and therefore it is label-free
- While a spectrum is a fingerprint of a molecule, further chemometric analysis can be carried out to analyse multiple chemicals at the same time

Example applications

- Pharmaceutical products, material purity testing, forensic analysis, graphene and advanced material
- Stress state determination, on-line monitoring of chemical processes

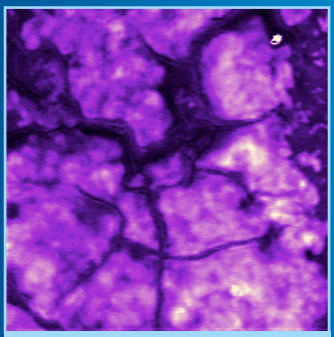
Stimulated Raman Scattering (SRS)

- Uses near IR laser to enhance Raman signal
- Chemical distribution in 3D at sub-cellular length scale without causing any significant damage to the sample. The signal is linear with concentration and semi-quantitative with the sensitivity currently at sub-micromolar range

Example applications

- 3D label-free imaging of living cell/tissue and small organisms, drug permeation through skin, sub-cellular drug and nanoparticle distribution

Attribute	Value	Unit
X-Y resolution	1	µm
Z depth resolution	1	µm
Time resolved	Yes	
Analytical information	Chemical	
Types of material	Raman active	
Sample preparation	None	
Quantitative	Can be	



Label-free SRS image of the distribution of unsaturated lipids in a lung tissue section

Attribute	Value	Unit
X-Y resolution	350	nm
Z depth resolution	700	nm
Sensitivity	Micro molar	
Time resolved	Yes	
Analytical information	Chemical distribution	
Types of material	Biological, organic and inorganic	
Sample preparation	Thin, 100 µm	
Quantitative	Relative concentration	

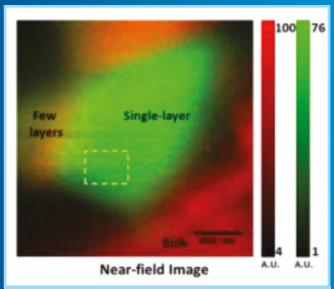
Raman techniques
– chemical mapping

Tip Enhanced Raman Spectroscopy (TERS)

- Combines Raman chemical mapping with high resolution of scanning probe microscopy
- Wide range of materials/chemicals including organic nanostructures, thin films, inorganic nanostructures and biological materials can be investigated

Example applications

- Raman-active materials such as carbon nanotubes, graphene, organic electronic polymers, phase separated polymers and biological materials



Single layer MoS_2

Attribute	Value	Unit
X-Y resolution	20	nm
Z depth resolution	1	nm
Sensitivity	Single molecule	
Time resolved	No	
Analytical information	Chemical	
Types of material	Raman active	
Sample preparation	None	
Quantitative	No	

Surface adsorption of biomolecules and surface wettability

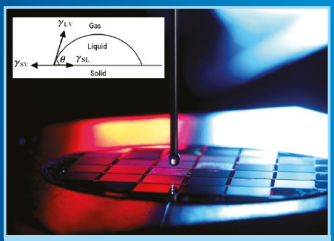
Contact Angle measurement – surface wettability

Surface wettability properties by means of sessile drop contact angle measurements in air using different liquids giving:

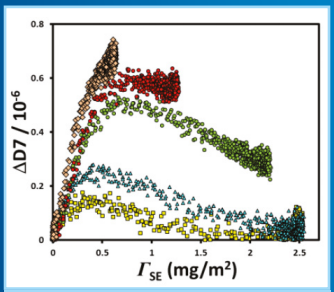
1) surface wettability
2) water contact angle
3) surface energy by Fowkes method
4) wettability mapping using micro-droplets as small as 100 pl

Which can help in understanding;

- Surface treatment and optimisation of coatings
- Adhesive properties and surface purity
- QC for wafers and microelectronics



Water contact angle measurement by sessile drop method



Dissipation variation (ΔD) due to changes in the amount of adsorption (Γ_{SE}) of molecules using QCM-D

Quartz Crystal Microbalance with Dissipation Monitoring (QCM-D)

- surface adsorption of proteins or biomolecules

- High sensitivity, low cost, real time, label free measurement and quantification of unlabelled adsorbates such as proteins, biomolecules and polymers
- Capability for surface mass binding and surface viscoelastic characterisation of the bound mass at the solid liquid interface down to 10^{-9} gm level

  - detects subtle changes in the solution-surface interface via frequency or dissipation changes

Nanoparticle characterisation techniques
- for powders and liquid dispersions

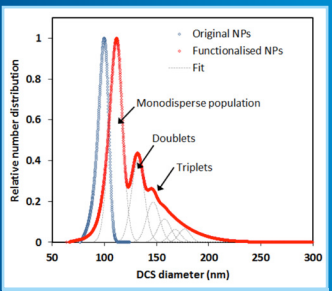
- Characterisation of a wide range of micro- and nano-sized materials, including metal, oxide, latex, silica, emulsions, bubbles, capsules and biological particles
- Measurement of size, high resolution size distribution, density and surface area using multiple techniques
- Measurement of production of reactive oxygen species
- Distribution of size and zeta-potential across a heterogeneous sample
- Measurement of mechanical properties of individual particles and capsules
- Accurate measurement of particle chemical composition, impurities and thickness of particle coatings

Example of applications:

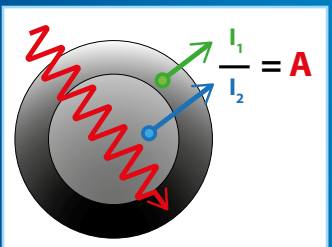
- Protein-functionalised particles for biosensing, drug delivery and lateral flow cytometry
- Catalysts; metal oxide nanoparticles for cosmetic formulations
- Core, core/shell and core/shell/shell quantum dots for biological labelling and electronics

Instrumentation:

Dynamic light scattering (DLS); Differential centrifugal sedimentation (DCS) / Centrifugal liquid sedimentation (CLS); Nanoparticle tracking analysis (NTA); Tuneable resistive pulse sensing (TRPS); Surface area; X-ray photoelectron spectroscopy (XPS); Atomic force microscopy (AFM); Electron microscopy



Size distribution of functionalised nanoparticles using differential centrifugal sedimentation



Schematic of method to calculate chemical composition and shell thickness of nanoparticle coatings using XPS

Attribute	Value	Unit
Size range	1 - 10,000	nm
Size distribution	Mono- and poly-disperse samples	
Time resolved	Yes	
Analytical information	Size, size distribution, coating, density concentration, zeta potential	
Types of material	Organic, inorganic and biological particles	
Sample preparation	Technique dependent	
Quantitative	Yes	

Molecular and membrane biophysics

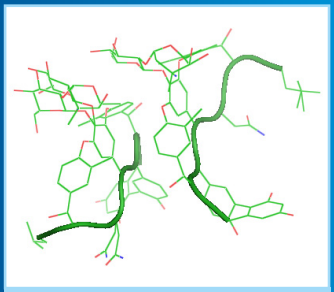
Biomolecular measurements in aqueous and membrane environments using circular and linear dichroism spectroscopy, Langmuir Blodgett trough, FTIR, UV-vis, fluorescence and Raman spectroscopy, for the following applications:

In solution:

- Biomolecular (proteins, peptides, DNA) folding, dynamics, orientation and self-assembly
- Secondary and tertiary structure analysis, stability and aggregation
- Analysis of post translational modifications (methionine oxidation)
- Intrinsic protein fluorescence and anisotropy

At interfaces:

- Label free analysis of drug interactions with lipid membranes
- Relative orientation of proteins, peptides, DNA and organic molecules at bio-interfaces, lipid membranes



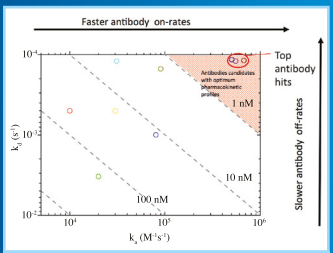
Secondary structural analysis of the antibiotic vancomycin

Protein functional assays

Biomolecular binding & affinities

Biomolecular affinity analysis using surface plasmon resonance sensor technology, and isothermal titration calorimetry. Point of care assay development using lateral flow platforms.

- Label free analysis of molecular interactions with µM to pM affinity constants
- Antibody/antigen screening, binding specificity (off target reactions, toxicity) and low affinity drug scaffolds
- Immunogenicity testing, patient sera screening, isotype host antibodies
- Drug screening using membrane bound biological receptors
- Dissociation constants (Kd), enthalpy changes (ΔH), and binding stoichiometry (n)
- Analysis of protein coating onto nanoparticles
- Lateral flow assays with fluorescent, gold and SERS active detection mono- and multiplexing formats



Iso-affinity plot - ranking antibody lead candidates based on binding kinetics

Surface plasmon resonance biosensor

Biomolecular chemistry & molecular biology

To aid in the design and construction of complex biomolecular systems (peptides, DNA) for functional analysis in native and near-native environments including synthetic and complex biological matrices, membranes and fluids by employing synthetic, imaging, electrophoretic, chromatographic and mass-spectrometry methods.

- Custom peptide synthesis (purity grade: crude to >95%)
- Isotopic and covalent labelling (fluorescence, biotinylation), cyclisation and lipidation
- Generation of peptide arrays, libraries and antigens
- Biomolecular purification and analysis by liquid chromatography (SEC, HPLC, FPLC) and electrophoretic methods
- Protein expression in bacteria and yeast
- Protein purification, characterisation, solubilisation and re-folding (exclusion bodies)
- Site directed mutagenesis, molecular cloning, plasmid preparation (from Mini to Maxi prep)
- Quantitative Polymerase Chain Reaction
- Biopolymer mass analysis, post-translational modifications and peptide mapping (LC-ESI and MALDI-ToF)

AKTA purification system for protein and DNA separation and analysis

Bacterial protein expression

Mammalian and microbial cell culture & monitoring

Culture facilities for primary and immortalised cells, yeast/fungi and non-pathogenic bacteria. We provide the following analytical services:

Mammalian cell culture

- Cell adhesion, proliferation, invasion, viability and death assays (apoptosis, necrosis)
- Extracellular and intracellular measurements: non-viral transfections, matrix niches, scaffolds, using fluorescence confocal microscopy and flow cytometry
- Tissue skin culture models for drug delivery and toxicity
- Short and long term, end-point and real time cell responses (drug treatment, post irradiation, transfection) monitored by fluorescence microscopy and impedance sensing

Bacterial cell culture

- Minimum inhibitory concentration (MIC) assays, haemolytic and co-culture assays
- Real-time live-dead assays and biokinetic assays

Aspergillus fumigatus bioaerosol emissions from composting sites

- Detection limit of 100 spores/m3 (cyclone air sampling and qPCR)
- Detection of total spore count (viable and non-viable)
- Differentiation between background spore levels and site specific emissions

Composting site bioaerosol monitoring

Aspergillus fumigatus detection using qPCR

Super-resolution and live cell imaging

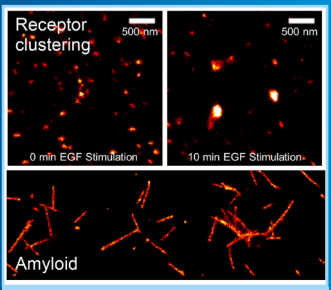
Fluorescence microscopy methods to achieve imaging below the "diffraction limit" of conventional light microscopy.

Localisation microscopy (dSTORM)

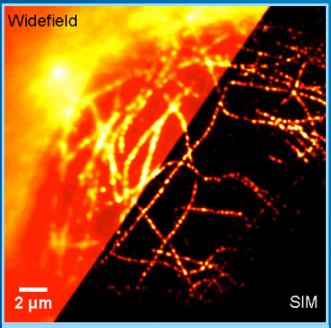
- To probe single molecule localisation with 10-15 nm precision (gives 20-30 nm resolution) in extracellular and intracellular environments, for in vitro and tissue samples
- Probes can be fluorescent proteins – "PALM" or organic fluorophores "dSTORM". Fluorophores can be coupled to antibodies or other molecules for specific recognition
- Multi-colour and 3D imaging; 3D slabs ~500 nm thick
- Fixed cells, biomolecules in vitro (DNA, protein filaments, etc.)
- Imaging of high content arrays

Structured illumination microscopy (SIM)

- Doubles the resolution of a given imaging system (typically achieves ~100 nm with high NA objectives)
- Real-time live-cell imaging, lower phototoxicity than STED
- Multi-colour and 3D imaging with most types of fluorophores
- Optical sectioning, increased spatial resolution for moderate thickness (typically < 10 µm)



Super resolution fluorescent images generated using dSTORM



Wide field and SIM images of fluorescently labelled actin filaments

Attribute	Value	Unit
X-Y resolution	20-30	nm
Z depth resolution	50-60	nm
Sensitivity	yoctomole	
Time resolved	No	
Analytical information	Specific biomolecule	
Types material	Cells, immobilised biomolecules	
Sample preparation	Standard fixation/ immunostaining	
Quantitative	Possible but not routine	

Additional Complementary techniques

Scanning Electron Microscopy (SEM) – image and elemental analysis

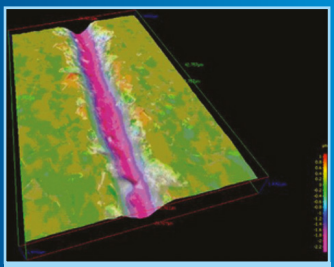
- High magnification imaging
- Study surfaces with complex topography
- Focused ion beam – SEM (FIB-SEM) for milling, 3D microstructure
- Electron backscattered diffraction (EBSD) – structure, orientation, phase of crystalline materials
- Energy Dispersive X-ray analysis (EDX) – elemental analysis
- Simultaneous in lens and backscattered detectors (e.g. for nanoparticle sizing)

3D microscopy / Confocal laser scanning microscopy (LEXT)

- 3D microscope images
- High resolution optical images with depth selectivity
- Lateral resolution 120 µm
- Vertical resolution 10 nm
- Also measures surface roughness

Microtome and ultra-microtome

- Methods to produce cross sectional slices of samples or flat regions of samples for analysis



Colour coded height map of micro-tribology experiment on WC/Co

How we can help you

Our breadth and depth of expertise and ability to combine techniques across disciplines, time and length scales makes us unique.

We deliver:

- Quick turnaround measurements
- In depth problem solving to identify the best technique or combination of techniques to address and solve your measurement challenge
- Longer term partnerships for repeat measurements to support quality control or R&D support
- Collaborative research for example Innovate UK and EU H2020
- Consultancy
- Training
- Instrumentation
- Free, no obligation quotes provided on all jobs

Please contact us to discuss your needs:

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www.npl.co.uk/biotechnology