Swallowable-Capsule Technology

Swallowable-capsule technology looks set to enter the realm of pervasive patient monitoring.

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The 1966 movie *Fantastic Voyage* showed a group of miniaturized scientists journeying through a living human body. Although the film's science was entirely fictional, the idea of exploring the human body captured the imagination. This vision is now becoming more achievable with recent advances in electronics, microsystem fabrication, and wireless communications, and a greater understanding of human physiology. Electronic microsystems can now be ingested to explore the gastrointestinal (GI) tract and can transmit the acquired information to a base station (see figure 1).

Annually, over 3 million people in the US alone suffer GI disease serious enough to require hospitalization. In over one-third of these cases, the cause is never found. Despite standard invasive examination techniques, much of the GI tract's inner workings remain a mystery. Procedures exist for examining the esophagus and stomach (gastroscopy) and the colon (colonoscopy), delivering some information at a cost of much distress to the patient. However, the small intestine remains inaccessible.

Swallowable capsules have been evolving for almost half a century and are now helping uncover GI tract mysteries in diagnostic and therapeutic applications. Here, we briefly review the history of the technology, present the state of the art, and describe ongoing research.

Capsule basics

In general, a swallowable capsule is a self-contained microsystem that performs a sensing or actuating function in the body. Usually the system consists of the core components in figure 2 encapsulated in a biocompatible material.

At one end of the chain are the sensors (or alternatively, actuators) that interface with the body. Sensors convert physical properties such as light, pressure, or temperature into electrical signals, while actuators perform the opposite function. The signal-conditioning block provides analog processing such as amplification and filtering to "clean" the detected signal. The system's brain, the CPU, digitizes the signal and might perform additional processing. The communication block can then transmit the signal to a receiver module outside the body. The communication medium can be RF, a magnetic field (inductive coupling), or ultrasound. Finally the power supply, based on either batteries or inductive coupling, provides energy for the system.

Technical challenges

In addition to the standard constraints in electronic design, a number of main challenges arise for systems that operate inside the human body. The foremost challenge is miniaturization to obtain an ingestible device. The availability of small-scale devices can place severe constraints on a design, and the interconnection between them must be optimized. Also the alternative, full integration on silicon, can be a long and expensive process. The size constraints lead to

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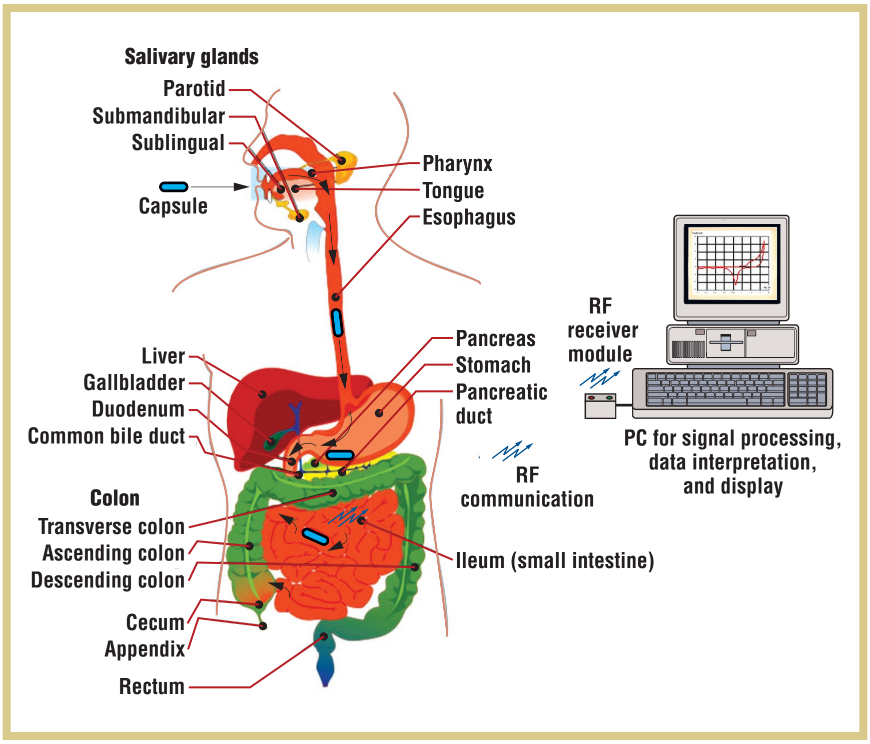


Figure 1. An ingested capsule transmits data wirelessly to an external base station.

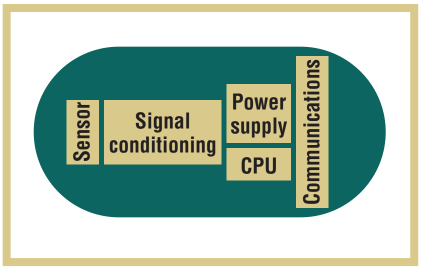


Figure 2. A block diagram of a swallowable capsule.

another challenge, noise. The coexistence of digital integrated circuits, switching converters for the power supply, and communication circuits in close vicinity of the analog signal conditioning could result in a high level of noise affecting the input signal. Therefore, capsule designers must take great care when selecting and placing components, to optimize the isolation of the front end.

The next vital challenge is to reduce power consumption. In battery-powered devices, the battery itself is likely the largest system component. Also, inductive links can handle only low levels of energy. Therefore, designers must minimize both supply voltage and current consumption while using high-efficiency topologies to achieve the required system performance.

Another challenge involves communication. In particular, the generated wireless signal must not interfere with standard hospital equipment but still be sufficiently robust to overcome external interferences. A dedicated RF communication standard is the Medical Implant Communication Service, operating in the 402–405 MHz range, although other Industrial Scientific and Medical bands such as 433.92 MHz are acceptable. The transmit power must be low enough to minimize interference with users of the same band while being strong enough to ensure a reliable link with the receiver module. Lower frequencies are used for ultrasound (100 kHz to 5 MHz) and inductive coupling (125 kHz to 20 MHz).

The human body is no place for operational obscurity, so the control software must enforce specific rules to ensure that all devices operate as expected. For that reason, key programs must be developed in a low-level (often assembly) language.

The last challenge concerns encapsulating the circuitry in appropriate biocompatible materials to protect the patient from potentially harmful substances and to protect the device from the GI's hostile environment. The encapsulation of contactless sensors (image, temperature, and so on) is relatively simple compared to the packaging of chemical sensors that need direct access to the GI fluids.

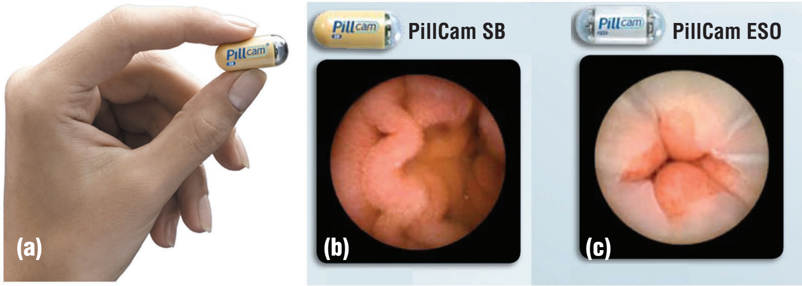
Obtaining FDA approval for the US market or CE (European Conformity) marking in Europe involves additional requirements. Capsules must undergo extensive material-toxicity and reliability tests to ensure that ingesting them causes no harm.

Early capsules

The swallowable-capsule concept first appeared in 1957 in R. Stuart Mackay and Bertil Jacobson's groundbreaking paper on RF transmission of temperature and pressure from within the human body.[1] Because transistors were rare and miniature batteries were unavailable, most of the early concepts used inductive links. In the early 1960s, Carlos A. Abella[2] and Jean-Pierre Perrenoud[3] each received a patent for systems based exclusively on mechanical devices (capillary structures) to extract or deposit fluids in the GI tract. These systems achieved control through strong external electromagnetic fields. Researchers also worked on optimizing the coil geometry to improve energy and data transfer.[4] In 1972, Matsushita further developed and patented Mackay and Jacobson's early concept to implement simple sensing capsules for pH, temperature, and pressure.[5] These concepts provided a design platform for many of the subsequent commercial capsules.

As the 1990s began, the snowball of the semiconductor revolution had

Figure 3. PillCam: (a) the capsule's relative size, and PillCam-produced images of (b) a healthy small intestine and (c) an esophagus. (images courtesy of Given Imaging)



become an avalanche. In its wake, new worlds of digital computing and microprocessing held unimaginable potential in all areas of electronics. The previously unreachable goal of performing detailed sensing and signal processing inside the body was slowly becoming a reality, as new technologies offered the accuracy, control, and miniaturization necessary to implement many ideas patented decades earlier. The introduction of smart technology and microelectromechanical systems (MEMS) in the last decade has greatly accelerated capsule development. Despite the long history of swallowable-capsule research, most of the early patented devices never made it outside the laboratory. The commercialization of such devices has occurred only in the last few years.

Commercial capsules

Some of the early concepts are now on the market. Families of sensing capsules provide temperature, pressure, imaging, and pH data to complement classic diagnostics, and one capsule delivers medication.

Temperature

One of the first commercial successes was the Ingestible Thermometer Pill, developed in the late '80s at John Hopkins University with NASA's support.[6] The initial aim was to monitor the core temperature of astronauts working in hostile space environments with temperatures varying from 120°C to –150°C. The device contained a single-cell nickel-cadmium battery that was wirelessly recharged before its use, giving a long shelf life. The frequency of the transmitted near-field signal was directly proportional to the temperature to a resolution of approximately 0.1°C, thanks to a temperature-sensitive crystal oscillator.

Heat-exhaustion-related deaths in American football sparked the pill's evolution into CorTemp in 2001.[7] Researchers carried out tests on the University of South Florida football team in 2005; many US National Football League teams have since used the capsule. More recently, the pill has seen use in other sports including soccer and hockey and in areas such as firefighting, deep-sea diving, and the military.

Similar real-time core-temperature-monitoring systems such as VitalSense (www.minimitter.com/Products/Brochures/900-0138-00_VS.pdf) have also emerged. VitalSense, targeted at unobtrusive patient monitoring, combines an ingested capsule (Jonah) and a dermal patch to monitor core and surface body temperatures.

Imaging

Capsule endoscopy emerged through the '80s and '90s and has become a realistic alternative to standard wired endoscopy.[8] Capsule endoscopes couple one or more imaging devices with a lighting source to capture images of the GI tract, including the small intestine. For the patient, such capsules offer a convenient examination with minimal preparation and immediate recovery. The main vendors are Olympus Optical (www.olympus-global.com/en/global), Given Imaging (www.givenimaging.com), and the RF System Lab (www.rfsystemlab.com). Specific challenges to capsule endoscopy include effective illumination of the region to be imaged and the relatively large volume of data associated with captured images.

Olympus received one of the first major patents in 1981.[9] The proposed device applied strong magnetic fields outside the body to control the capsule's displacement and orientation in the stomach, to turn the light on, and to trigger the shutter opening. It initially contained no intelligence or processing capability, and the capsule had to be opened to retrieve the images. The design has evolved to miniaturize the capsule and improve image quality.[10] The latest capsule boasts excellent image quality, brightness adjustment, real-time video viewing, and the ability to activate and deactivate the capsule. This device's specifications aren't as freely available as some others on the market. Olympus is reported to be investigating different methods of communication, powering, and imaging, while considering additional functions such as drug delivery, tissue sampling, internal ultrasound, and propulsion systems. Olympus released the device in Europe under the name EndoCapsule in October 2005. However, FDA approval is still pending for the capsule, so its use has been restricted to Europe, Australia, and several Asian countries.

Given Imaging has developed a similar endoscopy capsule, initially called the M2A.[11] Competition is intense between Olympus and Given Imaging, evident in ongoing lengthy and expensive patent litigation regarding the ownership of the endoscope pill concept and its developments. Given Imaging has developed two distinct capsules: PillCam ESO[12] for the esophagus and PillCam SB for the small bowel (see fig-

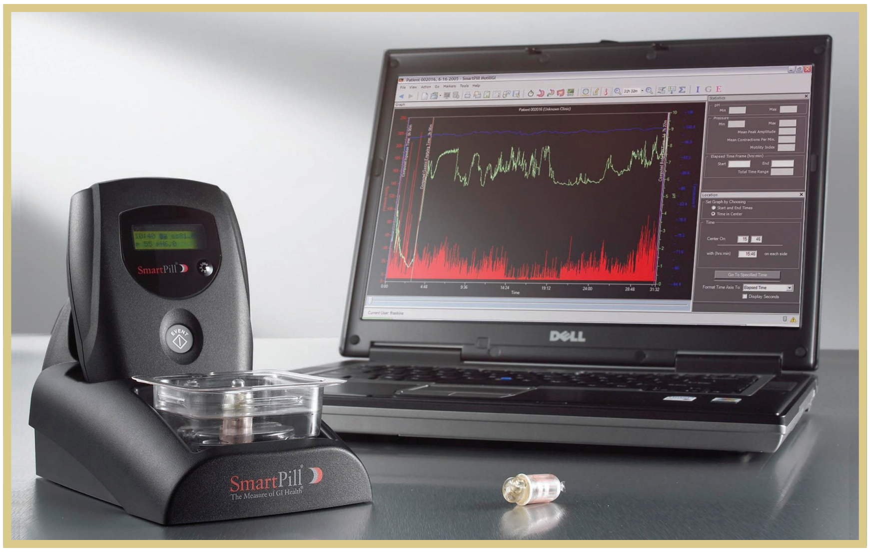


Figure 4. The SmartPill GI Monitoring System includes the SmartPill pH.p, a receiver, a docking station, and a PC user interface. (image courtesy of SmartPill Corp.)

ure 3). Both capsules measure 11 mm in diameter and 26 mm in length. RF data transmission at 433.10 MHz to an external antenna network enables the transfer of two to eight frames per second. The device, powered by silver-oxide batteries, can provide over five hours of continuous video recording.

Figure 3 shows PillCam-produced images of healthy patients. (To view other images from PillCam, see www.given.com/given/pdf/Platform_Brochure_2006.pdf.)

Given Imaging provides a complete analysis system including the pill, a data recorder, a docking station, and RAPID, a software package for displaying and analyzing images and generating full medical reports. The company is developing a third capsule, PillCam COLON, for the colon and large intestine. It will also soon release the recently FDA-approved second generation of SB and ESO capsules. Full FDA approval has given the company an advantage over its competitors; as a result, PillCam is available in almost every developed country.

The RF System Lab has been developing the Norika3 system since 1998. Unlike PillCam, which uses CMOS (complementary metal-oxide semiconductor) image sensors, this device uses a CCD (charge-coupled device) image sensor. This results in superior image quality but with much greater power consumption due to the intense digital signal processing involved. To tackle the power requirement, the capsule transmits raw sensor data, while the processing, which consumes over 90 percent of the power, occurs outside the body. The capsule, 9 mm in diameter and 23 mm long, is the smallest endoscopy capsule. It has four illumination LEDs with different light wavelengths. Three-dimensional coils within the capsule allow optimum power recovery from the inductive link.

The system consists of the capsule; a vest with power transmission coils; a joystick-like device to control the capsule; and a PC system for signal processing, image display, and data storage. The second-generation capsule Sayaka (www.rfamerica.com/sayaka/index.html), introduced in December 2005, operates on the same principle but has the lens on its lateral surface instead of its end. The imaging device is rotated within the capsule by steps of 7.5 degrees and provides approximately 30 frames per second, giving overall higher resolution.

Multisensor

The SmartPill Corporation has integrated temperature, pressure, and pH sensors into a single capsule, the SmartPill pH.p (www.smartpillcorp.com/index.cfm?pagepath=home/products/the_smartpill_pHp_capsule&id=395). The company promotes the device as a complement to endoscopy with the potential to replace gastric-emptying scintigraphy. The SmartPill GI Monitoring System (see figure 4) includes the capsule, a wireless data receiver, a receiver docking station, and MotiliGI software. A powerful magnet activates an internal latching switch that provides a connection between the electronics and the battery. Once the capsule is activated, it begins working and transmits data to the mobile-phone-sized receiver (worn on the patient's belt). The receiver, in turn, transfers the data wirelessly to a PC in real time.

The SmartPill, which has a 13-mm diameter and is 26 mm long, measures temperature to an accuracy of ±0.5°C, pressure resolution to ±3.6 mm HG, and pH to ±0.28. It uses the sensor data in addition to real and elapsed time measurements to provide gastric-emptying time, combined small and large intestine transit time, contraction patterns, and a motility index. To optimize the device's performance, the pill samples at a high rate for the first 24 hours and then at a decreased rate as the pill approaches the end of its journey. MotiliGI can plot the acquired data against time, providing invaluable information in the diagnosis of motility disorders such as gastroparesis (slowed passing of solids from the stomach). The pill underwent extensive clinical trials and consequently received FDA approval in July 2006.

Drug delivery

Another interesting area of swallowable-capsule technology is in-vivo drug delivery or, conversely, sample extraction. Pharmaceutical Profiles is researching drug absorption using

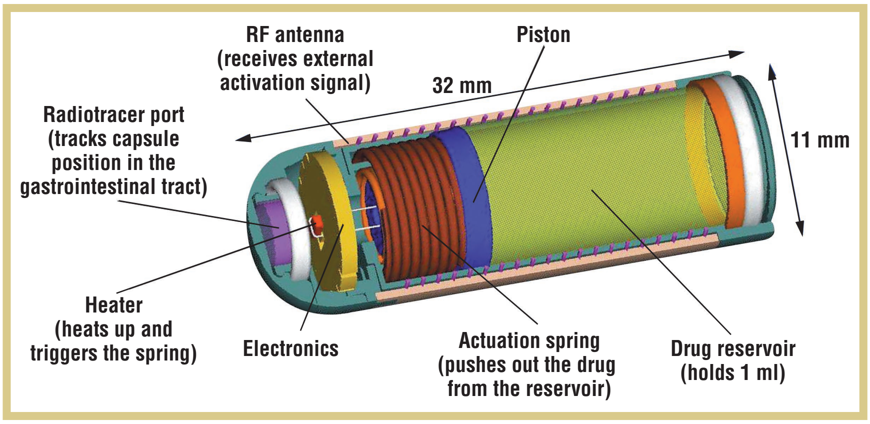


Figure 5. The Enterion drug delivery capsule. (image courtesy of Pharmaceutical Profiles)

the patented Enterion capsule (www.enterion.co.uk), developed by Phaeton Research. The capsule (see figure 5) is 32 mm long and 11 mm in diameter. It can hold up to 1 ml of liquid or powder, which it can expel at a target site in the body. The capsule contains a small amount of gamma-emitting tracer, allowing precise tracking in real time using an external gamma camera. When the capsule reaches the target area, an external electromagnetic field actuates the capsule's piston, ejecting the payload. The shell then passes harmlessly out of the body. Another piston-based capsule, developed at the University of New York, extracts substances from a target location in the GI track in a similar fashion.[13]

Research

The commercial successes we've described center on capsule endoscopy and very simple sensing applications. However, swallowable-capsule research is becoming more and more ambitious, encompassing far more complex and interesting developments. In particular, the evolution of MEMS is profoundly affecting what you can do in a device small enough to be swallowable.

Controlling locomotion

One of the simplest locomotion devices is a microbot that mimics a worm's rhythmic contractions through the linear movement of four surfaces on opposite sides.[14] These moving surfaces make contact with the intestinal wall and push the capsule forward. Another method of motion involves the electrical stimulation of the small-intestine wall.[15] The capsule moves along the small intestine by emitting electric pulses that activate the motor nerves, causing muscle contraction. The University of Colorado is developing a Vortex Drive system, which generates tiny puffs of air to provide propulsion, and could potentially drive a capsule through the intestine.[16]

Tracking location

One way to determine rough location is to place an antenna array around the body and measure signal strengths at each antenna, as Given Imaging has proposed. As we mentioned before, the Enterion capsule uses a radioactive tracer and a gamma camera to provide more accurate positioning. Another recently developed location system involves ultrasound signals.[17] The capsule can emit ultrasound waves for external detection, or it can echo waves emitted externally.

Tracking movement

The ESO-Pill monitors the bolus transit time in the esophagus.[18] Current techniques for diagnosing esophageal motility disorders include catheter-based impedance monitoring and radiography of radio-opaque liquid. The capsule, developed at the University of Calgary, contains a capacitive MEMS accelerometer. After conditioning the signal from the accelerometer, the capsule transmits the signal to an external module for processing. Through successive mathematical integrations, the propagation velocity and the capsule's displacement can be retrieved. The first-generation capsule is limited to the esophagus because acceleration levels in the stomach exceed micro-accelerometers' monitoring range.

Integrating multiple sensors

The IDEAS (Integrated Diagnostics for Environmental and Analytical Systems, www.elec.gla.ac.uk/groups/nano/mst/IDEAS_BROCHURE.pdf) project uses *system-on-a-chip* technology to integrate all electronic functionality onto one chip.[19] The project also employs the biological *lab-on-a-chip* technique to enable microscale implementation of chemical and biological processes. The team claims to have invented Laboratory in a Pill, which combines SoC and LOAC technologies.

The capsule contains a range of classic sensors for temperature, conductivity, and pH in conjunction with a chemical sensor for measuring dissolved oxygen in the intestine. It samples intestinal fluids through a series of microchannels. A low-frequency inductive link provides real-time data transfer to an external module, while batteries provide power. A specific communication protocol (based on TCP/IP) was developed for wireless data transfer to a remote clinician. This protocol may be easily adapted for GSM or 3G networks. Figure 6 shows the latest prototype of the 35-mm pill.

In early 2007 Wireless bioDevices (www.wirelessbiodevices.com), a spin-off of the IDEAS project, became the first company to specialize in swallowable biosensors. The company's pill targets the early diagnosis of bowel cancer and contains a sensor to detect intestinal bleeding.

Figure 6. In the Ideas (Integrated Diagnostics for Environmental and Analytical Systems) project's Laboratory in a Pill, a plastic shell encapsulates the device electronics. (image courtesy of the Ideas team)

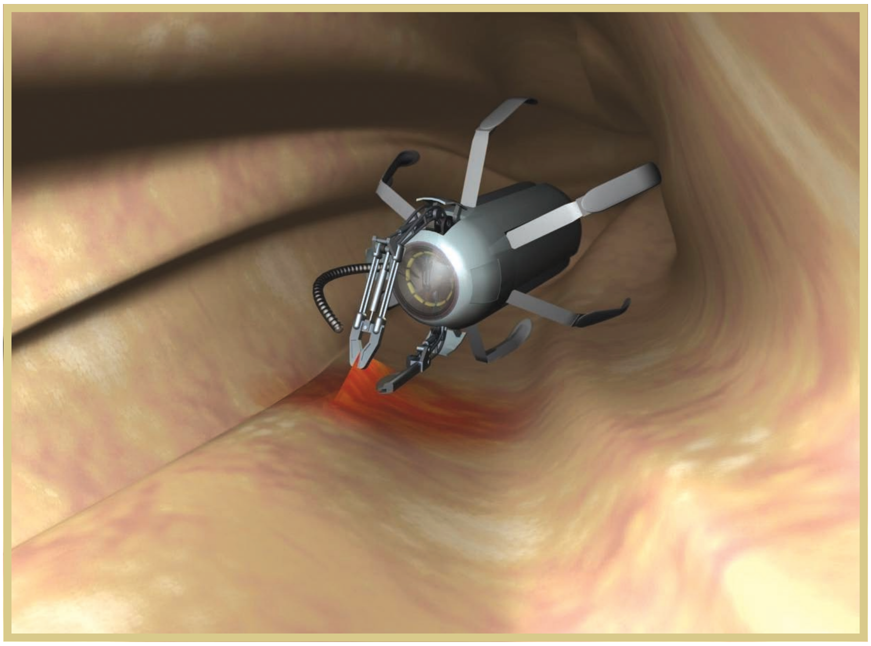


Figure 7. An artists' impression of the Vector (*V*ersatile *E*ndoscopic *C*apsule for Gastrointestinal *T*umor *R*ecognition and Therapy) capsule, which would use its imaging lens and mechanical arms to perform therapy. (image courtesy of Mats A. Heide, Sintef)

Providing therapy

Vector (*V*ersatile *E*ndoscopic *C*apsule for Gastrointestinal *T*umor *R*ecognition and Therapy, www.vector-project.com), funded under the European Union Sixth Framework Program, is an ambitious integrated project. Running from September 2006 until August 2010, it's investigating the use of complex robotic systems for advanced therapy inside the human body. Using the latest microelectronics and nanotechnology advances, it intends to make significant advances in the diagnosis and treatment of digestive cancers. Novineon Healthcare Technology Partners GmbH is leading a consortium of 19 companies, research groups, and medical clinicians.

The capsule, called a "robotic beetle" (see figure 7), would contain an endoscopy system employing ultrasound transducers and bioanalytical and mechanical sensors. Robotic arms would obtain tissue samples and provide treatment such as targeted drug releasing and thermal tissue destruction. The project is also studying a locomotion system that uses retractable legs to control capsule movement; a clinician would maneuver the capsule using live video navigation.

Integrated biomedical technology might well be the key to the first major scientific revolution of the 21st century, comparable to the semiconductor revolution of the late 20th century. Advances in areas such as nanotechnology, microrobotics, micro power generation, and materials science will present more interesting and exciting opportunities for capsule research projects to exploit. As capsule hardware evolves so too will computing and communication capabilities. Full integration of multiple capsules with implants of other kinds and external diagnostic equipment will move swallowable-capsule technology toward body sensor networks for pervasive patient monitoring. In the years to come, capsules will become smaller and perform more complex diagnostic and therapeutic functions in the human body.

ACKNOWLEDGMENTS

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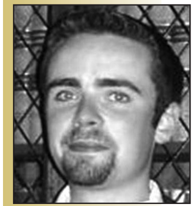

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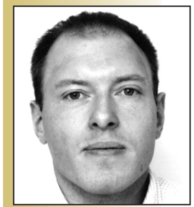

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