Institution: The University of Nottingham

Unit of Assessment: 9

Title of case study: Testing Functional Foods and Pharmaceutical Formulations using Dynamic Imaging of the Gastrointestinal Tract

1. Summary of the impact

New methods to study the biophysical action of the human digestive system were developed in Nottingham using high speed magnetic resonance imaging (MRI) and have been used by: (i) the food and drug industry (Unilever, Proctor & Gamble, Mitsubishi Chemicals, Reckitt Benckiser, Glaxo and McNeil Pharmaceuticals) to develop new products; (ii) Plant Bioscience Limited (PBL) to develop an artificial Dynamic Gut Model (DGM) which is now being applied commercially to characterise drug and food ingestion; (iii) the BBC and other media agencies in programmes related to the promotion of better understanding of nutrition in an effort to combat obesity.

2. Underpinning research

Echo planar imaging (EPI), invented by Sir Peter Mansfield in Nottingham in the 1970s, remains the fastest MRI technique, capable of generating images in times as short as 10 ms, and is thus an excellent tool for studying dynamic processes. Furthermore, EPI is the most robust magnetic resonance (MR) imaging method for quantifying biophysical parameters. The use of this technique to study the function of the gastrointestinal (GI) tract has been pioneered by *Gowland*, a member of the Nottingham MRI group, who, since 1993, has collaborated closely with Professor Robin Spiller, a clinician specialising in gastroenterology at the University of Nottingham. This collaboration has grown to encompass a large research team including industry-sponsored research assistants and CASE-funded PhD students, and, in particular, an interdisciplinary senior research fellow (Dr Luca Marciani), a physicist who was a member of our MRI group until 2003, when he transferred to the University's Division of Gastroenterology. Through this collaboration, we have used our unique expertise in quantitative and high speed MRI to develop novel non-invasive methods for measuring key physical parameters that characterise the function of the GI system, including:

- the measurement of gastric emptying and intraluminal viscosity of model meals (1997) [1,2], and the intragastric distribution of different meal components (fat in 1999, foams in 2001 and gelation in 2004 [3]);
- methods for assessing intraluminal emulsification of fat (2001);
- GI motility measurements (using a locally-developed analysis algorithm similar to m-mode ultrasound, 2001), intraluminal forces (studying the breakdown of model particles that we designed and fabricated, 2001) [4];
- evaluation of intraluminal flow rates, from which shear rates can be deduced (1997);
- transit time measurements (acquired using tailored pulse sequences in combination with labelled tracer particles that were designed and fabricated within the group, 2012);
- the only method available to measure small bowel water content (2007) [5].

More recently, we have developed methods to study colonic volumes and the characteristics of the colonic content, and we are currently developing methods to assess colonic motility using MR tagging techniques.

We have also used these MR-based GI functional tests to make substantial contributions to improving our understanding of the function of the GI tract in health and disease. We characterised the interacting effects of meal viscosities and nutrient contents on gastric emptying, gastric accommodation and the sense of satiety [1,2], and also demonstrated the effect of posture on the emptying of mixed fatty meals (1997), and how this can be affected by meal formulation. We have also shown that many meals mix more slowly than expected in the GI tract, which is important for the design of drugs that are affected by the acidic environment of the gastric lumen. We quantified the forces exerted by the stomach for the first time (2001) [4] and have measured gastrointestinal motility and intra-gastric flow rates.

This body of work led us to propose an MRI-based single diagnostic examination for the comprehensive analysis of GI function; no other modality can provide such a wide range of measurements in a single examination and, for the vast majority of the measurements we make, no alternative non-invasive assessment method is even available. The ability to make repeated measurements has enabled the detailed study of the response of the GI tract to meals in healthy

volunteers and patients. Our work has been published in the leading journals in the MR, nutrition and GI fields and is highly cited. It has been strongly supported by UK research councils (BBSRC, MRC) [i,ii] and by industry (Unilever, Reckitt-Benckiser [6], McNeil Nutritionals, Scienta, McNeil Consumer Healthcare, Dow Chemical Company, Proctor and Gamble and Norgine) [iii].

3. References to the research (*denotes paper which best highlights the quality of the research)

1) **L. Marciani, P. A. Gowland, R. C. Spiller, P. Manoj, R. J. Moore, P. Young, S. Al-Sahab, D. Bush, J. Wright, A. J. Fillery-Travis,** *'Gastric response to increased meal viscosity assessed by echo-planar magnetic resonance imaging in humans',* Journal of Nutrition **130**,122 (2000).
URL: http://jn.nutrition.org/content/130/1/122.full.pdf+html

*2) **L. Marciani, P. A. Gowland, R. C. Spiller, P. Manoj, R. J. Moore, P. Young, A. J. Fillery-Travis, '***Effect of meal viscosity and nutrients on satiety, intragastric dilution, and emptying assessed by MRI',* American Journal of Physiology – Gastrointestinal and liver physiology **280**, G1227 (2001).
URL: http://ajpgi.physiology.org/content/280/6/G1227.full.pdf+html

3) **C.L. Hoad, P. Rayment, R.C. Spiller, L. Marciani, B. de Celis Alonso, C. Traynor, D.J. Mela, H.P.F. Peters, P.A. Gowland**, *'In vivo imaging of intragastric gelation and its effect on satiety in humans',* Journal of Nutrition **134**, 2293 (2004).
URL: http://jn.nutrition.org/content/134/9/2293.full.pdf+html

*4) **L. Marciani, P. A. Gowland, A. Fillery-Travis, P. Manoj, J. Wright, A. Smith, P. Young, R. Moore, R. C. Spiller**, *'Assessment of antral grinding of a model solid meal with echo-planar imaging',* American Journal of Physiology – Gastrointestinal and Liver Physiology **280**, G844 (2001).
URL: http://ajpgi.physiology.org/content/280/5/G844.full.pdf+html

*5) **L. Marciani, E.F. Cox, C. L. Hoad, S. Pritchard, J.J. Totman, S. Foley, A. Mistry, S. Evans, P. A. Gowland, R. C. Spiller,** *'Postprandial Changes in Small Bowel Water Content in Healthy Subjects and Patients With Irritable Bowel Syndrome*', Gastroenterology **138**, 469 (2012).
Listed in REF2; DOI: 10.1053/j.gastro.2009.10.055

6) **L. Marciani, S.L. Little, J. Snee, N.S. Coleman, D.J. Tyler, J. Sykes, I.G. Jolliffe, P.W. Dettmar, R.C. Spiller, P.A. Gowland**, '*Echo-planar magnetic resonance imaging of Gaviscon alginate rafts in-vivo'* Journal of Pharmacy and Pharmacology **54**, 1351-1356 (2002).
DOI: 10.1211/002235702760345428

Research council funding (6 projects, selection below, total value £1,385,199)

i. *'Targeted Validation of the IFR Model of Human Digestion'*, M. Wickham, R Faulks and PA Gowland, BBSRC, (2005-2006) £56,108.

ii. *Perception of flavour in fat emulsions: interactions in mouth, gut and brain*', RC Spiller, J Hort, ST Franics, W Taylor, PA Gowland, BBSRC and Unilever, (2005-2008) £447,080.

Industrial funding related to GI function since 1993 (15 projects, selection below, total £1,367,581)

iii. *'Investigation of Action of Gaviscon'*, PA Gowland, L Marciani and RC Spiller, Reckitt and Colman, (1999-2000) £23,000.

Educational Funding

iv. 'The Truth about Food', BBC education grant, (2006) £6000.

4. Details of the impact

Functional gastrointestinal (GI) disorders affect a significant proportion of the population. For instance gastro-oesophageal reflux disease (GORD), the main symptom of which is heartburn, is experienced by ~40% of the population in Western countries. Chronic sufferers (10-15%) can develop more serious conditions such as Barrett's oesophagus and erosive oesophagitis. GI disorders cost the UK economy £7.2 billion/year and the NHS > £2.2 billion/year [*'Care of Patients with Gastrointestinal Disorders in the United Kingdom'*, British Society of Gastroenterology, March 2006]. Furthermore, the GI functional response also modulates behavioural responses to food and, hence, is key to designing meals and foodstuffs that increase satiation after a meal, which can play a part in controlling the increasing rate of obesity in the population. Health problems associated with being overweight cost the NHS more than £5 billion/year ['*Healthy Lives, Healthy People: A call to action on obesity in England*', HM Government, October 2011]. Despite the importance of GI

function in health and disease, until recently there have been very few techniques available to investigate the physiology of the GI tract repeatedly and non-invasively. The fast MRI methods that we describe in Section 2 overcome the effects of movement in the human abdomen, allowing the direct measurement of GI function *in vivo*.

Our work has influenced wider society through two principal routes: product development in the food and drug industry; and the commercial development of an *in vitro* model of the gut. In addition we have contributed to television/online programmes related to public health and nutrition. We now consider knowledge transfer into these areas in turn:

- **Product development in the food and drug industry**

Our demonstration that gastrointestinal motility and flow, together with a range of digestive processes, could be monitored directly in human subjects attracted the interest of companies who were seeking to optimise meal and drug formulations, and has led to funding from major multinational companies including Proctor and Gamble, Mitsubishi Chemicals, Unilever, Reckitt Benckiser, Glaxo and McNeil Nutritionals. Detailed information about how the data obtained in many of these trials were used by the companies in product development remains confidential (in most cases even to the Nottingham researchers involved). However, the value of these studies to the relevant organisations can be gauged by the rapid increase in the value of research contracts which they placed with the Nottingham MRI group. In the period up to 2008 the commercial contracts averaged ~£44.5k/annum; since 2008 this annual funding level has more than trebled to £135k/annum, totalling £678k (2008-2013).

We consider two examples of how our research influenced companies and products. Firstly, an investigation funded by Reckitt and Colman (now Reckitt Benckiser) [iii; 1999-2000] showed that *'Gaviscon Advance'* was more efficacious at forming an alginate raft within the stomach, preventing oesophageal reflux with only half the dose of normal Gaviscon. The visual detail (Fig. 1), which is taken from our paper [6], was reproduced by Reckitt Benckiser in their *"Gaviscon Advance 2006 campaign"* to promote the medicine by informing general practitioners, and to substantiate claims regarding the health benefits of Gaviscon Advance (GA) ([A]; see also [6]).

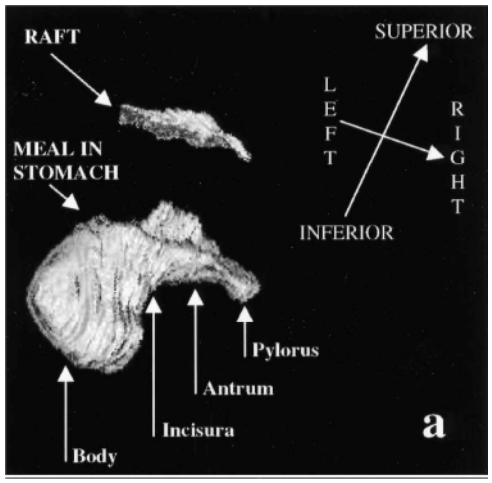

Figure 1: 3D MRI reconstruction of a Gaviscon Advance raft and underlying meal (NB: This figure is from [6] and is also used in [A]).

To quantify the on-going impact of the development of this product through the assessment period (2008 onwards) we estimate that NHS patients benefitted from 14.6M prescriptions of GA (2008-2012 [B]; these figures do not include over-the-counter sales). We present this as a prime example of how our expertise and facilities are being used to understand and improve the mode of action of products, and to substantiate claims about foods or drugs, with the ultimate beneficiaries being patient groups world-wide.

Secondly, we highlight a long-term collaboration with Unilever aimed at developing functional foods. This collaboration was built on the application of our methods to: studies of the fate of different components of a meal in the GI tract; the testing of prototype Unilever products; and an investigation of GI physiology relevant to Unilever's current and future product range. This relationship has led to support for 2 BBSRC CASE studentship awards and contract research funding worth £273k to our group since 2008. In describing this work, the Strategic Science Group Director Advanced Measurement in Unilever has stated [C]:

"*One particular example that was critical to a full product development cycle included the collaboration with, Dr Harry Peters' (R&D Manager, Unilever, Vlaardingen) and included research findings from a c£250k Unilever commission project (2004-2007). The quality of the MRI data and expert interpretation greatly increased prototype efficiency whilst reducing related costs. The obvious benefit to the company has been quicker time to market with reduced overheads, stronger data package in support of claims and authority whilst maintaining product quality and excellence for our customers.*

This success catalysed 5 further studies with Nottingham between 2008-2013, including two CASE studentships. It is worth noting new mechanistic and hence scientific insights into gastric

processing were delivered in the stomach, and both the small and large colon as a result of aspects of these studies. In this particular field alone Dr Pip Rayment (Unilever Colworth) has generated 6 patents…….".

These successes in MRI were instrumental in the decision by Unilever to enter into a strategic partnership with the University of Nottingham across all subject areas. The relationship with Unilever provides clear evidence of a multinational organisation making changes in its strategies for research and product development as a consequence of our research.

- **Commercial development of an *in vitro* model of the gut**

The costs, difficulties and lengthy time-scales associated with *in vivo* studies of the gut have motivated the development of an *in vitro* model. Researchers from the Institute of Food Research (IFR) in Norwich worked with us on a project funded by joint BBSRC grants (2005-06) [i], in which our research provided comparative data for the development and certification of the Dynamic Gut Model (DGM) [D]. This *in vitro* model is a machine which replicates the grinding forces and the slow rate of intra-gastric mixing of viscous meals that we measured *in vivo*, which is important since it determines the rate at which a product is exposed to the low pH of the gastric secretions.

Plant Bioscience Limited (PBL; a technology management company), the owners of the DGM intellectual property, successfully patented the machine in the EU (EP1907108B1), USA (US8092222) and Australia (AU2006271423). The role of Nottingham research, including in the protection of intellectual property, is confirmed by the PBL Business Development Manager [E],

"Nottingham's MRI group provided world leading research facilities and expertise that provided critical underpinning to the design and development of the DGM, and played a significant role both in establishing IP protection and marketing evidence."

The DGM has proven to be an ideal vehicle to study the dynamics of oral drug release, and has been widely applied in the pharmaceutical industry to help develop and refine new formulations without the risk and expense of human trials. PBL initially (Nov 2006) offered a fee-for-service from their established business unit *Model Gut*. More recently (Feb 2013) they have licenced the technology and contract research business to Bioneer Farma, a Danish company. In parallel, PBL have also secured over £900k follow-on funding from BBSRC for further development of the DGM [F].

- **Public Health and Nutrition**

Our research results have been used in health education television programmes about human nutrition, *"The Truth about Food"* (BBC and SBS (Australia)) [G]. This work was funded by the BBC (iv), and also included in an associated book [H]. The programmes were first broadcast in Jan 2007 and have been available online [G] throughout the assessment period (2008 onwards). The book was published in 2007 and is still available. Through their continuing availability, the programmes and book provide information that is intended to educate and inform the public about optimum food choices in an effort to combat obesity.

5. Sources to corroborate the impact (available on request)

A. "The science of alginates", Pulse, June 2006.
B. Data reported by the Health & Social Care Information Centre, http://www.hscic.gov.uk; the information for Gaviscon Advance can be found under the 'Prescribing' tab; then under 'Prescription Cost Analysis'. A summary document is available on request.
C. Letter from Strategic Science Group Director: Advanced Measurement at Unilever.
D. Model Gut Marketing presentation (contains direct reference to our research [2,3] on pages 7 & 9 respectively and extensive further reference to *in vivo* results).
E. Letter from PBL Business Development Manager.
F. PBL press release (25th January 2013) & "BBSRC Business" (Spring 2013) [page 7].
G. Weblinks: http://www.bbc.co.uk/sn/humanbody/truthaboutfood/ and http://www.sbs.com.au/shows/foodinvestigators/listings/detail/i/2/article/3021/Episode-4-The-Truth-About-Chicken-Soup; electronic copies are available on request.
H. "The Truth About Food", Jill Fullerton-Smith, Bloomsbury Publishing Plc, London 2007 ISBN 9780747586852. (Please see page 232 and credits to Prof Gowland and Dr Marciani).