Institution: Keele University

Unit of Assessment: B15 General Engineering

Title of case study: SIFT-MS: instruments for breath analysis and trace gas analysis in medicine and industry

1. Summary of the impact

A novel technique named Selected Ion Flow Tube-Mass Spectrometry, SIFT-MS, has been researched and developed by Professor David Smith and Professor Patrik Spanel at the Institute for Science and Technology in Medicine (ISTM), Keele University. This technique allows real time, on-line analysis of trace gases in air and exhaled breath. This development stems from basic research into the reactivity of ions in the gas phase, in which Smith & Spanel are recognised international experts, combined with a complete understanding of the engineering and technical requirements of successful analytical instrumentation. SIFT-MS instruments have been developed initially from large laboratory devices to the current, transportable commercial instruments that are produced by two independent manufacturers and sold worldwide. They are used in various fields of research, including immediate analysis of exhaled breath and urine headspace for clinical diagnosis and therapeutic monitoring, cell biology, and in environmental and food sciences. They have important practical use in the safety of customs workers in container ports and in prospecting for oil and gas. SIFT-MS instruments manufactured in the UK have been exported to Austria, Czech Republic, China and the USA.

2. Underpinning research

The SIFT-MS technique for trace gas analysis was developed under the leadership of Professor David Smith FRS (DS, currently Professor of Chemical Physics and a Head of the Trace Gas Analysis Group), who also pioneered the selected ion flow tube, SIFT, technique for the study of ion-molecule kinetics that continues to be used in laboratories around the world to elucidate the ion chemistry of terrestrial and other planetary atmospheres and interstellar clouds (see Smith & Spanel 1995). DS is still considered as a world leader in astrochemistry and his extensive published works (>400) continue to attract great numbers of citations (>13000). It is his understanding of ion chemistry in the gas phase that underpins accurate SIFT-MS analyses of trace gases. In SIFT-MS, selected reagent ions react with molecules of an air/breath sample introduced into the flow tube and the resulting product ions are quantified by mass spectrometry. Using the known reaction rate coefficients, the concentrations of several trace gases present in the sample (e.g. breath exhalations) can be immediately calculated. The rate coefficients and the product ions for hundreds of reactions of H_3O^+, NO^+ and O_2^+ reagent ions with a wide range of (largely) organic compounds have been determined at Keele University since 1996 (see Smith & Spanel 2005). These results have been reported in many peer-reviewed research and review publications and similar studies are ongoing for many more compounds as SIFT-MS is more widely applied to the analysis of new analytes detected in exhaled breath and evolving from cell cultures and foods.

The SIFT-MS analytical method was first conceived during the collaboration between DS and Professor Patrik Spanel (PS, Professor of Chemical Physics) in 1995 when they commenced their research at Keele, specifically to develop SIFT-MS, focusing on breath analysis for clinical diagnosis and therapeutic monitoring with initial probing experiments relating to health and safety and food science. The first proof-of-principle experiments were carried out on a large SIFT instrument (2000 kg). Development of numerical algorithms and software for automated quantification also began. Years of intensive

research (1995 to 2006) in the areas of flow dynamics, gas sampling methodologies directed towards a wide range of applications (for example, analysis of breath from children and frail patients), and the formation of an extensive library of ion-molecule kinetics, combined with development of instrument rigs and software, resulted in the smallest and most versatile SIFT-MS instrument, *Profile 3* (*120 kg*), that is transportable and can be located at the point-of-care in the clinical environment. Using such instruments, quantification of trace amounts of volatile organic compounds (down to the parts-per-billion by volume, *ppbv*) is achieved. Interdisciplinary studies have been carried out at ISTM, Keele, and the North Staffordshire Hospital Trust (now UHNS) during the period from 1997 to the present, involving the following specialists: Professors Simon Davies (nephrologist), Professor James Elder (GI surgeon), Professor Warren Lenney (respiratory paediatrician), Professor Alicia El Haj (cell biologist), Dr. Josep Sule-Suso (oncologist), together with external collaborators who have also adopted SIFT-MS.

Notable research results that demonstrate the impact of SIFT-MS are:

- reference ranges for several breath metabolites in the healthy population
- quantification of breath ammonia in renal failure and during haemodialysis
- volatile biomarkers in urine from patients with prostate and bladder cancer
- characterisation of volatiles from *in vitro* cell and bacterial cultures
- HCN in the breath of cystic fibrosis patients as a marker of *Pseudomonas* infection
- measurement of total body water in haemodialysis- and peritoneal dialysis patients

Breath analysis is now a recognised new and attractive tool in medicine (diagnosis and therapy) and physiology (transport of metabolites from cells to exhaled breath from nose and mouth, pharmacokinetics), not least because it is totally non-invasive. SIFT-MS researchers at Keele are amongst the pioneers and leaders in this field. The SIFT-MS quantitative approach to breath analysis has changed the paradigm in this field from the search for qualitative patterns to the discovery of objectively measurable biomarkers.

3. References to the research (Three key references are underlined.)

P. Španěl, D. Smith. Progress in SIFT-MS: breath analysis and other applications *Mass Spectrom. Rev.* 2011 **30**(2):236-267. doi:10.1002/mas.20303 (cited 40 times)

D. Smith, P. Španěl. Ambient analysis of trace compounds in gaseous media by SIFT-MS *Analyst* 2011 **136**:2009–2032. doi:10.1039/c1an15082k (cited 12 times)

D. Smith, P. Španěl. Selected ion flow tube mass spectrometry (SIFT-MS) for on-line trace gas analysis. *Mass Spectrom. Rev.* 2005 **24**(5):661– 700. doi: 10.1002/mas.20033 (cited 210 times)

D. Smith, T.S. Wang, J. Sule-Suso, P. Španěl, A.J. El Haj. Quantification of acetaldehyde released by lung cancer cells *in vitro* using selected ion flow tube mass spectrometry *Rapid Comm. Mass Spectrom.* 2003 **17**(8):845-850 (cited 62 times).

S. Davies, P. Španěl, D. Smith. Rapid measurement of deuterium content of breath following oral ingestion to determine body water. *Physiol. Meas.* 2001 **22**(4):651-659. (cited 25 times)

P. Španěl, D. Smith. SIFT studies of the reactions of H_3O^+, NO^+ and O_2^+ with a series of alcohols *Int. J. Mass Spectrom. Ion Proc.* 1997 **167-168**:375-388. doi: 10.1016/S0168-1176(97)00085-2 (cited 108 times)

S. Davies, P. Španěl, D. Smith. Quantitative analysis of ammonia on the breath of patients in end-stage renal failure *Kidney Int.* 1997 **52**(1):223-228. doi:10.1038/ki.1997.324 (cited 103 times)

D. Smith, P. Španěl. Ions in the Terrestrial Atmosphere and in Interstellar Clouds. *Mass Spectrom. Rev.* 1995 **14**(4-5):255-78 doi: 10.1002/mas.1280140403 (cited 98 times)

Grants

Name	Title	Sponsor	Period	Value
D. Smith	TSIFT Instrument	NHS West Midlands LORS (Locally organised research scheme)	1996-1997	£80,000
D. Smith	Application of SIFT-MS for breath analysis	EPSRC	1999-2002	£260,000
S. Davies	FA-MS for total body water	Wellcome Trust	2002	£65,000
W. Lenney	Paediatric SIFT-MS in North Staffordshire	GlaxoSmithKline	2004	£60,000
D. Smith	SIFT-MS instrument	SRIF (Science Research Infrastructure Fund)	2005	£135,000

4. Details of the impact

SIFT-MS is now a valuable method for ambient trace gas analysis, and the transportable instrument, built by a local company (Crewe, UK, corroborating source 1) according to the design of PS and DS, allows on-line analysis at the point-of-care obviating sample collection. Thus, examples of the research carried out are the pilot studies at Keele and UHNS of the metabolites in the exhaled breath of healthy volunteers and patients with renal failure; analyses at the health and safely laboratory, HSL, Buxton, of the exhaust gas from a diesel engine of the kind used in coal mines; establishment of concentration reference ranges for a number of common breath metabolites prior to the study of patients with various diseases at the Silsoe Research Institute, SRI.

Canterbury University, New Zealand, adopted the SIFT-MS method and replicated these instruments in 2001. Their spin-off company, SYFT Technologies (source 2), then began to commercialise the SIFT-MS method implemented in their own design of instruments (*Voice 100* (*200 kg*) and *200 (400 kg)*), that draw heavily on the many published results of the Keele research and development group. More than 50 of these *Profile 3* and *Voice* instruments have been sold (£70 - 200,000 each) and are in use around the world.
The international dimension of SIFT-MS is seen by its adoption in the UK: Keele, Open University, Imperial College London. Czech Republic: Academy of Sciences, Prague. Canada: Lakehead University Ontario. New Zealand: Canterbury and Otago Universities. U.S.A: Ohio University. Spain: IATA Valencia). SIFT-MS instruments are also being used to monitor cargo containers in ports in Australia and Europe (source 3), for oil and gas prospecting in Australia and New Zealand, and in other important areas where volatile compound analysis is valuable, as summarised in the Table below.

Worthy of special mention is the work carried out by Professor Simon Davies at Keele and UHNS on the measurement of total body water, TBW, using Flowing Afterglow-Mass Spectrometry, FA-MS (a variant of SIFT-MS). This is accomplished by measuring the deuterium content of exhaled water vapour following the ingestion of a known quantity of deuterated water (Davies et al, 2001). A multi-centre study is now (2012) demonstrating the benefit to end-stage renal patients of regular and accurate monitoring of TBW, using FA-MS and SIFT-MS, by assessing added value of measuring body composition in the clinical management of dialysis patients.

	Biomedical	Food science		
Liquid headspace analysis	Volatile biomarkers of cancer and infection in urine. Ketones in urine Tissue cell cultures. Bacterial cultures	Quantification of aroma compounds in fermentation Food flavour analyses	**Resources; Environment; health and safety**	
Breath analysis	**Clinical diagnosis:** renal failure diabetes cancer infection in cystic fibrosis **Therapeutic monitoring:** total body water (dialysis) chemotherapy and radiotherapy halitosis	Flavour release	Biological monitoring	**Security**
Ambient air, fumes or emissions	Release of volatile compounds by skin compounds in tobacco and cannabis smoke	Volatile organic compounds related to sensory qualities	Oil prospecting Customs work safety Emissions from waste incineration, sewage and landfills	Detection of volatile markers of explosives Products and fumes of explosions

The related analytical method known as PTR-MS is also directly based on the above-mentioned research into the ion chemistry of H_3O^+ at Keele (source 4). PTR-MS instruments are more sensitive but lack the absolute accuracy of SIFT-MS. Recently, NO^+ and O_2^+ were introduced as reagent ions in PTR-MS in an attempt to make this technique more competitive with SIFT-MS. These instruments are widely used in atmospheric monitoring, but have had limited application in breath analysis and food technology.

SIFT-MS has contributed to a paradigm shift in breath analysis. In the area of healthcare the increasing availability of SIFT-MS instruments has resulted in joint projects with medical groups, since breath biomarkers can distinguish healthy and disease states. Evidence for this are the joint publications with clinical specialists, which have attracted hundreds of citations. Thus, in 2007, The *Journal of Breath Research* (*JBR*) was introduced, published by *IOP Publishing*, and DS and PS were invited to be founder members of the Editorial Board. Currently, the papers co-authored by PS and DS fill 5 of the top 10 most cited papers in JBR and attracted some 20% of all citations to JBR papers (source 5, citations from *Web of Science*). DS is co-editor of two published books:

- *Breath analysis for clinical diagnosis and therapeutic monitoring*. World Scientific, 2005.
- *Volatile biomarkers. Non-invasive diagnosis in physiology and medicine*. Elsevier, 2013.

5. Sources to corroborate the impact

1. Chief Executive Officer at Instrument Science, a UK company selling SIFT-MS instruments http://www.instrumentscience.com/.
2. Chief Technical Officer at Syft Technologies, a New Zealand company selling SIFT-MS instruments http://www.syft.com/.
3. SIFT-MS at seaports http://www.nzine.co.nz/features/syfttoxicityscreening.html
4. Chief Technical Officer at Ionimed Analytik GmbH, a European company selling PTR-MS instruments http://www.ionicon.com/
5. Journal of Breath Research http://iopscience.iop.org/1752-7163/
6. Material World, BBC Radio 4. http://www.bbc.co.uk/radio4/science/thematerialworld_20061123.shtml