Lab-on-a-Chip Technology, as a Remote Distributed Format for Disease Analysis:
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Previously, Lab-on-a-Chip technologies have exploited many aspects of microsystems technology, including sensor miniaturisation and microfluidics, in order to deliver a variety of applications, particularly those associated with DNA analysis, proteomics and diagnostics. Despite the numerous analytical advantages that are delivered as a consequence of device miniaturisation, the vast majority of all devices that have been proposed either as commercial instruments or as research projects, have required to be based on a laboratory bench. In contrast, Lab-on-a-Pill technology now has the proven ability to deliver both remote and-or distributed analysis, resulting in a wide range of potential applications, including those associated with biomedical analysis in the gastro-intestinal tract, process control in industry and the functional foods industry.

Lab-on-a-Pill: The International Context of the Work: The invention of the transistor enabled the implementation of the first radiotelemetry ingestible capsules, which utilised simple circuits for *in vivo* telemetric studies of the gastro-intestinal (GI) tract [1]. These units could only transmit from a single sensor channel, and were difficult to assemble due to the use of discrete components [2]. The measurement parameters consisted of *either* temperature, pH or pressure. These first attempts of conducting real time non-invasive physiological measurements (understandably, given the extent of technology in 1957) suffered from poor reliability, low sensitivity and short lifetimes of the devices. Despite this, the first successful pH gut profiles were achieved in 1972 [3], with subsequent improvements in sensitivity and lifetime [4, 5]. Single channel radiotelemetry capsules have since found limited applications for the detection of disease and abnormalities in the GI tract [6-8] where restricted access prevents the use of traditional endoscopy [9]. Most radiotelemetry capsules utilise laboratory type sensors such as glass pH electrodes, resistance thermometers [10] or moving inductive coils as pressure transducers [11]. However, the relatively large size of these sensors limits the functional complexity of the pill for a given size of capsule.

The concept of *remote and distributed* miniaturised sensing has been most dramatically exemplified by the camera-on-a-pill technology, associated with video endoscopy within the gastro-instestinal tract [9]. The important contrast between this seminal work in video imaging (e.g. that produced by IMC, Korea and Given Imaging), and of our own work is that whilst the camera-on-a-pill seeks to create a visual image of the remote area being sensed, we wish to develop a remote chemical image of that site.

Name of Manufacturer	Technology	Main Technical Specifications	Comparison
Mackay/Jacobson, Nature, 179, 1239-40 (1957)	Endoradiosonde, Single transistor	Battery, single channel (9x28 mm).	Temperature or pressure Wireless communication
HC Noiler, Telefunken, Germany (1965)	Heidelberg pH capsule	Battery, single pH sensor (8x20 mm)	Small, utilised in medical research
M2A, Given Imaging, Israel (2001)	Video Capsule CMOS camera	Battery, 2 frames/s, 6 hour lifetime (11x26 mm).	Video imaging (single channel)
Norika 3, RF System Lab , Japan (2002)	Video Capsule, CCD camera	Induction, 30 frames/s, drug, prop, tracking, sampling (9x23 mm).	Video imaging, multiple function, excl. battery
IMP, IMC, KIST Korea (1999-2009)	Endoscopic Microcapsule	Battery, camera, drug release actuator, ultrasound (10x30 mm).	Evolutionary. Contract negotiation with GU
IDEAS, Glasgow Uni. UK (2001-2004)	Microelectronic pill Chemical imaging	Battery, ASIC, □-sensor, program, 40 hour lifetime (16 x 55 mm).	Sensor & system integr. multi capsule protocol.

Current Activity at the University of Glasgow: Our current research on sensor integration and onboard data processing has focused on the development of microsystems capable of performing simultaneous multiparameter physiological analysis both in vivo and in vitro. The technology has a range of applications in the detection of disease and abnormalities in medical research. Our overall aim has been to deliver enhanced sensor functionality, reduced size and low power consumption, through system level integration on a common integrated circuit platform comprising sensors, analogue and digital signal processing, and signal transmission. We have therefore created a platform which comprises a novel analytical microsystem incorporating a four channel microsensor array for real time determination of temperature, pH, conductivity and oxygen (work pioneered by Professor Jon Cooper and Dr Erik Johanessen). The sensors have been fabricated using standard photolithographic pattern integration, and are controlled using a custom made application specific

integrated circuit (ASIC), designed in Glasgow (by Dr Dave Cumming and Dr Wang Li) and fabricated by Europractice. The ASIC samples the data with 10 bit resolution prior to communication off chip as a single interleaved data stream. An integrated radio transmitter sends the signal to a local receiver (base station), prior to data acquisition on a computer. A receiver allows remote control of the Lab-on-a-Pill's function, switching sensors and-or power on and off, on demand.

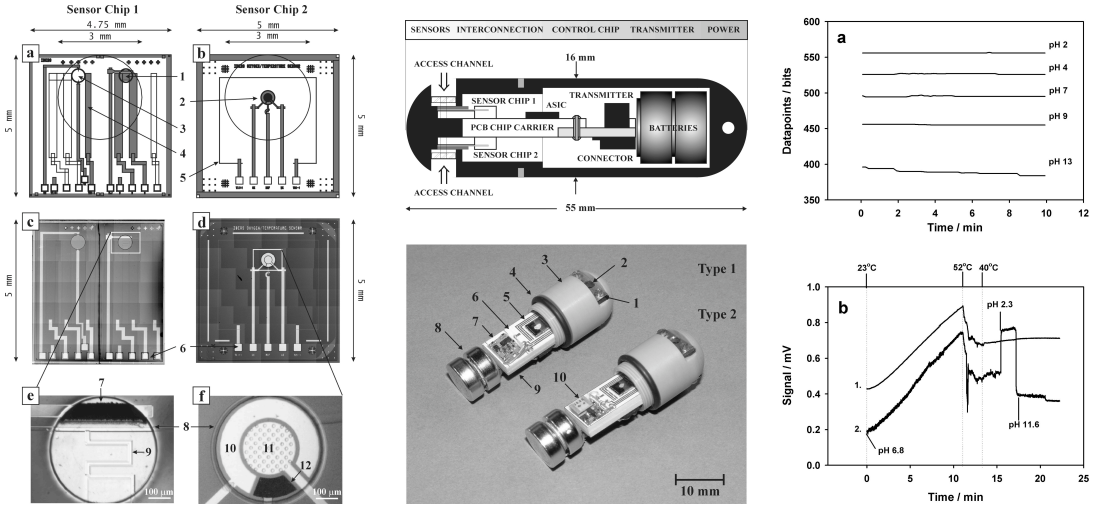

Figure 1: (Left) showing the ISFET, temperature and conductivity sensor (Chip 1, a,c) and the electrochemical oxygen sensor (Chip 2, b, d). Figures e and f show detail of the pH and oxygen sensor, respectively; (Middle) Schematic (top) and photo (below) of the Glasgow IDEAS capsule. Although the capsule is currently too large to swallow, the hybrid approach towards its construction provides considerable experimental flexibility. It is estimated that the volume of the pill could be readily reduced by ca. 40% through careful layout of the packaging and surface mount; (Right) a recoding of pH and temperature using wireless transmission of data from a model gut system, showing the importance of temperature sensing. As expected the response of the pH sensor has a Nernstian dependence on temperature (although the reverse is not true, and the temperature sensor does not have a pH dependence). The Figure also shows that there is no signal cross-talk across the capsule, between sensors, despite the fact that they are located proximal to each other on the chip (and share the same microsystem for signal collection and transmission).

The sensors comprise a silicon diode to measure the body core temperature, whilst also compensating for temperature induced signal changes in the other sensors; an ion selective field effect transistor, ISFET to measure pH; a pair of direct contact gold electrodes to measure conductivity; and a three-electrode electrochemical cell, to detect the level of dissolved oxygen in solution. All of these measurements will, in the future, be used to perform *in vivo* physiological analysis of the GI-tract. These four sensors (pH, □, T, pO_2) not only provide useful information for applications in industry and biomedicine *per se*, but also are a platform that will enable greater sensor functionality to be created (e.g. the electrochemical oxygen sensor could be readily modified in order to develop a sensor interface for the implementation of immunoassay technology).

We have now presented real time wireless data transmission from a model *in vitro* experimental set-up, for the first time, and are currently working with the Veterinary School at the University of Glasgow on performing multi-channel *in vivo* experiments. Extensive literature searching has revealed that we are the only group world-wide working at this state of the art in multi-channel remote wireless sensing (e.g. there is already a class of oesophageal pH sensors that are available in clinical practice). There has also recently been serious interest from two multinational electronics companies in obtaining IP generated through this work.

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