



Trends in Epidermal Stretchable Electronics for Noninvasive Long-term Healthcare Applications

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Abstract: Stretchable electronic devices hold the potential to revolutionize noninvasive healthcare diagnostics and treatments. Current clinical healthcare technologies are of limited use in ambulatory, long-term settings. A new class of epidermal electronics is designed to conform closely to and with the irregular shape of the human body is emerging, providing an improved functional interface even during motion, while being imperceptible to the user. This review discusses challenges associated with long-term interactions between electronic devices and the skin without interfering with its regulatory and protective function. We report on the current state of the art of monitoring devices for the detection of temperature, motion, biopotentials or biomarkers alongside therapeutic approaches for thermal treatment or drug delivery. In particular, focus is brought on the long-term application of such devices with the associated challenges in terms of materials, wearability, communication and energy supply. With a number of obstacles left to tackle, epidermal stretchable electronics represents a powerful tool in the rising field of personalized medicine.

Keywords: stretchable electronics, noninvasive, wearable, healthcare, long-term, continuous, skin, epidermal

Introduction

A Current high-performance, integrated electronics heavily rely on crystalline inorganic materials, such as silicon or gallium arsenide. Produced from wafers that are fundamentally planar and rigid, they are designed for the use under narrowly defined conditions. In contrast, humans are curvilinear, soft and almost constantly in motion. Moreover, biological systems are generally wet and packed with salts and proteins. When combining conventional silicon based electronics with tissue, these discrepancies quickly lead to adverse body reactions such as inflammation, fibrosis, or the malfunctioning of the electronics due to the harsh biological environment [1]. However, the increasing demand for wearable electronics, real-time health monitoring as well as invasive and noninvasive therapeutic devices has led to the development of flexible, soft and stretchable electronic

devices [2]. Their materials are carefully chosen to seamlessly adapt to the curved surfaces, complex chemistry and dynamic tissue of the human body. Flexible and stretchable electronic devices have already been realized to record a wide variety of physiological signals such as EEG, ECG, pulse, temperature or glucose levels, which provide important information on physiological functions as well as the state and progression of various diseases [3,4]. Besides monitoring body functions for diagnostic purposes, flexible and stretchable electronic devices have also been used therapeutically for drug delivery, phototherapy, electrical stimulation of tissues or in conjunction with prostheses as human-machine interfaces [5]. However, most of these solutions are not yet routinely applied. This is due to a number of issues, such as difficulties with power supply, complicated interfacing with traditional electronics or unsatisfactory long-term performance, that are still associated with many stretchable electronic technologies. In the case of



medical devices, regulatory hurdles for new solutions can be hard to overcome which further hinders the translation from the lab to the clinic.

There are already multiple, comprehensive reviews on the topic of stretchable electronics [2-9]. This review gives an overview on noninvasive, stretchable medical devices and technologies that are intended to better monitor, analyze and react to body functions from outside the body. We will discuss the associated challenges and

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provide insight as to how these issues are being solved, especially in respect to continuous, long-term applications.

Material Consideration for Long-term Skin Interfaces

Generally, noninvasive therapies or diagnostics are clearly favored over invasive approaches as long as the sensitivity and therapeutic outcome is satisfactory. The challenges faced by noninvasive medical devices are much different from those of invasive devices. Implanted devices for example are quickly encapsulated by a foreign body reaction [10,11]. On the other hand, noninvasive devices lack tissue access and can interfere with the natural function of the skin. Therefore, understanding the mechanical and physiological properties of the skin is crucial to create a seamless long-term interface. The skin not only protects the body against microorganisms, chemicals, solar radiation and mechanical impact but it is also crucial for temperature regulation, electrolyte fluid balance and sensory feedback. For noninvasive skin interfaces, the epidermis and the underlying dermis are the most relevant part of the skin because they are defining the interaction between device and body.

The human skin surface consists of sweat pores, hairs and has wrinkles and folds with deep furrows in the range of 20 to 100 μm , finer grooves of 5-40 μm and nanoscale roughness as displayed in Figure 1A [12]. A close, direct contact to the underlying tissue of interest is thus limited with conventional hard electronics. Additionally, the skin is an elastic, soft tissue that can stretch up to 30% [13]. During dynamic motion this can cause changes in position and signal stability as well as device delamination. The elastic modulus of the epidermis is roughly 1 MPa and highly dependent on skin hydration and temperature [14]. Finally, the outermost layer of the skin, the stratum corneum, consists mainly of 15-20 layers of dead cells that continuously renew and shed with an average turnover of about two weeks [15]. Bridging this nonconductive, protective barrier in a noninvasive fashion is one of the main challenges for long-term healthcare devices. Here, the choice of material can significantly improve the interface and thus the quality of the signal because it has a direct influence on important properties such as conformability, adhesion, breathability or impermeability.

In order to electrically bridge the skin to connect a device to the underlying tissue, the clinical gold standard uses an electrolyte gel in contact to a metal electrode as depicted in Figure 1B. The gel wets the skin and decreases the impedance of the stratum corneum enabling high quality electrical recording of tissue activity. However, such gel electrodes are not suitable for long-term



monitoring due to signal quality degradation caused by gel drying and lack of user comfort including skin irritations. Approaches to establish a good electrical contact through the skin without using gels have been studied for decades by using direct contact surface electrodes, penetrating electrodes or noncontact capacitive electrodes [17]. However, most approaches are unable to translate to clinics due to worse signal quality and motion artifacts, despite improvements in readout technology that reduce but not eliminate these drawbacks. Novel soft and stretchable conductive materials can improve the electrical contact through the skin because they better conform to its rough surface, thereby increasing the contact area as illustrated in Figure 1.C-E.

The formation of a high area contact between the device and the skin is also crucial to achieve significant adhesion for fixation and stable measurements. Soft electrodes with matched mechanical properties can lower motion artifacts by reducing the relative movement between the electrode and the skin [18]. However, achieving good adhesion to the skin is challenging. Its roughness and low surface energy, as well as the presence of hair and a significant amount of water, salts and oils hinder a stable interface. In addition to a tough adhesion during repeated skin stretch, the devices need to be removable without causing skin trauma, maintaining this ability upon repeated attachment. To meet those requirements, general medical skin adhesives are based on acrylic polymers, polyurethane rubbers, silicone rubbers or hydrogels. These materials have a sufficiently low surface tension for skin wetting and are soft enough to conform to the skin. Stretchable electronics are usually based on the same class of materials including silicone rubber, polyurethane and other flexible polymers. However, most of them are not specifically designed to be directly used as a skin interface. Nevertheless, these materials can be easily improved by tailoring the elastic modulus, their wetting and fluidity properties or overall

geometry accordingly. Simple treatments like adding small amounts of ethoxylated polyethyleneimine to polydimethylsiloxane (PDMS) can already enhance its adhesion factor more than ten times [19]. Nature-inspired dry adhesives use hierarchical structures to substantially improve contact area to surfaces with multiscale roughness enabling adhesion by van der Waals interactions [20]. Those are interesting approaches for medical skin patches to provide simultaneously a soft dry adhesion and improved breathability. Using Gecko feet inspired elastic micropillars as depicted in Figure 1D, Kwak et al. demonstrated a dry adhesive patch with an increase in air ventilation beneficial to avoid undesirable side effects such as redness and pain during the peel-off compared to acrylic adhesives [21]. Bae et al. demonstrated modulus tuned micropillars for improved, repeatable skin adhesion of the device [22]. Also, they had an improved ventilation of air and moisture and were less skin-irritating and biocompatible for prolonged exposure. Another approach uses cephalopod-inspired miniaturized suction cups in the soft elastomer, increasing the adhesion force three times compared to a plain elastomeric patch [23].

A high breathability is crucial for long-term application of epidermal devices that are not hindering the physiological function of the skin [24]. However, the control of evaporation and resistance to water still seems to represent an unsolved challenge for the devices to fully adapt to the human skin. Various efforts are made to resolve these issues, since lack of water permeability can result in undesirable irritations or infections that limit device functionality [25].

A membrane is defined as a breathable interface when it allows to pass water vapor through, while it has a resistance to water entering into the layer [26]. Typical basal values of transepidermal water loss in adults with healthy skin are in the range of $5\text{-}10\text{ gm}^{-2}\text{h}^{-1}$ [27]. In order to achieve comparable permeability to the human skin,

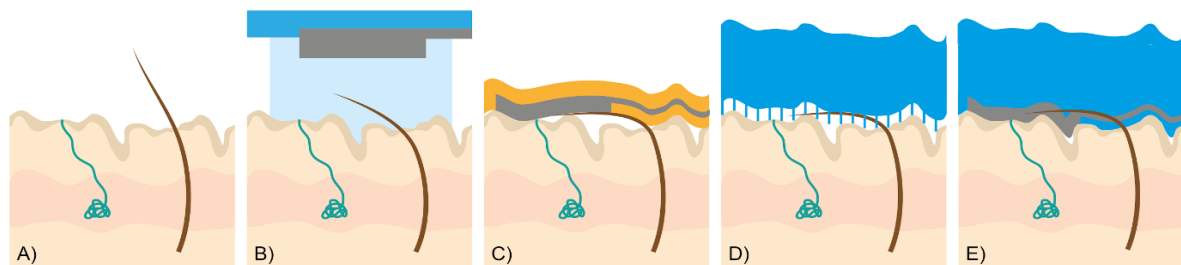


Figure 1. A schematic cross section of the human skin, interfacing devices made of different materials. A) The human skin consists of the hypodermis, dermis and epidermis with the outermost layer, the stratum corneum. Sweat ducts and hair shafts are spread throughout the entire skin. B) Wet, conductive gel electrodes, which can penetrate into the wrinkles of the stratum corneum, help to improve the electrical contact through the skin. Compared to common, dry and hard electrodes, stretchable electronics can conform tightly to the roughness of the skin improving adhesion and device functionality. C) Electrodes, consisting of ultrathin flexible polymer with low Young's modulus embedding to the uneven interface, allow close adaptation to skin strains. D) On the other hands, biomimetic micro and nanostructured stretchable substrates allow for repetitive dry adherence and removal as well as improving device sensitivity. E) Ultrasoft polymer sticking to the skin maximizes surface contact generating a compact interface similar to gel electrodes.

Jang et al. used ultralow modulus silicone for skin-mounted sensors [28]. It showed higher transepidermal water loss values compared to that of other standard silicone rubbers. Another promising candidate for epidermal noninvasive devices is polyurethane [29,30]. It is biocompatible, flexible and shows good breathability since the size range of nanoholes in polyurethane is between the size of water molecules and water droplets [31]. Various other ways have been proposed to improve the breathability of porous polymer membranes [26], including polysulfone and polyvinylidene fluoride [32,33], but they haven't been integrated with skin-mounted devices as of now.

One approach to successfully solve most of these issues was demonstrated by Kim et al [34]. They developed an ultrathin, low modulus device structure that matches the elastic modulus of the skin. As a result, it can conform tightly to the epidermis with integrated electronics and sensors. The lightweight and conformal contact allows for adhesion based solely on van der Waals interactions and makes it mechanically imperceptible to the user. The substrate consists of a 30 μm thick, low modulus, gas-permeable elastomer and supports interconnects employed as stretchable serpentine ribbon electronics. Even thinner devices were presented by Kaltenbrunner et al., where sensors and transistors were implemented on polymer foil with 1 μm thickness [35]. To improve wearability lifetime of such devices to up to two weeks in everyday life including personal hygiene, Yeo et al. used a biocompatible spray-on bandage acting as adhesive and encapsulant of those devices [36]. Interestingly, failure of those devices was not caused by adhesion loss, but rather from fracturing into smaller pieces. The authors assume it is caused by the continuous shedding of dead cells. Finally, Yu et al. recently showed extremely high skin conformity using a siloxane based polymer. The polymer is crosslinked *in situ* and shows skin-like mechanical properties [25]. Such materials are well suited as matrix materials for stretchable electronics applications.

Current Skin Devices for Health Monitoring and Diagnostics

Nowadays, monitoring vital signs of body function, for example after surgical intervention, is mainly used in stationary clinical settings. Few wearable devices for ambulatory, continuous, long-term monitoring are yet available for sensing health parameters on a clinically satisfactory level. Stretchable electronic devices in direct contact with the skin can overcome current limitations especially for continuous, long-term advanced health monitoring and diagnostics on and through the skin as

schematically illustrated in Figure 2.

Tight contact to the skin is a prerequisite for continuously monitoring its properties. Spatial mapping of skin temperature and hydration state can provide information on wound healing and skin disease like atopic dermatitis or edema [37,38]. Webb et al. demonstrated an array of epidermal temperature sensors to continuously map the temperature on the skin. Combined with heating elements, they can estimate the moisture level by measuring differences in thermal conductivity [39]. Using this approach, Hattori et al. reported an integrated sensor platform that monitors both temperature and thermal conductivity during wound healing for up to 30 days [40]. These thermal sensing approaches can also be used to continuously monitor blood flow with an ultrathin, skin conforming device [41]. Furthermore, conformal piezoelectric devices have been used to noninvasively characterize the mechanical properties of the epidermis and underlying skin [42]. This allows for noninvasive, continuous monitoring of changes in the tissue properties, for example caused by diabetes, or the detection of pathologies such as tumors [43,44].

The measurement of blood oxygen level is an important indicator for the diagnosis of ventilation-perfusion mismatch, hypoventilation and shunts [45]. Pulse oximetry is a noninvasive technology based on the oxygen-dependent absorption of light in the blood and is routinely applied in clinical diagnostics and emergencies. In contrast to existing bulky and obtrusive devices, Yokota et al. presented a stretchable pulse oximeter with 3 μm thickness that is nearly imperceptible to the wearer [46]. The technology combines polymer light-emitting diodes with organic photodetectors and could potentially be used to display results directly on the patient's skin. Such flexible, optoelectronic sensors can not only be used to detect blood and tissue oxygenation but were also applied to detect muscle contraction [47].

Detecting body motion can provide feedback about vital functions such as respiration rate, heart rate and blood pressure [3]. Similarly, monitoring arterial and venous blood pressure is widely used to determine a person's health state. Monitoring pulse pressure waveforms can help to detect and continuously assess cardiovascular diseases like hypertension and enable real time response to changes. This was implemented by Schwartz et al. who combined thin-film transistors with microstructured PDMS as gate dielectric to create a highly sensitive pressure sensor with fast response time [48]. Dagdeviren et al. developed such a skin sensor based on a conformable piezoelectric pressure sensor technology [49]. Improved adhesion and skin-device coupling using micro suction cups made it possible to measure arterial pulse waves without the need of constant external



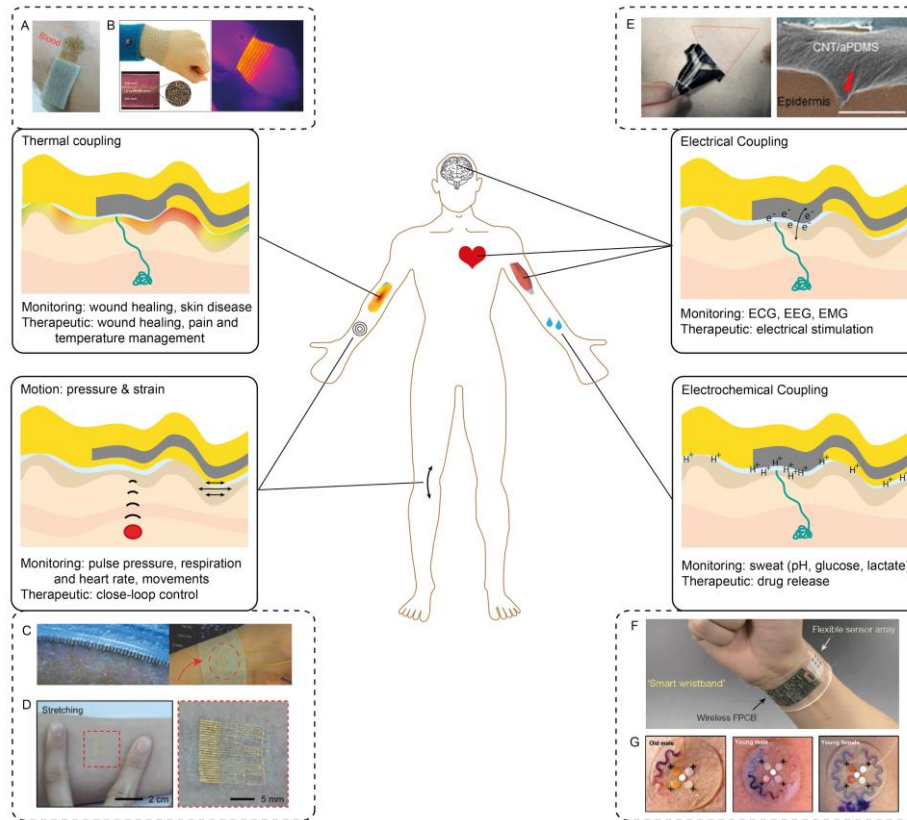


Figure 2. Vital signs, such as electrical signals, pressure, strain, pH or temperature can be measured continuously with stretchable devices. Thereby, close conformal contact between the rough skin and the device not only increases device adhesion but also allows for a good physical and chemical coupling. A) Thermal sensor for the continuous mapping of blood flow [41]. B) Stretchable heating element that conformally integrates with the wrist [91]. The mesh heater is fabricated from an AgNW composite. C) Highly skin conforming, gecko feet inspired pulse sensor [50]. The micro hairs improved skin coverage of the device. D) Suction cups based dry adhesive for pulse monitoring and drug delivery [23]. The cephalopod inspired cups allow for repeated reapplication of the device and improves the mechanical coupling. E) Self-adhering dry ECG patch for long-term, robust electrical coupling [66]. The electrode was made of CNT and adhesive PDMS and can conformally laminate into the wrinkles of skin. F) Fully integrated electrochemically coupled sensor array [82]. The device features glucose, lactate, sodium, potassium and temperature sensing. G) Epidermal microfluidic sweat monitoring device [83]. Biomarkers such as chloride, hydronium ions, glucose or lactate are analyzed externally in a colorimetric fashion. Images reprinted with the permissions from A) Ref. 41 © 2015 AAAS, B) Ref. 91 © 2015 ACS, C) Ref. 50 © 2015 Wiley, D) Ref. 23 © 2016 Wiley, E) Ref. 66 © 2014 NPG, F) Ref. 82 © 2016 NPG and G) Ref. 83 © 2016 AAAS.

pressure [23]. Also, pressure signal strength on the skin can be enhanced substantially by using micropillars with a highly conformable capacitive pressure sensor [50]. This signal amplification not only enables the measurement of arterial but also jugular venous pulses, used to track the recovery of heart surgery patients.

Monitoring of human motion, like gait, joint movement and posture, is important for rehabilitation and personalized health monitoring, but also interesting in consumer electronics [51,52]. Here, continuous, daily recording potentially provides more beneficial and intuitive feedback than short term monitoring during rehabilitation trainings and clinical settings. Various flexible, skin-mountable and wearable strain sensors have been developed for human motion detection and the development methods and its performances are discussed in a recent review [53]. Nanomaterials, like metallic nanowires [54,55], nanotubes [56,57] and graphene [58], have been used to create accurate sensors for high strains. For example, Wang et al. developed a

sensor based on graphene woven fabrics using a copper mesh template with a special crisscross configuration to detect weak human motions such as hand clenching, expression change, blinking, breath and pulse [59]. Another interesting example of motion detection has been enabled by mounting carbon nanotubes (CNTs) silicone rubber based strain sensors on different parts of the body such as finger, wrist, and elbow joint [60]. Ultrasoft silicone rubber was used to realize high stretchability while strong adhesion of the CNTs resulted in reliable measurements even at large strains. Recently, a strain sensor with high stretchability, sensitivity and a wide sensing range has been demonstrated [61]. The sensor consists of double layers of reduced graphene oxide on pre-strained substrates. The structure allows the adjacent overlapped graphene layers to readily change their overlapping areas under strain. This could enable the detection of human motion in full-range, from pulse to finger bending.

Accessing signals of electrically active organs like

muscle or nervous tissue from outside the body enables fast and efficient mapping of critical health parameters. For example, biopotential recording of the heart activity, i.e. ECG, allows to monitor and diagnose pathological heart conditions including myocardial infarction, ischemia, and arrhythmias, which are potentially life-threatening. Monitoring cardiac problems for patients at risk during everyday life and exercising would be highly interesting. Routinely, wearable consumer electronics can only monitor the simplest parameter, the heart rate. However, the clinical relevance of pulse monitoring is rather limited. As discussed above, novel soft electrodes aim to bridge the gap in electrode-skin interface quality for enabling high-quality recording over extended periods of time [18]. Recently, dry polymer electrodes were shown to have a performance close to wet electrodes with only slightly lower signal-to-noise-ratio (SNR) by using conductive pillar structures [62]. Since the pillar contacts less skin area, it has less influence on skin perspiration. However, the pillars with an elastic modulus of 100 MPa are too hard for the fixation pressure, leading to minor discomfort and erythema after ten hours or longer wear time. Earlier, a simple PDMS-based dry electrode with higher impedance and motion artefacts was shown [63]. With this electrode it was possible to measure up to seven days without producing visible changes of the skin. More recently, with CNTs incorporated into PDMS, ECG measurements over seven days without signal quality degradation and no adverse skin reactions were demonstrated [64]. Soft silver nanowires (AgNWs) based dry electrodes could reduce the effect of motion artifacts compared to standard Ag/AgCl electrodes [65]. However, fixation remains an issue and long-term stability is not clear yet. Lee et al. solved the adhesion problem by using an adhesive PDMS with incorporated CNTs [66]. This electrode had a higher impedance but signal quality remained comparable to standard electrodes. Also, biopotential measurements using conductive gecko-inspired pillar electrodes were shown [67]. Even though the electrode patches in this work seem too big to be of clinical relevance, good repetitive adhesion properties could be shown. Norton et al. demonstrated an interesting approach to measure brain activity using their self-adhesive epidermal electrodes. With their fractal mesh electrodes, which are stretchable above 50% with a Young's modulus of 20 kPa, they interfaced the auricle for long-term EEG, capable of good recording quality for 14 days without adverse effects. By this approach, they circumvent the problem of interfacing the brain through the hair. However, power supply or wireless communication systems have yet to be integrated [68]. This problem is tackled by Jang et. al by providing an integrated platform allowing for direct and reversible bonding to external wireless recording and

transmission electronics using magnets [69]. Their adhesive electrode showed stable SNR for EMG measurements over eight days. As an alternative, hydrogels represent an interesting interface to the skin for electrical and electrochemical exchange [70-73]. However, drying out and fragility of the hydrogel is a problem. Recently, tough hydrogels with high adhesion properties have been emerging [74-76]. Such hydrogels can be combined with elastomers to form robust stretchable hydrogel-elastomer hybrids through covalent bonding [76]. The elastomer can act as an anti-dehydration layer for the hydrogel, showing no weight change over 48 hours, and without affecting the mechanical properties of the hydrogel [77].

The continuous point-of-care monitoring of electrolytes and metabolites in biofluid, such as blood, urine, sweat and tears provide important information for the treatment of chronic, homeostasis-related diseases. Using an invasive sensor, such as sampling the blood for glucose detection, has limitations for continuous monitoring, since it requires the acquisition of the sampling media [78]. On the other hand, noninvasive devices enable continuous monitoring of a wearer's health. The growing interest in wearable sensors shifts hospital-based patient care to a more home-based personal management, which is beneficial to lower health-care costs. Sweat contains metabolically rich information and sweat analysis can be used for disease diagnosis, drug detection and athletic performance improvement [79]. For continuous monitoring of human perspiration, a noninvasive, enzymatic temporary-transfer tattoo biosensor has been demonstrated for the first time [80]. The flexible printed tattoo was functionalized with lactate oxidase and provides time dependent analysis of sweat lactate during exercise without hindering the wearer. The measurement of the glucose concentration in sweat correlates to the level of blood glucose thus providing a noninvasive control for diabetes patients [81]. Gao et al. developed an *in situ* perspiration sensor to detect variations in the concentration of biomarkers such as glucose, lactate, sweat potassium and sodium levels [82]. The device showed good real-time monitoring stability while a subject was exercising for two hours. Koh et al. used a stretchable microfluidic device to sense different biomarkers including glucose using a colorimetric reaction of pre-deposited chemicals. The devices were successfully tested on cyclists demonstrating the potential of soft and unobtrusive sweat analysis [83]. Alternatively, tears can be used as an easily accessible fluid for noninvasive monitoring of glucose. Even though tear and blood glucose levels have been shown to correlate well, there can be a peak to peak delay times of 10-30 minutes [84-86]. Other flexible electrochemical



sensors have also been reported [87-90]. Yao et al. even demonstrated a contact-lens sensor with integrated wireless electronics for data recording [90]. However real-life applications of the wireless electrochemical glucose sensor has yet to be demonstrated.

Current Skin Devices for Therapeutic Healthcare Applications

Most work on flexible devices has focused on sensing and signal processing for electronic applications such as artificial skin and health-monitoring devices. Lately, human-interactive devices that simultaneously sense signals from the human body and respond to the wearer's needs, have been investigated extensively for the next generation of wearable electronics.

Thermal therapy is one of the classic physiotherapies used in orthopedics to alleviate symptoms such as pain, swelling and muscle weakness. There are several conventional heat therapy methods, such as heat packs or wraps [92,93]. Usually these solutions are relatively heavy, bulky and temperature control can be difficult. The device is required to achieve stable and uniform heating during repeated deformation especially at articular regions such as wrists or knees. Choi et al. presented a soft and stretchable heating element that is lightweight and conformally integrated with the human joints for effective thermotherapy [91].

This mesh heater was made of a homogeneous nanocomposite of AgNWs and styrene-butadiene-styrene elastomer [94]. For better temperature control, Hong et al. adjusted the applied voltage to keep the temperature constant along with the higher strain [95]. Recently, Dinh et al [96] demonstrated heaters for thermal therapy based on graphite and polyvinylchloride, which has a good thermal stability since it has lower temperature coefficient of resistance than that of graphite on paper [97]. The temperature profile could be regulated with an integrated circuit though lacking feedback from the body. Local heating of chronic wound sites is known to promote healing [98,99]. Until now skin-mountable sensors which are integrated with heating elements to assist wound healing have not been demonstrated. Although micro heaters have been integrated into sensors they have been used to examine the thermal conductivity and thus state of wound healing, and not for therapeutic purpose [40]. However, Kim et al. have presented an ultrathin suture strip, which is composed of temperature sensors and heating elements based on Au serpentine structures [100]. The stripe was used to monitor and support wound healing thermally. Even though this can be considered an invasive technique, it also demonstrates that medical devices can be used for monitoring and providing

therapeutic treatment to wound sites simultaneously.

Wearable soft devices promise to significantly advance point-of-care technology by enabling the controlled release of drugs in response to a diagnostic result. Ideally this is achieved transdermally, providing a convenient and pain-free solution for patients [101]. For a precise control of transdermal drug delivery, thermal elements have already been integrated into a wearable electronic patch, to successfully combine diagnosis and therapy in one device [102]. Here, motion sensors mounted on the patch are able to detect movement disorders of subjects. In return, this can trigger the transdermal release of drugs using the integrated heater. Furthermore, temperature regulated drug delivery has been improved using microneedles [103]. Lee et al. developed bioresorbable polymer-based microneedles that were coated with a phase-change material [104]. There, a glucose sensor activates the heating elements leading to drug-release into the bloodstream. Recently, bendable microneedles based on SU-8 and maltose were proposed to overcome the safety issue associated with the microneedle breakage during the application or strain [105]. However, this can also be achieved using bioresorbable materials. Another promising technique for transdermal drug delivery is iontophoresis, which is known to increase delivery across the skin significantly [106,107]. Iontophoresis can help to avoid thermal denaturation of drugs or low-temperature burn injury which can occur for thermal diffusion approaches. Lately, wearable electronic patches with dry adhesives have been combined with iontophoresis electrodes to control transdermal delivery of mesoporous silica nanoparticles loaded with drugs [23].

Such wearable epidermal devices can not only be used for therapeutic drug delivery but also for prosthetic and patient-assistant research [108]. Sensitive movement of artificial or assistive robotic limbs can be controlled in real-time in a closed loop manner [109]. One example used a composite material for a closed-loop human-machine interface with skin-conformable sensors [110]. The used graphene heterostructures not only provided effective feedback for the stimulation of the robotic motion, but also high flexibility, transparency and low power consumption. This demonstrates how the adaption of soft electronics in the rising field of soft robotics opens new paths for healthcare devices and biomedical applications that can be controlled over a closed loop by a wearable sensor. These approaches are still far from commercial use but represent the tremendous potential this combination can have for therapeutic devices [111-113].



Future Trends for Skin Electronics

Many of the current noninvasive, soft healthcare devices show proof of concept results. However, significant challenges are still unsolved. As seen in Figure 3, there are some approaches that manage to overcome the limitations of current devices, e.g. energy supply, processing, storage and transmission of data as well as unperceived wearability and longevity.

In order for a device to execute a monitoring or therapeutic function continuously over extended periods of time, a constant supply of energy needs to be ensured. The gold standard in energy supply today is batteries due to the wide availability, low cost and high power density. In contrast to emerging stretchable devices, batteries are rigid and bulky, therefore limiting both overall size and wearability of the device. However, new approaches aim to reduce the size of the energy storage and embed it in stretchable substrates. The work of Xu et al. represents

such an approach, incorporating the basic principle of rechargeable lithium ion batteries embedded in Ecoflex and interconnected in a serpentine like manner [114]. This design can be reversibly stretched up to 158%. As an alternative energy storage Yun et al. presented a micro-supercapacitor (MSC) array embedded in a stretchable substrate and used it to power a stretchable gas sensor [115]. One individual MSC has millimeter dimensions and both energy storage and sensor can withstand reversible stretching up to 50%.

Although ultralow power electronics reduce the energy demand of wearable devices, batteries and capacitors might not be a sufficient solution for long-term applications and imperceptible devices. The use of energy from harvesting technologies, for example using thermal energy or mechanical motion, displays an attractive alternative. Flexible thermoelectric generators (TEG) were demonstrated based on polymeric substrates [116] or thermocouples [117] and achieved power densities in the

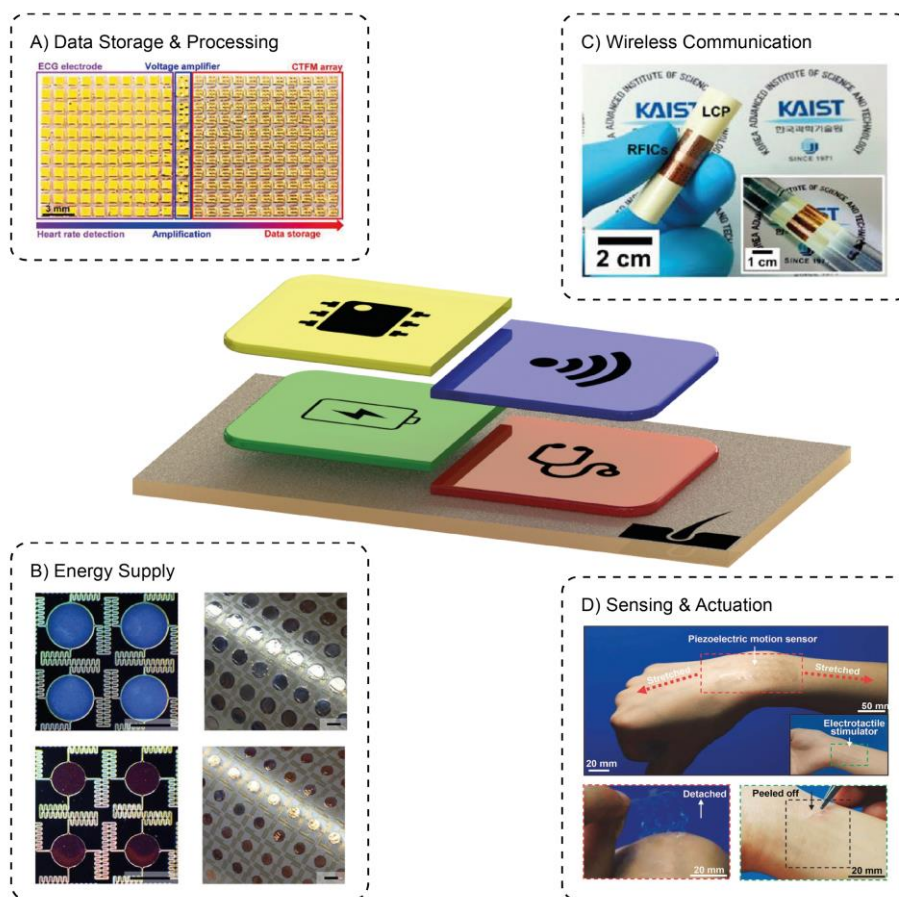


Figure 3. Future stretchable health-care devices combine power supply, sensing, processing and data supply in one device. Many of these elements have already been realized with stretchable materials. A) An Au nanoparticle enhanced CTFM mounted on a thin PDMS membrane [122]. Here, the gate interconnects were realized with wave like interconnects. B) Rechargeable battery based on conventional lithium ion technology, embedded in Ecoflex [114]. The device can be reversibly stretched above 150%. C) Liquid crystal polymer encapsulated wireless transmitter. The electrical performance and biocompatibility of the flexible RFICs was confirmed in vivo. D) Highly transparent and flexible mechanical sensor and stimulator for human-machine interfaces. The device was realized with a graphene/CNT/AgNWs embedded in a Poly(L-lactic acid) matrix. These early examples demonstrate the successful combination of conventional with stretchable technologies resulting in hybrid devices that can cope with the electrical and biological requirements of health monitoring. Images reprinted with the permissions from A) Ref. 122 © 2016 AAAS, B) Ref. 114 © 2013 NPG, C) Ref. 123 © 2013 ACS and D) Ref. 110 © 2015 NPG.

microwatt range. Advances in the thermoelectric figure of merit and flexibility can make them a viable option for future wearable power supplies. Similarly, piezoelectric materials have been utilized to harvest energy from human motion. Again, the power density generated this way is in the range of nano to microwatts per square cm, which requires large-area harvesters if wireless, wearable devices need to be supplied with energy in a long-term manner [118]. The introduction of the triboelectric nanogenerator (TNG) promised new possibilities for the power supply in wearable devices. The TNG receives the energy from the triboelectric effect, a contact electrification mechanism that occurs when two oppositely charged surfaces touch and detach, generating a current flow that has to be compensated [119]. Because the harvested energy is directly coupled to the movement of the wearer, not every user scenario can provide sufficient power. Ha et al. suggested to stack several TNG layers to improve the generated power or to combine different energy harvesting techniques into one device [119]. Using micro-patterned co-polymers and CNT-PDMS composites, Lee et al. demonstrated a stretchable generator that is both piezo- and pyroelectric, generating power during movement and temperature changes simultaneously [120]. In addition to being stretchable, TNGs can be transparent using graphene and other nano-scale active materials [121]. A common problem for all energy harvesters is power conditioning, which is currently still based on rigid and bulky discrete components such as coils and capacitors. Overall, stretchable energy harvesters represent an interesting new approach that has to be further developed and adapted to fully exploit them as a wearable electronic energy supply.

In order to access and process collected data, a continuous data storage in a device is needed to prevent data loss prior to transmission. This is especially important for ambulatory sensors, which are not always connected to an external device monitoring or analyzing the collected data. Recent approaches to create stretchable nonvolatile memory storage use CNT based soft electronic devices high performance Si nanomembrane based deformable charge trap floating gate memory (CTFM)[122]. The CTFM consists of Au nanoparticles floating gates to increase the stability, performance and efficient charge confinement. The whole substrate is mounted on a thin layer of PDMS with wave like interconnections between the gates. This stretchable device was then used for successful ECG recording of cardiac function. Also, other innovative approaches that use biocompatible materials like cellulose might be usable to generate novel energy efficient and long-term stable memory storage devices [124,125]. However, even if the

stretchable data storage units could comply with the physical and physiological requirements for modern healthcare applications, the data storage capacity cannot yet fully reach current conventional devices.

Early designs for wearable sensors have used wires to connect sensors with external processing units. However, wired connections cannot cope with the elevated mechanical needs of stretchable interfaces present in newer wearable devices. Besides the minimization trend complicating this interface even further, the attachment of cables reduces the desired imperceptibility. Here, wireless feedback systems that monitor body functions and respond according to the evaluated data can facilitate healthcare and medical applications [126,127]. These kind of feedback loops are necessary to gain a user friendly healthcare device for long-term incorporation in daily life activities as needed in many cases. Guenther et al. made use of the wireless approach for invasive implants to regain speech in an individual with a stroke determined speech inability, where the signals from brain electrodes were wirelessly linked to the speech motoneurons [128]. Although this demonstrates the potential of fabricating complex wireless triggering devices, many problems related to the rigidity, powering and long-term performance of such devices need to be overcome. Hwang et al. focused more on the flexibility and long-term stability of their wireless device when exposed to a wet environment [123]. Recently, Hussain et al. presented a stretchable far-field antenna that can operate during physical shape deformation [129]. Finally, a wireless glucose sensor on a contact lense capable of long-term data acquisition and feedback loops is a leap in the right direction [90]. For advanced, multifunctional wireless devices, hybrids that combine stretchable with standard electronics can take advantage of both technologies. Xu et al. used fluidic enclosure of standard electronics and stretchable interconnects to mechanically decouple them from the elastic substrate [130]. This allows for biaxial stretchability above 100% with an increase in overall modulus by less than 5% compared to the elastomeric substrate itself [90].

Finally, for patients under continuous diagnostic and therapeutic observation, one of the most important factors is user convenience and comfort [131]. Transparent, electronic nanomaterials can help to render wearable devices nearly invisible, resulting in a natural look and aesthetics. Especially metal mesh or grid structures are emerging as promising solutions since they exhibit high flexibility and optical transparency, while maintaining low sheet resistance [110,132]. Such mesh structures are easy to fabricate and integrate with microprocessing technologies [133,134]. Together with the ultrasoft substrates mentioned earlier, this can result



in a near seamless integration for daily applications.

Conclusions

This paper reviewed the various current approaches for skin-contacting, stretchable electronic devices for healthcare applications. The biggest benefit of this new class of devices is that they have an inherently good contact to the skin even during motion, thanks to their softness and flexibility that adapts well to the complex surface of the skin. Therefore, stretchable devices tend to cause less skin irritation and seem to have better long-term stability than conventional rigid electronics. Although many systems are already available and more are emerging continuously, there are several critical elements that still need to be resolved. Skin contact, power supply and data transmission are among the most relevant. This probably means that in the future, more and more hybrid systems will be developed where the direct body interface, i.e. the stimulating and the sensing aspect, will be provided by the soft electronics while the intelligence, i.e. data processing and communication, will be taken care of by regular CMOS components. Nevertheless, present devices are already capable of recording a wide variety of parameters by continuously monitoring various skin-related signals. However, this has to be managed properly in order to find correlations with medical conditions. Although this might be straightforward in certain cases, other more complex conditions require even larger amounts of information for conclusive diagnosis. Therefore, besides measuring temperature, pressure, movement and electrical signals, we will have to increase the capabilities of skin-contacting devices further. For example, towards obtaining more and more biochemical information which will ultimately require to access the bloodstream using minimally invasive devices.

Overall, it is clear that skin-contacting soft electronic devices are on the verge of changing our life by providing more and more information about our body with a tremendous impact on the future of healthcare technologies.

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