

Impact case study (REF3b)

Institution: Lancaster University
Unit of Assessment: B9 Physics
Title of case study: Commercial exploitation of entirely new forms of microscopy providing chemical analysis of materials at the nanoscale based on photo-thermal techniques developed and patented at Lancaster.
1. Summary of the impact Basic research combining scanning probe microscopy with thermal, spectroscopic and chemical analysis has enabled the development of powerful, entirely new forms of analytical microscopy. Commercialisation of instruments for micro-thermal analysis began by TA Instruments, in 1998, based on four patents, followed by a Lancaster start-up company Anasys Ltd. These instruments have since been extensively used in multidisciplinary applications by scientific industry and government laboratories. Anasys has sold over 100 units of these nanoscale thermal analysis instruments (total turnover £3M) and many leading polymer industries, research institutes and academic programs worldwide are now users of this technology.
2. Underpinning research Fundamental research led by H.M. Pollock and A. Hammiche during the mid-1990s in Lancaster University Physics Department into the thermal properties of materials on the nanoscale resulted in the development of a cantilever with an ultra-miniature resistive element on its tip, which can act either as a temperature sensor or as a point-like heat source. Pollock and Hammiche were the first in the world to develop the ability to simultaneously deposit thermal energy and measure temperature changes on a sub-micron scale. This breakthrough was expanded into a new generic scanning thermal probe microscopy (SThM) technology, where purely thermal modes of imaging are complemented with localised analysis. For the first time individual regions of a solid sample could be selected by means of surface or even sub-surface imaging to combine spatial discrimination and chemical fingerprinting using calorimetry, thermomechanometry, infrared spectroscopy and pyrolysis mass spectrometry. The outcome was a powerful new form of analytical microscopy. Building on the results of their basic research into the interaction of solid surfaces with thermal stimulus and thereafter on the realisation that this could be combined with the precision of the scanning thermal probe, academic findings were disseminated in high impact scientific journals, web pages and specialist conferences. The 1st International Workshop on Spectral Diagnostics (2007) proved to be a landmark event pointing the way forwards for clinicians to make use of spectroscopic instrumentation. From the beginning the research was carried out in close collaboration with chemists (D. Hourston, Loughborough University and M. Reading, UEA), biologists at Lancaster (N.J. Fullwood & F. Martin) and more recently with clinicians in the NHS (P. Martin-Hirsch, Consultant, Royal Preston Infirmary). Consequently, new applications in polymer blends, pharmaceuticals and biomaterials were developed. The research was funded (> £2.1M) by EPSRC, BBSRC and EU and attracted strong industrial interest throughout, which led to instrument development and subsequent commercialization by TA Instruments and Anasys Ltd. Since 1995 four patents were successfully filed, three of which were

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initially assigned to TA Instruments. In March 1998, the "Micro-thermal Analyser" (marketed by TA Instruments Co., based upon this research) was awarded the PittCon Gold Award for the best new product at PittCon '98 (the world's largest annual scientific instruments conference – 3000 exhibits, 25000 attendees), as judged by a panel of editors of the leading international scientific instrumentation journals. The instrument subsequently won the R & D 100 award in September 1998 and received a Design Council "Millennium Award" in 1999 following its exhibition in the Millennium Dome.

In 2005 a Lancaster Start-Up company "Anasys Instruments" was formed, having negotiated the re-assignment of the first three patents from TA Instruments to Anasys. Since then Anasys Instruments has developed and introduced multiple major award-winning technologies: nanoscale thermal analysis (nano-TA™), transition temperature microscopy (TTM™), AFM+ thermal analysis (afm+™), and AFM+ IR Spectroscopy (nanolR™). The afm+ was a 2007/2008 R&D 100 Award winner, and the nanolR won the honour in 2010 as well as a Microscopy Today Innovation Award.

3. References to the research

(1) H. M. Pollock and A. Hammiche, *J Phys D: Appl Phys* 34, R23-R53 (2001), Micro-thermal analysis: techniques and applications.

Describes the underpinning research work performed at Lancaster leading to instrument development, (144 citations).

(2) A Hammiche, H M Pollock, M Reading, M Claybourn, P Turner and K Jewkes, *Applied Spectroscopy* 53, 810-815 (1999). Photothermal FTIR spectroscopy: a step towards FTIR microscopy at a resolution better than the diffraction limit.

Describes a technique for near-field infrared spectroscopy with sufficiently high spatial resolution for chemical analysis of sub-micron-sized volumes to be performed. Has led to further patents, commercial application, and biomedical research on tissue samples at the near-single-cellular level.

(3) F L Martin and H M Pollock, *Oxford Handbook of Nanoscience and Technology 2* (A V Narlikar and Y Y Fu, eds.), pp. 285-336 (2010), Microspectroscopy as a tool to discriminate nano-molecular cellular alterations in biomedical research.

This O.U.P. book chapter is a keynote review with high citations and a standard reference in the field.

(4) Jemma G. Kelly, Júlio Trevisan, Andrew D. Scott, Paul L. Carmichael, Hubert M. Pollock, Pierre L. Martin-Hirsch and Francis L. Martin, *Biospectroscopy to metabolically profile biomolecular structure: a multi-stage approach linking computational analysis with biomarkers. J Proteome Res.*, 10(4), pp 1437–1448 (2011)

This is a keynote article, published in a journal with high citation index (5), and will be a standard reference in the field for many years.

(5) Discrimination of human stem cells by photothermal microspectroscopy, O Grude, T Nakamura, A Hammiche, A J Bentley, F L Martin, H M Pollock, S Kinoshita and N J Fullwood, *Vibrational Spectroscopy* 49, 22-27 (2009).

One of the first examples of the use of nano-IR in biomedical research.

(6) FTIR micro-spectroscopy identifies symmetric PO₂- modifications as a marker of the putative stem cell region of human intestinal crypts, Michael J. Walsh, Tariq G. Fellous, Azzedine Hammiche, Wey-Ran Lin, Nigel J. Fullwood, Olaug Grude, Fariba Bahrami, James M. Nicholson, Marine Cotte, Jean Susini, Hubert M. Pollock, Mairi Brittan, Pierre L. Martin-Hirsch, Malcolm R. Alison and Francis L. Martin, *Stem Cells* 26, 108-118 (2008) Includes some nano-IR data, published in a journal with a high citation index (7.9).

4. Details of the impact

In localised calorimetry and thermomechanometry, the probe heats any microscopic feature of interest so that events such as glass transitions, crystallisation, melting and decomposition are induced and detected. This capability transformed SThM into a powerful new form of analytical microscopy with wide-ranging applications. Meanwhile, photothermal nano-IR is used to obtain infrared spectra from sub-micron sized regions, and improved methods involving chemometrics and/or fuzzy logic enable detection of minute compositional differences between otherwise identical samples.

The direct beneficiaries of our research include two companies who have successfully developed and sold instruments based on our high spatial resolution near-field thermal methods for analysis and characterization. The first range of instruments, namely the “Micro-thermal Analyser”, was commercialized by TA Instruments Inc. (New Castle, Delaware USA). An improved version, the “Nano-TA”, was subsequently developed by our start-up company Anasys Instruments. The second range of instruments (nano-IR, Anasys) uses the same type of probes, combining thermal microscopy with infrared spectroscopy to yield a new technique, namely nano-infrared microspectroscopy.

The research organisation TNO in the Netherlands has used the micro-TA instrument extensively for the microthermal analysis of durability and to determine glass transition temperatures in polymers. Subsequently, Borealis who are a leading provider of chemicals and plastics used the instrument for quality control of polypropylene to detect inclusions and impurities and to investigate customer claims in the development of polymer films and packaging for the healthcare and electronics industries. Our research has also led to development of high-resolution biomedical imaging techniques applicable to tissue engineering; drug testing and discovery for amyloid diseases (e.g., Alzheimer’s disease) and DNA studies. For detection of minute compositional differences between otherwise identical samples, our research has also helped develop improved chemometrics and/or fuzzy logic.

The wider beneficiaries include a variety of scientific and industrial end users of our technology. Micro-thermal analysis is now being widely used commercially to visualize the spatial distribution of phases, components, and contaminants in polymers (Kimberly Clark), pharmaceuticals (Molecular Profiles Ltd., 3M Healthcare, Pfizer, AstraZeneca), foods, biological materials and electronic materials, nanoscale spectroscopy, electronic and heat transport properties of novel macromolecular systems, (such as carbon nanotubes), manipulations of atoms and macromolecules into nanostructures; development and investigation of submicron- and nano-structures of novel inorganic and organic semiconductor materials. For example, *Tom Eby of Kimberly Clark Corporation, states that “Reverse engineering based on IR is an important application in most industrial labs and the spatial resolution breakthrough of the AFM-IR technique now enables this for a wide range of materials with sub-micron features.”* Being based upon extensive basic nanophysics research in novel materials, our cross-disciplinary research was also fundamental to the development of non-invasive scanning techniques for biological and biomedical applications. These include studies of bio-chemical processes in plant cells; for example, the Micro-TA has been used to help Syngenta develop a better model for understanding herbicide interactions with leaf surfaces. Meanwhile, work by Molecular Profiles Ltd. on solid dispersion formulations using the NanoTA in collaborations with Nottingham University and Janssen Pharmaceuticals has led to the development of formulations for poorly soluble drugs (such as the anti-AIDS drug etravir, now in the product Intelence®).

5. Sources to corroborate the impact

- (1) Factual statement by key user at Nottingham University which articulates applications in Pharmacy and healthcare together with industrial users (-available on request)
- (2) Report from Kimberley Clark Corporation : Spectroscopy Europe **24**(3)18-21, (2012)
- (3) List of references (10 papers) provided by TNO describing different aspects of microthermal analysis of polymers (-available on request)
- (4) Paper from Borealis describing identification of inclusions in polymers (-available on request)
- (5) Nano-TA instrument developed by Anasys Instruments based on Lancaster research wins the R&D 100 award. <http://www.rdmag.com/Awards/RD-100-Awards/2007/09/RD100-Awards-Bridging-The-Gap-With-AFM/> validates that the instrument brings new capability and measures both thermal and nanoscale properties quantitatively.
- (6) A further Anasys instrument (Nano-IR) derived from Lancaster research won the 2010 R&D award <http://www.rdmag.com/Awards/RD-100-Awards/2010/08/AFM-gains-chemical-composition-power/> and enables chemical analysis of samples down to 100 nm in spatial resolution, an improvement of up to two orders of magnitude over conventional transmission IR micro-spectroscopy.

Patents

- (7) "Method and apparatus for performing localized thermal analysis and sub-surface imaging by scanning thermal microscopy" US 6,491,425 & US 6,095,679,
- (8) "Method and apparatus for high spatial resolution spectroscopic microscopy" US 6,260,997,
- (9) " Method and apparatus for localized dynamic mechano-thermal analysis with scanning probe microscopy" US 6,200,022
- (10) "Microspectroscopy Apparatus and method" , Reading, Montagu-Pollock, Wood, WO2,011,007,168