Institution: University of Strathclyde

Unit of Assessment: 9

Title of case study: Market leading sales of fluorescence spectrometers for multidisciplinary applications.

1. Summary of the impact (indicative maximum 100 words)

Fluorescence lifetime research since 1993 in Strathclyde's Photophysics Group led by Prof. David Birch contributed to the success of the University spin-out company IBH (Imhof, Birch, Hallam), and its successful merger with the £1Bn multinational company Horiba. The Strathclyde research has helped Horiba to be, since 2008, the market-leading supplier of fluorescence spectrometers, which comprise steady-state, lifetime and hybrid instruments. The commercial success of the company has led to economic benefits and employment. Through production of an improved spectrometry product range, the Strathclyde research has also facilitated multidisciplinary molecular and materials research globally, across Industry, Government and University sectors, bringing benefits to diverse disciplines such as life sciences, healthcare, chemistry, and nanotechnology.

2. Underpinning research (indicative maximum 500 words)

Context

Fluorescence is the emission of light by a molecule when excited with light. The fluorescence spectrum and excited state lifetime (typically nanosecond) are fingerprints of the emitting molecule and its local environment. The properties of fluorescence, including quantum yield, single molecule sensitivity, and polarization, and implementation in tracking molecular kinetics, imaging and microscopy, have served to establish fluorescence globally as a primary analytical technique. Sequencing the human genome and immunoassay for disease diagnostics are two well-known applications. Indeed, fluorescence has particular importance in medical research and the life sciences, disciplines that require routine operation of equipment by users who are not usually instrumentation specialists. This case study is based on research that improved performance in the main growth area of fluorescence spectroscopy, namely excited state lifetime studies, which opened up new application opportunities and led to considerable commercial success.

Key findings

Research published in the period 1996 – 2004 resulted in a number of important discoveries and innovations as indicated below [numbers refer to the references in section 3].

[1] An inexpensive, miniaturized and portable blue-green InGaN light-emitting diode (LED) source and drive electronics for obtaining pulses of ~ 1.9 ns at up to 10 MHz repetition rate. It was shown to be ideal for faster acquisition of fluorescence decay data using the most popular method of time-correlated single-photon counting (TCSPC). Previously LEDs operated only at ~10 kHz. Fluorescence and rotational decay times of the dye rhodamine 6G agreed with previous values obtained with a Ti:Sapphire laser at ~100x the cost. The approach opened up new markets involving molecules/samples that changed rapidly e.g. silica nanoparticle growth [5], and sensing e.g. glucose for diabetes [6].

[2]. This joint paper with IBH describes a disruptive new LED technology that enabled for the first time the routine and inexpensive excitation of protein intrinsic fluorescence decay using a semiconductor source. Until this work the alternatives were expensive mode-locked lasers or unreliable and unstable spark lamps, which limited applications. The paper reported excitation of the amino acid tyrosine at 280 nm. Subsequent joint publications with IBH addressed the fluorescent amino acids tryptophan and phenylalanine, and protein. The technology propelled the IBH NanoLED global market [text removed for publication]. Dr David McLoskey led the IBH contribution.

[3]. The capability of fluorescence lifetime measurement was enhanced when the Photophysics Group were the first to demonstrate in this work multi-photon excitation (MPE) combined with TCSPC data acquisition. The different selection rules for MPE can provide extra selectivity, but this paper demonstrated an increased dynamic range of anisotropy decay, aiding precision in particle metrology [5]. MPE-TCSPC is now widely used in fluorescence lifetime imaging (FLIM).

[4]. This paper developed our patented invention of multiplexed TCSPC in the first application specific integrated circuit (ASIC) designed for fluorescence lifetime. The ASIC enabled 16 channels of fluorescence data e.g. decay vs. wavelength, position etc., to be recorded simultaneously. The paper shows some of the first TCSPC lifetime images, thus helping to pave the way to fluorescence lifetime imaging , which is now used universally e.g. in the Horiba DynaMyc. Prof. P Hicks of UMIST led the ASIC design.

[5]. There is a global environmental and healthcare requirement for better alternatives to expensive scattering techniques and electron microscopy for measuring nanoparticle size in the critical 1-10 nm range that easily traverses cellular membranes. This paper showed the accepted model of the bi-exponential fluorescence polarization anisotropy decay observed during the gelling of silica sols, and based on the co-existence of dual viscosities, was in fact incorrect and proposed a new model in terms of Brownian rotation of free dye and dye bound to nanoparticles. This led to a new method for nanoparticle metrology in-situ. The work was in collaboration with Unilever.

[6]. The ongoing collaboration, since 1997, with Kings College London School of Medicine/Guys Hospital on in-vivo glucose sensing for diabetes management using fluorescence, demonstrated the usefulness of TCSPC in the quest for a non-invasive sensor. Prior to this work frequency domain lifetime measurement had been the main approach. The paper also described an improvement in a sensor for serum glucose based on Concanvalin A by compatibility with the therapeutic window in skin. Prof. John Pickup led the medical part at KCL.

Key researchers at Strathclyde
Prof. D Birch academic in Department of Physics from 1/09/78 to present,
Dr O Rolinski. Senior Lecturer in Department of Physics from14/04/94 to present.
Prof. D Sherrington academic in Pure and Applied Chemistry 1/09/71 to 29/02/12 now retired.

3. References to the research (indicative maximum of six references)
Outputs 2, 5 and 6 best represent the quality of the underpinning research.

[1] *MHz LED source for nanosecond fluorescence sensing*. W J O'Hagan, M McKenna, D C Sherrington, O J Rolinski, & D J S Birch. Meas. Sci. Technol. 13, 84-91, 2002.
[2] *A new sub-nanosecond LED at 280 nm: application to protein fluorescence.* C D McGuiness, K Sagoo, D McLoskey & D J S Birch. Meas. Sci. Technol. 15, L19-22, 2004.
[3] *Time-resolved non-linear fluorescence spectroscopy using femtosecond multi-photon excitation and single-photon timing detection.* A Volkmer, D A Hatrick & D J S Birch, Meas. Sci. Technol. 8, 1339-49, 1997.
[4] *Multiplexed single-photon counting 1: A time-correlated fluorescence lifetime camera.* D McLoskey, D J S Birch, A Sanderson, K Suhling, E Welch & P J Hicks, Rev. Sci. Instrum. 67, 2228-37, 1996.
[5] *Sol-gel particle growth studied using fluorescence anisotropy: An alternative to scattering techniques.* D J S Birch & C D Geddes. Phys. Rev. E. 62, 2977-80, 2000.
[6] *Near-infrared fluorescence lifetime assay for serum glucose based on allophycocyanin-labeled concanavlin A*. L J McCartney, J C Pickup, O J Rolinski & D J S Birch. Anal. Biochem. 292, 216-21, 2001.

Other evidence for quality of research (Numbers refer to the references above).
[1]. Supported by a £128k EPSRC Award "Fluorescence lifetime sensors for metal ions" during 1998-2001. Overall assessment: "Tending to outstanding."
[2]. The UV-LED source described received global scientific press coverage e.g. Biophotonics International and Chemistry World.
[3]. Chosen as 1 of best 5 papers in Meas.Sci.Technol. in 1997. Led to a £150k GSK award in 2002.
[4]. The Birch-Imhof invention of a 2 channel version was patented by the University of Strathclyde (International Patent WO 85/03352) and in 1990-93 EPSRC funded a 3 channel version "Optical fibre fluorometry" with £108k. Overall assessment: "Very significant contribution to the field."
[5]. Our technique has been used by many other research groups [text removed for publication]. The

work formed part of the1997-9 £198k EPSRC Award "Fluorescence dynamics in confined water: application to the structure of silica hydrogels." Scientific/technological assessment: "Very significant contribution to the field." Follow-on funding was through the 2000-3 £240k EPSRC Award "Nanometre silica particle metrology in sol-gels using fluorescence anisotropy." Overall assessment: "Outstanding."
[6]. The collaboration with KCL was highlighted as 1 of 5 excellent research outcomes in the 2011 EPSRC review of Science & Innovation Awards (SIA). Press coverage included EPSRC Impact Case Study 36. Collaborations with KCL led by David Birch, include the £5m SIA in nanometrology and the £500k EPSRC Adventure Fund proposal “Single molecule sensing in clinical medicine,” [text removed for publication] (overall final assessment: "Tending to Outstanding").

4. Details of the impact (indicative maximum 750 words)

Process/events from research to impact

IBH was incorporated in 1977 and its acquisition by Horiba in 2003 to form Horiba Jobin Yvon IBH Ltd brought together IBH-Strathclyde’s leading technology in pulsed fluorescence lifetime systems, with Horiba's steady-state (SS) fluorescence systems to produce a joint product line (Source 1) that paved the way to market supremacy. David Birch co-founded IBH and the Photophysics Group in 1977/8, served as IBH Chairman 1977-2003 and is presently Horiba Jobin Yvon IBH Director of Science and Technology. His role, bridging between research, new products and the market, has been crucial to achieving commercial success. The process to impact started by demonstrating new instrument capabilities and applications through publications, which developed the field, attracted the market to related instrument products, and built the brand and reputation of IBH and Horiba.

Description of impact

Since 2008, Horiba and IBH together have won the largest market share of fluorescence spectrometer sales. From this flows a sustainable business, investment for innovation, and an extensive global customer base pursuing diverse applications.

Improved products: The fluorescence spectrometer market is comprised primarily of three parts. Fluorescence spectrometers, incorporating steady-state (SS) sources, stand-alone fluorescence lifetime spectrometers incorporating pulsed sources, and hybrid spectrometers that combine both spectra and lifetime capabilities. Following the IBH-Horiba merger, market impact was realized by upgrading Horiba’s global SS spectrometer user base with IBH’s lifetime capability and the sale of new instruments. [Text removed for publication.] Specifically, the present IBH-Horiba lifetime-SS spectrometer range offers a more complete measurement solution for non-specialist users than was hitherto available from any supplier, as evidenced by the market leading position.
The seminal breakthrough was the transition from ~ 30 kHz pulsed spark lamp sources to the more reliable and higher repetition rate semiconductor sources (References 1 and 2). This launched a new range of spectrometers based on the laser diodes and LEDs of the 1 MHz NanoLED and 100 MHz Delta product ranges. These offered higher time resolution, stability, data acquisition rate and ease of use, all at a reduced price (down to < $30k). This enabled expansion into key research markets in life-sciences, medicine and bionanotechnology. In his definitive book “Principles of Fluorescence Spectroscopy” 3rd ed., Springer 2006, JR Lakowicz wrote about papers 1 and 2 *“Perhaps the most important development for TCSPC since 2000 is the introduction of pulsed-laser diodes and pulsed light-emitting diodes……While this chapter was being written, the first report appeared on excitation of intrinsic protein fluorescence using a pulsed LED.”* This research was crucial to the instrument developments that had such a significant market impact from 2008.

Market leading sales: The combined global market for fluorescence SS and lifetime spectrometers exceeds £100M. It has been reported, *“Horiba has a solid lead in the market due in part to its wide range of popular lifetime fluorescence instruments, which is a segment of the market in which it dominates"* (Source 3). Sales of the joint product line of IBH’s fluorescence lifetime technology and Horiba's SS systems grew by [text removed for publication] from 2008-2012 to secure, since 2008, the largest global market share of 15% [text removed for publication]. This is significantly higher than that of other well-known brands e.g. PerkinElmer (11%), Thermo-Scientific (10%), Shimadzu (9%) and Hitachi (9%). The data is from market analysts Strategic Directions Inc. who

highlight in Sources 2 and 3Horiba's dominance due to IBH's fluorescence lifetime technology.

Global adoption of technology across research laboratories: Adoption of the Strathclyde research in the fluorescence spectrometer products has benefited customers and their research outcomes across the globe, serving diverse disciplines such as life sciences, healthcare, chemistry, and materials. Sequencing the human genome and immunoassay for disease diagnostics are two important areas the products have supported. Research into improved healthcare is over 50% of the market and grand challenges addressed include diabetes, neurodegeneration and cancer. An expert in fluorescence at Brown University (Source 4) wrote *"Without your research and your successful commercial exploitation there is no doubt fluorescence lifetime would not be the major technique it is today"* and expert in fluorescence at Texas Christian University (TCU) wrote *"The instrument systems you have helped design and develop, and that have been manufactured by the company you started, Horiba Jobin Yvon IBH Ltd in Glasgow, are used by leading laboratories all over the world"* (Source 5).

Skilled employment: The IBH market-leading position helps generate and sustain employment. [Text removed for publication.] Its business model makes significant use of UK sub-contractors and a highly skilled staff. The success of IBH contributed directly to the start-up, by former IBH Director Dr Anthony Hallam, of Sim4t Ltd. in 2012, an educational software and research training company, with its first products based on the simulation of TCSPC fluorescence lifetime decay data.

Training: The impact of the research has been fostered by global dissemination activities such as the FluoroFest workshop series (Source 6) initiated by David Birch, sponsored by Horiba and launched in Prague in 2009, with subsequent events in California (2010,2011) Munich (2011), Maryland (2012), Kyoto (2012) and Texas (May 2013). An expert in fluorescence at Brown University comments in his letter to David Birch "*Finally, let me mention the great job you have done in disseminating research in fluorescence through your initiation of the globally acclaimed FluoroFest hands-on international workshop series. I have personally attended … these events and they are to the benefit of the whole fluorescence community"* (Source 4). In collaboration with Sim4t, the CPD course "Fluorescent nanoparticles and molecules for nanomedicine", was trialled at the Czech Technical University in 2013 (Source 7).

5. Sources to corroborate the impact (indicative maximum of 10 references)

1. Products described at: http://www.horiba.com/scientific/products/fluorescence-spectroscopy/
2. Independent analysis in Strategic Directions International Inc. Global Assessment Report 11th Edition and Market forecast 2009-14. The Laboratory Analytical & Life Science Instrumentation Industry. Oct.2010. Page 245
3. Strategic Directions International Inc. Global Assessment Report 12th Edition and Market forecast 2012-16. The Laboratory Analytical & Life Science Instrumentation Industry. Oct.2012. Page 265
   Note: Taken together 2 and 3 show that Horiba's overall market lead in the combined fluorescence steady-state and lifetime based systems is due to the fluorescence lifetime products produced by IBH, these in turn being underpinned by the Strathclyde research.
4. Statement from US expert in fluorescence Brown University
5. Statement from US expert in fluorescence Texas Christian University.
6. International training workshops at:www.fluorofest.org/ (past workshops tab)
7. International training workshop http://box.fbmi.cvut.cz/index.php/en/