Institution: Imperial College London

Unit of Assessment: UoA 15 (General Engineering)

Title of case study: Real-time monitoring of tissue health by rapid-sampling microdialysis gives better outcomes during surgery and intensive care

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

The Boutelle team has developed a biosensor that uses rapid-sampling microdialysis (rsMD) to detect ischaemia (restricted blood supply to tissue) during surgery and intensive care. The rsMD biosensor is implanted into tissue at risk and provides a real-time readout of chemical markers of metabolism. By 2009, technical improvements researched in the Department of Bioengineering had made the system suitable for routine clinical use. The system has reduced morbidity and mortality by alerting the surgical team to otherwise undetected ischaemia. It has been used by an international consortium of clinical centres to help decide treatment in approximately 100 patients with brain injury. More recently it was adopted by a Portsmouth hospital to monitor cancer patients undergoing reconstruction of the face and jaw; the biosensor detected a failure of perfusion in transplanted tissue in two of the first ten patients, prompting the surgical team to remove otherwise undetected blood clots that could have led to death from septicaemia.

2. Underpinning research (indicative maximum 500 words)

Professor Martyn Boutelle has pioneered the development of enzyme-based rsMD biosensors for continuously monitoring multiple metabolites - principally glucose and lactate – that indicate tissue health during surgery and intensive care. In this method, a probe is inserted into the tissue of interest; substances that diffuse across its dialysis membrane are washed towards an electrochemical sensor that relies on immobilised oxidase/peroxidase enzymes to convert specific analytes into oxidised species, which are then detected by reduction.

An initial prototype was developed by the Boutelle group when they were based at King's College London. However, it could only detect large metabolite changes, seen rarely in patients. Following Dr Boutelle's appointment to the Department of Bioengineering in December 2004, proof-of-principle tests were conducted, sensitivity was improved by an order of magnitude, and pre-clinical and clinical validations were carried out. This research made the sensor suitable for routine use in hospitals for a number of clinical conditions.

The first target application was detecting brain ischaemia during spreading electrical depolarisation, a common adverse consequence of brain injury. Trials in 8 patients undergoing surgery for cerebral aneurysm gave proof-of-principle that glucose and lactate can be continuously monitored in the human brain by rsMD, and that their concentrations change detectably when the blood supply is deliberately interrupted; the system had 30s temporal resolution and a response time of only 9 minutes [1]. (This makes it far more applicable than the only commercially-available microdialysis device, which provides hourly samples that require manual handling and a lengthy chromatographic analysis; timely information is essential in the clinic.) Sensitivity sufficient for routine use on spreading depolarisation patients was obtained by developing novel noise reduction algorithms [2]; subsequent optimisation of the microfluidics chamber where analytes contact the electrodes has further improved sensitivity (and also response time). Pre-clinical trials in cats determined the reciprocal relation, time course and absolute value of glucose and lactate concentrations during induced depolarisations [3]. A clinical trial [4] in 10 brain-injured patients demonstrated reciprocal changes in glucose and lactate during periods of spontaneous spreading depolarisation; multiple depolarisations were associated with a stepwise depletion of glucose of sufficient severity to compromise tissue viability.

Although originally developed for monitoring injured brain, further underpinning research has been required to make the technology suitable for other conditions. To make it useful for gastrointestinal surgery, for example, a series of studies was conducted in collaboration with Professor George Hanna and Professor Lord Ara Darzi. Pre-clinical trials using pigs showed that changes in glucose and lactate concentrations could be detected within 5 minutes of interrupting the blood supply [5]. Such changes were also observed in 7 patients undergoing bowel resection. A stable, highly-selective ATP biosensor has also been developed to assess metabolic problems in gut tissue.

The research has been published exclusively in international peer-reviewed journals [ref 3 features on the journal cover]. It has been supported by peer-reviewed funding including a £1.3M Wellcome Trust / Department of Health Healthcare Innovation Challenge Fund grant. Industrial interest is demonstrated by a BBSRC CASE studentship with Sharp Europe and a BBSRC Industrial CASE studentship with GSK, whilst two internally-allocated translational grants totalling £135k demonstrate institutional support [6]. Recent esteem indicators include Boutelle's Chairmanship of the symposium of the International Society for Monitoring Molecules in Neuroscience.

3. References to the research (indicative maximum of six references)
* References that best indicate quality of underpinning research.

1. Bhatia R, Hashemi P, Razzaq A, Parkin MC, Hopwood SE, Boutelle MG, Strong AJ. Application of rapid-sampling, online microdialysis to the monitoring of brain metabolism during aneurysm surgery. Neurosurgery. 2006;58:ONS-313-321. DOI: 10.1227/01.NEU.0000208963.42378.83..
2. *Feuerstein D, Parker KH, Boutelle MG. Practical methods for noise removal: applications to spikes, nonstationary quasi-periodic noise, and baseline drift. Anal Chem. 2009;81:4987-4994. DOI: 10.1021/ac900161x.
3. *Hashemi P, Bhatia R, Nakamura H, Dreier JP, Graf R, Strong AJ, Boutelle MG. Persisting depletion of brain glucose following cortical spreading depression, despite apparent hyperaemia: evidence for risk of an adverse effect of Leão's spreading depression. J Cereb Blood Flow Metab. 2009;29:166-175. DOI: 10.1038/jcbfm.2008.108. Cited 32 times by 15.10.2013.
4. *Feuerstein D, Manning A, Hashemi P, Bhatia R, Fabricius M, Tolias C, Pahl C, Ervine M, Strong AJ, Boutelle MG. Dynamic metabolic response to multiple spreading depolarizations in patients with acute brain injury: an online microdialysis study. J Cereb Blood Flow Metab. 2010;30:1343-1355. DOI: 10.1038/jcbfm.2010.17.
5. Corcoles EP, Deeba S, Hanna GB, Paraskeva P, Boutelle MG, Darzi A. Use of online rapid sampling microdialysis electrochemical biosensor for bowel anastomosis monitoring in swine model. Anal Methods 2011;3:2010-2016. DOI: 10.1039/c1ay05306j.

Grants:
(i) Boutelle and E. Drakakis. "Real-time detection of the onset of secondary brain injury in the intensive care unit," Wellcome Trust/Department of Health, 30/9/2011-29/09/2014, £1,332,289.
(ii) Boutelle. Sharp Laboratories Of Europe Ltd. "CASE Studentship for Dominic Lawrance." £13,500. 1/10/2009 - 30/9/2012
(iii) GlaxoSmithKline Services Limited. "Industrial CASE studentship for Michelle Rogers." £83,470. 1/10/2007 - 30/9/2011.

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

The majority of patients benefitting from the rsMD technology have suffered a brain injury that reduces the blood supply to their brain. Brain tissue can cope with the consequent reduction in the supply of oxygen and nutrients if its metabolic rate is sufficiently low. Unfortunately, however, as

shown by the Boutelle group, a common consequence of such injury is the occurrence of synchronised waves of electrical depolarisation in the brain; generating the synchronised waves requires lots of energy and the injured brain consequently suffers from the ischaemia. It is therefore unsurprising that the occurrence of waves is associated with a worse outcome [A]. Since the unsupported metabolism is itself a direct cause of damage, diagnostic precision can be increased by monitoring it locally, continuously and in real time. Currently this can *only* be achieved with the Boutelle group's methods.

Professor Boutelle is a founding member of COSBID [B], an organisation established for the investigation and treatment of patients with brain injury depolarisations resulting from head trauma or vascular stroke. Its 16 Centres are distributed worldwide. Six of them (Charité Hospital, Berlin; King's College Hospital, London; University Hospital, Cologne; St Mary's Hospital, London; Charing Cross Hospital, London; and University of Pittsburgh Medical Center) monitor eligible patients not only for depolarisation waves but also for ischaemia, using rsMD equipment made by Professor Boutelle. He also trained 15 neurosurgeons and other clinical staff, and has run briefing courses for approximately 30 intensive care nurses every 6 months, during the REF period.

The introduction of routine monitoring of brain ischaemia by rsMD represents a change in clinical practice. For example, Cologne uses rsMD to screen every patient with sub-arachnoid haemorrhage and some with traumatic brain injury (approx. 10 patients/year) [C]; approximately 100 patients have been screened across all Centres within the assessment period. The method provides greater precision in the diagnosis of the patient's condition and hence helps to guide the selection of treatment options such as administering glucose, raising blood pressure or performing radical hemispheric craniectomy [D]. It was highlighted as being of "outstanding interest" in a recent expert clinical review [E].

The method has been extended to clinical practice in other surgical areas. For example, it is employed in reconstructive surgery of the tongue or jaw where a flap of the patient's own tissue is used as a transplant, usually following cancer treatment. Success in this procedure depends on adequate perfusion of the flap with blood; it therefore requires clot-free blood vessels, and microsurgical techniques to interface the vessels in the flap with those of the surrounding tissue. Inadequate perfusion occurs in 9% of cases (and many more in patient groups with adverse conditions such as diabetes); the failure rate at salvage is then up to 66% [F]. It causes flap ischaemia and necrosis, ultimately leading to life-threatening septicaemia if left uncorrected. Mortality for septicaemia in intensive care is approx. 80-90%. Perfusion is traditionally assessed only by the feel and appearance of the flap; signs of failure appear late, by which time surgical rescue is difficult or impossible.

To overcome this problem, rsMD biosensors from the Boutelle team have been used to monitor 3 patients per month, starting in November 2011, at the Queen Alexandra Hospital, Portsmouth; monitoring takes place during both surgery and intensive care [G]. This represents a change of clinical practice at the hospital, and improves outcome. After only ten patients had been examined, the system had detected a failure of tissue perfusion in two patients after initial flap placement. The surgical team responded by disconnecting the flap, where they found blood clots. These were cleared and the flap metabolic state dramatically improved. Without rsMD technology, the clots would have remained undetected, causing the tissue flap to become ischemic and then necrotic, probably leading to septicaemia with its associated high incidence of mortality. The paper [H] describing these cases was "highlighted" in the American Chemical Society's Chemical & Engineering News [I] 2013;91:30. The surgeon is currently trying rsMD in other, related classes of operation including, with colleagues, reconstructive breast surgery.

Overall, the impact of this technology during the REF period has been to reduce patient morbidity and mortality, reduce medical costs, and relieve burden on medical infrastructure at the hospitals in which the device has been used: Charité Hospital, Berlin; King's College Hospital, London; University Hospital, Cologne; St Mary's Hospital, London; Charing Cross Hospital, London; University of Pittsburgh Medical Center; and Queen Alexandra Hospital, Portsmouth. Discussions on commercialisation of the latest version of the rsMD technology are underway with M Dialysis, a Swedish company that dominates the clinical microdialysis market [J]. The technology will be patented using the translational funds obtained for that purpose.

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

A. Hartings JA, Bullock MR, Okonkwo DO, Murray LS, Murray GD, Fabricius M, Maas AI, Woitzik J, Sakowitz O, Mathern B, Roozenbeek B, Lingsma H, Dreier JP, Puccio AM, Shutter LA, Pahl C, Strong AJ; Co-Operative Study on Brain Injury Depolarisations. Spreading depolarisations and outcome after traumatic brain injury: a prospective observational study. Lancet Neurol. 2011;10:1058-1064. DOI: 10.1016/S1474-4422(11)70243-5 *By showing that ischaemia-causing waves worsen outcome, this paper explains why the rsMD device provides increased diagnostic precision in traumatic brain injury.*

B. www.cosbid.org *The clinical-research collaborative network through which rsMD is applied to traumatic brain injury in hospitals.* Site Archived on 24/10/2013 at https://www.imperial.ac.uk/ref/webarchive/p1f

C. Deputy Managing Director, Multimodal Imaging, Max Planck Institute for Neurological Research, Cologne. *Describes the number of patients and clinical benefit of using rsMD at University Hospital, Cologne.*

D. Emeritus Professor of Neurosurgery, Department of Clinical Neuroscience, Institute of Psychiatry, King's College London. *Describes the origin of COSBID in Boutelle's work, and the number of patients and clinical benefit of using rsMD at King's College Hospital London.*

E. Goodman JC, Robertson CS. Microdialysis: is it ready for prime time? Curr Opin Crit Care. 2009;15:110-117. DOI: 10.1097/MCC.0b013e328325d142. *This expert review highlights the clinical value of Boutelle's rsMD technique, particularly the research in Reference 3 of Section 3, above.*

F. Garg S, Deschler D. Saving a free flap with close clinical postoperative monitoring. JAAPA 2013; 26: 47-49. *This publication highlights the severity of the clinical problem that is addressed by use of Boutelle's rsMD maxillofacial surgery.*

G. Consultant Oral and Maxillofacial Surgeon and Professor of Surgery, Queen Alexandra Hospital, Portsmouth. *Describes the number of patients and clinical benefit of using rsMD at Queen Alexandra Hospital, Portsmouth.*

H. Rogers ML, Brennan PA, Leong CL, Gowers SA, Aldridge T, Mellor TK, Boutelle MG. 'Online rapid sampling microdialysis (rsMD) using enzyme-based electroanalysis for dynamic detection of ischaemia during free flap reconstructive surgery. Anal Bioanal Chem. 2013;405:3881-3888. DOI: 10.1007/s00216-013-6770-z. *Describes the clinical benefit of using rsMD at Queen Alexandra Hospital, Portsmouth.*

I. American Chemical Society's Chemical & Engineering News April 15th 2013, page 30: http://www.heterobetainas.uah.es/intranet/REVISTA%20CHEM%26ENG%20NEWS/cen20130415-dl%20(3).pdf . *Describes the clinical benefit of using rsMD at Queen Alexandra Hospital, Portsmouth.* Archived here on 24/10/2014

J. Sales & Marketing Director, M Dialysis AB will attest to the commercial discussions between Prof Boutelle and M Dialysis concerning rsMD.