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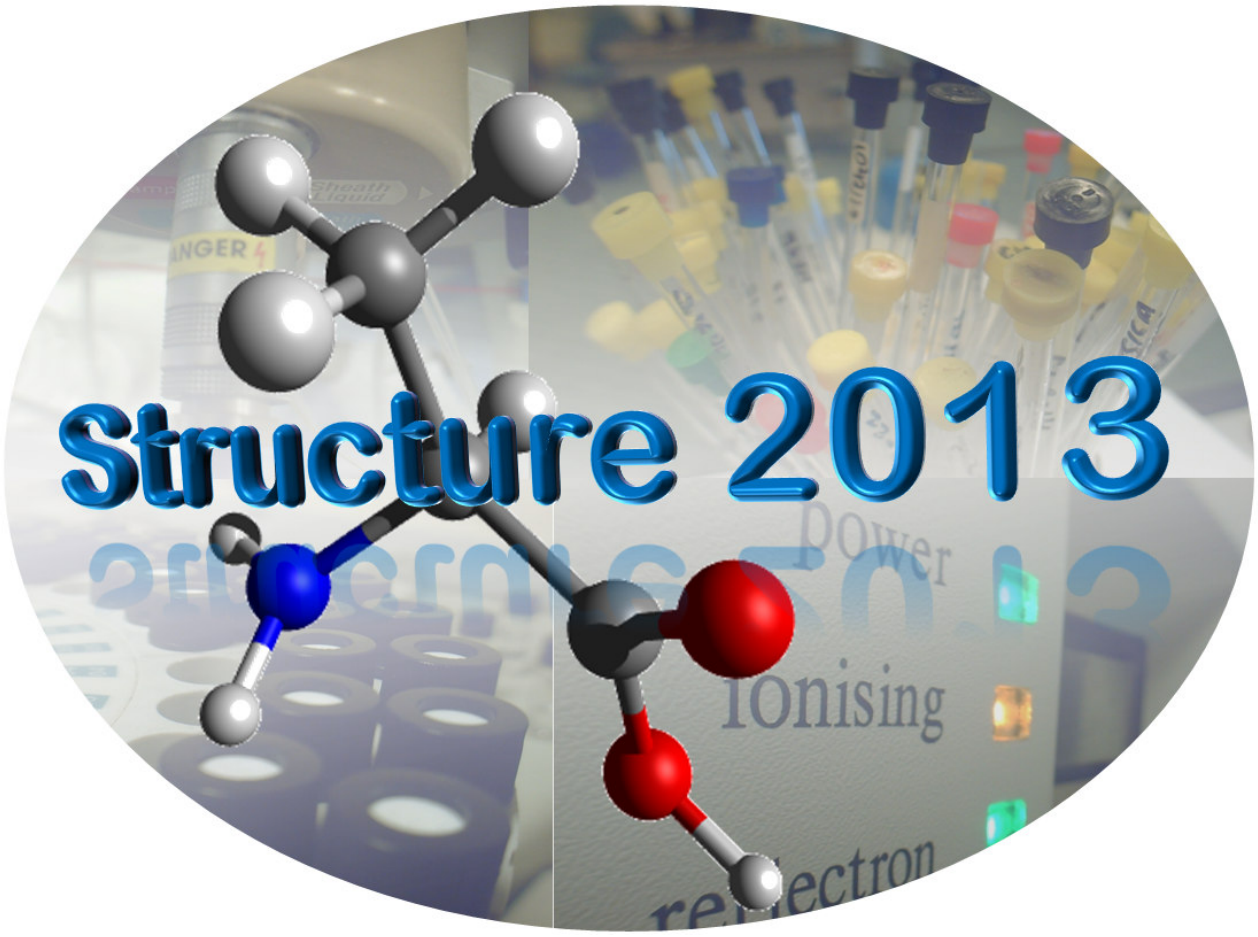
BMSS BRITISH MASS SPECTROMETRY SOCIETY



How Low Can You Go?

Detection, Identification and Elucidation at Low Level

A scientific meeting organized jointly by the Royal Society of Chemistry Molecular Spectroscopy and NMR Discussion Groups and the British Mass Spectrometry Society

Holywell Park and Burleigh Court
Loughborough University Campus, Leicestershire, U.K.
26th–27th February 2013

Contents **Page**

Dear Delegate,

The organizing committee are very proud to welcome you to **"Structure 2013"**.

This is the second meeting in the "Structure" series following on from "Structure 2010 – Advances in Structure Elucidation". As with the previous meeting, Structure 2013 is organised under the auspices of the Royal Society of Chemistry NMR-Discussion Group (NMR-DG), the Royal Society of Chemistry Molecular Spectroscopy Group (MSG) and the British Mass Spectrometry Society (BMSS). The continuing concept is to showcase new and evolving techniques, workflows and applications within the broad framework of molecular structure elucidation as applied to small molecules.

Increasingly, the challenge exists today for detecting and identifying molecules at low levels, in some cases at the limits of detection for a number of analytical techniques. How do we ensure accuracy and reproducibility in the identification process? How can improvements be made over existing techniques to enable the elucidation of molecular structures at lower detection limits? Continuing the theme of cross-disciplinary science has again resulted in the invitation of speakers from a wide diversity of backgrounds with common interests in structure elucidation at these limits of detection. The organisers gratefully acknowledge the willingness of all our invited speakers who contribute to Structure 2013 in sharing their ideas, concepts, discoveries and vision.

This year's Structure meeting includes presentations not only from the academic community but also from among representatives of the industries that enable new techniques to be made available to a wider audience through their commercialization ventures, thereby providing this meeting with a unique opportunity to see the best of the science that such commercial ventures can address.

Structure 2013 has been generously supported by sponsors and exhibitors, without whose financial support the meeting would not have been made possible, especially within the current economic climate. Their contribution is extremely gratefully acknowledged. Please take time to visit the exhibitor stands throughout the course of the meeting to discuss your particular application needs.

We thank you for your valued support of Structure 2013 and trust you will make the most of the opportunities that the meeting provides.

Structure 2013 Organising Committee

Steve Coombes, AstraZeneca, Macclesfield (MSG)

Tim Claridge, University of Oxford

Tony Sullivan, Agilent (BMSS)

Paul Thomas, University of Loughborough (MSG)

John Parkinson, University of Strathclyde (NMR-DG)

February 2013

Sponsorship

Structure 2013 is most grateful for the very generous sponsorship provided by the following companies and agencies:

AstraZeneca UK

Syngenta UK

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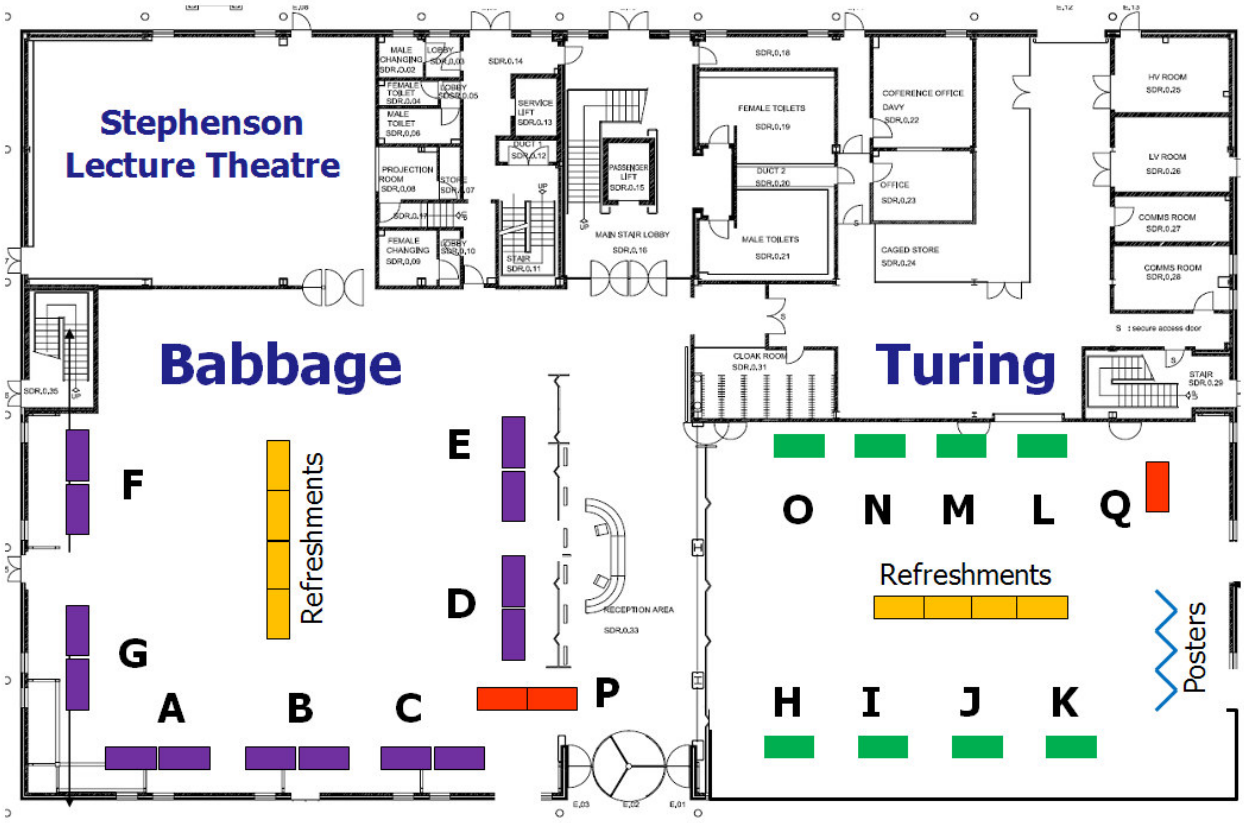
Royal Society of Chemistry

Exhibition

The contribution made by a wide cross-section of manufacturers to **Structure 2013** is very gratefully acknowledged. The exhibition provides opportunity for product manufacturers that supply equipment to research fields allied to molecular structure elucidation to display products, to distribute advertising material and to provide delegates with the opportunity to discuss their experimental needs with those most closely allied to their areas of interest on a one-to-one level. A plan of the exhibition area with exhibitor allocation is provided below. Please make the most of the time provided throughout the course of the meeting to explore the exhibition area.

Structure 2013 Exhibitor, Poster Display and Refreshment Areas



Exhibition KEY

A. Agilent
B. Bruker UK
C. Jeol
D. Mestrelab Research
E. Oxford
F. Shimadzu
G. Thermo
H. ACD/Labs
I. Cole-Parmer
J. GPE
K. KR Analytical
L. Leco
M. Presearch
N. VRS
O. Waters
P. Registration/BMSS
Q. RSC

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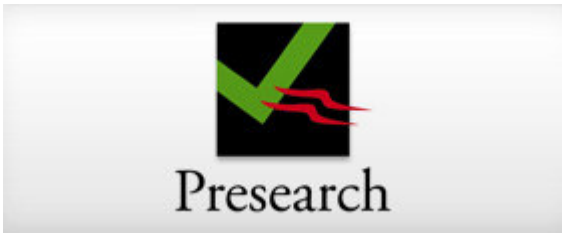
Presearch


vrs


Waters
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Software and Careers Workshops

Software Workshop demonstrations lasting 45 minutes each will be provided at Structure 2013 by **ACD/Labs** and **Mestrelab Research** in the Stephenson Lecture Theatre. Following this a student careers advice seminar will be provided by representatives of **VRS** for those who may be interested.

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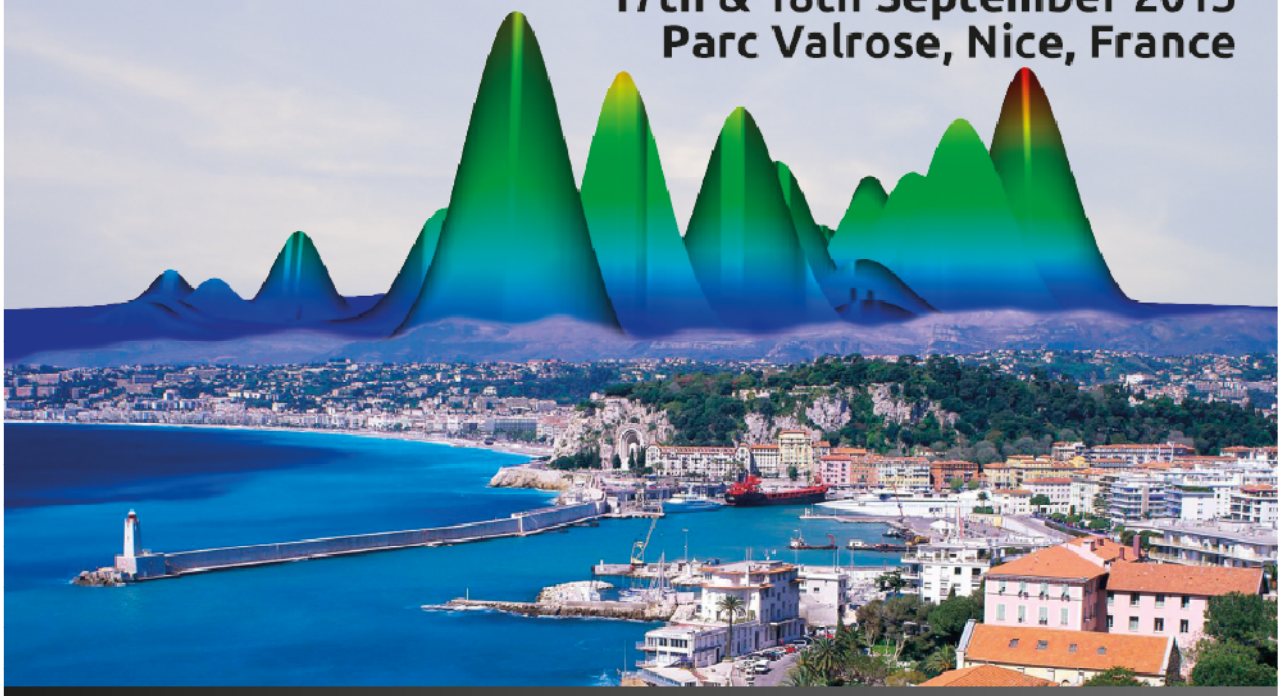
3rd European GCxGC Symposium

17th & 18th September 2013
Parc Valrose, Nice, France



From 2009 the symposium has grown and evolved in to a significant bi-annual European conference that each year has attracted an increasing number of delegates. This year, the symposium is organised in close collaboration with ***Prof. Dr. Uwe Meierhenrich****, University Nice Sophia Antipolis.*

Exploring the area of **Comprehensive Chromatography and Mass Spectrometry**, the symposium program is based on presentations from leading industry experts in the areas of Aroma and Flavour, Food Safety, Environmental Forensics, Drugs of Abuse and Omics applications. The **Routine application of GCxGC and GCxGC-MS techniques** are presented by professionals in the field during the 2-day symposium.

Learn how to address today's analytical challenges using Comprehensive Chromatography and Mass Spectrometry from the speakers personal experience and knowledge in the Life Science, Industrial and Environmental Application fields. Registration is open to all members of the Separation Science and Mass Spectrometry community with an interest in these advanced techniques

Preliminary program includes lectures in:

- GCxGC and GCxGC-MS Technical skills & development
- Aroma, Flavour, Fragrance
- Food Ingredients & Food Safety
- Forensic - Scene of Crimes, Environmental Forensics, Drugs of Abuse
- Omics

The definitive program and speakers will be communicated shortly.

CC-Antonio Zugaldia

The organizing committee looks forward to welcoming participants to the beautiful area of Côte d'Azur and to an outstanding technical conference.

For more information, please contact:

Mrs Birgit Zahel
Phone : +49 2166 687 305
E-mail : birgit.zahel@leco.de

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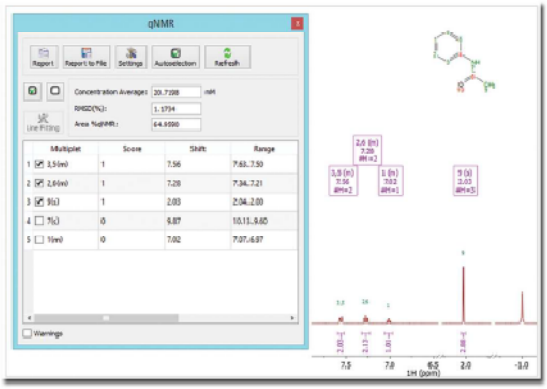
As in 2010, Mestrelab Research is proud to sponsor Structure 2013.

Mnova qNMR

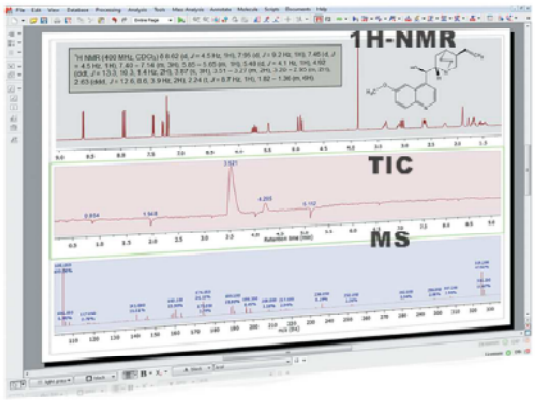
Quantitation lies at the heart of thousands of analytical procedures that impact on virtually every scientific endeavour.



With qNMR the integral of a set of peaks assigned to a nucleus is proportional to its concentration. This "response factor" is the same for all species.

Mnova MS

Processing & analyzing LC GC MS data that emphasizes agility.



By providing a common interface for different vendor data and automating all functionality (data import and display, integration, background subtraction and computational analysis), Mnova MS opens the power of the technique to all non expert users.

We will be holding a Users' Meeting to coincide with our support of the Structure 2013 Conference (Monday 25th February). Please join us!

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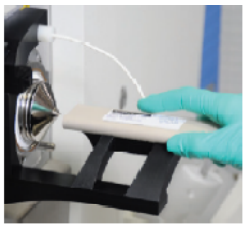

NEW OBJECTIVE

PicoChipNanospray column: designed for high sensitivity LC-MS research

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Student Bursaries

Student bursaries have been awarded to the following delegates:

Maria Grazia Concilio	University of Manchester
Kwong Kit Chan	University of Manchester
Alex Hill	University of Loughborough
Liam Heaney	University of Loughborough
Shou Gang	University of Loughborough
Dorota Ruszkiewicz	University of Loughborough
Rob Smith	University of Loughborough
Cecilia Fenech	Dublin City University
Fay Probert	University of Warwick

Acknowledgements

We thank **Oxford Instruments** for sponsorship of the Drinks Reception during the poster session.

Posters

Posters should be mounted in the Turing Area of the conference venue as soon as possible after your arrival and certainly prior to the formal start of **Structure 2013**. Allocated poster board numbers may be found within this abstract book. Posters should remain mounted until the formal close of the meeting.

Poster session arrangements

Posters should be manned during the poster session between 18.00 and 19.00 during Day 1 of Structure 2013.

Feedback

Feedback is welcomed by the organising committee following on from this meeting. Comments should be sent to **structure2013@gmail.com**

Program

Refreshments and meals will be available from the Babbage and Turing areas of the Holywell Park Conference Centre. All lectures will be presented in the Stephenson Lecture Theatre. The conference dinner will be held in the Burleigh Court Restaurant.

Day 1: 26th February 2013

09:00-10:25 Registration and Coffee

10.25-10.30 Structure 2013 Opening Remarks and Welcome by Prof. Paul Thomas

10.30-12.00 Session 1 Session Chair: Dr. John Parkinson, University of Strathclyde

10.30-11.00 Prof. David Cowan, Kings College, UK
London 2012 – Olympic and Paralympic Games – the latest science behind the anti-doping tests

11.00-11.30 Dr. Tony Bristow, AstraZeneca, UK
When Big is Brilliant and Small is Beautiful – Mass Spectrometry diversity for a huge range of analytical challenges

11.30-12.00 Dr. Sandra Groscurth, Bruker, Switzerland
Structure elucidation and verification with different analytical methods – a case study

12.00-13.00 Lunch

13.00-15.00 Session 2 Session Chair: Dr. Tim Claridge, University of Oxford

13.00-14.00 Plenary Lecture: Prof. John Lindon, Imperial College, UK
Bringing molecules into medicine using metabonomics: the challenges of patient phenotyping for diagnosis, optimising treatment and prognosis

14.00-14.30 Dr. Madalina Oppermann, Thermo Fisher Scientific
m/z Cloud – Novel Spectral Library for Metabolite Identification

14.30-15.00 Prof. Jörg Baumbach, B&S Analytik and Technical University, Germany
Volatile metabolites of humans, animals, cells and bacteria – detected using ion mobility spectrometry

15.00-15.30 Tea

15.30-17.00 Software Seminars (main lecture theatre):
15.30-16.15: ACD Labs
16.15-17.00: MestreLab Research

17.00-18.00 Vendor Exhibition; including student careers advice session from ***VRS***

18.00-19.00 Poster Session with drinks sponsored by ***Oxford Instruments***
Vendor Exhibition continues

19.00-20.00 Free Time

20.00-22.00 Conference Dinner: Burleigh Court
22.00-24.00 *Vendor discussions, mixing, bar*

Day 2: 27th February 2013

09.00-10.30 Session 3 Session Chair: Prof. Paul Thomas, University of Loughborough

09.00-10.00 Plenary Lecture: Prof. Michael Phillips, Menssana Research, USA
Breath tests for biomarkers of disease

10.00-10.30 Simon Noble, Quotient Bioresearch, UK
The challenges of high sensitivity MS detection in bioanalysis

10.30-11.00 Coffee

11.00-12.30 Session 4 Session Chair: Dr. Tony Sullivan, Agilent

11.00-11.30 Prof. Aldrik Velders, Wageningen University, Netherlands
Nanolitre NMR Spectroscopy

11.30-12.00 Prof. Peter Fielden, University of Lancaster, UK
Cheap as Chips? – Analysis with Low Cost Sensing Systems

12.00-12.30 Dr. Jonathan Williams, Waters Corporation
Applications of Travelling Wave Ion Mobility Mass Spectrometry in Small Molecule Studies

12.30-13.30 Lunch

13.30-15.00 Session 5 Session Chair: Dr. Steve Coombes, AstraZeneca

13.30-14.00 Dr. Hiroaki Sasakawa, JEOL, UK
New Solid NMR Probes and Applications for Structure Analysis

14.00-14.30 Dr. G. John Langley, University of Southampton, UK
Unravelling complexity through experiment design

14.30-15.00 Dr. Andy Phillips, AstraZeneca, UK
The use of NMR for trace analysis within pharmaceutical development

15.00-15.30 Closing Remarks and Tea

15.30 Formal Close of Structure 2010

The main programme will be followed by the **ACD/Labs Symposium at Structure 2013** *in the Stephenson Lecture Theatre; 15.30-17.00.*

Index to Poster Presenters

Lecture Abstracts

Lecture 1

Prof. David Cowan,
Department of Forensic Science & Drug Monitoring, Kings College, London, UK

London 2012 - Olympic and Paralympic Games – the latest science behind the anti-doping tests

London 2012 is now but a memory but one that will live with the world for many years. What of the science? Many advances were made in preparation for delivering a world-class anti-doping analytical service. Our goal was to deliver a programme of such strength that it would help deter drug misuse. Put simple, our task was encapsulated in the phrase "super-fast and super-sensitive". We developed an infrastructure that would allow us to analyse more than 6,000 samples in less than six weeks with turnaround times as short as 24 hours. In order to achieve these goals we made of use of tandem MS, UHPLC, high resolution MS providing total data capture, sensitive combustion isotope ratio mass spectrometry through to biomarker testing for the administration of human growth hormone. Most of the results are now in the public domain and a personal insight will be provided in this presentation.

Lecture 2

Dr. Tony Bristow[1], Andy Ray[1], Marie-Claire Lacassin[1], Hilary Major[2], Jackie Mosely[3], Colin Creaser[4] and Peter O'Connor[5]
[1] Pharmaceutical Development, AstraZeneca, Macclesfield, SK10 2NA, [2] Waters Corporation, Wythenshawe, Manchester, M23 9LZ, [3] Department of Chemistry, University of Durham, Durham, DH1 3LE, [4] Department of Chemistry, Loughborough University, Loughborough, LE11 3TU, [5] Department of Chemistry, University of Warwick, Coventry, CV4 7AL.

When Big is Brilliant and Small is Beautiful – Mass Spectrometry diversity for a huge range of analytical challenges

The range of analysis problems to which mass spectrometry can be applied continues to grow. This expansion has resulted from the continued innovation in the development of all aspects of mass spectrometry instrumentation. This includes ionisation techniques, mass analysers and new experiments. This presentation will describe a number of recent mass spectrometry innovations that have been investigated for a diverse range of analytical challenges within the pharmaceutical industry. The examples will include the application of novel ion source designs, on-line mass spectrometry, advanced mass analysers, novel techniques for structural characterisation and new approaches for the characterization of complex polymeric systems. The impact of these developments will be discussed.

Lecture 3

Dr. Sandra Groscurth
Bruker, Switzerland

Structure Elucidation and verification with different analytical methods- a case study

Mass Spectrometry (MS), Nuclear Magnetic Resonance (NMR) and Single Crystal X-ray Diffraction (SC-XRD) are known to be extremely powerful analytical methods to verify and elucidate molecular structures. Therefore they form essential tools for successful chemical and biological research.

Today's hardware and software has made analytical data acquisition more convenient and efficient than ever before. However, subsequent experimental data analysis can be time consuming and is often the bottleneck in the structure verification and elucidation process. Therefore Bruker has focused on the development of software packages assisting the chemist with the interpretation of experimental data. Based on a case study, we present these developments in the process of computer-assisted structure verification and elucidation with different analytical techniques, including MS, NMR and X-ray crystallography.

Lecture 4 (Plenary)

Prof. John C. Lindon
Biomolecular Medicine, Imperial College, London, UK.

Bringing molecules into medicine using metabonomics: the challenges of patient phenotyping for diagnosis, optimising treatment and prognosis

NMR- and MS-based based metabolic profiling (metabonomics) of mammalian biofluids and tissues has proved to be a useful approach for understanding physiological effects, for disease diagnosis, for prognosis of future treatment and outcome, and for the investigation of interactions between the host and its gut microbial ecology. Such applications require the employment of multivariate statistics for efficient data interpretation. This talk will provide a brief overview of metabonomics technologies, provide some recent examples of clinical metabonomics, and highlight new developments in metabolic phenotyping of hospital patients with the aim of achieving stratified or more personalised treatment. This is a challenging task and if the approach is also to be used for real-time medical and surgical applications then new technologies and organisational approaches will be needed and these will be discussed.

Lecture 5

Robert Mistrik[1], Juraj Lutisan[1], Yingying Huang[2], Rose Herbold[2], **Dr. Madalina Oppermann[3]**, Eric Genin[4]
[1]HighChem, Ltd., Bratislava; Thermo Fisher Scientific, [2]San Jose, CA, [3]Stockholm and [4]Paris

m/z Cloud - Novel Spectral Library for Metabolite Identification

Analysis of numerous small molecules and structural assignments of individual metabolic components is a major bottleneck in various areas of metabolomics. In mass spectrometry widely used library search systems are designed to identify compounds represented in the reference library. If the unknown compound is not represented in the library, the compound cannot be identified by this method. We will present a new type of mass spectral library providing the functionality required for elucidation of unknowns even if compounds are not present in the library.

A few years ago, Precursor Ion Fingerprinting (PIF) was developed. This approach identifies sub-structural information through the comparison of product ion spectra of structurally related compounds. Structural information is derived by utilizing previously characterized ion structures stored in reference libraries of tandem mass spectral data and matching them with unknown product ion spectra. PIF is a powerful technique that takes advantage of the structural continuum and conservation of eukaryotic metabolism.

The library is implemented in a relational database that will be accessible through a public domain web site of an emerging consortium named "m/z Cloud". Since the consortium is predominantly oriented towards high-resolution, accurate mass spectra, the database design, spectral management, and library search algorithms require a completely new architecture compared to traditional spectral databases. The idea of this project is to create a library of comprehensive spectral ion trees based on structurally characterized product ion spectra to enable the identification of substructures in unknowns.

Each structurally characterized product ion spectrum will contain the precursor ion m/z value, a list of product ion m/z values with mass accuracies, corresponding absolute and relative intensities, ion polarity, charge state, the structure of the precursor ion, and the structure of the parent molecule. For the assignment of fragment structures to a precursor ion in the process of creating structurally characterized product ion spectra, it is extremely beneficial to have high-resolution spectra since the accurate m/z values of precursor and product ions greatly reduce the number of possible molecular formulas for fragment structures. Also, the determination of the structural arrangement for the elucidated molecule benefits from exact mass measurements by constraining the elemental composition of the elucidated molecule and consistently validating the calculated mass of recognized fragment structures and accurate m/z values of precursor and product ions.

The m/z Cloud public domain database aims to provide complete library technology based on spectral ion trees to enable elucidation of unknowns using the precursor ion fingerprinting method.

Lecture 6

Prof. Jörg Ingo Baumbach
B&S Analytik GmbH and Technical University, Dortmund, Germany

Volatile metabolites of humans, animals, cells and bacteria - detected using ion mobility spectrometry

Volatile metabolites in human exhaled breath, in the exhale of animals or over cell cultures and bacteria could be detected down to the pg/L-range (pptv) using ion mobility spectrometry coupled to multi-capillary columns within less 10 minutes total analysis time and in rather complex und humid matrixes. Normally, about 10 mL of exhaled breath will be analysed and characterized with respect to identification and quantification. Some proven medical applications will be considered (e.g. lung cancer, anaesthesia, SEPSIS, bacterial infections) and recent results in metabolomics and breath gas analysis will be presented. The advantages and disadvantages compared to GC/MS are discussed with respect to information content, analysis time, instrumentation requirements and analytical and separation power. In addition, the improvement of results using modern methods of bioinformatics will be shown (including data mining, statistics, decision trees and correlation analysis).

Lecture 7 (Plenary)

Prof. Michael Phillips
Menssana Research Inc., Newark, USA

Breath tests for biomarkers of disease

Researchers hope to screen for disease with rapid, cost-effective, and safe breath tests for biomarkers. However, every step towards this goal from research bench to bedside is fraught with obstacles:

Collecting a breath sample: The majority of volatile organic compounds (VOCs) in breath are excreted in low concentrations: parts per billion or parts per trillion. A sample suitable for analysis must be free of artefactual contamination, and must also be alveolar (deep lung) breath with compensation for background VOCs in room air. This requires a specialized breath collection apparatus (BCA) that preconcentrates VOCs.

Analyzing a breath sample on a discovery platform: The workhorse of breath VOC analysis has been 1D gas chromatography mass spectrometry (GC MS), which yields around 200 different VOCs in a single sample of alveolar breath. Recently, comprehensive 2D (GCxGC) with time of flight MS has improved the yield by an order of magnitude, to 2,000 VOCs in a sample.

Making sense of the data: Biomarker discovery requires carefully designed clinical studies to compare subjects with and without disease. When the number of candidate biomarkers is greater than the number of human subjects, there is a high risk of false positive outcomes ("seeing faces in the clouds"). Rigorous statistical analysis e.g. with Monte Carlo methods, is essential to separate signal from noise. Several different biomarkers may need to be combined in a multivariate predictive algorithm, and then tested in a blinded pivotal study.

Analyzing a breath sample on a point-of-care platform: Discovery platforms are too expensive and slow for routine clinical care. Current R&D focuses on migrating predictive algorithms to less expensive point-of-care platforms e.g. GC with surface acoustic wave (GC SAW) or differential mobility spectrometry (GC DMS). In a multicenter international study at sites in India, UK and Philippines, a 10-min point-of-care breath test using GC SAW identified active pulmonary TB with 84% accuracy [1].

Getting regulatory approval and getting paid for the test: FDA approval is required in the USA and CE Marking in the EU. Self-payment by early adopters will probably precede insurance reimbursement.

[1] Phillips, M., et al., Point-of-care breath test for biomarkers of active pulmonary tuberculosis. Tuberculosis, 2012. 92(4): p. 314-20.

Lecture 8

Simon Noble
Quotient Bioresearch Ltd.

The challenges of high sensitivity MS detection in Bioanalysis

As drugs become more potent and the use of low abundance endogenous biomarkers becomes more prevalent in drug development, the development and validation of sensitive mass spectrometry (MS) based bioanalytical methods is increasingly key to providing the necessary pharmacokinetic and pharmacodynamic data. This presentation will look at the challenges of high sensitivity MS methods, and how the structures of the analytes relate to the various strategies in extraction, chromatography and detection are employed to achieve them.

Lecture 9

Prof. Aldrik Velders
BioNanoTechnology Group, Wageningen University & Research Centre , Wageningen, The Netherlands

Nanolitre NMR Spectroscopy

Analysis of mass-limited samples with NMR spectroscopy is a major challenge, which has triggered the development of expensive and technologically demanding solutions, such as cryoprobes, ultra-high magnetic fields and hyperpolarization strategies. A relatively cheap alternative approach regards the use of miniaturized coils and, over the past two decades, microcoils of different geometries have proven this to be a successful strategy.[1] We are particularly interested in microfluidic chip designs with planar spiral transceiver coils and detection volumes in the lower nanoliter range. These chips can be used in static mode, e.g. for observation of supramolecular interactions by ^{19}F NMR spectroscopy,[2] or on-flow, e.g. for high-throughput (^{1}H-NMR) monitoring and optimization of reactions.[3] Currently, we are designing NMR-chips for observation also of low-gamma nuclides, for 1D as well as 2D NMR experiments.

[1] R. M. Fratila, A. H. Velders, Annu. Rev. Anal. Chem. 2011, 227-249

[2] M. V. Gomez, D. N. Reinhoudt, A. H. Velders, Small 2008, 4, 1293-1295.

[3] M.V. Gomez, H.J.J. Verputten, A. Díaz-Ortíz, A. Moreno, A. de la Hoz, A.H. Velders, Chem. Commun. 2010, 4514-4516.

Lecture 10

Prof. Peter Fielden
Department of Chemistry, University of Lancaster, UK

Cheap as Chips? - Analysis with Low Cost Sensing Systems

Sensing systems based on polymer substrates may be fabricated at very low cost by manufacturing techniques, such as injection moulding, normally associated with mass production. Whilst such systems cannot ultimately compete with high-end laboratory-based analytical techniques, there are many examples where sensing systems can provide sensitive and selective assays, with the added attraction of portability. Microseparations, such as chip-based isotachophoresis, coupled to simple sensors may be employed to address a significant range of target species within complex samples. Electrochemical assays have been demonstrated where plastic composite and screen-printed ink-based electrodes have been used, rather than expensive rare metals such as gold and platinum, to fabricate electroanalytical sensing systems. Optical microresonator sensors may be fabricated in a microreactor as spheres, or by stereolithography as rings, with specificity added through molecular imprinting or immunoassay chemistry. Consideration of the direction and future of low-cost sensing systems will be made.

Lecture 11

Dr. Jonathan Williams
Waters Corporation

Applications of Travelling Wave Ion Mobility Mass Spectrometry in Small Molecule Studies

A hybrid quadrupole / ion mobility / oa-ToF mass spectrometer (Synapt G2 HDMS, Waters, UK) has been used in both CID and ETD modes of acquisition. The instrument incorporates three Travelling-Wave SRIG's prior to the ToF mass analyser. For fragmentation using ETD, a glow discharge source was used to fill the Trap T-Wave cell with quadrupole mass selected ETD reagent anions. During an acquisition, the source polarity and quadrupole set mass are switched to allow multiply charged cations to interact with stored reagent anions in the Trap T-Wave. This interaction allows an ion-ion type reaction resulting in ETD product ions which are separated according to their ion mobilities in the second cell (IMS T-Wave cell). Upon exiting the IMS cell the ions enter the Transfer T-Wave which can be used to transfer ions into the ToF or optionally provide CID prior to the ToF.

A number of diverse application areas will be described. These will include the utility of both CID and ETD combined with ion mobility for some isomeric permethylated oligosaccharides and low molecular weight polymers. Ion mobility has been used to separate two singly charged ion species differing only by the site of protonation of a number of fluoroquinolone antibiotics. The enhanced mobility resolution of the Synapt G2, together with differing drift gas evaluation, has facilitated baseline separation of the 'protomers' formed from the fluoroquinolones investigated. A description of how to calculate the CCS values of ions using T-Wave ion mobility will be shown.

Lecture 12

Hiroaki Sasakawa
JEOL UK Ltd, Welwyn Garden City, Herts, UK

New Solid NMR Probes and Applications for Structure Analysis

We released a new 0.75 mm solid state NMR probe on last April. Its probe is capable of ^{1}H high resolution analysis by sample spinning at 110 kHz. This new probe is expected to be effective in applications that are difficult for conventional NMR systems, including micro analysis of drugs, natural products, and thin films. We will show some example data with this new probe. Also, we released 8 mm solid state NMR probe for narrow bore magnet. This is very large volume MAS probe (606 μL). Its sensitivity boosts by a factor of around 4, comparing to 3.2 mm MAS probe. This means more than 10 times shorter experiments and promises very quick observation of small peaks. In case of large volume MAS probe, it is not easy to adjust resolution to get high quality spectra, but we developed a simple method to automatically shim at the magic angle spinning [1]. This is introduced based on the gradient shimming approach. We can achieve the less than 1 Hz line width on ^{13}C NMR adamantane within few minutes.

[1] Y. Nishiyama, Y. Tsutsumi, and H. Utsumi, J. Magn. Reson. 216 (2012) 197-200.

Lecture 13

Dr. John Langley
Department of Chemistry, University of Southampton, UK

Unravelling complexity through experiment design

Generic hyphenated methods have become common place and can solve a number of issues, e.g. high throughput needs, analysis of analogues etc. These approaches use generic methods and as such often ignore the needs of the specific analyte. By considering the analytical need and the analyte(s) in question, the optimum hyphenated technique can be determined. This presentation will discuss biodiesel analysis at Southampton, in particular oxidation of FAMEs, through the use of HPLC-MS, GC-MS and SFC-MS (and MS-MS) to aid structural elucidation.

Lecture 14

Dr. Andrew R. Phillips, Ian C. Jones and Steve Coombes
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The use of NMR for Trace Analysis within Pharmaceutical Development

NMR is a well-established quantitative technique for looking at relatively small amounts of material – for example residual solvents within an active pharmaceutical ingredient down to levels of 0.1% w/w. Recently there has been considerable concern from pharmaceutical regulatory agencies over the control of potential genotoxic impurities (PGI) in medicinal products. The Threshold of Toxicological Concern (TTC) for PGIs in commercial products is 1.5 µg/day, or single-figure ppm with respect to a typical drug substance. Consequently, methods for the measurement of impurities in the single-ppm range are required – presenting a significant analytical challenge. We have recently shown that NMR can detect down to these low level often with significant advantages over other more traditional techniques in terms of method development, sample preparation and experiment time. [1] The key to the success of NMR is overcoming the inherent lack of sensitivity so this presentation will focus on some of the important factors that determine the level of detection, such as the performance of the NMR system, substrate concentration, linewidth, resolution and dynamic range. This will include how new state of the art equipment in our laboratory has been utilised to overcome some of these challenges. In addition a number of new genotoxic impurities examples analysing both pure compounds and formulated products will be presented. Furthermore it will shown that the use of NMR can be expanded to other trace analysis problems such as cleaning validation: confirming vessels used for chemical reactions are not contaminated with material from previous experiments.

[1] Andrew R. Phillips 'Analysis of Genotoxic Impurities by Nuclear Magnetic Resonance Spectroscopy' in 'Genotoxic Impurities: Strategies for Identification and Control' edited by Andrew Teasdale, 2011, Wiley-Blackwell

Poster Abstracts

P01

Automatic Structure Elucidation and Determination of Small Molecules

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The results of a study consisting of the comparison of automatic structure elucidation and determination are presented. Structure elucidation was carried out with data from 1D and 2D nuclear magnetic resonance spectroscopy (NMR) and accurate mass spectrometry (MS and MS/MS). The data were analysed using Bruker CMC-SE software for computer-assisted structure elucidation [1,2]. Fully automatic 3D structure determination was carried out using SMART X2S [3]. Our results clearly highlight the advantages of using complimentary techniques to aid in the structure elucidation process. In particular, introducing the molecular formula is key for full automation and the addition of user defined fragments can drastically decrease the calculation time.

References

[1] http://www.bruker.com/products/mr/nmr/nmr-software/software/complete-molecular-confidence-cmc/cmc-se-struture-elucidation/overview.html. Accessed 15/11/2012.
[2] Elyashberg, M. E.; Williams, A. J.; Martin, G. E. *Prog. Nucl. Mag. Reson. Spectrosc.* (2008) **53**, 1–104.
[3] Eccles, K. S.; Lawrence, S. E.; et al. *J. Appl. Cryst.* (2011) **44**, 213-215

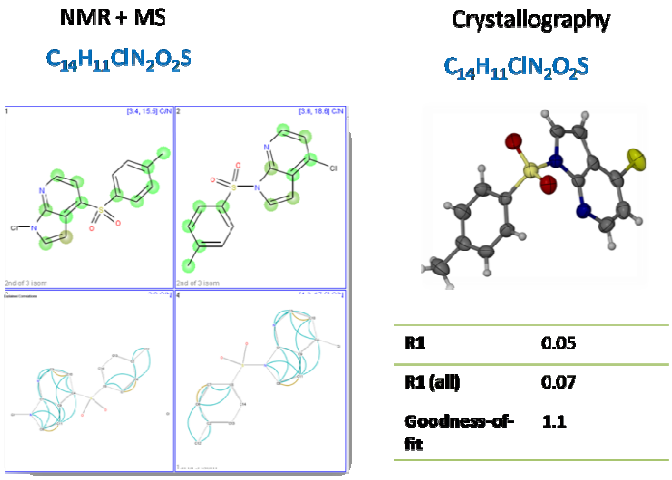

Fig. 1: Structures obtained by CMC-SE (left) and SMART X2S (right) for compound 1

P02

Trace analysis for environmental forensics applications: The case of low level chronic contamination

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Interest in environmental forensics applications for nitrate source determination has increased in recent years. To date, nitrate stable isotope compositions have largely been used for this purpose; however, they only identify the predominant source and do not differentiate sewage and manure nitrate sources. Therefore, they are not suitable in scenarios where multiple-sources co-occur and particularly in scenarios where these sources are at low chronic levels.

To overcome the limitations of the current approach, the presence of human and veterinary pharmaceuticals was exploited as co-occurring sewage and manure discriminators. By understanding their use, occurrence and fate, point and diffuse sources of sewage and manure contamination can be identified and characterised, e.g. differentiation of raw and treated sewage. Pharmaceutical analysis is typically achieved using SPE-LC-MS/MS techniques. A single method has been developed and validated for an analytical suite of pharmaceuticals at detection limits of up to 50 pg/L. This allows for low-level sources of contamination, such as from septic tank infiltration, to be identified.

However SPE-LC-MS/MS is time intensive and costly. The potential of the novel application of alternative analytical tools, such as NMR and immunoassays for the detection and identification of trace levels of the chemical markers within surface waters was assessed, by identifying and optimising the relevant parameters within the methodology. The use of immunoassay techniques for pharmaceutical detection showed great promise in this regard, allowing for low ng/L detection limits to be achieved, whilst requiring reduced sample volumes and being more cost and time effective.

P03

NMR characterisation of the conserved RNA motifs making up the 4-way junction of the EMCV IRES element

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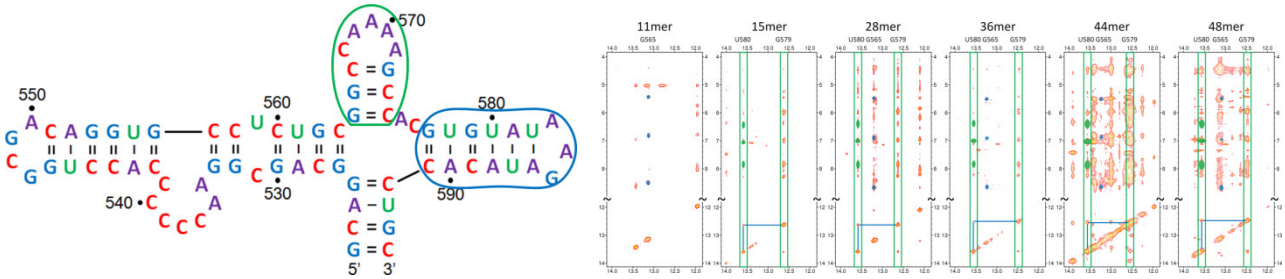
The apical 'hammerhead' region of the I-domain of EMCV IRES RNA element plays a vital regulatory role in the novel, cap-independent translation initiation mechanism (Figure, left). The region is endowed with highly conserved and functionally important stem loop secondary structural RNA motifs and determining their structure function relationship is essential for a better understanding of the IRES mechanism. We have determined the NMR structures of a stable 11mer and the adjoining 15mer RNA stem loop motifs separately on their own and when they are both combined together by a bridging, unstructured AC dinucleotide to produce a larger and more stable 28mer RNA motif.

To monitor the change in tertiary contacts due to the increase in RNA size, NOESY spectra of the 11-, 15-, 28-, 36-, 44- and 48mer RNAs were measured (Figure, right). The conserved patterns of NOE cross peaks due to the imino protons of U580 (13.6 ppm) (shaded green) and the sequential imino–imino proton connectivity between U580 (13.6 ppm) and G579 (12.6 ppm) (blue lines) observed across all RNAs have demonstrated that the tertiary contacts as observed in the 15mer were uniformly conserved in the larger RNAs.

^{19}F-NMR study of selectively fluorine labelled (U580) 15-, 28- and 44mer homo duplex RNAs has shown a conservation of the unique fluorine resonance at -168 ppm, indicating conservation of structural environment. These results support the formation of the highly conserved 4-way junction (4WJ) of the hammerhead motif.

Reference: K.K.Chan and V. Ramesh, Chem. Commun. (2012) **48**, 11573–11575



P04

NMR characterisation of a novel neamine antibiotic and its interaction with a conserved RNA motif A-site 16S rRNA.

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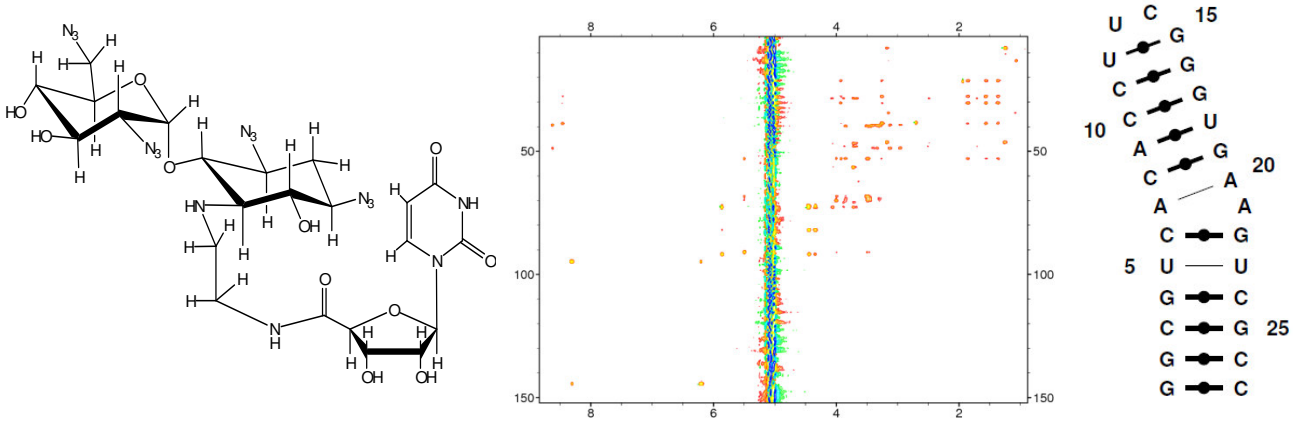
The growing challenge of antibiotic resistance being witnessed in recent times has prompted intense efforts to elucidate the mechanism of action of antibiotics at the molecular level, using techniques such as NMR spectroscopy. Blocking protein synthesis is an effective way of combating bacterial infection and many antibiotics function in just this manner. Interest in the involvement of RNA in protein biosynthesis has increased following extensive studies on the binding of antibiotic drugs to specific target sites on ribosomal RNA.

We have carried out a systematic NMR study of a novel antibiotic derived from neamine and its interaction with a conserved and highly stable 27mer RNA motif of the A-site 16S rRNA. The antibiotic shows well resolved and dispersed resonances including exchange retarded amide protons suggesting a stable, folded conformation of the drug. Similarly, the 27mer RNA exhibits well resolved and stable exchangeable imino protons in the lowfield region of the NMR spectrum.

After the addition of 1 molar equivalent of the antibiotic to RNA discrete changes to the NMR spectra of both the molecular components can be clearly identified indicating the formation of a stable and specific binary RNA-antibiotic complex. These results provide a very good opportunity to elucidate the molecular basis of antibiotic action and resistance in three dimensional structural terms.

Acknowledgement: We thank Prof Li-He Zhang and co-workers at SKLNBD, Peking University, Beijing, China for the supply of the neamine antibiotic. We also thank Kwong Kit Nicholas Chan, University of Manchester, for his valuable help and support.



P05

Observations of [TATP+M]+ complexes of triacetone triperoxide with alkali metals

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The peroxide based explosive triacetone triperoxide (TATP) has gained notoriety through its use by terrorist organisations. Its straightforward synthesis and an explosive power comparable to TNT, make it the explosive of choice for illicit use. Reaction with metal ions can improve the stability of TATP and the ability to detect the explosive, with examples of Li, Na and K complexes being used with desorption electrospray ionization. Ion mobility spectrometry (IMS) measurements of [TATP+M]+ complexes have demonstrated the use of ESI-High Resolution IMS for detection of the sodium complex. However, other reported IM detection systems rely on the use of a NH4+ adduct due to its suitability for atmospheric pressure introduction.

The structural analysis of [TATP+M]+ (M = Li+, Na+, K+, Rb+, Cs +) adduct ions, generated by electrospray ionization has been carried out using ion mobility-mass spectrometry (IM-MS) and tandem mass spectrometry (MS/MS), . The use of group one metal ions yields characteristic alkali metal adducts and fragment ions of the peroxide ring, with the formation of sandwich complexes ([2TATP+M]+) observed for Li and Na ions only. All the alkali metal complexes of TATP showed greater stability to fragmentation than protonated TATP, enhancing detectability. A trend of increasing drift time with increasing metal ion radii is observed, accompanied by a reduced parent ion abundance, suggesting weaker complex binding energies between TATP and the larger alkali metal ions

P06

Analysis of Volatile Organic Compounds in the Breath of Elite Swimmers

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Elite swimmers show a higher prevalence of lower airway disorders, such as asthma and exercise-induced bronchoconstriction.1 It has been postulated that the inhalation and absorption of volatile, toxic disinfection by-products (DBPs) may be causing this increased incidence of respiratory disorders.2 The aim of this work is to analyse and compare the pre- and post-swimming levels of DBPs in the breath of asthmatic and non-asthmatic swimmers to determine DBP levels in pre- and post-swimming exhaled breath profiles.

Breath samples were obtained using a portable 100 mL Bio-VOCTM breath and passed through a pre-conditioned and blanked mixed-bed sorbent tube (Markes Int., UK); this was repeated to give a sample of 200 mL. Background pool and sampling room air samples (200 mL) were passed through the sorbent tubes by flushing the Bio-VOCTM with ambient air and via the use of a sampling pump. The samples were analysed by thermal desorption-gas chromatography-mass spectrometry.

Four DBPs ($CHCl_3$, $CHBrCl_2$, $CHBr_2Cl$ and C_2HCl_2N) were identified in the breath of the swimmers and in the pool air, along with CCl_4; suggesting the chemicals to be of exogenous origin. Significant differences in pre- and post-swimming were present for $CHCl_3$ and $CHBrCl_2$ in asthmatics, non-asthmatics and as a combined group. Multivariate analysis of the four components was conducted and a clustering of the non-asthmatics was shown. However, the asthmatic individuals showed no distinct clustering or separation from the non-asthmatics.

Elevated levels of potentially harmful DBPs, as shown by high intensities of $CHCl_3$ and $CHBrCl_2$, are present in the breath of swimmers post-swimming.

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2. Bernard et al. (2003) *Occup Environ Med* **60**(6), 385-394

P07

Development of a protable breath sampler for remote exhaled breath VOC sampling

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Currently, adaptive breath samplers employed in clinical studies for collecting exhaled breath VOCs are restricted to usage only in clinical station or laboratory. This restriction forces participants to travel for breath sampling, limiting the scope of clinical studies.

This work describes the development of a portable breath sampler to allow collection of breath samples in the field. The portable sampler is compartmented into sampling station, air purification unit and air supply units enabling exhaled breath VOCs collection at remote locations. The portable breath sampler was tested in a study with a panel of healthy participants, where the reproducibility of breath samples and air samples taken using the portable sampler and a conventional adaptive breath sampler were compared. The collected breath samples were analysed using thermal desorption/gas chromatography/mass spectrometry. By using a combination of high capacity re-generable activated carbon and molecular sieve filters, the portable breath sampler can achieve consistently higher air supply purity level than stationary adaptive breath sampler. This enables standardised high purity background for exhaled breath samples; improving breath sample reproducibility and enhancing the biomarker prospecting process.

P08

Piezoelectric injections as a systematic approach in fundamental study on dopants and modifiers to control atmospheric pressure chemical ionization process in differential mobility spectrometry

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The concept of using piezoelectric injection (PZX) to control levels of dopants in ion mobility spectroscopy (IMS) [1] and differential mobility spectroscopy (d-IMS) [1] has been proposed previously. This research seeks to fully digitise the control of PZX and use blends and formulations to simultaneously control the levels of dopant and modifier level in the d-IMS.

Digital control has been demonstrated using 2-butanol. Previously optimised bi-polar waveform was used to control the droplet formulation process and changing frequency was used to control the level of the injection. Under continuous operation of the injector, between 1 and 15 Hz (concentration between 23 and 440 μg m^{-3}), the reproducibility study was done, based on hundreds of successful injections. The RSD of the d-IMS 2-butanol signals were < 10% in all cases.

Six dopants: 2-butanol, acetone, dichloromethane, ammonia 1-chlorohexane and ethanol are being studied with water, methanol, toluene and carbon dioxide modifiers. The dopants were introduced using PZX technology, when modifier was introduced in the continuous matter using exponential dilution approach. Experimental design and methodology is described, with over a hundred undergoing experiments, along with the results from the 2-butanol with methanol tests. Concentrations of methanol were varied between and 2600-0.6 mg m-3 while 2-butanol was varied between 50 and 500 μg m^{-3}. Changes to RIP and compensation field resolution were observed with the most significant effects observed at the concentration level of methanol between 700-300 mg m^{-3}.

The results are encouraging and serve as a useful case study for the utility of a PZX-based experimental approach for systematic studies of modifier/dopants interactions.

P09

Structural Studies of Small Molecules, Peptides and Proteins by Field Asymmetric Waveform Ion Mobility Spectrometry-Mass Spectrometry

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Miniaturised high-field asymmetric waveform ion mobility spectrometry has been interfaced with time-of-flight mass spectrometry (FAIMS-MS) to enable the analysis of ions by differential mobility prior to mass-to-charge ratio. The miniaturised FAIMS device (Owlstone Ltd.) exploits the structural and ion mobility differences between ions under high and low electric fields allowing rapid, gas-phase separations that are orthogonal to mass spectrometry. The chip-based FAIMS features a 100 µm electrode gap to enable high dispersion fields (<300 Td) with a 700 µm path length to give short ion residence times (50 – 250 µs) for rapid compensation field (CF) scanning. Sample introduction by direction infusion, high performance liquid chromatography and thermal desorption has been demonstrated. The prototype FAIMS-MS system has been used for structural studies of a wide range of analytes including active pharmaceutical ingredients and excipients, a urinary drug metabolite, isobaric potentially genotoxic impurities, peptides and proteins. FAIMS selection of ions prior to in-source collision-induced dissociation (FISCID-MS) enables tandem experiments to be performed on differential mobility-selected ions and mass analysis of the resulting fragment ions using a single mass analyser. Production of characteristic fragments of FAIMS pre-selected ions is shown to aid the identification of a drug metabolite in urine and of plasma proteins as a result of improvements in the product ion spectra of FAIMS-selected peptide precursor ions.

P10

Simultaneous generation of structural and quantitative metabolism data using nominal mass and high resolution mass spectrometry

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In order to understand metabolic clearance in drug discovery, a recent DMPK initiative has been the simultaneous generation of qualitative and quantitative metabolism data (the 'qual/quan' approach). This work describes an investigation of the benefits and limitations of different LC-MS approaches for the generation of qual/quan data.

Human liver microsomal incubations for a range of test compounds were analysed on API 5000, Q-ToF Premier and LTQ-Orbitrap instruments using a range of LC conditions. The data showed that intrinsic clearance values compared well with literature data whether generated using a triple quadrupole (TQ) or high-resolution (HR) instrument, although cycle times were quicker using a TQ. MRM analysis on a TQ enabled detection of predicted metabolites and some structural elucidation. However, the approach commonly failed to detect unexpected metabolites. The use of HR-MS with data-dependent MSMS acquisition resulted in the detection and detailed structural elucidation of a broad range of metabolites. However, the reduced scanning speed for the LTQ Orbitrap at maximum resolution necessitated longer LC run-times in order to ensure adequate data – an issue less pronounced for the Q-ToF due to its lower resolution. Overall, the data showed that whilst qual-quan analysis is possible using TQ or HR instruments, a balance is required between speed and the thoroughness of the metabolism information. Whilst MRM screening on a TQ can deliver rapid metabolism data, the potential to miss unexpected metabolites may impact drug design strategies. The use of HR-MS will reduce the likelihood of missing important metabolites, but may necessitate reduced throughput.

P11

A fuzzy-logic expert system for the automatic identification, confirmation and quantification of LC/MS data sets

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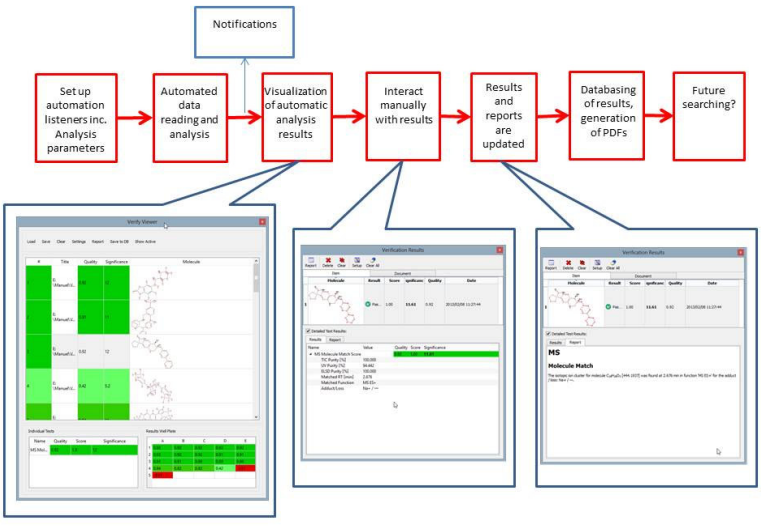
In this work we present an automated integrated software solution aimed at answering the following questions: (1) is my structure consistent with my data and (2), would it correspond with the major species in my data?

The first question is tackled by an efficient algorithm (MolMatch) comparing spectral features predicted from the molecular structure with experimental MS and MS/MS data to determine whether the structure is present in the sample.

The second question is addressed by analysing all available traces in the dataset in order to assess the purity of the putative structure, provided that the first step has succeeded.
The significant novelty presented in this work is a fuzzy-logic expert system that allows the combination of all the information gathered from the different traces (i.e. UV, ELSD, CLND, etc.) and provides a consistent overall answer taking into account the strengths and weaknesses of the available data.

The expert system consists of a mathematical framework applicable in many situations where a decision (such as pass / fail) must be taken on the basis of a number of elementary indications (i.e. tests based on the individual traces) which, taken individually, need not be sufficiently significant and sometimes are even contradictory.

This expert system has been implemented in Mnova MS. For maximum flexibility, it can be placed online allowing the automatic analysis of any number of samples as they get acquired and is capable of using additional analytical information (i.e. NMR) if available.



P12

NMR Spectral Alignment Approaches

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Spectra recorded on similar but non-identical samples, the same sample over time, or in an experiment where pulse-program conditions vary, can show changes in peak positions, and these small changes in signal position can significantly disrupt data analyses. Previous to any form of analysis which involves the comparison across different spectra, the one step which is crucial and often overlooked is the alignment of peaks in these similar spectra. In this poster we will review our own experience using different algorithms and workflows to combat this difficulty and present solutions to common problems that are based on sophisticated algorithms

Depending on the nature of the data to be analysed as well as on the type of analysis to be performed or even if this is of manual or an automatic approach, the choice of alignment strategy may change.

We describe three distinct methods for the alignment of NMR data, of the many which can be implemented, and which situations we find them to be of most use. These are:
Absolute referencing
Auto-Tuning
Global alignment
The correct application of the algorithms to the data being analysed, whether these are metabolomics, ligand screening, reaction monitoring or any other set of experiments, will be one of the critical factors for the rigorous analysis of the data, and certainly the first condition which has to be met to facilitate the automatic analysis of experiments. Ultimately, the pre-processing of data so all are correctly aligned, when required, is critical to the analysis of groups of data acquired through any analytical technique.

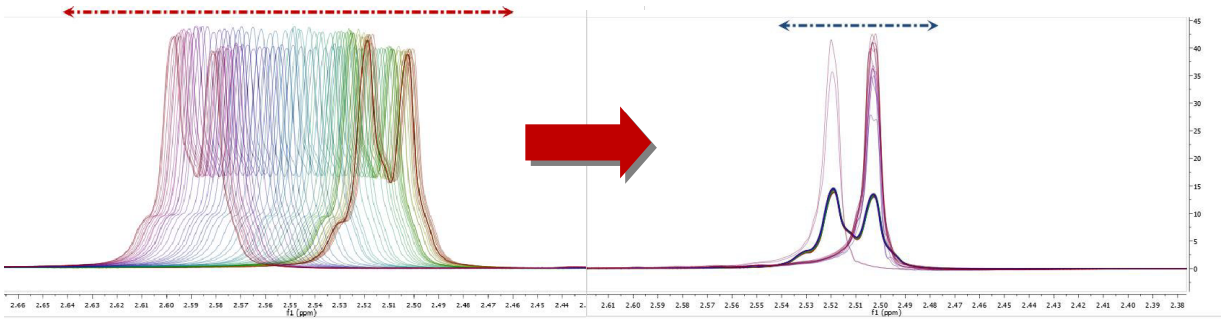

Fig 1. Results of applying global alignment to a series of RM spectra, where we can clearly observe the almost perfect alignment of data

P13

Real-time Fingerprinting of Breath by PTR-ToF-MS for Non-Invasive Diagnostics

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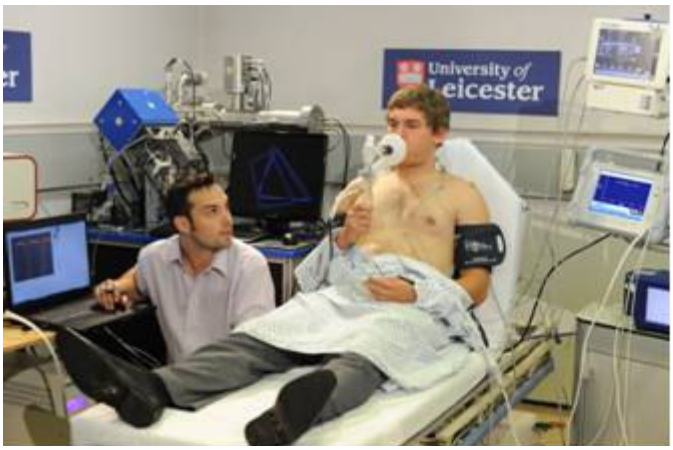
Preliminary results are presented from the diagnostic development unit's (DDU) pilot study into the potential of Proton Transfer Reaction-Time of Flight- Mass spectrometry (PTR-ToF-MS) for fingerprinting breath. The DDU is a multidisciplinary initiative which encompasses non-invasive technology in order to rapidly assess metabolic and disease state by monitoring cardiovascular health, thermal- and hyperspectral-body imaging and breath sampling. The pilot scheme involves patients administered to the Emergency Department at Leicester Royal Infirmary, UK with the 20 most common presentations and diagnoses.

Breath sampled during both controlled single exhalations and normal, tidal breathing was analysed for volatile organic compounds (VOCs) using PTR-ToF-MS alongside simultaneous measurements of nitric oxide and carbon dioxide. The results highlight both the challenges and the potential surrounding the deployment of this technology into the clinical environment towards real-time multi-marker measurement for non-invasive diagnostics.



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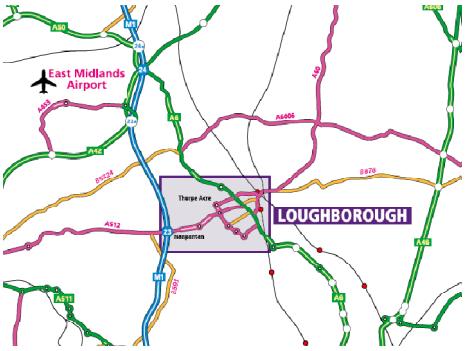

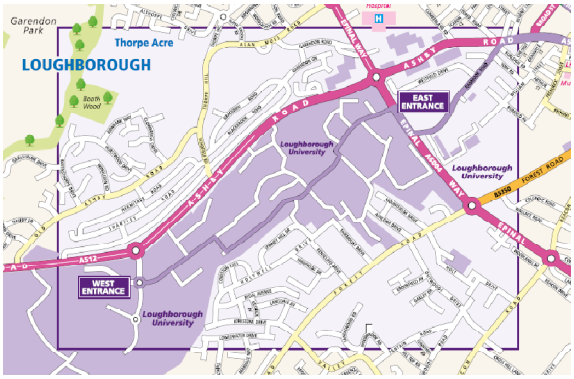

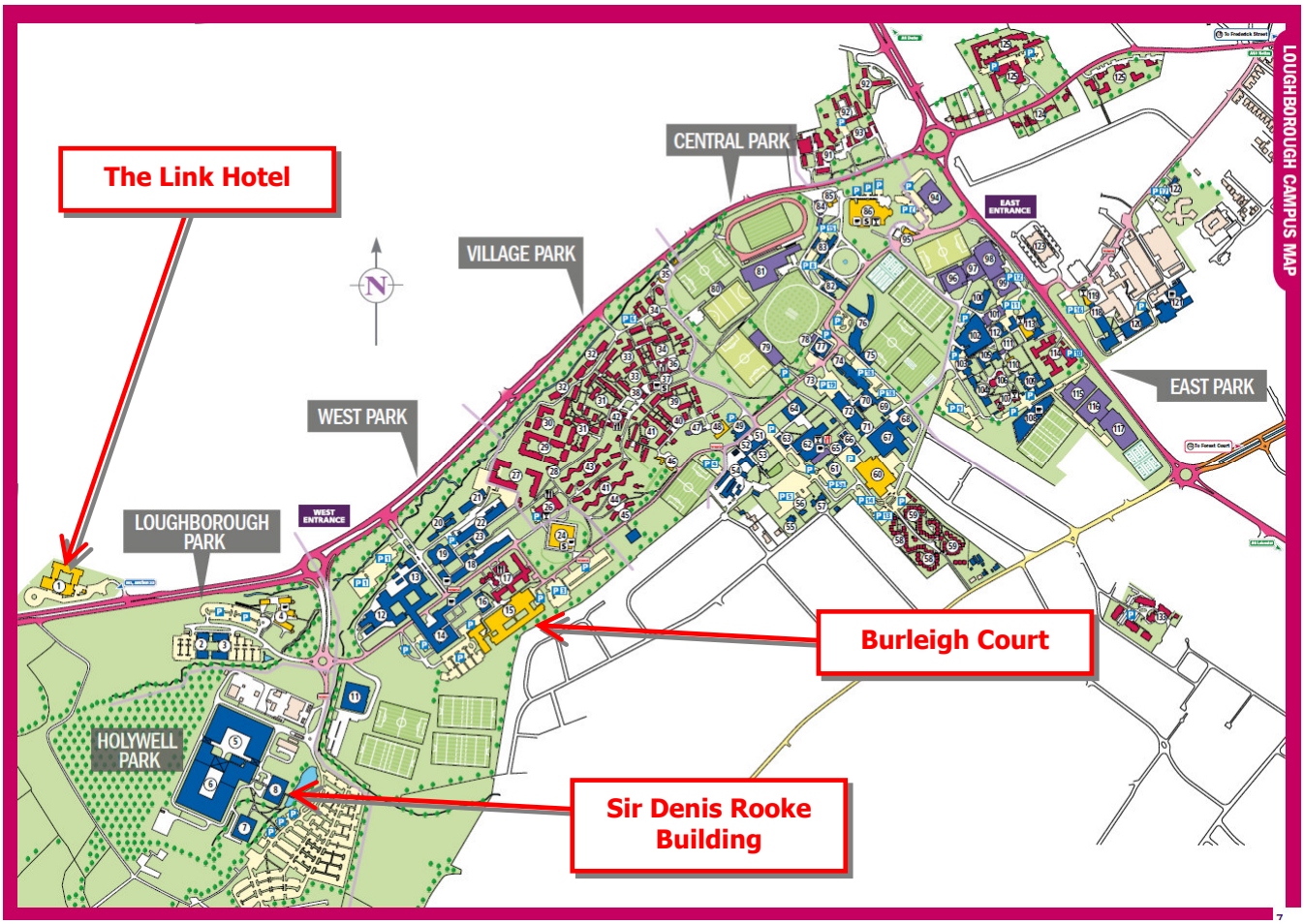

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