Institution: Imperial College London

Unit of Assessment: 9 Physics

Title of case study: P1 - The commercial applications and economic success of fluorescence lifetime imaging (FLIM)

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

Imperial researchers in Prof Paul French's photonics group demonstrated one of the first practical FLIM instruments in 1997 using a prototype gated optical intensifier (GOI) developed by Kentech Instruments Ltd and a home-built solid-state ultrafast laser. They subsequently pioneered the use of ultrafast supercontinuum sources (USS) for FLIM. Today wide-field time-gated FLIM is a commercial success and is being widely applied for biomedicine, including for imaging of diseased tissue [e.g. 5] and for FRET (Fluorescence resonance energy transfer) microscopy to assay protein interactions [e.g. 3, 4]. This research thus helped translate FLIM to a wider community, highlighting the potential for tissue imaging, cell biology and drug discovery. It stimulated about £5M of GOI sales for Kentech [section 5, source A], with whom they developed time-gated FLIM technology and applications, and millions of pounds worth of sales of supercontinuum sources for Fianium Ltd [B].

2. Underpinning research (indicative maximum 500 words)

Fluorescence lifetime measurements are a means to analyse the radiation emitted by fluorescent molecules in order to distinguish different molecular species, to probe the local molecular environment and to monitor molecular interactions. FLIM is the measurement of fluorescence lifetime in every pixel of an image and was first implemented in microscopes, although now it has been extended to endoscopy, tomography and other imaging modalities. Although fluorescence lifetime measurements date back decades, FLIM was first demonstrated around 1990 but was not widely taken up because of the complexity of the technology required. The Imperial group demonstrated one of the first "practical" FLIM instruments in 1997 [1, 2] using wide-field time-gated imaging with a prototype gated image intensifier (GOI) and a home-built novel solid-state ultrafast laser source that replaced complex and cumbersome ultrafast dye laser systems. It also developed suitable software tools to analyse FLIM data since none were commercially available. Subsequently it demonstrated the potential for applications in biomedicine (e.g. cell biology using FRET to read out cell signalling processes [3] and for clinical diagnosis [5]), high content analysis for drug discovery [e.g. 4] and in the physical sciences. This work has underpinned the impact of time-gated FLIM in the wider user community and helped establish a market for the technology.

Research by Professor French's group included demonstrating the initial practical system in 1997 [1,2] and subsequently refining it, and integrating novel laser sources with gated optical image intensifiers (GOI) in FLIM instrumentation. This work was initiated and has continued with close interaction with industry, particularly Kentech Instruments Ltd but also AstraZeneca, GE Healthcare, GSK and PerkinElmer. The Imperial group co-authored several papers with industry [1-4] that raised the profile of time-gated FLIM.

The group has continued to develop novel FLIM instrumentation. It demonstrated FLIM using a high repetition rate gated image intensifier operating at ~80 MHz with a mode-locked Ti:Sapphire laser and this approach has become wide-spread. In 2004, the group also demonstrated the potential for rapid FLIM endoscopy using the Kentech GOI technology and also demonstrated the first FLIM with an ultrafast supercontinuum source (USS) [6], which, in turn, stimulated the market

for USS. They have also demonstrated the potential for rapid imaging in microfluidic devices using GOI FLIM in 2005 and the extension of the technique to wide-field time-resolved fluorescence anistropy imaging.

Key researchers: Prof Paul French (Head of Photonics group) has led the FLIM development and application since initiating it in 1996, later working with Prof Mark Neil (Professor of Photonics), Dr Christopher Dunsby (Lecturer in Photonics) and Dr James McGinty (Lecturer in Biophotonics). The other authors on the cited references are Imperial PhD students and Research Associates, colleagues from industry and biomedical collaborators. Three PDRAs (Sam Hyde, Richard Jones and Keith Dowling moved to industry following their FLIM research.

3. References to the research (* References that best indicate quality of underpinning research)

[1] Dowling K, Hyde SCW, Dainty JC, French PMW, Hares JD, "*2-D Fluorescence Lifetime Imaging using a Time-Gated Image Intensifier*", Opt. Commun, 135, 27 (1997). DOI, **30 citations (on 29/11/12)**

[2] *Dowling K, Dayel MJ, Lever MJ, French PMW, Hares JD, Dymoke-Bradshaw AKL., "*Fluorescence Lifetime Imaging with picosecond resolution for biomedical applications*", Opt Lett., 23, 810-812 (1998). DOI, **90 citations (on 29/11/12)**

[3] Grant D, et al., "*High speed optically sectioned fluorescence lifetime imaging permits study of live cell signaling events*", Opt. Expr., 15, 15656–15673 (2007). DOI, **23 citations (on 29/11/12)**

[4] Talbot CB, et al., "*High speed unsupervised fluorescence lifetime imaging confocal multiwell plate reader for high content analysis*", J. Biophoton. 1 (2008) 514–521. DOI, **17 citations (on 26/06/13)**

[5] *Galletly NP, et al., "*Fluorescence lifetime imaging distinguishes basal cell carcinoma from surrounding uninvolved skin*", British Journal of Dermatology, 159, pp. 152-161, 2008, DOI, **35 citations (on 26/06/13**)

[6] *Dunsby C, et al., "*An electronically tunable ultrafast laser source applied to fluorescence imaging and fluorescence lifetime imaging microscopy*", J Phys D: Appl. Phys., 37, 3296-3303 (2004). DOI, **45 citations (on 29/11/12)**

Research Grants:

32 FLIM related research grants (including ESPRC - GR/L34273/01, GR/N16464/01, EP/F040202/1, BBSRC, EU and Wellcome Trust) since 1996 summing to £8.2M including £2.8M from DTI/TSB/industry. Most of this funding relates to biomedical applications of FLIM rather than technology development.

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

As part of the research and development of FLIM technology, the Imperial group has worked closely with several industrial partners, including Kentech Instruments Ltd, AstraZeneca, GE Healthcare, GSK and PerkinElmer. This resulted in several papers being co-authored with industry [1-4] which raised the profile of time-gated FLIM and helped to establish a market for this technology. This was particularly important in helping to create a new market for Kentech Instruments' GOI and high repetition rate gated optical imaging intensifiers (HRI) products, as well as stimulating the development of further products.

In addition to collaborative work with industry, key routes to impact have been to seek funding to demonstrate specific applications, e.g. BBSRC for cell imaging, EPSRC for medical imaging and a DTI/TSB Technology Award (2006-2010) for drug discovery with Kentech Instruments Ltd,

AstraZeneca, GSK and GE Healthcare, who are looking to include FLIM in their activities.

The Imperial group's research underpins the adoption of the technology in FLIM systems and since 2005 has led to a sharp increase in Kentech's GOI sales. Kentech, manufacturers of specialised and custom built electronics and imaging equipment, state that since 2005 sales of FLIM systems based on GOI technology "*have reached around £5M, (with ~£2.5M having been sold since 01/01/2008), with typical individual sales having a value of ~£100k*" [A]. Kentech attribute the increased sales "*to the interest generated by [Imperial's] research and note that customers have frequently asked for the technology 'developed by the Imperial College Group'."* [A].

The Imperial group's demonstration of the use of ultrafast supercontinuum sources for FLIM and their subsequent development of new instrumentation, particularly for FRET readouts of cellular signalling processes, *"helped stimulate significant world-wide demand for…supercontinuum products*" [B] and led to an increase in sales of ultrafast fibre laser-pumped supercontinuum sources by Fianium Ltd, who had recently pioneered this technology and launched the first commercial product. Fianium Ltd, a fiber laser company focused on the manufacture and development of ultrafast, high power laser systems, estimate that "*approximately half of more than 600 supercontinuum devices that [Fianium] have delivered to date are being used for fluorescence lifetime measurements and that this follows directly from [Imperial's] pioneering research*" [B]. The "*devices are currently priced between £12,000 and £80,000"* and therefore *"this number of sales [approx. £3-25M in value] represents a significant impact on the commercial development of [the] market"* [B]. Fianium further commented that Imperial's "*application of their ultraviolet ultrashort pulse sources …. to clinical imaging has stimulated interest in FLIM for medical diagnosis*" and that they "*have sold further systems to customers interested in following [Imperial's] work in this area*" [B]. Fianium currently market 'fluorescence lifetime measurements' as an application for three supercontinuum lasers series (the Whitelase SC series, Whitelase UV and Whitelase Micro) and two supercontinuum filter systems (SC-AOTF and SuperChrome) in their product line [C, D].

The Imperial group undertook, and continues to run, a number of collaborative research projects with industry exploiting FLIM including [1, 2, 3, 4]. Information from these research projects, in particular with Kentech and Fianium, has fed back into better device designs and development of more compelling products. Kentech testify that they have "*benefitted from working with [the Imperial] research group through [Imperial's] feedback and suggestions, which have helped…to improve our products and broaden the applications and markets into which our products are sold. [The]…impressive system integration talent build up in [the Imperial] group has guided [Kentech] in the continuing development of our control systems, further improving product performance*" [A].

In addition to the translation of the technology into industrial application that is detailed above, the FLIM research programme at Imperial has resulted in knowledge transfer via delivery of skilled technical staff into industry. Four postdoctoral research staff and PhD students within the group developed technical expertise enabling them to acquire positions with companies including Intel (ultrafast silicon based photonics), GEC Marconi and then Narragansett Imaging (business aspects of imaging technology), Evotec and Genentech (technology development in drug discovery), Powerlase Ltd and the technology development company The Technology Partnership (TTP).

GE Healthcare, AstraZeneca, GSK and Kentech Instruments Ltd joined Imperial in a DTI (TSB) Technology award (01/01/2006-31/10/2010) to develop and evaluate a prototype FLIM multiwell plate reader. [text removed for publication]. It is too early to judge societal/health impact but FLIM instruments based on GOI technology are currently being used for biomedical research across the world (for instance [E, F]). Kentech confirm the biomedical use of time-gated FLIM in a letter – the Imperial group's "*work demonstrating the biological and medical applications of time-gated FLIM – particularly [the] demonstration of rapid FLIM for real-time endoscopy and live cell imaging –*

created significantly increased demand in [Kentech's] HRI products across our international market and we frequently had customers wanting to purchase HRI technology so that they could do similar work." [A]

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

[A] Letter from Managing director, Kentech Instruments Ltd, 20th November 2012. Letter confirms Imperial's role in the development of FLIM technology and their sales of GOI and HRIs. [Letter available from Imperial on request]

[B] Letter from Founder and CEO, Fianium Ltd, 27th November 2012. Letter confirms the significant impact that Imperial's pioneering research on the development of FLIM technology has had on sales of their supercontinuum devices. FLIM has become a major application of Fianium's technology. [Letter available from Imperial on request]

[C] Fianium WhiteLase Supercontinuum products page, http://www.fianium.com/supercontinuum.htm (Archived at https://www.imperial.ac.uk/ref/webarchive/pkf on 02/05/13)

[D] Example product datasheet for Fianium supercontiuum source which markets 'Fluorescence lifetime measurement' as an application - the WhiteLase SC Series, http://www.fianium.com/pdf/WhiteLase_SC4x0_v2.pdf (Archived here)

[E] The Scientist article, 'Eyes on Cancer: Techniques for watching tumors do their thing', 1/4/12, http://www.the-scientist.com/?articles.view/articleNo/31889/title/Eyes-on-Cancer/ (archived at https://www.imperial.ac.uk/ref/webarchive/wpf on 7/8/13)

[F] Three example biomedical papers using time-gated FLIM technology: DOI(1), DOI(2), DOI(3)