

# WARWICK CENTRE FOR ANALYTICAL SCIENCE

Grant Ref:EP/F034210/1

## KEY PERSONNEL

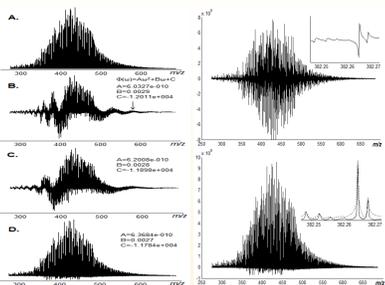
**Principal Investigator:** Professor Mark Smith, Deputy Vice Chancellor  
**Centre Director:** Professor Pat Unwin, Department of Chemistry  
**MSc Course Director:** Dr Claudia Blindauer, Department of Chemistry  
**Co-investigators:** Professor Peter Sadler (Chem), Professor Malcolm Cooper (Phys)  
 Professor Jane Hutton (Stats)

**Academic Appointees:** Professor Peter O'Connor, Department of Chemistry  
 Dr Jeremy Sloan, Department of Physics Dr Fabio Rigat, Department of Statistics  
**Heads of Department:** Professor Mike Shipman, Department of Chemistry,  
 Professor Robin Ball, Department of Physics, Professor Saul Jacka, Department of Statistics  
**Administrative Coordinator:** Mrs Fiona Friel

WCAS was established in November 2008, with the principal aim of establishing 3 new research groups in mass spectrometry (Prof. Pete O'Connor from Boston, USA), high resolution transmission electron microscopy (Dr Jeremy Sloan, from QMW) and statistics/chemometrics (Dr Fabio Rigat, Warwick). With significant additional funds from the University of Warwick, appointments were made at the levels of Full Professor, Associate Professor and Assistant Professor. As highlighted herein, the University has made substantial further commitments to its infrastructure in Analytical Science and the grant has arguably given Warwick the most comprehensive coverage of Analytical Science in the UK, strengthening existing internationally-leading activities in magnetic resonance spectroscopy, mass spectrometry, electrochemistry and interfacial science, surface analysis, metallomics, bioanalytical science, analytical neuroscience and sensor systems. The initial goals of the Centre have been achieved: (i) to set the 3 groups up with an excellent level of support from the grant and University, providing the groups a platform from which they have the opportunity to develop and grow; (ii) the development of a high value Masters programme in Analytical Science which feeds through to PhD programmes; and (iii) to establish new multidisciplinary programmes at Warwick and beyond.

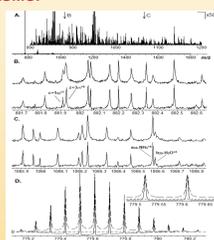
### MASS SPECTROMETRY

**Solving the phasing problem:** in FTICR mass spectrometry, as in FTNMR spectroscopy, if the initial phase of the sample ions rotating in the centre of the magnet is known, then the signal can be mathematically rotated to align with the real axis, providing an accurate 'absorption mode' spectrum. Solving the correct phase function in FTICR has been difficult and to date all FTICR experiments have therefore presented their data as lower resolution magnitude mode spectra. We have discovered a simple technique to iteratively solve the FTICR mass spectrometry phase function using quadratic least-square fitting and iterating through the whole range of predicted phases (see Figure on the right).



This technique increases the resolution of all FTICR instruments worldwide by 50-100% at no cost. A paper [1] was accepted without revision for JASMS.

The relevance of this work can be appreciated by the ECD MS/MS spectrum of the 8.5 kDa protein ubiquitin (on the right). A) the normal magnitude mode spectrum showing a large number of peaks. B) an expansion of A shown as a magnitude mode spectrum (upper) and an absorption mode spectrum (lower) demonstrating the resolution and peak-shape improvements obtained when the spectrum is properly phased. C) same as B, different region of the spectrum. D) the molecular ion region showing the magnitude mode and absorption mode spectra.



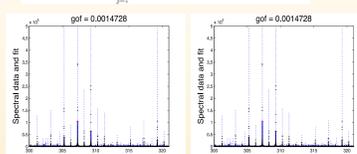
Our studies of the isomerization of aspartic acid and the deamidation of asparagine has continued with another 6 publications in the last two years [2-7]. These publications have applied our existing methods to new systems (alzheimer's amyloid beta peptide, the beta-2 microglobulin protein, and glutamine deamidation) and to some fundamental experiments on beta-linked peptides and similarly modified peptides.

### STATISTICS

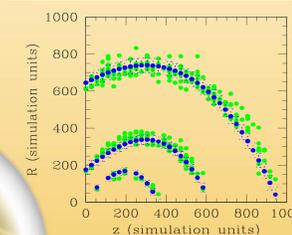
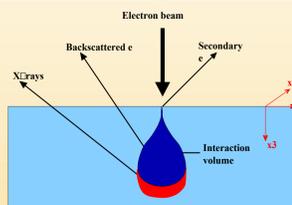
A collaborative project between Statistics and Mass Spectrometry WCAS groups focuses on incorporating all relevant physical and chemical constraints underpinning the generation of empirical FTICR spectral data in a fit-for-purpose statistical model (model equations on the right). This is a major improvement on current practices in mass spectrometry, where data are fitted using off-the-shelf models and a large proportion of an investigator's time is spent in the manual interpretation of the fitted results. A research paper [8] is being prepared illustrating the statistical methodology and a set of preliminary results applying our structural FTICR mass spectra models to petroleomics applications (on the right of this text). A dynamic version of this model for pharmaco-dynamic applications is being planned leveraging on [9].

The model equations are:

$$\begin{aligned} \kappa &\sim \text{Binomial}(N, p), & (4) \\ \sigma_k &\sim \text{Exp}(\lambda), & (5) \\ \omega_k &\sim \exp(-\gamma \mu_k), & (6) \\ \mu(k) &\sim U(1, \dots, M), & (7) \\ \varphi(r) &\sim U(1, \dots, J) \text{ without replacement for each } k, & (8) \\ l(\varphi(r)) &\sim F(\theta_1, \dots, \theta_{J(\varphi(r))}) \text{ the empirical abundance distribution,} & (9) \\ \mu_{i,k} &\sim \text{Poisson}(\eta_i), & (10) \\ \mu_k &= \sum_{i=1}^J \mu_{i,k} \omega_i(\varphi(r)), & (11) \\ \theta_i &= \sum_{j=1}^J \omega_j(\sigma_i + \delta | \mu_{i,j}, \sigma_{i,j}), & (12) \\ \mu_i &\sim \text{Beta}(\theta_i, \sum_{j=1}^J \theta_j), & (13) \end{aligned}$$

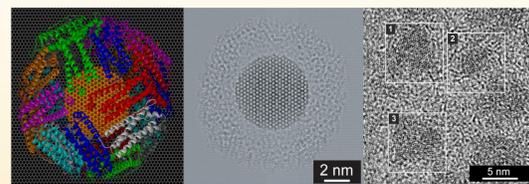


A collaboration between the Statistics and Electron Microscopy groups focuses on estimating 3D sample microstructure using 2D TEM and EPMA image projections taken at multiple energy resolutions [10]. This is an inverse problem requiring identifiability constraints and an appropriate representation of the Physics underpinning the observed projections. The former are imposed using a piece-wise constant and site-specific 3D density function within a model where both the zero-count noise and the correction function are taken as Gaussian. Physical constraints defining the expected 2D projections are modeled using an axisymmetric and energy-dependent interaction volume (schematic representation on the right) leveraging on recent related work [11], illustrating the statistical methodology and fitting the 3D microstructure of inorganic samples (model fit for simulated data on the right).

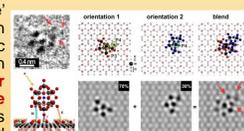
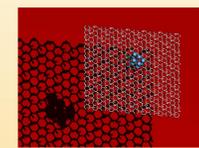


### HIGH RESOLUTION MICROSCOPY

The first use of graphene oxide (GO) as a chemically modified support for transmission electron microscopy (TEM). This work was highlighted in two high-profile publications [12,13], where GO was used as a low-background support for TEM imaging of ferritin/ferrihydrate. This work has generated significant interest. The figure below depicts a composite model showing the protein ferritin with an embedded nanocrystal of ferrihydrate supported on GO (right). The middle image depicts a simulation showing how the obtained image contrast in transmission electron microscopy is dominated by the specimen and not the support. The image on the right shows ferrihydrate nanocrystals embedded in ferritin.



GO can also be used for visualising much smaller species, as demonstrated the imaging of discrete polyoxometalate ions on GO for the first time. For instance, the image on the right shows a schematic depiction of the [7-SiW<sub>10</sub>O<sub>36</sub>]<sup>8-</sup> ion being supported on GO and forming a projected image. Further dynamical imaging studies demonstrated the retarded rotation/translation behaviour of individual ions on GO thought to occur as a result of hydrogen bonding between the substrate and the supported anions. The three right models (top) and simulations (bottom) show how the experimental image is in fact a 'freeze-frame' capturing the oscillation of the anion between two orientations/locations. The schematic diagram at lower left indicates the hydrogen bonding that retards this motion. This paper has received significant press coverage through a University press release. It was noted in Graphene Times and Microscopy and Microanalysis and elsewhere.



## Scientific Advances

## Building Capacity Research Strategy

We have established 3 new research groups which are now up and running in important areas of analytical/measurement science. The areas complement existing University strengths in mass spectrometry, magnetic resonance spectroscopy, sensor systems and electrochemistry, interfacial science, surface analysis, analytical neuroscience, metallomics and bioanalytical science. Each of these areas typically comprises several academic groups (more than 100 PhDs and post docs), all of whom are highly successful in research and delivering impact to end users, including industry.

To directly support the S&I Award, investment has been made in enhancing instrumentation (a 12 Tesla FTMS system and a UHR-TOF system have recently been acquired) and purpose built accommodation (£1.2M extension to the Magnetic Resonance Centre at Millburn House) has been constructed to house Professor O'Connor's instrumentation and research group.



£1.2M extension at Millburn House

Links to have been established to related projects, for example, the Birmingham – Warwick Science City project in Advanced Materials, which involves considerable analytical and measurement activity. The Advanced Materials project has led to ca. £20M investment in analytical and materials characterisation equipment in the University of Warwick and University of Birmingham.

A new Materials and Analytical Sciences (MAS) Building (£24M) has been planned around state of the art space to accommodate high resolution transmission electron microscopy and will be completed by September 2011. NB. This facility goes well beyond the original vision to develop a £1.3M Analytical Science extension to Chemistry supported by the University to a level of £0.75M (S&I Grant providing the balance). The sum of £0.55M from the grant has been used towards the MAS Building.

Substantial investment (ca. £3M) has been made in state of the art TEM, together with focussed ion beam scanning electron microscopy (FIB SEM), advanced AFM and other facilities which, along with the investment in academic infrastructure from the WCAS initiative, will propel Warwick to be one of the leading nanofabrication/characterisation centres in the UK.

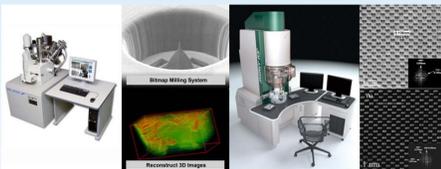
Computing facilities in the Centre for Scientific Computing are also being significantly enhanced with contribution from the WCAS grant and other sources.

Strong management and oversight ensures the success of this important project. A Management Committee reports to a University-level Steering Committee with external advice from an International Advisory Board. This structure has ensured that WCAS has delivered on initial aims successfully and on time.



The O'Connor Group with the distinguished Professor Fred McLafferty who opened the new FTICR Laboratory and also gave a lecture on "Top-down analysis of proteins" to our Warwick Analytical Graduate School (WAGS) students.

A fundamental aspect of the Centre's mission is to collaborate with industry with the objective of providing a platform for the identification, definition, and implementation of new analytical science research goals. This is progressing, an example being the establishment of a long-term collaborative partnership with Bruker-Daltronics in the development of both applications and fundamental instrument technology in the area of extreme resolution mass spectrometry.



State of the art FIB-SEM facility (left three panels), enabling nanofabrication and 3D elemental mapping of sectioned samples and ultrahigh resolution JEOL ARM200F microscope (right three panels) capable of <math>\times 1.0\text{-}0.8\text{\AA}</math> resolution in HRTEM and STEM to be installed in the MAS building.



Artist's impression of the new MAS Building

### Research Aims

- To promote world-leading research in Analytical Science in its broadest sense
- To provide an environment that encourages multi-disciplinary ventures in Analytical Science, for example, by working closely with the MOAC DTC and Science City Project
- To ensure that Warwick is recognised as the UK's leader internationally, putting it in a strong position for future bids in Analytical Science, for example as a Doctoral Training Centre
- To build on initial success of WCAS through further academic appointments – the first of these in Solid State NMR (Dr Josef Lewandowski, European Centre for High Field NMR, Lyon, France) has been appointed (commences Sept. 2011)
- To be a hub for academic and industrial partnerships in Analytical Science

### National and International Links

The WCAS appointees have established a network of international collaborations (Brazil, India, Italy, USA) and are actively involved in the construction of research links with industrial R&D and public bodies.

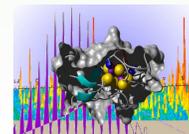
- Syngenta
- AstraZeneca (Macclesfield site; pharmaco-dynamics)
- Pfizer
- Novartis Vaccines and Diagnostics (Siena, Italy; modelling support for bacterial vaccinology)
- GlaxoSmithKline (London site, HIV dynamics)
- Unilever (Colworth site; data integration for skin sensitization modelling)
- The Forensics Service, Northamptonshire Police (value of analytical forensic evidence for crime prosecution)
- The Home Office (modelling of social networks)

### WCAS Added Value

Affiliated research groups in Analytical Science have already won considerable support from industry and European Sciences as a result of the increased visibility through WCAS. For example:

- Co-investigators Pat Unwin and Peter Sadler have each won major European Research Council Advanced Investigator Grants (£2M each) to develop fluorimaging and metallomics
- Mark Newton (Physics), Julie Macpherson (Chemistry) and Pat Unwin have won £600k funding for sensor development from the UK company Element 6
- The Warwick Electrochemistry and Interfaces Group has developed numerous science projects with the following since WCAS started:

- BP
- Lubrizol
- GSK
- National Physical Laboratory
- Unilever
- AstraZeneca

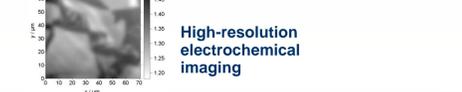
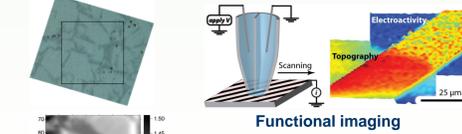


Combining High-resolution Mass Spectrometry and multidimensional NMR for a comprehensive understanding of metallo-protein structure and molecular function

### Teaching and Training in Analytical Science at Warwick

Launched new MSc course in Analytical Science: Methods and Instrumental Techniques (AS:MIT)

- Highly multidisciplinary: teaching and training by colleagues from Chemistry, Physics, Statistics, Life Sciences and Engineering
- Close links with MOAC DTC, including shared modules
- Surge in interest and enrolments: MSc student numbers up by 250% since 2008
- MSc projects act as "centres for nucleation", bringing together different disciplines and collaborations with industry
- Warwick Analytical Graduate School (WAGS) – established to provide expert workshops for UK PhD students in Analytical Science



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