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Towards device technologies non-invasive to our daily lives

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Recent advances in non-invasive technologies have shown disruptive potential for biomedical applications. However, while surgically non-invasive, they may introduce other types of limitations which interfere with the patient's quality of life, from impracticalities and discomfort in daily life to social stigma.

One way to define the terminology 'invasive' technology refers to the case 'involving the introduction of instruments or devices into the body regardless of the method of access to the body (incision, natural orifice, percutaneous access, etc.)'[1]. Invasive procedures and implantable devices are common in clinical practice and typically offer excellent performance. They also come with risks associated with implantation, operation, and explanation, including long-term degradation of the device because of the accumulated microorganisms, biocompatibility issues (toxicity, rigidity), energy source problems, and wireless communication[2].

Therefore, there has been a continuous demand for alternative technologies that are capable of comparable functions and performances in a non-invasive or in a *minimally* invasive manner. A multitude of non-invasive wearable technologies that can sense, decode, cure, and modulate the inner tissue have been on the rise, with hefty investments from both academia and industry. Beyond conventional mechanical or electrophysiological signals, novel approaches were introduced and suggested to investigate physiological states and activities. For example, secreted biofluids can be analyzed with skin-conformable electronics to derive physiological conditions. Moreover, non-invasive wearable devices adopting penetrative wave media (light, ultrasound, etc.) can reach into the inner tissue without damage, not only to decode biomechanics of the inner body but also to conduct therapies and to modulate tissues' characteristics[3].

Sometimes, however, it is unclear whether a device or a therapy is invasive, non-invasive, or minimally invasive. This confusion is exacerbated by the appearance of technologies located on the border of the two boundaries e.g. microneedles, edible electronics, and injectable devices/materials, for which the classic definition of "surgically invasive" may not cover the full scope and duration of the operation. While being surgically non-invasive, non-invasive approaches may be more interfering (with life), and introduce other limitations.

Here we discuss the scope of fully 'non-invasive' technology, which is expected to be helpful for users and clinicians to understand and utilize novel technologies with clear understanding. Moreover, we suggest technical endeavors to render invasive technology more human-friendly and *unobtrusive*, while maintaining the advantages of invasive technology, to build device technologies non-invasive to our daily lives.

Rising non-invasive device technologies

Conventional electrophysiological signal decoding methods including electrocardiography, electromyography, electroencephalography, electrooculography, and skin potential measurement are non-invasive, as they do not harm or intrude into body tissue during the measurement. The electrical signals from the internal body tissue can be conveyed through the surface electrodes attached to the skin, which contain physiological information about our internal organs including the heart, muscles, brain, and eyes. As these technologies can be efficiently integrated with wearable devices, they can be easily applied to several biomedical applications, from cardiac monitoring to motion recognition, from respiration analysis to stress detection[4].

Magnetometry-based non-invasive quantum sensors are also started to show their feasibility for biomedical signal sensing[5]. For example, optically pumped magnetometers and magnetometry based on nitrogen-vacancy (NV) centers in diamond enable detection of weak magnetic fields from the brain for injury investigations. Especially, NV magnetometry does not require bulky superconducting quantum interference devices and can work without cryogenic temperature, which sheds light to its wearable applications.

Beyond electrophysiology, monitoring the chemical composition of body fluids e.g. sweat, tear, saliva, wound exudate and exhaled breath can be achieved via skin-adhesive electronics, and exhaled breath can be detected from mask-based wearable devices.

Other rising non-invasive methods harness penetrative wave media: ultrasound imaging and/or stimulation (ultrasound wave), photoplethysmography (PPG), photoacoustic imaging (optical wave), impedance plethysmography (IPG) (electrical wave), and stethoscopes (mechano-acoustic wave) analyze biomechanics of the inner tissues by decoding waveforms of the emitted and/or reflected wave media from the tissue[3]. Ultrasound imaging can be efficiently harnessed for anomaly detection, blood pulse wave monitoring, organ volume measuring, and organ stiffness estimation. PPG is a commercially popular method for blood pulse monitoring and photoacoustic imaging can also decode blood pulse and do imaging of the small molecules inside the body. IPG utilizes electrical wave to measure the resistance of the body, which can be harnessed for heart monitoring with a form of thorax belt. Mechano-acoustic methods can acquire sound waves from different organ movements including heartbeat, pneumatic movement, intestinal movement and body movement. This method is efficient for decoding multiple signals simultaneously by applying signal decomposition methods to the collected sound, which has been conducted in the form of auscultation by physicians. Utilizing such penetrative wave media has broadened the scope of the wearable device into the body without causing damage to the body tissue, which enables painless investigation of the physiological status for various biomedical applications[3,6,7].

Technologies on the border between invasive and non-invasive

Several new technologies appear to the public to be on the border between invasive and non-invasive technology because of their surgery-free and painless procedures. The most confused technology is a microneedle-based device. Although the devices have needles and penetrate the body tissue, patients usually do not feel pain as the needles are very small (<100 μm). The microneedle array is effective for injecting drugs with controllable release rate into the body, biofluid sampling, electrostimulation and photodynamic/photothermal therapy. When the technology first appeared, several researchers mentioned that the technology is non-invasive; however, recently most researchers have recognized that microneedles are minimally 'invasive' as the core function of the microneedle is to physically gain access under the outer layer of the skin[8].

Similarly, injecting materials into the body can also be considered a minimally invasive technology when considering the whole process[9,10]. Recent technologies accompanying processes of injecting nanomaterials, liposomes, light-sensitive proteins and nanodevices reactive to external stimuli, or helping outer devices to track the internal physiological status of the body with them, appear to be non-invasive when only considering the device functioning. These methods can harness ultrasound to stimulate mechano-luminescent liposomes for optogenetics applications or nanoparticles to deliver drugs and can utilize fluorescence spectrum analysis to detect the concentration of chemotherapeutic agents. However, when the injection of such materials is indispensable prior to the device operation and the injected materials or devices remain inside the body for a certain period of time, the whole technology can be considered as invasive. Moreover, the accompanying device for external stimulation may be bulky and impractical.

Another interesting field of cutting-edge biomedical devices is the device with edible form[11,12]. This edible form of devices enables interactions between the swallowed device with the surface of mucosa inside the organ, without surgical operation. Various biomedical applications, including hunger-regulating hormone modulation by electrical stimulation of mucosa, electrophysiological signal decoding from gastric mucosa, and intestinal reanimation for improved motility, have been successfully demonstrated in the animal model. These devices can operate in the digestive system, and can be excreted after a few days in animal models without harmful effect to the animal. For example, the devices were confirmed not to induce serious inflammation or fluid blockage, and showed proper biocompatibility. This method can be considered non-invasive in terms of its operation (electrophysiological decoding, drug delivery, etc.), as the devices do not intrude into the tissue. Technically, if biologics or substances are delivered through transdermal, oral, transmucosal, and inhalational means, the delivery can be considered as non-invasive, as it does not physically damage the tissue[13,14]. However, as this technology also includes a process of inserting devices into a natural orifice, the whole technology can be considered as another minimally invasive technology. Moreover, if a swallowed device penetrates into the mucosa for delivering substances or for decoding bio-signals, the device operation should also be considered as invasive[15].

The terminology 'invasive' does not necessarily highlight a negative aspect of a given technology. Nor that a non-invasive alternative offers only advantages. In fact, invasive procedures and devices may the most efficient methods for specific applications including pacemaking, drug delivery, and deep brain stimulation[16], and the most accepted by the users. Several state-of-the-art implanted and invasive technologies are less intruding in our daily life than other surgically non-invasive technologies which may feature metal electrodes, or polymer substrates inducing skin rash for long-term usage. Moreover, they may be bulky gadgets that can interfere with our motion and daily life. Therefore, it is desirable for researchers to carefully consider each aspect of a technology, describe it comprehensively, demonstrate it in a transparent and sophisticated way in order to avoid misunderstanding by users and clinicians regarding its physical (and life) *invasiveness*.

Beyond this classification, researchers keep demonstrating innovative methods to alleviate the limitations of each technology. Non-invasive devices are emerging to be more seamless and better able to conduct more complicated analysis with smaller device dimensions. Integration of these technologies into familiar accessories such as wrist watch, ring, and earbuds enhanced user acceptance of these unfamiliar healthcare possibilities. Invasive technology keeps suggesting innovative strategies, for example, biodegradable devices without any need for extraction[17], the single-injection method of engineered particles for compartmental drug delivery[18], and novel injection technology including stiffness-tunable needles for painless and safe intravenous injections[19]. Furthermore, beyond the technical improvement, relatively undervalued sociocultural elements such as shared beliefs, stigma, social messages, and psychological context among users should be addressed to enhance the user acceptance[20]. Such endeavors are expected to render current biomedical devices more human-friendly and unobtrusive, which would make them non-invasive to our daily life.

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H.Y. and C.D. conceived and wrote the article. All authors approved the submitted version of the article.

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