combinations between *C. maxima*, *C. reticulata* or other yet-to-be-identified wild species might provide superior varieties resistant to abiotic and biotic stresses[7], such as that caused by the bacterium responsible for the citrus greening or Huanglongbing disease[8], which is decimating orchards across the world and threatening the global citrus industry. Finally, the work of Wu *et al.*[2] will lead to a better understanding of the genetic basis of the extraordinary diversity in the colors, flavors, sizes and aromas of citrus fruits and whether these might be engineered in novel varieties.

COMPETING FINANCIAL INTERESTS
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Next-generation wearable electronics

Michael J Cima

New fabric-like sensors measure and transmit mechanical strain on the skin with unprecedented sensitivity.

Motion, an act we take for granted until it is stolen by disease, age or injury, can now be measured by a growing array of portable electronic devices for consumer and medical use. Whether for fun, fitness or medicine, these simple wearable devices rely on tiny accelerometers that capture only the gross motion of a limb or entire body. Writing in *Nature Nanotechnology*, Son *et al.*[1] describe a new class of integrated electronic sensors and memory elements packaged in fabric-like material that can record mechanical strains when applied to the skin, offering unprecedented fidelity for analyzing human motion. Devices built on this technology could find broad uses in medicine ranging from diagnostic tools to mechanically assisted prostheses.

Portable electronics, originally devised for communication and entertainment, are expanding rapidly into the area of health metrics as they become more 'wearable' through form factors such as wristwatches, bracelets and eyewear. For example, Fitbit and similar products are worn like a watch and contain accelerometers or other sensors for tracking movement and recording vital signs. The clinical equivalent, such as systems by ActiGraph, can securely manage information across cohorts of study subjects or patients. These products presage a future in which measurements from wearable devices form the basis of clinical decisions.

The transition to electronic health management builds on a long history of medical electronics. The first fully implanted pacemakers were developed in the 1960s, and since then similar devices have been developed for a large number of indications. Implanted devices for cardiac defibrillation, cardiac resynchronization, peripheral and vagus nerve stimulation and deep brain stimulation have saved many thousands of lives. All of these products were created by packaging existing electronic and microelectromechanical systems in ways appropriate to the application. An implanted device, for example, must have a package that is biocompatible and hermetic. This often takes the form of a welded titanium enclosure. Such devices are not truly integrated with tissue as they have completely different mechanical properties.

The article by Son *et al.*[1] is representative of a new trend in medical electronics: the design of discrete electronic and microelectromechanical systems devices for clinical measurement and actuation, embedded within packaging that can be worn directly on skin or contained in clothing. Such devices have been difficult to develop because they must conform to the contours of the skin while also accommodating the large strains experienced during physical activity. Son *et al.*[1] succeeded by incorporating device elements within an elastic matrix.

The authors integrated mechanical strain sensors with arrays of data-storage elements, called resistive random access memory, into the elastic matrix (**Fig. 1**). When applied to the skin, the device's onboard sensors record the strains that it experiences when the skin moves. These data are stored locally in the resistive random access memory and read at a later time. Several other groups are pursuing similar approaches, for example, multifunctional epidermal electronics[2] from the group of John Rogers.

Continuous strain measurements using the devices of Son *et al.*[1] provide new opportunities for analyzing human motion. Mobility is a strong predictor of health outcomes in older adults[3], and people who lose proficiency in balance and mobility are at increased risk of morbidity and mortality. Simple wearable accelerometers that measure gross motion of a limb or entire body have already been adopted in clinical settings. Indeed, a recent article in the *Journal of the American Medical Association* describes the use of accelerometer data as an outcome measure in evaluating structured physical activity to prevent mobility impairment in older adults[4]. Continuously monitored motion data generated by arrays of strain sensors[1] could provide diagnostic information on the complicated interplay between individual muscles needed for motion and balance.

Another application of strain-sensitive arrays would be to control input signals for exoskeleton assist devices—externally worn robotic hardware that assists human motion. The popular press depicts these technologies as part of the future, but they are already a reality in rehabilitation training for patients with stroke and other conditons[5]. Although chronic mechanical assist prostheses have improved substantially in recent years, the control systems integral to their operation[6] are still inadequate. The primary control interface is surface electromyography, in which electrodes on the surface of the skin measure voltage signals within the depolarization zone of skeletal muscles. However, the relationships between the magnitude of the signals, the force exerted by a prosthetic and the displacement of the limb are difficult to determine. Strain-sensitive arrays could easily be integrated with surface electromyography to provide the high-quality measurements needed to more effectively control a prosthesis.

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Son *et al.*[1] also describe devices that deliver drugs to the skin, but they are less compelling. These devices include drug-containing silica nanoparticles and electroresistive heaters and temperature sensors. Transdermal drug delivery has two main limitations: transport and dose. Transport is limited by diffusion through the stratum corneum, the ~10-µm-thick outermost layer of the skin composed primarily of dead keratinocytes surrounded by a lipid-rich extracellular matrix. This tissue functions to keep things out of the body and poses a formidable barrier to transport of drugs through the skin. Enhancing drug transport through the stratum corneum has been achieved by altering either the formulation or the delivery method. Son *et al.*[1] propose to apply heat using the integrated electroresistive heater and temperature sensor. Ultrasonic heating, for example, has been shown to enhance transport for some molecules.

Most systemic drug therapies require doses at the milligram level or higher. In general, the total volume of payload becomes prohibitive if more than a few doses must be contained in the transdermal device. It is difficult to envision how to incorporate large volumes of drug into the devices described by Son *et al.*[1]. The devices could, however, be useful for certain classes of very potent drug. For example, the synthetic opioid fentanyl requires microgram doses and can be delivered transdermally. A wearable electronic delivery device for fentanyl, based on the drug's unique electrophoretic properties, is already available[7]. Other drugs that could be considered are hormones that regulate growth and reproduction. These are considerably harder to formulate for stability and bioavailability reasons but are often very potent. Finally, doses may be lower for nonsystemic therapies targeted to the tissue adjacent to the device.

The pervasive reach of consumer electronics is being extended to medical applications. The first of these devices use existing technologies, but they are being followed by devices, such as those of Son *et al.*[1], tailor-made to the application. Wearable electronics demands custom packaging and custom embedded devices. The future will no doubt include devices worn on the skin or contained within clothing. Such formats will provide a completely passive, nonintrusive interaction between the user and the device.

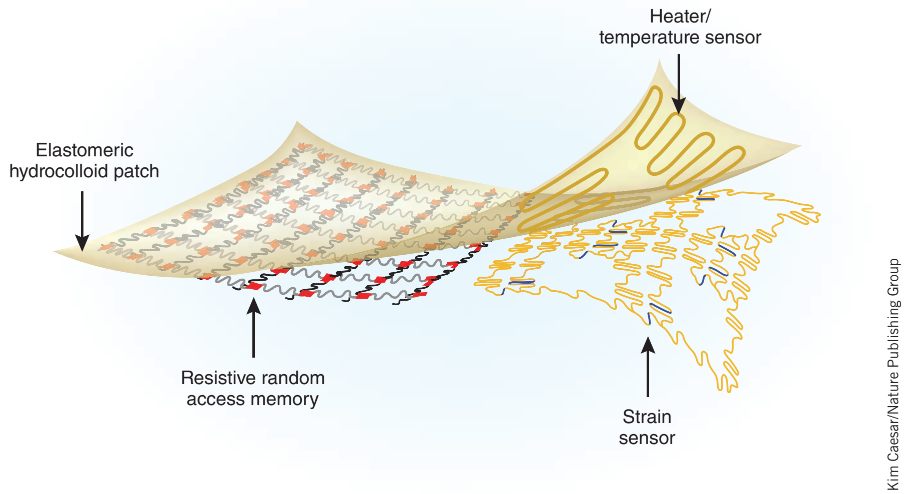

Figure 1 Stretchable, wearable, electronic device for measuring motion. Silicon nanomembrane strain sensors measure mechanical strain placed on the device, which is packaged in an elastic hydrocolloid patch. Resistive random access memory stores sensor data. Integrated heater and temperature sensors can provide localized heat to enhance the delivery of drugs encapsulated in mesoporous-silica nanoparticles embedded in the device. (Figure adapted from Figure 1 in Son *et al.*[1].)

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