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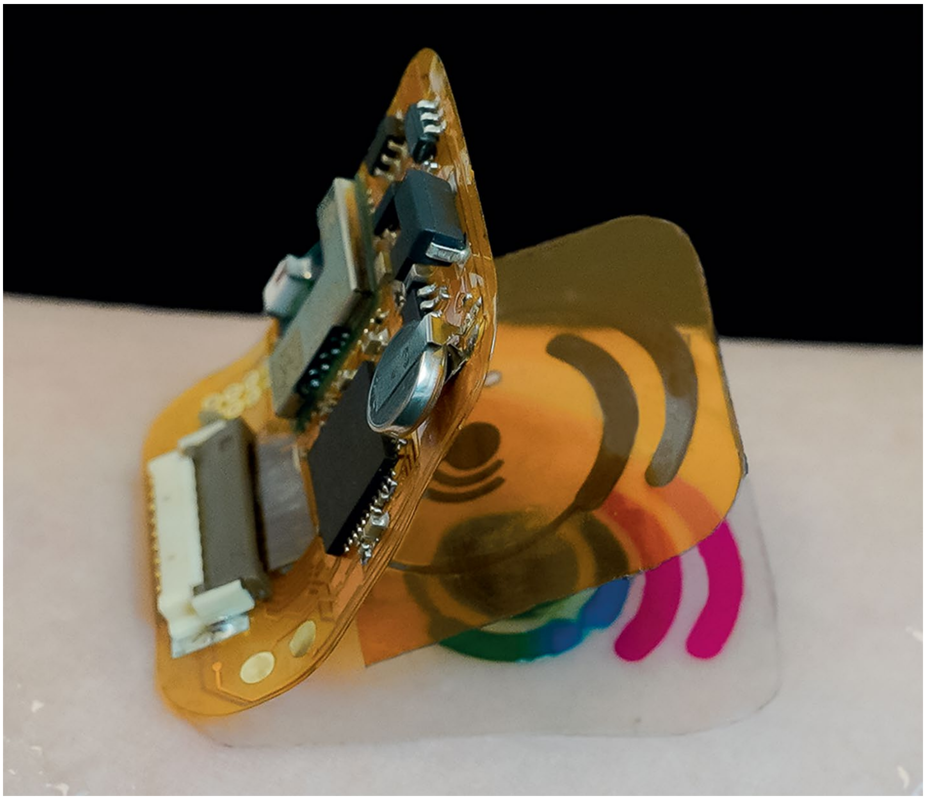
Ever easier health monitoring

The management of health and of disease conditions will eventually be supported by ever more integrated and less conspicuous wireless bioelectronic devices designed to continuously monitor multiple biomarkers.



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What features and capabilities are desirable in devices for the continuous monitoring of health? Taking today's smartwatches and other wearables for fitness tracking as a guide, three general characteristics seem to be essential: wearability without wires, multifunctionality without parts, and reliability without bulkiness. Health-monitoring devices — or at least their interfaces with the body — should be largely inconspicuous and ideally wireless so that they are comfortable to use, should be able to measure multiple physiological signals to provide rich health data preferably within a single device or interface, and the measurements should be reliable without sacrificing device footprint.

These functionalities and engineering constraints can be better balanced by taking advantage of the ever greater miniaturization and power efficiency of electronics[1,2], as well as advances in materials, device designs and fabrication strategies[3]. Naturally, each intended health application (such as monitoring health status, detecting the onset of disease, or following the progression of a known condition or the effectiveness of a treatment for it) and, in particular, the bodily source and types of biomarker to be monitored, will determine the specific functionalities and constraints for the device and technologies used. And each type of sensing technology, material and fabrication method comes with its own set of limitations. For example, a decision of where to measure the concentration of a biomarker (in blood, in interstitial fluid or in sweat, for example) needs to take into account accuracy (specifically, sensitivity), reliability and device invasiveness. And monitoring biomarkers from distant body parts (for instance, in the heart and in the peripheral vasculature) may require multiple separate sensors, and bring about challenges in device integration and data management.

This issue of *Nature Biomedical Engineering* highlights seven advances in the application of wearable, ingestible and implantable bioelectronic devices for the continuous monitoring of health status, of disease progression or of the effectiveness of treatment. All the highlighted research advances are at a relatively early stage of technology development and provide proof-of-concept evidence for the technology's intended use. They all involve the rational design, use, adaptation or optimization of state-of-the-art materials, sensors and methods to best navigate the specific needs and constraints of the intended application.

Individuals with cardiovascular conditions would benefit from small and untethered devices that can monitor vascular haemodynamics in real time. Today, devices for the monitoring of the cardiovascular system in patients involve catheters and wired connections to external electronics, and hence are typically unsuitable for outpatient settings. And wireless devices for measuring blood haemodynamics have so far tracked either blood pressure or blood flow. John Rogers and colleagues now demonstrate an integrated miniaturized implant that can continuously and simultaneously track blood pressure, flow rate and temperature, and that transmits the data and receives power wirelessly. The sensor is intended for use in patients at risk of heart failure or stroke, can be implanted via a minimally invasive transcatheter procedure, and can also be mounted on surgical clips, intravascular stents, cardiac-valve prostheses and other standard clinical devices. The device performed as well as clinical devices for the monitoring of blood flow and pressure, as the researchers show in pigs (with the device implanted in the pulmonary artery) and sheep (with the device mounted on a stent placed in the aorta). Because the implant is in contact with blood, the device will have to meet the requirements of long-term biocompatibility and reliability of use.

Patients with a very high risk of heart failure undergo invasive monitoring of cardiac output and vascular resistance through catheter-based devices. When risk is lower, the patient is often instructed to perform frequent measurements of blood pressure at home and to report any relevant symptoms (such as dizziness or fatigue). In another Article by John Rogers, Daniel Franklin and colleagues, the researchers report a non-invasive wearable technology for the continuous measurement of multiple biomarkers of cardiovascular health. The technology involves sensors placed on different parts of the body (on the chest next to the heart; and close to peripheral arteries, such as on a wrist or a finger), and the recording of metrics related to vascular resistance, cardiac output and blood-pressure regulation via synchronized sensors for chest electrocardiography, seismocardiography and peripheral multispectral photoplethysmography. The researchers show that the synchronized wearables could be used to classify haemodynamic states resulting from a number of stimuli (such as exposure to heat or cold, physical exercise, or breath holding, as well as from vasopressor administration during post-operative hypotension) in healthy individuals, individuals with hypertension, and patients recovering from cardiac surgery.

Cardiovascular conditions and many other diseases can raise the levels of inflammatory biomarkers in blood. However, their quantification at sufficient sensitivity requires a blood draw and laborious analytical procedures. Instead, the real-time monitoring of inflammatory biomarkers, ideally in sweat and hence non-invasively, would allow for the tracking of the progression of disease. Yet, reliably measuring the levels of proteins in sweat involves addressing the challenges that arise from large interpersonal and intrapersonal variations in sweat composition. Wei Gao and colleagues now show a wearable and wireless on-skin patch (pictured) for the real-time detection of the inflammatory biomarker C-reactive protein in sweat, as well as ionic strength, pH and temperature. The device combines technologies for autonomous sweat induction (via iontophoresis), sweat sampling and reagent routing and replacement (via microfluidics) and in situ immunosensing (electrochemically, via a graphene-based electrode functionalized with antibodies for C-reactive protein). The researchers show that the levels of the inflammatory biomarker in blood and sweat were highly correlated, and that the device measured high levels of it in the sweat from patients with chronic obstructive pulmonary disease, with active or past infections, or who had heart failure. The device will, however, need to be optimized for usability, to make it easier to wear it for longer, and to allow for the reagent cartridges to be easily replaced.

Biomarkers that can be measured in sweat can also be helpful in the monitoring of brain conditions. For example, measuring lactate levels while recording electroencephalograms can aid the discrimination of epileptic seizures from non-epileptic confounders[4]. In addition, metabolic biomarkers have been associated with brain function[5]. Gert Cauwenberghs, Joseph Wang, Sheng Xu, Patrick Mercier and colleagues report wearable sensors, mounted on an earbud, for simultaneous metabolic and electrophysiological sensing inside the ear canal. Specifically, the researchers show that the device can be used to detect lactate levels in sweat and to monitor brain states via electroencephalography, electrooculography and electrodermal activity, as demonstrated with volunteers performing acute bouts of exercise.

The mechanical behaviour of tissue can also be considered as a source of biomarkers of disease. For example, the Young modulus of diseased tissue can reflect underlying pathophysiological conditions[6]. Tissue modulus can be measured through elastography via magnetic resonance imaging, ultrasound or optical coherence imaging, but the devices are commonly bulky, and portable versions do not typically allow for frequent measurements with sufficient spatial resolution. Techniques based on tissue suction, indentation or compression can also probe tissue, but only its superficial layers. To enable frequent and serial measurements, Sheng Xu and colleagues now describe an ultrasonic array of electrodes that conforms to tissues in the human body and that allows for serial, non-invasive elastographic measurements of tissues deep under the skin at spatial resolutions below a millimetre. The researchers exemplify the utility of the arrays by mapping and monitoring microstructural damage before the delayed onset of soreness in the muscles of volunteers and by monitoring the recovery of muscle injury during physiotherapy. However, the device prototype requires wires for data and power transmission and a desktop-based control system, but low-power integrated circuits and lithium–polymer battery technologies could make the technology portable or even wearable.

Treating neoplasms of the nervous system often requires surgical excision and the use of intraoperative neurophysiological monitoring to preserve the structural and functional integrity of the nerves. However, it is difficult to maintain stable and reliable recording of near-field potentials during microsurgery (and far-field potentials are weak, requiring long-time acquisitions). Wang Jia, Zhenan Bao, Deling Li and colleagues leveraged soft and stretchable conducting polymers to fabricate nerve-wrapping electrodes that record near-field action potentials continuously during microsurgery, allowing for the precise localization of the target nerve without the need for anatomical landmarks. The researchers validated the performance of the device by monitoring the post-operative behavioural and neurophysiological function of rats and rabbits after tumour-resection microsurgery.

For tumours in the gastrointestinal tract, radiotherapy is sometimes used as adjuvant therapy before or after surgical removal of the neoplasm. Monitoring the dose of X-ray radiation in the gastrointestinal tract can enhance the precision of radiotherapy, yet the accuracy of clinical dosimeters, which are placed near the skin, is hindered by photon attenuation by tissue and by tissue heterogeneity. Xiaogang Liu, Bin Zhou, Zonghai Sheng and colleagues designed a swallowable X-ray dosimeter containing lanthanide-doped nanoscintillators with persistent luminescence for the wireless monitoring of the absolute absorbed radiation dose (from measurements of radioluminescence, afterglow intensity and temperature) within the gastrointestinal tract. But as noted by Louis Archambault in an accompanying News & Views article, “a swallowable capsule is convenient, yet it comes at the cost of precise control of the position of the detector.”

For all these prototypes to have meaningful clinical prospects, they will require stronger validation of their functionality and safety for the intended uses and users. Many design considerations would need to be optimized, for instance, for optimal fit to specific body areas, to minimize overall device footprint, for low-power data acquisition and data transmission, or for long-term reliability. The benefits of doing so to enable the continuous monitoring of multiple biomarkers, particularly when done wirelessly and non-invasively, are clear – most notably, the ever easier monitoring of health, disease and treatment outcomes, and the earlier detection of disease onset.

References

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