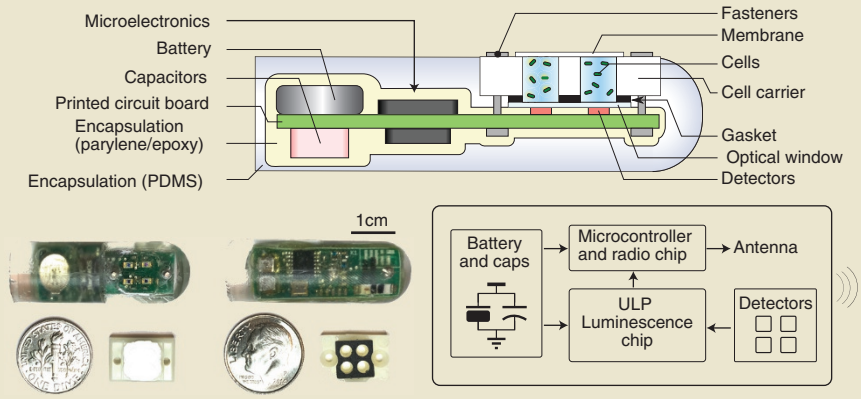
Reportage from the gut

Sensors that track our health could enable earlier disease detection and therapeutic intervention. Few applications are more intriguing than ingestible sensors that report on the health of the gastrointestinal (GI) tract in real time. But engineering these devices has not been trivial and progress has been slow. Writing in *Science*, Mimee *et al.*[1] describe a device that combines electronics and engineered bacteria to monitor intestinal bleeding[1]. They encapsulate bacteria that sense heme, and the versatile system they describe might form the basis for future ingestible sensors.

A swallowed pill that detects biomarkers and sends wireless reports as it journeys through the GI tract is a goal of twenty-first century precision medicine. Towards this aim, capsules that are able to, for example, sense gases (oxygen, hydrogen and carbon dioxide), carry a camera, measure pH, or report on medication compliance have been devised. But on the whole, progress in the field has been disappointing, particularly in the development of sensors that can measure a range of useful biomarkers.

Ideally, "ingestible sensors would be able to detect multiple biomarkers that together indicate the health of the GI tract," says Kourosh Kalantar-Zadeh, a professor of engineering at RMIT University in Melbourne, Australia. He points out that "the lumen of the gut is in constant contact and exchange with other bodily fluids, which we can access non-invasively with ingestible sensors." A wealth of data could potentially be obtained with effective sensors.

The sensor developed by Mimee *et al.*[1] is the first to combine synthetic bacterial circuits with electronics. It detects heme using bacteria that express a gene circuit from a promoter that is regulated by a heme-sensitive repressor. The output of the circuit is luciferase, which is recognized by photodetectors present in the electronics. The signals are processed, and the data are transmitted by radio to a computer or phone. The device is watertight and encapsulated in a semipermeable membrane that enables constant contact with the lumen of the GI tract.



Modified with permission from ref. 1.

To demonstrate the capabilities of their device, the authors present a proof-of-principle experiment in pigs[1]. The animals, after being placed on a liquid diet for a day, received a neutralizing solution with or without a bolus of blood, and the capsule was deposited in the gastric cavity using endoscopy. The researchers obtained data from the capsule over a two-hour period and observed induced luminescence within 30 minutes.

These results are a good starting point, and prove that the capsule can detect blood *in vivo* in real time. Although occult blood tests enable non-invasive diagnosis of bleeds in the colon, hemorrhages are more difficult to detect in the small intestine. How the capsule compares with imaging in terms of sensitivity is unclear, in part because of difficulties in modeling this in animals.

As Timothy Lu, a professor at MIT and a senior author in the study[1], readily admits, the position of the sensor in the GI tract cannot easily be tracked. And Kalantar-Zadeh says, "Being able to determine where the device is in the GI tract at any given moment is critical." Both oxygen levels and pH are good indicators of position within the gut, so sensors that incorporate one of these two measurements would enable trackability.

Lu also recognizes that the capsule prototype is relatively large. "We need to make it smaller and to automate its assembly," he says. "The first ones we pretty much built by hand."

Using bacteria as the sensing module could provide opportunities for detection of the many biomarkers for which synthetic circuits can easily be built. "We could also multiplex by placing several optical sensors and engineered bacteria on the same chip," says Lu. "We believe the bacteria can be made to be quite sensitive," he adds.

As with small children learning to walk, every attempt is an opportunity to celebrate. In this case, the combination of synthetic biology and bioengineering could be the start of a sprint to engineer a new class of gut sensors.

Irene Jarchum,
Senior Editor

1. Mimee, M. *et al.* An ingestible bacterial-electronic system to monitor gastrointestinal health. *Science* **360**, 915–918 (2018).