

IMPLANTED DEVICES

A biodegradable wireless blood-flow sensor

A soft implant wirelessly senses arterial blood flow post-surgery before being gradually resorbed.

Krishna Yeshwant and Roozbeh Ghaffari

Implantable devices for measuring intravascular pressures and blood flow are essential for the management of patient health and for the surveillance of disease progression. Because sensing devices implanted during vascular and surgical interventions have to be extracted after they are no longer needed, morbidity risks (such as major complications and infections) associated with surgical extraction can constitute a significant cost burden. Biodegradable soft materials, sensors and actuators have enabled fully integrated implantable systems that can wirelessly sense pressure, flow, temperature and electrophysiological variables, such as voltage or current changes^{1,2}. Such biodegradable devices have accuracy and sensitivity profiles that match conventional electronic systems, and can be designed to dissolve in a controlled manner (ideally over a narrow time window, and leaving behind innocuous by-products) after their period of function, thereby circumventing device extraction. For vascular surgical procedures (such as vessel anastomosis), sensing devices need to be highly miniaturized, soft, flexible and biodegradable, so that they can wrap around arteries and ideally operate wirelessly over extended periods without the need for batteries. Reporting in *Nature Biomedical Engineering*, Paige Fox, Zhenan Bao and colleagues now demonstrate a biodegradable and battery-less implantable cuff-like device that wraps around an artery to measure pulsatile blood flow and that wirelessly transmits the captured data to an external receiver³. Pulsatile blood flow causes detectable changes in the capacitance of the device, which consists of a fringe-field capacitive sensor that couples to the exterior vessel wall, and this in turn generates a shift in the resonant frequency (on a cycle-by-cycle basis) of an inductor–capacitor–resistor circuit. These data are transmitted wirelessly via inductive coupling to an external reader coil positioned on the surface of the skin (Fig. 1a–c).

To make a biodegradable device that interfaces with a blood vessel,

and achieves high performance and a stable operation, Fox and co-authors created a multilayered stack of materials that provided a mechanically robust yet soft interface with well-established biocompatibility. They used poly(octamethylene maleate (anhydride) citrate) and polyhydroxybutyrate/polyhydroxyvalerate, as packaging layers (each thinned to 10 μm) that provided a soft mechanical interface around the vessel wall, with minimal mechanical loading, so as to capture the effects of pulsatile blood flow. A 50- μm -thick magnesium layer as an electrical interconnection was deposited in between the packaging layers, coupled directly with a microstructured poly(glycerol sebacate) 40- μm -thick dielectric layer and a 50- μm -thick insulating layer of poly(lactic acid) to space the magnesium coils (Fig. 1d). This design approach allowed for rapid iterations in electronics architecture to test for optimal capacitance and resonant-frequency responses, while considering cost and size trade-offs.

Advances in high-volume and low-cost fabrication of biodegradable electronics and packaging are critically important for establishing biodegradable electronics as a broadly deployed technology. To facilitate wide-scale adoption beyond proof-of-concept prototypes, Fox and co-authors used simple benchtop lamination-and-deposition techniques that could be implemented in existing manufacturing facilities and foundries. Although there are additional electronics and communication building blocks that would be needed for continuous wireless monitoring, the authors' benchtop and in vivo results (Fig. 1d–f), enabled by capacitance sensors, electronics for near-field-communications, and inductive power and data transmission, highlight the potential for this technology to be used in many surgical procedures. The authors observed stable sensor function and blood-flow recordings for over one week of operation in vivo, yet noted changes in the quality factor of the signal over this time period. Naturally, materials-science

challenges related to maintaining stable operation over an extended lifetime, while concurrently initiating the bioresorption processes, would have to be addressed before first-in-human tests and broad clinical deployment of biodegradable electronics can be carried out.

A growing body of research has focused on the critical importance of tuning the geometries and physical properties of the materials encapsulating biodegradable electronics so as to avoid biofluid exposure to active electronic modules and thus prolong the lifetime of the devices. A variety of existing encapsulating materials, including poly(lactic acid), silk fibroin and poly(lactic-co-glycolic acid), are attractive candidates because of their biocompatibility and easy-processing properties⁴. However, these classes of encapsulating material can undergo microcracks, nanocracks and fractures, creating leakage pathways that prematurely disrupt sensor function. Additional coating layers consisting of protective thermally grown silicon dioxide could provide a robust barrier, enabling controlled dissolution primarily via hydrolysis⁵ without impacting sensor accuracy, and facilitating operating times that span weeks or months.

The effects of mechanical loads caused by local movements and body deformations pose another major challenge to the long-term stability and performance of biodegradable implants. Future histological studies that characterize the effects of cyclical mechanical stresses at the device/tissue interface, and of the bioresorption of the biodegraded products, will help create the necessary safety data to support clinical studies in humans. Even when the key materials are water-soluble and lead to biocompatible end products, the distribution of dissolved materials in the blood stream and vital organs will require preclinical and clinical surveillance studies of immune response, blood toxicity and blood chemistry over extended periods following bioresorption.

Although inductive coupling enables wireless and battery-free operation,

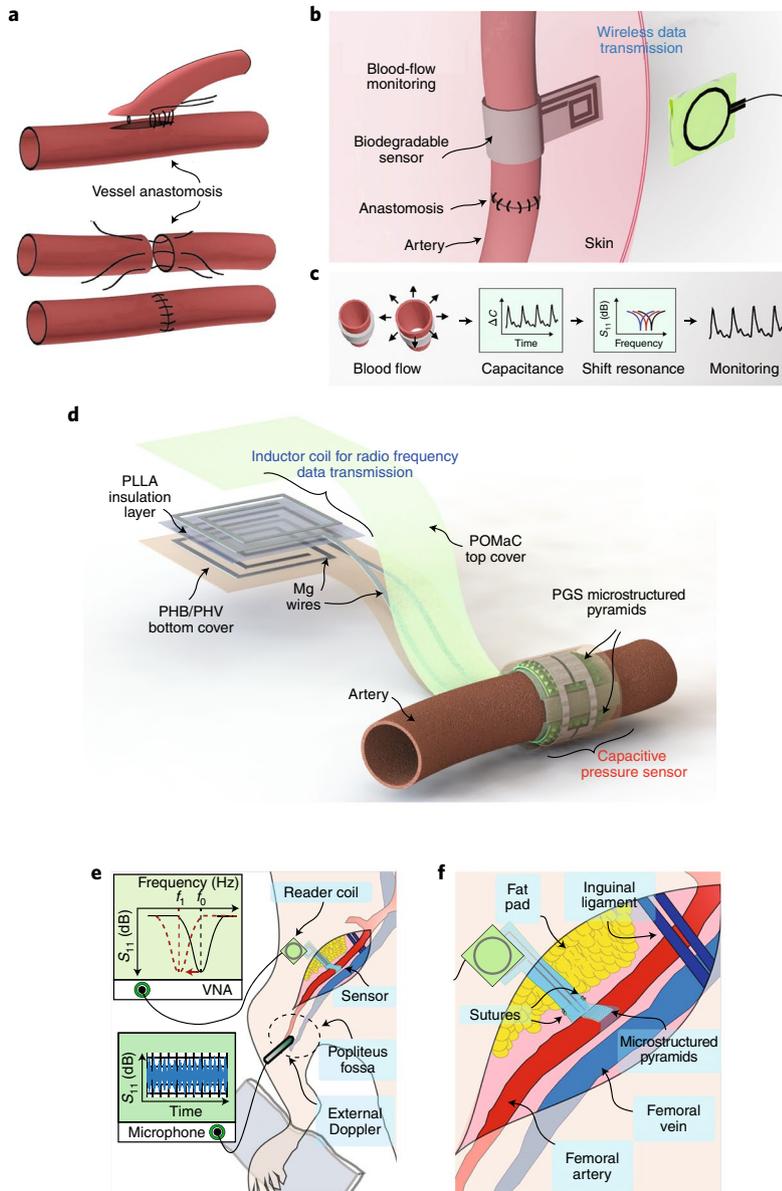


Fig. 1 | Biodegradable implantable device for monitoring arterial blood flow in cardiovascular, reconstructive or organ-transplant surgery. **a**, Vessel anastomosis³. **b–d**, The biodegradable sensor, made of magnesium wires laminated with layers of dielectric (poly(glycerol sebacate), PGS), insulating (poly(lactic acid), PLLA) and packaging (polyhydroxybutyrate/polyhydroxyvalerate, PHB/PHV; and poly(octamethylene maleate (anhydride) citrate), POMaC) materials, and wrapped around the anastomosed artery, generates capacitance and resonant-frequency data. These data are transmitted via inductive coupling to an external reader coil in contact with the skin. S_{11} , reflection coefficient. **e, f**, The biodegradable device implanted in a small animal for in vivo testing. A Doppler ultrasound detects the pulse rate, and a microphone records the Doppler ultrasound signal. VNA, vector network analyser. The pyramidal microstructure of the PGS dielectric layer enables improved sensor sensitivity and response time. f_0 and f_1 , resonant frequencies. Figure reproduced from ref. ³, Springer Nature Ltd.

continuous monitoring would require a biodegradable power source. Conventional battery technologies are typically sealed off from biofluids and contain toxic chemicals that are largely incompatible with biological tissues. This mismatch has led to new opportunities for robust biodegradable power sources. For instance, a fully biodegradable encapsulated magnesium–molybdenum trioxide (Mg–MoO₃) battery with high energy density and capacity (6.5 mWh cm⁻²) and stable output voltage (~1.6 V) has been shown to power a light-emitting device for up to 13 days⁶.

Biodegradable implantable monitoring systems are poised to provide critical insights in the weeks and months following vascular surgeries and reconstructive procedures. Assuming that the stability challenges and long-term safety risks are addressed in animal models, the biodegradable device demonstrated by Fox and co-authors could lead to medical-implant technologies that detect changes in haemodynamics and vascular health in clinical settings, and at home once patients are discharged. The physical designs, soft materials and tissue-like mechanics underpinning these biodegradable devices could lead to fully integrated biodegradable systems with multifunctional diagnostic and therapeutic capabilities, thereby eliminating the need for device-extraction surgeries and fundamentally changing patient-care management post-surgery. □

Krishna Yeshwant¹ and Roozbeh Ghaffari^{2*}
¹Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. ²Center for Bio-Integrated Electronics, Department of Biomedical Engineering, Northwestern University, Evanston, IL, USA.
 *e-mail: rooz@northwestern.edu

Published online: 8 January 2019
<https://doi.org/10.1038/s41551-018-0345-4>

References

- Hwang, S. W. et al. *Science* **337**, 1640–1644 (2012).
- Yu, K. J. et al. *Nat. Mater.* **15**, 782–791 (2016).
- Boutry, C. M. et al. *Nat. Biomed. Eng.* <https://doi.org/10.1038/s41551-018-0336-5> (2019).
- Shin, J. et al. *Nat. Biomed. Eng.* <https://doi.org/10.1038/s41551-018-0300-4> (2018).
- Chang, J. K. et al. *Proc. Natl Acad. Sci. USA* **114**, 5522–5529 (2017).
- Huang, X. et al. *Small* **14**, 1800994 (2018).