Electrical Stimulation for Wound Healing: Opportunities for E-Textiles

Tom Greig, Russel Torah, Kai Yang

Abstract—Ulcers and chronic wounds are a large and expensive problem, costing billions of pounds a year and affecting millions of people. Electrical stimulation has been known to have a positive effect on wound healing since the 1960s and this has been confirmed in numerous studies, reducing the time to heal, and the incidence of adverse events such as infections. However, because each study used different parameters for the treatment, inclusion criteria and metrics for quantifying the success, it is currently hard to combine them statistically and gain a true picture of its efficacy. As such, electrical stimulation has not been universally adopted as a recommended treatment for various types of wound.

This paper summarises the biological basis for electrical simulation treatment and reviews the clinical evidence for its effectiveness. Notable is the lack of research focused on the electrodes used to deliver electrostimulation treatment. However, a significant amount of work has been conducted on electrodes for other medical applications in the field of e-textiles. This e-textile work is reviewed with a focus on its potential in electrostimulation and proposals are made for future developments to improve future studies and applications for wound healing via electrical stimulation.

I. Introduction

Chronic wounds are wounds which do not proceed through the natural healing process in an orderly or timely fashion. They are a significant problem for health systems, often leading to further harm to patients and greatly increasing the chances of long term hospitalisation.

All types of wounds can become chronic, but they are most prevalent as a result of pressure or vascular ulcers. These are breaks in the skin which occur because of a lack of blood flow to the underlying tissue, caused by prolonged pressure or by other problems with the circulatory system, often associated with diabetes [1], [2].

Ulceration is a very common problem. Between 2015 and 2018 the UK's National Health Service treated 33 155 cases of diabetic foot ulceration, though at any one time, more than 64 000 people with diabetes in the UK have at least one ulcer [3]. Only half of these heal within 12 weeks. Diabetic foot ulceration is also a leading cause of amputations, resulting in 7 000 each year in England. Having an ulcer is also associated with a high chance of mortality for diabetic patients: only 60% survive for five years [3]. Pressure ulcers also present a significant healthcare burden: incidence rates of up to 45% have been recorded in hospitalised neurological patients [4], [5]. Significant percentages have also been seen in hospitals around the world [6]–[8]. All together, chronic wounds affect 2.2 million people in the UK costing the NHS £5.3 billion per year [3].

Current wound treatments mostly aim to create an environment which best allows the body to heal itself: dressings are applied to prevent further damage and blood loss and to maintain the ideal level of moisture and infections are treated. The causes of the wound are also alleviated, to the greatest extent possible. For example, pressure redistribution equipment may be used to alleviate the cause of a pressure ulcer [9]. In some cases though, particularly when the cause of the wound cannot be completely removed, the body is unable to repair itself and the wound becomes chronic.

One component that has been identified as being important to the wound healing process is the current of injury. This is a small, ionic current that starts flowing towards the wound when the skin is broken. It helps signal to cells that a wound has occurred and where it is located. This allows a quicker immune response and means that the rebuilding of damaged tissue can begin sooner. The cessation of this current is strongly correlated with a wound becoming chronic [10].

By applying an electric field to the wound manually, a treatment known as electrostimulation, the effects of the natural current of injury can be recreated and the cellular response to an injury increases even if the natural current has stopped. Electrostimulation has had promising results in a number of studies, in many cases, more than doubling the speed at which wounds heal [11], [12]. This equates to a difference of several weeks in healing time.

While electrostimulation has been adopted as a recommended treatment in some parts of the world, including the European Union and the United States of America [13], there are still several issues that hinder more widespread use. There are numerous parameters that can be varied when setting up an electrostimulation protocol: different studies have chosen different stimulation waveforms [11], [14], polarities [9], [12], durations of treatment [14], [15] and electrode locations [14], [16] making it difficult to combine their results into a cohesive body of evidence.

On top of this, electrostimulation apparatus can be bulky and inconvenient for the patient. Small e-patch based devices have made an improvement in this area. These are self-contained, wearable devices that adhere to the skin and have been widely used in biopotential monitoring, particularly as ECG loggers [17], [18]. However, these devices rely on rigid circuit boards and so cannot conform completely to the contour of the skin, particularly where the surface of the body is tightly curved.

These are limitations that new e-textile technologies have the potential to improve. E-textiles are textiles that include electronic components, either in or around the fabric structure [19]: it is now possible to incorporate conductive traces [20], [21], sensors [22], integrated circuits [23], and electrodes [24], [25] into textiles without compromising the textile's properties of comfort and flexibility. E-textile printing techniques make it possible to integrate electronics directly onto existing wound dressings [26], [27].

Additionally, as e-textile devices become easier to fabricate and as electronic integration increases, they may allow for more research into the effectiveness of electrostimulation with a more consistent and standardised approach. This would provide better understanding of its efficacy and

Tom Greig and Russel Torah are with the School of Electronics and Computer Science, University of Southampton, Southampton, UK (tg8g16@soton.ac.uk).

Kai Yang is with the Winchester School of Art, University of Southampton, Winchester, UK.

increase the number of qualified manufacturers that supply it as a wound treatment.

This review will discuss the biological factors that influence wound healing, summarise the existing evidence for its efficacy, and conclude with a discussion of the potential impact e-textiles could have in this area.

II. The Biology of Wound Healing

The natural processes that control wound healing involve numerous different types of cells and chemicals that form a complex web of interaction. Despite this, they can be divided into four chronological stages, though these stages overlap and will take place at different times in different parts of the wound.

Stage 1 is where the body attempts to minimise blood loss through a process called haemostasis. This usually takes place within a few minutes of the wound opening and is a task largely completed by platelets [28].

Platelets detect and bind to tissues as soon as a blood vessel's walls are broken. They then start binding other platelets to themselves and producing the chemical fibrin which is used to construct a temporary matrix around which the tissue can be rebuilt [28].

Stage 2 is the inflammation stage, used to prevent infections. A break in the skin will inevitably allow pathogens to enter the body and it is important that they are killed before an infection can take hold.

When the skin is broken, skin cells release chemicals, called mediators, that trigger the inflammatory response [29]. Immune cells: first neutrophils, then macrophages; detect these mediators and move into the wound site. Once there, they engulf and break down pathogens as well as devitalised tissue [30].

Once this process is completed, macrophages release another set of mediators to initiate the proliferation stage [31].

Stage 3, the proliferation stage, is when the damaged tissue is replaced. Fibroblast cells move into the wound when they detect the mediators released by macrophages and once there, replace the fibrin matrix with one made of type II collagen, allowing granulation tissue to grow and replace the damaged dermis [32].

Once this new matrix is in place, new blood vessels can be grown in a process called angiogenesis [33] and reepithelialisation can begin. Reepithelialisation is the regrowth of the skin, wherein keratinocytes from the bottom skin layer move out over the wound, the begin dividing to build up the rest of the skin's layers shown in figure 1 [34].

Stage 4 is the final stage of wound healing: remodelling. It exists to improve the work of the earlier stages: the type II collagen matrix is replaced again by a more organised type I matrix with higher tensile strength and capillary density is reduced as small blood vessels merge to form larger ones.

A. Chronic Wounds

A wound may become chronic if anything prevents it from moving through the four stages. Most commonly, this occurs when a wound gets stuck in the inflammatory stage as a result of a prolonged infection. The immune response to infection in a wound involves the release of enzymes and chemicals that can inflict significant damage to host cells which, combined with the biological burden of the pathogens themselves, create an environment in which it is very difficult to begin rebuilding tissue. This is particularly in cases where the original cause of the wound is still being felt [32].

Another cause of delayed wound healing is physical damage to delicate, newly grown tissue. Should new capillaries be broken for example, the whole process of wound healing may have to start again from stage 1 [32], [33].

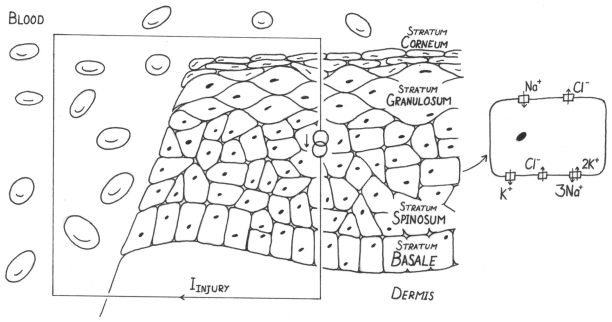

Fig. 1. The structure of skin and source of wound current. Cells in the stratum basale proliferate and move outwards, changing morphology as they go from one layer to the next [34]. These cells move charged ions through themselves, providing a current source and the circuit is completed when a conducting fluid, e.g. blood or wound exudate, connects the surface of the skin with the dermis [34], [35].

III. Electrical Currents in Wound Healing

A. The Natural Current of Injury

During wound healing, a current naturally flows into the wound from the surrounding tissue. This is a result of the potential differences across the skin being short circuited by conducting fluids such as blood and wound exudate [10].

The potential difference across the skin is generated by moving sodium, potassium and chloride ions through the cells of the epidermis. Most cells predominantly move negative ions (Cl^-) towards the surface and positive ions (Na^+ and K^+) away from the surface [35]. On average, this causes the surface of the skin to have a potential 23 mV lower than the dermis, though this varies between different parts of the body and different people [36].

When the epidermis is broken, a conducting path can form between the dermis and the surface of the skin, see figure 1. Here, the current does not consist of free electrons as in a metallic conductor, but the same charged ions that were originally moved through the epidermis. As such, the natural current of injury is considered an ionic current.

How the properties of this current are affected by the depth of the wound has not been thoroughly studied, though it is known that the dermis is more conductive than the fat or muscle that lies below it [37] meaning that the returning current will likely be concentrated in the dermis regardless of the wound's depth.

B. Cellular Responses to Current

Many different types of cells migrate directionally in an electric field, an effect called electrotaxis [35]. Macrophages and neutrophils have been shown to exhibit this effect [38], [39], as have other immune cells: monocytes [38], and granulocytes [40]. Several studies have examined how fibroblasts behave in an electric field and most show them travelling cathodically: towards a wound site [41]–[45], but they have also been recorded moving towards the anode [46]. Keratinocytes also migrate cathodically [47].

There are a number of mechanisms through which this migration may be occurring. It is possible that charged

proteins on the cell's surface accumulate on one side when exposed to an electric field. Integrins, the proteins used by cells to pull themselves over a collagen matrix, are negatively charged in the region outside the cell and so accumulate cathodically when an electric field is applied [35].

The same mechanism applies to the receptor proteins cells use to detect dissolved mediators. Epidermal growth factor is a mediator that encourages keratinocytes to proliferate and move across the wound [48]. The proteins that detect it have been shown to accumulate of the cathodic side of their cells within 10 minutes of an electric field being applied [35].

C. Antibacterial Effects of Current

It is also thought that electrical current can inhibit the growth of bacteria [10]. Some clinical trials reported that electrostimulation treatment helped to heal infections and that the rates of infection were higher in control group patients than those receiving stimulation [14], [49], [50]. However, it is difficult to determine exactly how this inhibition occurs given the complex systems involved.

One potential reason for the lower incidence of infection is that electrical stimulation is aiding the body's own immune system. As stated above, monocytes and neutrophils are attracted to the cathode when placed in an electric field [38] so cathodic stimulation will cause a greater number of these cells to reach the wound site and increase the chance that an infection is quickly eradicated.

This cannot be the only mechanism involved though, as several in vitro studies have also demonstrated the antibacterial effect of electrical current. The first of these was by Rowley in 1972 [51]. He placed E. coli from a colony in its logarithmic growth phase into a liquid growth medium and applied DC or AC of varying frequencies in the range of 0.2 - 140 mA. AC had very little effect, but DC significantly reduced the growth rate of the bacteria. However, this effect was reduced when mesh filters were added, allowing ion molecules to pass through but keeping the bacteria away from the electrodes themselves, as these areas had a significant change in pH. With filters, 140 mA DC increased the intergeneration time - the time between a cell dividing and its daughter cells dividing - by 14.6%. Without filters, the increase was 38.8%. The electrodes used in the experiment were made of platinum-iridium to ensure that they did not leach into the growth medium.

Later, Spadaro et al. performed a similar test using four different types of bacteria: staphylococcus aureus, E. coli, pseudomonas aeruginosa and proteus vulgaris; and five types of electrode: platinum, stainless steel, gold, copper and silver. It was found that silver had a large bacteriostatic effect (it prevented growth, but did not kill bacteria) even at very low currents (0.4 µA) where no pH change was caused. With larger currents (40 & 400 µA), the other electrodes started to have an effect, though at this point, large changes in pH had occurred [52]. This implies that any effect were less a result of the current itself, but was caused but the antibacterial properties of silver or the environmental changes the larger currents caused.

These two studies show that electric current does create an environment which is less suitable for bacterial growth, though to what extent this is a result of the current itself or of the environmental changes it triggers (pH and chemical balance) is not clear.

IV. The Effectiveness of Electrostimulation in Wound Healing

The first true research into the effects of electricity on wound healing came in the 1960s, after is was found that applying gold leaf to ischaemic skin ulcers (those caused by arterial problems) increased the conductivity of the skin and significantly improving their ability to heal [53], [54]. Though this was in fact noted in 1668 by Sir Kenelm Digby in his Choice and experimented receipts in physick and chirurgery where it was described as 'a certain remedy for all Scars of the Small-pox' [55].

Reviewed below are the studies that tested an active electrostimulation treatment, observing its effects on wound healing in human patients. They were identified by searching the PubMed database and EBSCO MEDLINE with the query 'wound AND heal* AND electr* AND stimulation'. Each paper also had its references and, where available, papers that cited it, checked for other studies that fit the criteria.

A. Low Intensity Direct Current

The first type of active electrostimulation investigated is known as low intensity direct current (LIDC). It typically involves currents of under 1 mA delivered either continuously or as a low frequency square wave with pulses lasting at least one second [56].

The first study to investigate LIDC was carried out by Wolcott et al. in 1969 [14]. Here, patients with ischaemic skin ulcers were treated with a constant DC current of between 400 and 800 µA. Current was applied in sessions lasting two hours, three times per day. For the first three days, the electrode on the wound itself was negative with the positive electrode 15 cm proximal to the wound. The electrodes were then switched and the positive electrode kept on the wound until healing 'plateaued' (usually two to three weeks later), then switched back until there was a second plateau, and alternated daily thereafter. A plateau was implied to be when the wound size stopped decreasing, but precise criteria were not defined. The reason for the polarity switching, explained in [57], is that negative stimulation appeared to have an antibacterial effect but hindered wound healing, while positive stimulation aided healing but also encouraged bacterial growth.

Of the 75 ulcers treated during the 18 month study, most of which had not responded to previous treatment, 31 healed completely. Eight patients had two or more ulcers and so were able to serve as their own control. All eight of them saw a greater decrease in size in the stimulated wound than their control one.

This study was repeated in 1976 [15] using the same methodology but only reversing the polarity once. Here 48 out of 100 total ulcers healed completely and in six patients with control ulcers, the mean weekly healing rate was twice as high in wounds treated with electrostimulation.

Since then, there have been several other studies investigating LIDC, each with slightly different protocols. In 1985, Carley and Wainapel [58] tested the same LIDC stimulation using both steel mesh and carbon electrodes. Their study used 15 pairs of subjects, matched by age, wound type, wound size and wound location; one of whom received stimulation treatment, while the other received only standard wound care. Initially, the negative electrode was positioned over the wound. After three days, this was switched to positive and maintained until healing plateaued, at which point another three days of negative

stimulation was used. The duration of the treatment was five weeks.

The average wound volume in the two groups was similar at the start of the study, but by the third week, the treatment group's wounds were significantly smaller, showing a p-value under 0.05, thus confirming the efficacy of the treatment.

In 1987, Katelaris et al. [59] tested LIDC stimulation combined with dressings soaked in saline solution or povidone-iodine. They used a stimulator that provided 20 µA of current with the cathode over the wound. In this case, the investigators were unable to find any evidence that electrical stimulation accelerated the healing of venous ulcers. In fact, it was found that electrical stimulation combined with povidone-iodine significantly slowed healing. A likely cause of this is that the negative electrode over the wound would repel the negatively charged iodine molecules causing them to penetrate deeper into the tissue. Here, their slightly toxic effect on human cells wound hinder the growth of new tissue [60]. Additionally, the small sample size, only 24 patients, and particularly low current are potential flaws meaning that this study does not constitute proof that LIDC is generally ineffective. However, it does show that care must be taken when considering the material used alongside electrostimulation treatment to avoid detrimental side-effects.

In the same year, Fakhri and Amin [16] investigated the effects of LIDC on chronic burn wounds. Their treatment consisted of 25 mA of current, applied on either side of the wound for 10 minutes, twice a week. In all but one of their 20 patients, reepithelialisation, the regrowth of skin, began within three days and the wound completely healed within three months. In addition to this, several patients, on whom skin grafts had previously been attempted, had them succeed when retried after electrostimulation treatment.

Despite the majority of evidence suggesting the LIDC improves wound healing and it being the stimulation type that most closely resembles the natural current of injury, LIDC is rarely used in modern settings. This is because prolonged exposure to DC currents, even below 1 mA, can cause the tissue under the anode to become alkaline, and under the cathode acidic. This is because the anode attracts the negative hydroxide ions (OH^-) the make up alkalis, and the cathode attracts positive hydrogen ions (H^+) creating an acid. This can cause irritation and create a sub-optimal environment for the cellular processes necessary for a wound heal [56], [61].

B. Pulsed Current

Some of the issues with DC stimulation can be alleviated by using pulsed current. Pulsed current stimulation usually takes the form of a square wave with pulses lasting less than 1 ms, equating to less than 5% of the total duration (a duty cycle under 5%). This prevents it from causing the irritation and acid / alkaline build up that occurs with continuous current while still being a polar signal [56].

The first studies into pulsed current for stimulation were done to test wound healing stimulators made by Staodynamics Inc.: the Dermapulse [11] and Vara/Pulse® [62]. Both of these stimulators could be configured to provide a square wave with an amplitude of 35 mA and a frequency of 64 or 128 Hz. When set to 60 Hz, the duty cycle was 0.84%, at 128 Hz it was 1.68%. In both studies, the stimulation was applied in 30 minute sessions, twice a day for four weeks. Initially, the electrode over the wound was negative and the frequency set to 128 Hz. This was maintained until the wound cleared itself of necrotic tissue. After that, the polarity was switched every three days. Once the wound no longer descended as far as the muscle, the frequency was reduced to 64 Hz and polarity reversed every day. In both studies, the healing rate was twice as high in the stimulation group than in the control group.

In 1993, Wood et al. [63] tested a device that applied 300 - 600 µA of current at frequencies below 1 Hz. In their study, the electrodes were placed either side of the wound, on healthy skin. After eight weeks of treatment with one session (of unspecified length) each day, the treatment group's ulcers had healed by 80% on average and those from the control group had mostly deteriorated.

The Dermapulse® device was tested again by Jünger et al. over a period between 1997 and 2006 [64], [65] using a similar protocol to the original studies, except the stimulation was repeatedly cycled between 7 days of negative and 3 days of positive. After four months, stimulation was found to have a significant positive effect on wound size, reported pain, transcutaneous oxygen partial pressure (a measure of a tissue's oxygen level) and capillary density relative to a control.

In 2001, Adegoke and Badmos [66] tested an electrostimulation device that provided pulsed current with a duty cycle of one third and a frequency of 30 Hz. They found that the area of their treatment group's ulcers reduced by 22.2% while the control group's only reduced by 2.6%. While this does indicate that the stimulation improved healing, there were only three patients in each group and that there was a large variation between patients, therefore the result cannot be considered statistically significant.

One other study, published in 1996 by Baker et al. [67] used stimulation that could also be considered pulsed current. Here, three different stimulating waveforms were tested. The first consisted of a positive pulse of high intensity followed by a longer negative pulse at a lower intensity, such that the total charge transferred in each direction was equal. The second was the same except the negative was the same duration as the positive, but still at the lower intensity. The final waveform was the same as the first, but scaled to a lower amplitude overall: 4 mA for the positive pulse. The first two waveforms had their amplitudes set just below the motor threshold, the intensity that induces muscle movement, for each patient. No statistically significant difference was found between the healing rates of the three different stimulation groups or the control group. When just the patients that completely healed during their treatment were analysed, the balanced waveform appeared slightly better than the unbalanced and significantly better ($p < 0.05$) than the lower amplitude and controls. The applicability of this result is limited however, not just by the complicated method required to obtain a significant result, but also by the fact that both the electrodes were placed on intact skin either side of the wound, as opposed to the more common configuration of one on intact skin and the other directly on the wound itself. As such, this study does not provide any further clarity on what the effects of charge flowing into or out of the wound are.

C. High Voltage Pulsed Current

A sub-type of pulsed current that has become one of the most widely studied is high voltage pulsed current (HVPC). This continues the principal of using a higher current with a lower duty cycle, under the hypothesis that it would be even better at providing the benefits of electrostimulation

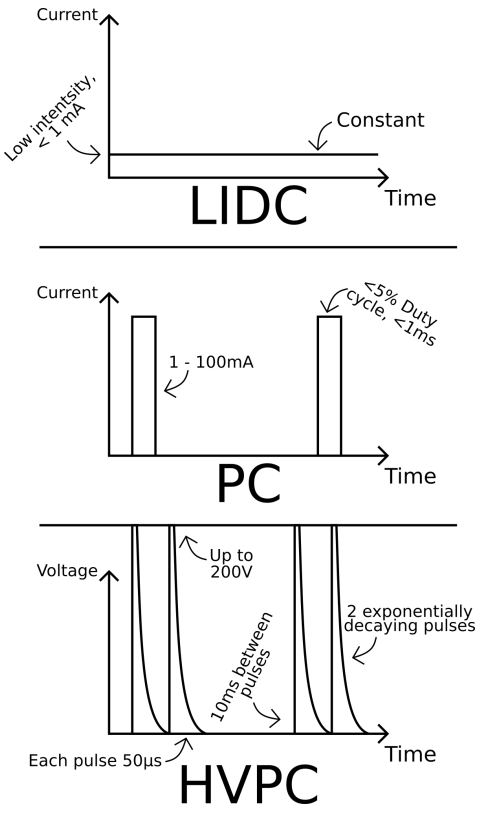

Fig. 2. The three common stimulation waveforms used in wound healing research [56].

while avoiding the side effects. HVPC treatments apply voltages of up to 200 V but only for a few microseconds and with a duty cycle under 1% [56].

An early study on HVPC was done by Kloth and Feedar in 1988 [68]. They applied HVPC to nine patients with ulcers that descended all the way into the muscle and compared the results to seven controls. Their stimulation waveform had two peaks, 50 µs apart repeated at 105 Hz, as shown in figure 2. The intensity of the peaks was set just below the motor threshold, between 100 and 175 V. After sixteen weeks of treatment with 45 minute sessions, five days a week, all of the treated patients had healed completely, while most of the control group's wounds had deteriorated.

In 1991, Griffin et al. [69] studied the effects of HVPC on pelvic ulcers in patients with spinal cord injuries. Using twin peaked pulses of 200 V, 100 Hz and 75 µs duration for 20 days, they found that the patients receiving treatment had a decrease in wound size significantly greater than the control patients' on days 5, 10 and 20 of the 20 day trial, though not on day 15.

HVPC was shown to have a positive effect on leg ulcers in 2000, when Franek et al. [70] showed that it performed better than topical medicine or Unna's boot (a type of compression therapy) both in terms of wound size decrease and rate of granulation tissue growth.

In 2001, Peters et al. [71] tested HVPC's effect on diabetic foot ulcers by having patients wear a Dacron-mesh silver stocking which delivered 50 V stimulation for 20 minutes each hour. It was found that patients that had the real stocking were much more likely to heal than those using a placebo, though in both groups, those who used the stocking for more than 20 hours a week were more likely to heal that those who did not.

The effects of HVPC specifically on diabetic vascular ulcers was shown by Houghton et al. in 2003 [12]. During negative HVPC stimulation (50 µs pulses, 150 V peak, 100 Hz), the weekly reduction in wound surface area among the treated patients was approximately double that of patients in the control group.

Another study lead by Houghton [72] assessed the effects of HVPC on the pressure ulcers of patients with spinal cord injuries. Treating patients with HVPC for 40 minutes each hour, 3 hours a day for three months, alternating between 10 and 100 Hz, also gave approximately twice the healing rate seen in controls.

Again testing pressure ulcers on the legs and feet, Franek et al. [73] found in 2012 that HVPC gave a doubling of the rate at which wound size and area decreased. This was with only 50 minutes of stimulation per day, 5 days a week for 6 weeks.

In 2012 and 2014, Ud-din et al. [74], [75] tested a device that measured the impedance of a patient's skin and applied an HVPC signal with an amplitude of 20 - 80 V based off that measurement. The details of how the skin impedance affected the signal were not given. At the beginning of the study, healthy subjects were given punch hole biopsies in both arms; one arm had electrostimulation applied, the other was used as a control. It was found that the arm that received stimulation predominantly had a smaller wound than the control arm at any given time after wounding. The authors also found that electrostimulation increased blood flow, levels of haemoglobin and the concentration of soluble mediators that trigger the regrowth of blood vessels such as vascular endothelial growth factor-A. This device had earlier been tested by Perry et al. [76] as a treatment for painful or itchy skin scars. That study had participants rate their levels of pain and itchiness. While there were conflicts of interest (the study was funded by the device's manufacturer) and there was no control group, it did give positive results.

In 2016, Zhou et al. [77] tested HVPC in conjunction with silver collagen dressings on 10 patients. They recorded a significant decrease in wound size, though there were no controls to compare against. Additionally, several adverse events occurred during the study including one wound becoming infected (which silver dressings are designed to prevent) and one patient noticing an increased foul odour after using the dressing.

In 2017, the effects of changing polarity were tested by Polak et al. [9]. Their study ran for six weeks with one group of patients receiving a typical cathodic HVPC treatment for the duration while the other group received cathodic stimulation for only the first week before switching to anodic. The results showed that the purely cathodic treatment resulted in slightly greater shrinkage, though the difference was not significant. Both were significantly greater than the control group.

D. Other Stimulating Waveforms

A number of studies have used waveforms that do not fit into the above categories. One such study was performed in 1988 by Kaada and Emru [78]. They investigated the effectiveness of TENS stimulation on leprous ulcers. TENS - transcutaneous electrical nerve stimulation - is used as a treatment for chronic pain because it can disrupt the nervous system's signals [79]. The waveform used by Kaada and Emru consisted of a pattern of 5, 0.1 - 0.2 ms pulses, 10 ms apart, repeated at 2 Hz. The pulses had an intensity of between 25 and 50 mA. Their study included 19 patients

all of whom had leprous ulcers lasting for at least 2 months with an average size of 5.2 cm². All 19 patients healed completely within 12 weeks. While this study does show that TENS stimulation has promise as a wound treatment, the lack of controls and the small sample size mean that it cannot be considered conclusive.

A second study conducted in the same year used a similar waveform to treat ischaemic skin flaps resulting from reconstructive surgery for mammary carcinoma. This study, by Lundeberg et al. [80], involved 24 patients, 10 of whom were used as controls and given a sham treatment. For the treatment group, stimulation was set at an intensity three times higher than the threshold at which a tingling sensation was felt. The results of this study were also positive, with electrical stimulation generally increasing blood flow and with no incidents of necrosis, compared to 80% incidence in the control group.

Lundeberg published a second study in 1992 [81], using the same stimulation method, this time investigating the effect on diabetic ulcers. This study had 64 subjects, 32 with a real stimulation and 32 with a sham, receive stimulation for 40 minutes a day over 12 weeks. At the end of the treatment, the average size of the stimulation group's ulcers was significantly lower than that of the control group's with an average of 39% of their original size, compared to 59% for the control group.

An entirely separate category of stimulation is that which uses a biphasic waveform, where the amount of charge transferred in each direction is equal. While this does have some advantages: most notably, it does not cause a pH change, some of the mechanisms discussed in section III are directional and so require a polar signal to function. As a result, research into biphasic stimulation has not been widely pursued. The exceptions are detailed below.

The first study investigating biphasic stimulation was published in 1994 by Jerčinović et al. [82]. They used a functional electrical stimulation (FES) waveform consisting of trains of pulses which, as they return to zero, overshoot slightly and slowly, exponentially decay back up, keeping the overall charge transfer balanced. This waveform, shown in figure 3, was used to treat 61 pressure ulcers in spinal cord injury patients while 48 patients received only traditional treatment and were used as controls. They recorded 1.5 to 2 times faster healing in wounds treated with electrostimulation.

Another study to investigate biphasic stimulation was conducted in 2019 by Ibrahim et al. [50] on patients with severe partial thickness burns. They compared the effects of electrical stimulation to negative pressure wound therapy, a treatment that involves applying a suction force to the wound to drain excess fluids as well as stimulate blood flow and tissue regrowth. The electrical stimulation used a 1 Hz, 300 µA amplitude square wave. Both the electrical stimulation and the negative pressure performed significantly better than the standard wound care control, both in terms of wound size decrease (1.6 and 1.3 times respectively) and bacterial colony count (both caused a slight decrease compared to the almost two times increase seen in controls). Patients treated with electrical stimulation showed slightly better wound size reduction while those treated with negative pressure showed fewer bacterial colonies. It is possible that combining both electrical stimulation and negative pressure could give superior results on both metrics, but this was not tested.

In 2007, Lawson and Petrofsky [83] published a further study investigating biphasic stimulation. They were interested in whether applying electrostimulation to chronic wounds while in a warm environment would increase blood flow and improve healing. Their study involved 10 patients with diabetes and 10 without, all of whom had an ulcer penetrating into the subcutaneous tissue that had not healed for two months. All patients received stimulation in the form of a biphasic square wave of width 200 µs, frequency 30 Hz and amplitude 20 mA for 30 minutes, 3 times a week for 4 weeks. It was found that electrical stimulation, given in a room with an ambient temperature of 32°C did increase the blood flow and that this correlated with increased healing among diabetic patients. This increase could only be measured against the baseline of no healing for the previous two months however, as there were no dedicated control patients. Additionally, there is no way of knowing to what extent the temperature of the room affected the results as there were no controls in that regard either.

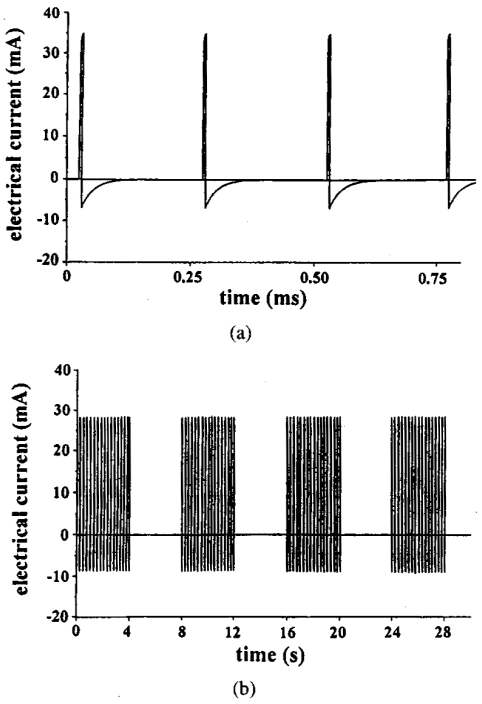

Fig. 3. The waveform used by Jerčinović et al, 1994, showing the trains of pulses used. The initial spike and the exponential decay were balanced so that the net charge transfer was zero (a). These 4 kHz pulses were grouped into trains 4 seconds long, with four second breaks in between (b).

FREMS - frequency rhythmic electrical modulation system - is a waveform similar to HVPC which has been used in a small number of studies. A FREMS signal consists of several short pulses occurring at a rapidly changing frequency. It was first used in 2004 to treat musculoskeletal pain [84]. Since then, much of the research into FREMS has been focused on its potential to lessen diabetic neuropathy (nerve damage caused by diabetes), a task at which it shows promise [85]–[87]. The reasoning behind the use of varying frequency pulses is that the variations 'probably permit a modulation of peripheral and central systems' [84].

Between 2008 and 2013, there were four studies published evaluating the efficacy of FREMS stimulation on chronic leg ulcers. The first of these was performed by Janković and Binić [88] and comparing standard topical treatment (15 patients) to topical treatment plus FREMS stimulation (20 patients), showed that FREMS reduced the size of

ulcers and the perceived level of pain significantly more than topical treatment alone ($p < 0.01$). In the same year, Magara et al. [89] found that wounds treated with FREMS shrunk significantly ($p < 0.05$) more than the control group's wounds 15 and 30 days into the treatment period, though this significance did not persist to day 60. The third study also found positive results when testing FREMS solely on venous ulcers, isolated from the effects of diabetes. This study, by Santamato et al. [90], had a treatment group of 10 patients who saw decreases in wound area approximately six times greater than those of the 10 patient control group after 15 days of treatment and 30 days of follow up. The levels of pain reported by treated patients were also significantly lower than those reported by the control group. The final study, by Magnoni et al. [49], contained 30 treated patients and 30 controls with chronic ulcers of any type. This study also reported significantly better results, both in terms of wound size and reported pain, in their treatment group. None of these studies used a sham treatment however, meaning that the patients knew whether they were in the treatment or control groups. Because of this, it is difficult to know whether the benefits to wound healing were a result of the treatment or the placebo effect.

Figure 4 provides a summary of the different electrostimulation studies from the literature which reported the rate of wound size reduction. Studies are grouped according to the stimulation waveform that was used and the number of patients enrolled in the study. Most studies, particularly those conducted more recently or with a large sample size, report an improvement in the rate of wound size decrease of roughly two times, but there is still a large amount of variation between studies.

V. Electrodes for Wound Healing

In general, little attention has been given to the electrodes used to deliver electrical stimulation for wound healing. The majority of early studies used steel [58], [62], [77] or other metallic mesh [12], [14], [16], [59], [69], [71] placed on top of a saline soaked gauze. Examples are shown in figures 5 and 6. Later studies mostly used carbon rubber electrodes [9], [11], [65], [67], [70], [73], though several studies simply do not specify. No clinical trials have compared the effectiveness of different electrodes, though one, Houghton et al. 2010 [72], did note that switching to a carbon rubber electrode alleviated redness caused by the original self adhesive one for one patient.

A. Existing Electrode Technologies

There are several electrode technologies that provide alternatives to the traditional metal and gauze system used in earlier studies. A common material used in modern electrodes is hydrogel. These electrodes use a mesh of hydrophilic polymers, capable of holding a very high water concentration, sitting between a metal cap and the skin [91]. Because of its gel like consistency and high water content, hydrogel is capable of forming a very low impedance contact with the skin [92]. Recent work has shown that carefully formulated hydrogels can have excellent conductivity and biological properties [93]. However, hydrogels do eventually lose their moisture to evaporation, at which point that advantage is lost and the electrode must be replaced. In addition, their inherent adhesive properties mean that they are prone to picking up dirt and skin cells, and thus become fouled over time, reducing their conductivity.

Another alternative, as mentioned above, is carbon rubber electrodes. These use carbon to add conductivity to a soft rubber pad, creating an electrode that is comfortable, conductive and able to conform to the surface it is placed upon [94]. While the carbon rubber itself does not suffer from drying out, it is usually necessary to moisten the interface between the electrode and the skin to lower the electrical impedance between them and improve user comfort. This is particularly important for stimulation requiring current above around 10 mA. This is because the reduced impedance allows for deeper penetration of the electric field away from the sensitive nerve endings close to the surface [95].

In the context of wound healing however, this moisture requirement is less relevant as the biological mechanisms of wound healing already necessitate that the wound be a moist environment. Moisture is needed to prevent cells from drying out and to allow the chemical mediators, used for inter-cell communication, to diffuse. Interventions already exist to increase wound moisture when it is required [33].

B. Electrode Layout

An area that has been shown to affect stimulation outcomes is the layout of the electrodes used. An early study investigating this was done by Petrofsky et al. [96] who studied the current output of self-adhesive hydrogel electrodes. They found that the size of the electrode had very little effect on how the current was passed into the skin. This was because the hydrogel had a relatively large resistance, meaning the current only flowed through the centre, close to where the lead wire was attached, see figure 7. Thus, adding extra electrode area, far from the lead wire had little effect on the current distribution. This was not the case with carbon rubber electrodes which have a lower resistance and create a constant current density over their whole area, whatever that may be.

Minimising electrode impedance and thus the current density passed into the skin is important because that determines the intensity felt by the patient [24]. Additionally, having all the current passing through a small area limits the total strength of current that can be passing into the skin, as regulations define the maximum current that a device can emit in terms of current density rather than absolute current strength [97]. However, the majority of modern electrodes use a conductive cap or mesh covering the would electrode area rather than a single lead wire, meaning the applicability of this result is limited [92].

In 2007, Petrofsky and Schwab modelled the flow of exogenous (externally generated) current through the body, particularly focusing on blood flow. They concluded that, because blood has such a low resistivity ($1.6\ \Omega m^{-1}$), current is likely to be concentrated wherever it flows: if there is a lot of blood near the surface of the skin, current flow will concentrate near the surface, otherwise it will penetrate deeper [98]. This means that the effect of applying electrostimulation could vary depending on the blood flow to a wound, often an issue in cases of vascular ulceration [2], as well as with the ambient temperature, as blood flow is concentrated near the skin when body is trying to cool itself down [99].

In 2009, Suh et al. [100] studied the effects of using a three electrode system for treating chronic diabetic wounds. They placed three electrodes in a triangle centred on the wound. One electrode was active and the other two were connected to ground. These roles were switched every second to create a rotating electric field across the

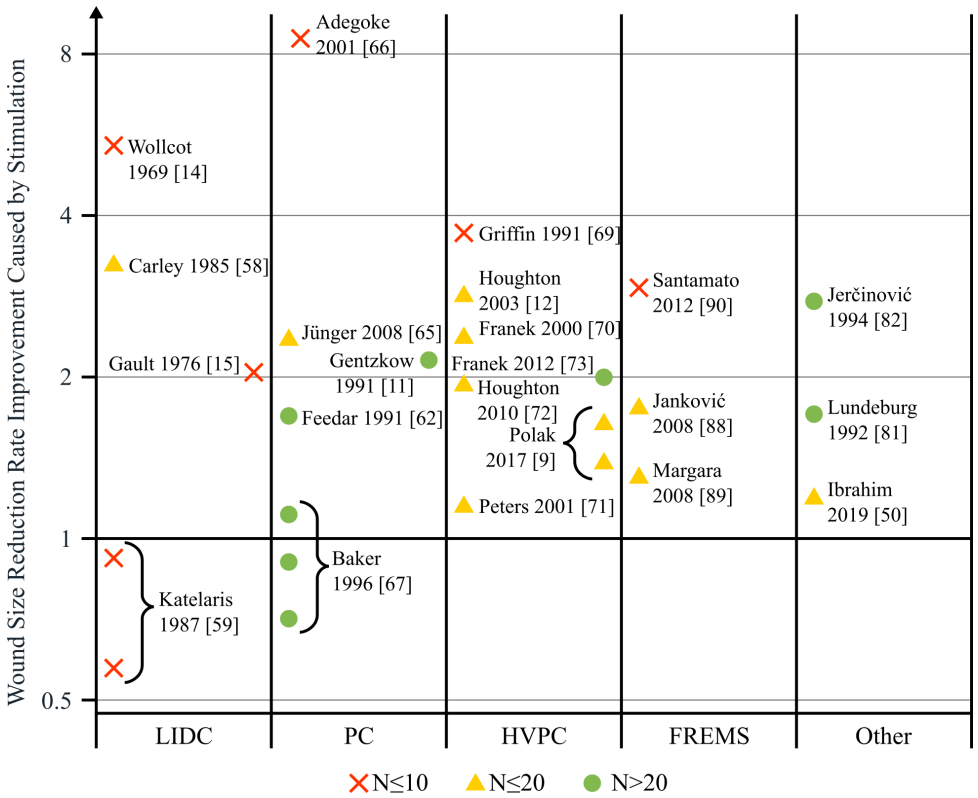

Fig. 4. Comparison of results from controlled studies that report wound area decrease. The y-axis shows the improvement in percentage decrease in wound area per week that the treatment group had over the control group. Data points are colour and marker coded by the number of participants in the study as shown at the bottom of the figure, where N is either the number of patients in the treatment group or in the control group, whichever was smaller. Where a study tested multiple treatments, the results of each treatment group are shown separately.

Fig. 5. Stimulator used by Gault and Gatens, 1976, showing the mesh electrodes used to deliver the current. Image taken from [15].

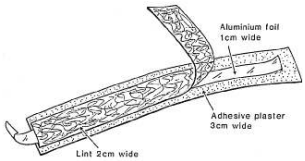

Fig. 6. Electrode used by Fakhri and Amin, 1987. Image taken from [16].

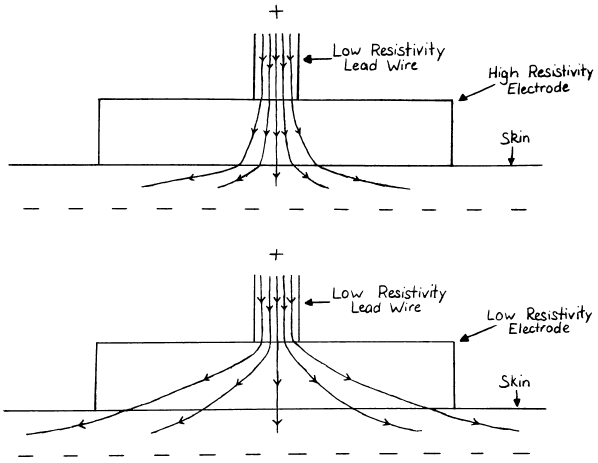

Fig. 7. Flow of current through high and low resistivity electrodes. When the electrode resistivity is high, the current can only travel a short distance and so remains concentrated under the lead wire. When the electrode resistivity is low, the current is able to spread out and enter the skin in a more distributed fashion [96].

wound. On healthy skin, the three electrode system caused a greater distribution of current and caused current to penetrate deeper into the muscle than an equivalent two electrode setup.

These results were supported in 2017, when Yung-Shin Sun [101] used the finite element modelling software COMSOL® to simulate the electric field that would result from applying electrical stimulation from various shapes of electrode with the aim of finding which electrode configuration would generate the largest electric field at the edges of the wound. Their results suggest that the best configuration was to have the negative electrode over the wound itself, with the skin around the edge of the wound covered by the positive electrode. With an applied voltage of 30 mV, this generated an electric field of 40 mV/mm at the edge of a 5 mm wound. Figure 8 shows three representations of this field. This study was limited however in that it dealt only

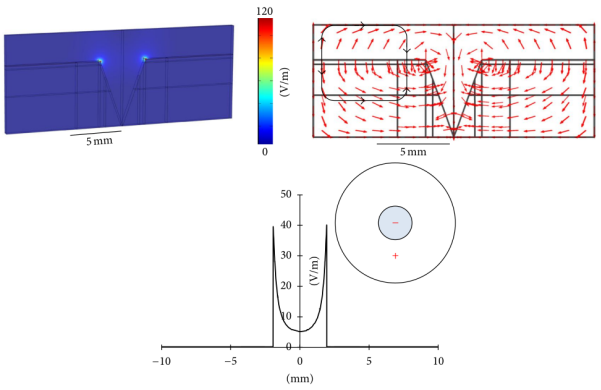

Fig. 8. Results of Sun's simulation of a concentric electrode over a circular wound. A 3D heat map to the generated electric field is shown in the top right, the direction of the field in the top left and the magnitude and electrode design at the bottom. This electrode design created a field with the highest magnitude at the edge of the wound of all the designs tested. Image from [101].

with constant DC stimulation, used a simplified model of the skin and only considered a circular wound of a single size.

VI. E-textile Opportunities

While it has been shown that choice of electrodes can affect several factors that are important to wound healing, relatively few research studies have been conducted into electrodes in that context. However, there has been a significant amount of research into electrodes within the context of e-textiles: electrode systems have been developed for functional electrical stimulation [102], transcutaneous electrical nerve stimulation [24] and for biopotential monitoring [23], [103]. The results of these efforts have not been widely applied to wound healing, however.

E-textiles are textiles that have electronic devices fabricated on or integrated within them: e-textiles have been developed which include sensors [22], energy harvesters [104], integrated circuits [23], antennas [20] and displays [21] as well as electrodes [23], [94], [102], [103]. The integration of electronics into textiles holds significant advantages for the user because it allows them to use body mounted electronic devices without the necessity for a bulky, rigid PCB. This is particularly true for wound healing devices: traditional wound dressings usually fit very close to the skin and do not interfere much with the patient's clothing or movement. As such, to avoid additional burden for the patient, any stimulation device would have to fulfil these requirements as well.

A. E-Textile Materials

One intuitive material choice for making e-textile devices are metals and this is often used when creating the connections to electrodes or any other electrical wiring. Silver is a common choice because of its high conductivity; stretchable, silver based inks have been developed with conductivities as high as 3200 S cm^{-1} [17]. It is also chemical stable and biocompatible, but, being a precious metal, its cost can be prohibitively high [105]. Copper also has a high conductivity and is significantly cheaper than silver, making it another common choice for e-textile applications, though it is more prone to corrosion [105]. Steel has been used to create conductive yarns for e-textiles because of its balance of good physical and electrical properties [106].

An alternative to metals are polymers, of which there are several suitable options, for example polyaniline [107], [108], polypyrol [109], [110], or poly(3,4-ethylenedioxythiophene) polystyrene sulphonate (PEDOT:PSS) [111], [112]. However, these polymer fibres have a conductivity at least one order of magnitude lower that metallic conductors so are less suited for long conductive paths. As shown by Merhi et al. [113] it is possible to combine metals with polymers to create a material that has the physical properties of the polymer but with much lower resistance. Merhi et al.'s work mixed PEDOT:PSS with silver nanowires - short silver fibres - creating a stretchable, screen printable ink with a sheet resistance of only 6 Ω/sq.

These materials can be made into yarns by a variety of spinning techniques, for example, electrospinning, where an electric field is used to pull a thin strand of the polymer out of a solution [114], or wet spinning, where the polymer precipitates from a solution in a liquid bath [107]. It is also possible to coat existing fibres or textiles with conductive polymers or metals.

A common material choice for the electrodes themselves is carbon loaded rubber, as discussed above [94]. When it is used in e-textiles, carbon rubber is often printed onto its substrate using one of the techniques described below.

When designing e-textile devices, careful consideration must be given to the choice of materials. To function on a textile substrate, they must be flexible, and in some cases stretchable, without breaking or losing their conductivity. In wearable contexts, particularly medical ones, biocompatibility is also essential. The materials must also be appropriate for use with e-textile fabrication techniques; they can either be used as a thread for weaving, knitting or embroidery, or as an ink for printing, as described in the following section.

When printing, there are also requirements placed on the substrate. It is desirable for the substrate to absorb some of the printed ink, in order to provide a more mechanically robust bond after curing [115]. Most printed electronic inks have curing temperatures between 100 and 150 °C, sustained for 5 - 30 minutes [92]. Some inks alternatively require exposure to high intensity ultra-violet light in bursts of 5 - 60 seconds [116]. Therefore, the substrate must be sufficiently robust to sustain this post-processing, typically repeated for several layers of printing [103].

B. E-Textile Electrode Fabrication Techniques

There are two broad categories of fabrication methods for textile electrode systems: the first is incorporating the conductive material into the textile itself using traditional textile manufacturing techniques such as weaving, knitting or embroidery. The second is printing or depositing the conductive materials onto the surface of an existing textile.

The methods in the first category require a conductive yarn. This could be a yarn manufactured using one of the techniques described above or simply a metallic wire with the right physical properties to be incorporated into the textile [24]. There are a variety of different weaving techniques that can be used to create the topography of yarns necessary for complex circuits [117], however, the conductive paths will always be limited to the orthogonal paths of the weave. Embroidery offers more geometric flexibility, though is more difficult to realise on an industrial scale as most conductive threads lack the necessary strength and elasticity for machine sewing [118].

There are numerous different methods by which it is possible to print conductive materials. The most simple of

these is stencil printing. Here, a stencil sheet with openings cut to the desired pattern is filled with conductive paste. The paste is then completely cured and the stencil removed [23], [94]. This method is most suited to simple patterns as the stencil will become too fragile if particularly fine details (< 1 mm) are required, resulting in deformation of the stencil and inaccuracies in the print. Additionally, all parts of the stencil must be connected meaning that free-standing, concentric designs are not possible. Stencil printing is good for thicker deposits of material (> 1 mm) as large amounts of material can be applied in one pass, while other techniques, originally designed for graphic printing, would need several layers to reach the same thickness [118].

A method which works on similar principles to stencil printing is screen printing. The screen in a screen printer is a dense wire mesh, partly covered by an emulsion to create a mask of the design. The material being printed is forced through the mesh openings with a squeegee, and onto the uncovered parts of the substrate [103].

Dispenser printing is a third method by which conductive material can be applied to fabrics. Here, a nozzle is moved around by a robotic actuator, while printing paste is pushed out by pneumatic or mechanical means. Because they can only print lines, typically under a millimetre in width, dispenser printers are slow to print large areas. They are however much more versatile than screen or stencil printers. Using one of those methods, changing the design requires the manufacture of a new screen or stencil; a dispenser printer can simply be reprogrammed with a new design. Dispenser printers also offer the ability to change the vertical position of the nozzle during printing, making it much easier to print on uneven surfaces or to vary the print thickness [119]. Dispenser printing is also a non-contact process: nothing touches the substrate apart from the paste, making it possible to print on adhesive or delicate substrates.

Inkjet printing uses a similar process to dispenser printing, in that a nozzle is positioned close to the substrate and inks are ejected from it. While dispenser printers typically print with a continuous stream of paste, the ink used in an inkjet printer is deposited as individual drops, typically only picolitres in volume. To form such small drops, inks used in inkjet printing have a much lower viscosity than those used for screen, stencil or dispenser printing [120]. Drops may be produced continually or only when needed depending on the desired pattern. Inkjet printing has benefited from large amounts of research interest, being one of the most common methods used in graphic printing.

There are a number of other printing methods that are less commonly used in the fabrication of e-textiles. Aerosol printing, a technique similar in principal to dispenser and inkjet printing, moves ink droplets from the nozzle to the substrate using a stream of gas, kept accurate by another sheath of gas around it [121]. Aerosol printing provides some of the same advantages of dispenser printing, though requires a significantly more complex system.

There are also a number of methods that involve setting up ink in the required pattern on one surface, before transferring it to the substrate. These include gravure and flexographic printing, where the design is engraved on a roller, the engraving filled with ink and the transferred onto the substrate [122]. The cost of producing the rollers and the stringent requirements on the properties of the inks [122] mean that these methods are not often used in small volume e-textiles production.

Printing techniques such as these generally require a very smooth surface that the ink can adhere to. If this requirement is not met, the ink may not adhere or may require increased quantities be deposited to create a complete conducting path. Because most textiles do not meet these requirements, interface layers can be placed between the conductive ink and the fabric. Polyurethane is common choice for this and can be printed as a paste [92] or applied as a laminated sheet [123].

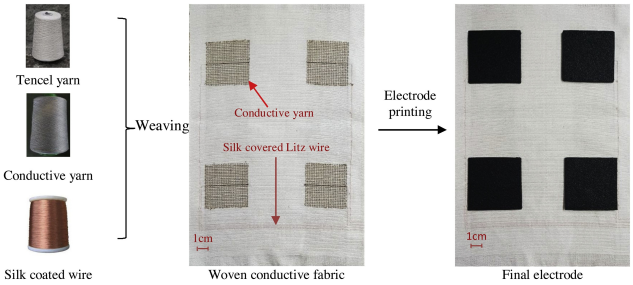

Fig. 9. Pain relief electrodes built by Yang et al. showing electrical connections woven into the fabric (centre) and the carbon rubber electrodes printed on top (right). Image from [24].

These printing techniques open up the possibility of building electrodes on top of existing wound dressings. This would allow doctors to retain their full choice of which dressing they use while still being able to apply electrostimulation at the same time.

Often, a number of different fabrication techniques will be used in the production of one device. For example, the electrical interconnections may be woven into a fabric before the electrode contact material is printed on top as in [24], see figure 9. It is also possible to combine prefabricated electronics with textiles using any number of adhesive or sewing techniques. This allows for the utilisation of standard electronics microfabrication techniques while, so long as any rigid components are sufficiently small, maintaining the benefits of a textile form-factor. This technique is particularly helpful when prototyping e-textile devices as it can be much quicker and more reliable to place several electronic components on to a single circuit board than to integrate them each into the textile separately [124].

Recent advancements have also been made, improving the physical characteristics of e-textile devices. In 2015, Komolafe et al. showed that optimising the thicknesses of the encapsulation above and below the conductive layer of a printed circuit so that the conductive path did not change length as it was bent, had the potential to reduce the change in a path's resistance caused by bending and washing [125]. A number of other techniques, including thermally bonding polyurethane interface layers [123] and introducing a catalyst to facilitate electroless deposition [126], have also been proven successful in this regard.

A greater understanding has also been gained of the failure modes of textile electronics. In 2019, Komolafe et al. showed that breaks in an etched flexible copper circuit were developing as a result of cracks in the copper or buckling as the traces came away from their substrate. It was found that these mostly occurred in the thin traces, close to the large connection pads [127]. This implies that the high stresses at the transition between more rigid and more flexible parts of the system are the primary cause of failures for flexible circuits.

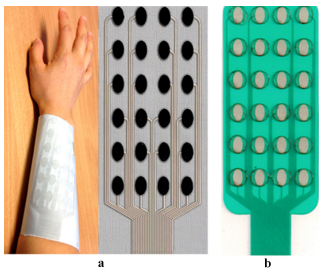

Fig. 10. Electrode array used by Yang et al. 2014, showing the 24 small carbon electrodes connected by screen printed traces. Image from [92].

Fig. 11. Shirt produced by Moineau et al. 2019 showing the fabric electrodes integrated into the right arm. The system used a hip mounted stimulator to provide the stimulation current. Image from [128].

C. E-Textiles in Electrostimulation

E-textiles have already been successfully used in other electrostimulation treatments. As such, a significant amount of work has been done on electrode design within the e-textile community.

Functional electrical stimulation (FES) is a treatment used to increase the functional movement available to patients with damage to their nervous systems, for example stroke survivors [25]. In 2014, Yang et al. published details of an FES system which uses 24, small, printed electrodes, shown in figure 10. The smaller electrodes, approximately 1 cm^2 in size, allowed more selectivity in which areas were stimulated and the system was able to produce multiple different hand positions including pointing, pinching and holding the hand open. The electrodes in this case were screen printed with interface and encapsulation layers of polyurethane sandwiching the conductive silver traces in between. The electrode pads themselves were printed using carbon loaded rubber paste. The interface layer served to provide a smooth surface on which to print the conducting traces, making printing more reliable and reducing the quantity of paste required to ensure a complete conductive path. The encapsulation layer provided electrical insulation and physical protection to the conductive traces. This system allowed printing of traces 0.6 mm wide and 5 µm thick with only a resistance of only 82 Ω/m on an industry standard polyester cotton fabric [92].

In 2017, Stewart et al. performed a test comparing hydrogel electrodes to ones made of a moistened, commercially available, conductive textile. They varied a number of parameters in the signal that was used to stimulate the subject's bicep including amplitude and ramp up time. In all cases, the textile electrode performed comparably or slightly better than the hydrogel one [25].

E-textile electrodes have also been incorporated into clothing, as in one study by Moineau et al. [128]. They designed and tested a pair of garments, a shirt and a pair of leggings, containing electrodes knitted of conductive yarn, see figure 11. An FES stimulator was connected to them and the system was used to identify the current required to reach the sensory threshold, the movement threshold, the full movement threshold (the point at which the stimulation caused the muscle to fully contract) and the maximal stimulation threshold (the point at which the subject could not withstand further intensity). These values were compared to those found with a gel electrode. The textile electrodes performed similarly to the gel electrodes: they had a lower sensory threshold implying that current was flowing close to the surface of the skin where there are more nerve endings [95]. It is also possible that the textile electrodes transferred current in a less even manner, creating "hot-spots" that were more easily felt. The textile electrodes also had a lower full motion threshold, but a higher maximal stimulation threshold. The authors noted two major issues with their system: first, that wires attached to each electrode made it harder to use the system as they could easily become entangled, and second, that the electrodes needed to be moistened every 10 to 15 minutes in order to perform well. Other works have made improvements to systems for integrating electrical connections into textile garments [129] and there are also studies reporting improved performance of dry textile electrodes, reducing the need for wetting.

Another treatment that e-textiles have successfully been used for is pain relief. It is possible to use electrical stimulation to interrupt the signals the body uses to communicate chronic pain and this stimulation can be delivered using e-textile electrodes. In 2020, Yang et al. tested a device that used interferential current, a signal consisting of two frequencies between 1 and 10 kHz delivered at < 100 mA, between two pairs of electrodes across the subject's knee. The electrodes used in this study were made of carbon loaded rubber, printed on top of a textile with copper wires woven into it. The soft rubber material was able to completely conform to the surface it was placed on and form a good electrical contact. Tests showed that the current was delivered uniformly and subjects reported that the device was comfortable and easy to use [24].

These successes imply that, if e-textile technologies were applied to wound healing, similar results to those seen in the studies presented in section IV could be achieved while creating a device that has all the ergonomic benefits e-textile technology can provide. In addition, a consistently manufactured e-textile device could lead to a greater number of studies using the same fundamental system and thus create a larger, more reliable body of evidence.

D. Remaining Challenges for E-Textile Based Stimulation

Several challenges still exist, which have hindered the development of e-textile based electrical stimulation. Primarily among them is the supply of power. The state of the art for powering small electronic devices is currently lithium based batteries due to their high energy density. While these are available at small sizes, down to a few cm^2, they are not flexible and are thus difficult to use while retaining the comfort and flexibility afforded by e-textiles [130]. For high voltage stimulation, the power requirements are more strenuous; while the power transferred to the skin is still low, boost converters require large amounts of power to maintain their output at a high voltage, and

can overwhelm even lithium batteries. Research is ongoing, developing battery solutions that better fit e-textile devices, however these are still far from providing the power output necessary for wound stimulation applications [130]. Alternatives such as energy harvesting have been considered [131]–[133], but there are currently very low power, in the nano- and micro-watt range, and therefore are insufficient for these applications.

A second challenge relates to sustainability. Wound dressings are inherently single use products and as such, any electronics integrated into them must either be removed or be safe and sustainable to discard. This is an area in which current e-textile solutions perform poorly and little consideration has so far been given [134]. Increasing the modularity of devices can alleviate this problem, but doing so requires impermanent connectors between modules, which remain difficult to realise without compromising the properties of the textile [135].

Another limitation of e-textile electrodes is the need for wetting. To maintain a low impedance connection to the skin, textile electrodes need to be kept moist. During use, electrodes will naturally dry out and so will need rewetting as often as every 10 minutes [128]. This is less of an issue in the context of wound healing because wounds must kept moist anyway, to allow effective healing. Interventions are available to accomplish this if necessary [33].

There are also practical challenges that hamper the development of medial e-textile devices. Running a trial with enough patients to get statistically valid results can be a difficult and time consuming, as evidenced by the low patient numbers in many studies in section IV. Once a device has been developed and tested, obtaining the regulatory approvals necessary to bring the device to market can still be a long and complicated process [136].

VII. Conclusions

Given the cost of chronic wounds, both to a patient's well-being as well as to health systems as a whole, any improvement to the current methods of wound treatment could have a large, positive impact. When reviewing all the evidence presented in the literature together, it is clear that electrostimulation can have a positive effect on the healing of many types of chronic wounds. Several studies have demonstrated electrostimulation doubling the rate at which their subjects' wounds healed suggesting that, if properly optimised, electrostimulation could greatly improve wound care outcomes. This would represent a significant improvement for patients by increasing quality of life and reducing the risk of further medical complications.

However, no single study has had enough participants to be considered conclusive evidence on its own. The median among all studies review is less than 40. The only study to have over 100 participants was the work by Gault and Gatens in 1976 [15] and another high participation study, Jerčinović et al. [82], noted that despite having 73 patients with 109 ulcers, there were still imbalances between their treatment and control groups due to the random allocation. In addition to this, few studies used the same treatment protocol and inclusion criteria meaning that it is hard to combine them into a single piece of evidence supporting a particular treatment.

The fact that different protocols have garnered different results, implies that future work should focus on optimising the stimulation parameters. However, organising a study with enough subjects not only to obtain significant evidence of electrostimulation's effectiveness, but also to identify the effectiveness of different protocols relative to each other presents a significant challenge.

The few studies that have investigated electrode types and patterns in the context of wound healing have shown that they do have some effect. However, there has not been sufficient experimentation in this area to say conclusively what the best options for electrode design are. E-textile technology has the potential to make electrodes that are more comfortable for the patient without compromising their medical effectiveness, as shown by studies into TENS and FES. Fabrication methods such as dispenser printing would make it easier to prototype and test different designs, with screen printing offering large scale and cost effective manufacturing. Additional benefits include the ability to embed electrodes into dressings making them easier to use and combine with existing wound treatment technologies.

References

[1] J. M. Monfre, "Pressure Ulcers," Wound Healing - New insights into Ancient Challenges, Oct. 2016.

[2] G. V. Torres et al., "Aspects Related to Venous Ulcer Healing and its Influence on Quality of Life," Worldwide Wound Healing - Innovation in Natural and Conventional Methods, Dec. 2016.

[3] NHS, "National Diabetes Foot Care Audit, 2014-2018." https://digital.nhs.uk/data-and-information/publications/statistical/national-diabetes-footcare-audit/2014-2018, May 2019.

[4] J. Nixon, G. Cranny, and S. Bond, "Skin alterations of intact skin and risk factors associated with pressure ulcer development in surgical patients: A cohort study," International Journal of Nursing Studies, vol. 44, pp. 655–663, July 2007.

[5] Y.-H. Choi and S. R. Kim, "The effect of uncoated paper application on skin moisture, risk of pressure injury and incidence of pressure injury in neurologic intensive care unit patients: A randomized controlled trial," International Journal of Nursing Practice, vol. 27, no. 4, p. e12919, 2021.

[6] P. M. G. Sardo, J. A. D. Guedes, J. J. M. Alvarelhão, P. A. P. Machado, and E. M. O. P. Melo, "Pressure ulcer incidence and Braden subscales: Retrospective cohort analysis in general wards of a Portuguese hospital," Journal of Tissue Viability, vol. 27, pp. 95–100, May 2018.

[7] E. K. Biçer et al., "Pressure Ulcer Prevalence, Incidence, Risk, Clinical Features, and Outcomes Among Patients in a Turkish Hospital: A Cross-sectional, Retrospective Study," Wound Management & Prevention, vol. 65, pp. 20–28, Feb. 2019.

[8] W. V. Padula and B. A. Delarmente, "The national cost of hospital-acquired pressure injuries in the United States," International Wound Journal, vol. 16, no. 3, pp. 634–640, 2019.

[9] A. Polak et al., "The Efficacy of Pressure Ulcer Treatment With Cathodal and Cathodal-Anodal High-Voltage Monophasic Pulsed Current: A Prospective, Randomized, Controlled Clinical Trial," Physical Therapy, vol. 97, pp. 777–789, Aug. 2017.

[10] J. Hunckler and A. de Mel, "A current affair: Electrotherapy in wound healing," Journal of Multidisciplinary Healthcare, vol. 10, pp. 179–194, Apr. 2017.

[11] G. D. Gentzkow, S. V. Pollack, L. C. Kloth, and H. A. Stubbs, "Improved Healing of Pressure Ulcers Using Dermapulse, A New Electrical Stimulation Device," Wounds, vol. 3, pp. 158–170, Jan. 1991.

[12] P. E. Houghton et al., "Effect of Electrical Stimulation on Chronic Leg Ulcer Size and Appearance," Physical Therapy, vol. 83, pp. 17–28, Jan. 2003.

[13] EPUAP, "PU Guidelines – EPUAP," 2019.

[14] L. Wolcott, P. Wheeler, H. Hardwicke, and B. Rowley, "Accelerated Healing of Skin Ulcers by Electrotherapy: Preliminary Clinical Results," Southern Medical Journal, vol. 62, pp. 795–801, July 1969.

[15] W. R. Gault and P. F. Gatens, "Use of Low Intensity Direct Current in Management of Ischemic Skin Ulcers," Physical Therapy, vol. 56, pp. 265–269, Mar. 1976.

[16] O. Fakhri and M. A. Amin, "The Effect of Low-Voltage Electric Therapy on the Healing of Resistant Skin Burns," The Journal of Burn Care & Rehabilitation, vol. 8, pp. 15–18, Jan. 1987.

[17] T.-G. La et al., "Two-layered and stretchable e-textile patches for wearable healthcare electronics," Advanced Healthcare Materials, vol. 7, no. 22, p. 1801033, 2018.

[18] M. M. H. Shandhi et al., "Estimation of instantaneous oxygen uptake during exercise and daily activities using a wearable cardio-electromechanical and environmental sensor," IEEE Journal of Biomedical and Health Informatics, vol. 25, no. 3, pp. 634–646, 2021.

[19] M. L. R. Liman, M. T. Islam, and M. M. Hossain, "Mapping the progress in flexible electrodes for wearable electronic textiles: Materials, durability, and applications," Advanced Electronic Materials, vol. 8, no. 1, p. 2100578, 2022.

[20] C. G. Bartone, L. Moore, and M. Kohli, "An e-textile antenna for body area network," in 2016 IEEE International Symposium on Antennas and Propagation (APSURSI), pp. 999–1000, June 2016.

[21] M. de Vos, R. Torah, and J. Tudor, "Dispenser printed electroluminescent lamps on textiles for smart fabric applications," Smart Materials and Structures, vol. 25, p. 045016, Mar. 2016.

[22] A. Komolafe, R. Torah, H. Nunes-Matos, M. Tudor, and S. Beeby, "Integration of temperature sensors in fabrics," in 2019 IEEE International Conference on Flexible and Printable Sensors and Systems (FLEPS), pp. 1–2, July 2019.

[23] G. Paul, R. Torah, S. Beeby, and J. Tudor, "Novel active electrodes for ECG monitoring on woven textiles fabricated by screen and stencil printing," Sensors and Actuators A: Physical, vol. 221, pp. 60–66, Jan. 2015.

[24] K. Yang et al., "Electronic textiles based wearable electrotherapy for pain relief," Sensors and Actuators A: Physical, vol. 303, p. 111701, Mar. 2020.

[25] A. M. Stewart, C. G. Pretty, and X. Chen, "An Evaluation of the Effect of Stimulation Parameters and Electrode Type on Bicep Muscle Response for a Voltage-controlled Functional Electrical Stimulator," IFAC-PapersOnLine, vol. 50, pp. 15109–15114, July 2017.

[26] T. Greig, R. Torah, and K. Yang, "Investigation of Nozzle Height Control to Improve Dispenser Printing of E-Textiles," Proceedings, vol. 68, p. 6, Jan. 2021.

[27] W. Lv et al., "A wireless flexible smart bandage for wound monitoring," in 2022 IEEE 35th International Conference on Micro Electro Mechanical Systems Conference (MEMS), pp. 864–867, 2022.

[28] A. Hoffbrand, J. Pettit, and P. Moss, "Platelets, blood coagulation and haemostasis," in Haematology, pp. 236–249, Blackwell Science, fourth ed., 2001.

[29] K. Murphey, Janeway's Immunobiology. Garland Science, eighth ed., 2012.

[30] P. Lydyard, A. Whelan, and M. Fanger, BIOS Instant Notes in Immunology. London, UNITED KINGDOM: Taylor & Francis Group, 2011.

[31] H. Sorg, D. J. Tilkorn, S. Hager, J. Hauser, and U. Mirastschijski, "Skin Wound Healing: An Update on the Current Knowledge and Concepts," European Surgical Research, vol. 58, no. 1-2, pp. 81–94, 2017.

[32] M. Flanagan, ed., Wound Healing and Skin Integrity: Principals and Practice. Wiley-Blackwell, 2013.

[33] M. J. Morison, L. G. Ovington, and K. Wilkie, eds., Chronic Wound Care. Mosby, 2004.

[34] R. Graham-Brown and J. F. Bourke, Mosby's Colour Atlas and Text of Dermatology. London: Mosby, 1st ed., 1998.

[35] C. Martin-Granados and C. D. McCaig, "Harnessing the Electric Spark of Life to Cure Skin Wounds," Advances in Wound Care, vol. 3, pp. 127–138, Feb. 2014.

[36] I. S. Foulds and A. T. Barker, "Human skin battery potentials and their possible role in wound healing," British Journal of Dermatology, vol. 109, no. 5, pp. 515–522, 1983.

[37] Z. Li, Textile Electrode Design and Simulation for Bio-Signal Recording. PhD thesis, University of Southampton, Oct. 2018.

[38] M. Zhao et al., "Electrical signals control wound healing through phosphatidylinositol-3-OH kinase-γ and PTEN," Nature, vol. 442, pp. 457–460, July 2006.

[39] M. R. Cho, H. S. Thatte, R. C. Lee, and D. E. Golan, "Integrin-Dependent Human Macrophage Migration Induced by Oscillatory Electrical Stimulation," Annals of Biomedical Engineering, vol. 28, pp. 234–243, Mar. 2000.

[40] K. Franke and H. Gruler, "Galvanotaxis of human granulocytes: Electric field jump studies," European Biophysics Journal, vol. 18, pp. 334–346, July 1990.

[41] C. A. Erickson and R. Nuccitelli, "Embryonic fibroblast motility and orientation can be influenced by physiological electric fields.," The Journal of Cell Biology, vol. 98, pp. 296–307, Jan. 1984.

[42] M. J. Brown and L. M. Loew, "Electric field-directed fibroblast locomotion involves cell surface molecular reorganization and is calcium independent.," The Journal of Cell Biology, vol. 127, pp. 117–128, Oct. 1994.

[43] E. Finkelstein et al., "Roles of microtubules, cell polarity and adhesion in electric-field-mediated motility of 3T3 fibroblasts," Journal of Cell Science, vol. 117, pp. 1533–1545, Mar. 2004.

[44] C.-H. Tsai, B.-J. Lin, and P.-H. G. Chao, "$A2\beta1$ integrin and RhoA mediates electric field-induced ligament fibroblast migration directionality," Journal of Orthopaedic Research, vol. 31, no. 2, pp. 322–327, 2012.

[45] A. Guo et al., "Effects of Physiological Electric Fields on Migration of Human Dermal Fibroblasts," Journal of Investigative Dermatology, vol. 130, pp. 2320–2327, Sept. 2010.

[46] H. K. Soong, W. C. Parkinson, S. Bafna, G. L. Sulik, and S. C. Huang, "Movements of cultured corneal epithelial cells and stromal fibroblasts in electric fields.," Investigative Ophthalmology & Visual Science, vol. 31, pp. 2278–2282, Nov. 1990.

[47] D. M. Sheridan, R. Rivkah Isseroff, and R. Nuccitelli, "Imposition of a Physiologic DC Electric Field Alters the Migratory Response of Human Keratinocytes on Extracellular Matrix Molecules," Journal of Investigative Dermatology, vol. 106, pp. 642–646, Apr. 1996.

[48] S. Barrientos, O. Stojadinovic, M. S. Golinko, H. Brem, and M. Tomic-Canic, "PERSPECTIVE ARTICLE: Growth factors and cytokines in wound healing," Wound Repair and Regeneration, vol. 16, no. 5, pp. 585–601, 2008.

[49] C. Magnoni et al., "Electrical stimulation as adjuvant treatment for chronic leg ulcers of different aetiology: An RCT," Journal of Wound Care, vol. 22, pp. 525–533, Oct. 2013.

[50] Z. M. I. I. S. W. O. Ibrahim, "Negative pressure wound therapy versus microcurrent electrical stimulation in wound healing in burns," Journal of Wound Care, Apr. 2019.

[51] B. A. Rowley, "Electrical Current Effects on E. coil Growth Rates," Proceedings of the Society for Experimental Biology and Medicine, vol. 139, pp. 929–934, Mar. 1972.

[52] J. A. Spadaro, T. J. Berger, S. D. Barranco, S. E. Chapin, and R. O. Becker, "Antibacterial Effects of Silver Electrodes with Weak Direct Current," Antimicrobial Agents and Chemotherapy, vol. 6, pp. 637–642, Nov. 1974.

[53] N. M. Kanof, "Gold Leaf in the Treatment of Cutaneous Ulcers," Journal of Investigative Dermatology, vol. 43, pp. 441–442, Nov. 1964.

[54] J. P. Gallagher and C. F. Geschickter, "The Use of Charged Gold Leaf in Surgery," JAMA, vol. 189, pp. 928–933, Sept. 1964.

[55] K. Digby, Choice and Experimented Receipts in Physick and Chirurgery, as Also Cordial and Distilled Waters and Spirits, Perfumes, and Other Curiosities. Collected by the Honourable and Truly Learned Sir Kenelm Digby Kt. Chancellour to Her Majesty the Queen Mother. Translated out of Several Languages by G.H. London: printed for the author, 1668.

[56] L. C. Kloth, "Electrical Stimulation Technologies for Wound Healing," Advances in Wound Care, vol. 3, pp. 81–90, Feb. 2014.

[57] B. A. Rowley, J. M. McKenna, and L. E. Wolcott, "Proceedings: The use of low level electrical current for enhancement of tissue healing," Biomedical Sciences Instrumentation, vol. 10, pp. 111–114, Apr. 1974.

[58] P. J. Carley and S. F. Wainapel, "Electrotherapy for acceleration of wound healing: Low intensity direct current," Archives of Physical Medicine and Rehabilitation, vol. 66, pp. 443–446, July 1985.

[59] P. M. Katelaris, J. P. Fletcher, J. M. Ltttle, R. J. Mcentyre, and K. W. Jeffcoate, "Electrical Stimulation in the Treatment of Chronic Venous Ulceration," Australian and New Zealand Journal of Surgery, vol. 57, no. 9, pp. 605–607, 1987.

[60] P. L. Bigliardi et al., "Povidone iodine in wound healing: A review of current concepts and practices," International Journal of Surgery, vol. 44, pp. 260–268, Aug. 2017.

[61] D. L. Nelson and M. M. Cox, Lehringer Principles of Biochemistry. Macmillan Higher Education, 7th international ed., 2017.

[62] J. A. Feedar, L. C. Kloth, and G. D. Gentzkow, "Chronic Dermal Ulcer Healing Enhanced with Monophasic Pulsed Electrical Stimulation," Physical Therapy, vol. 71, pp. 639–649, Sept. 1991.

[63] J. M. Wood et al., "A Multicenter Study on the Use of Pulsed Low-Intensity Direct Current for Healing Chronic Stage II and Stage III Decubitus Ulcers," Archives of Dermatology, vol. 129, pp. 999–1009, Aug. 1993.

[64] M. Jünger, D. Zuder, A. Steins, M. Hahn, and T. Klyscz, "Behandlung von venösen Ulzera mit niederfrequentem gepulstem Strom (Dermapulse): Effekte auf die kutane Mikrozirkulation," Der Hautarzt, vol. 48, pp. 897–903, Dec. 1997.

[65] M. Jünger, A. Arnold, D. Zuder, H.-W. Stahl, and S. Heising, "Local therapy and treatment costs of chronic, venous leg ulcers with electrical stimulation (Dermapulse®): A prospective, placebo controlled, double blind trial," Wound Repair and Regeneration, vol. 16, no. 4, pp. 480–487, 2008.

[66] B. O. Adegoke and K. A. Badmos, "Acceleration of pressure ulcer healing in spinal cord injured patients using interrupted direct current," African Journal of Medicine and Medical Sciences, vol. 30, pp. 195–197, Sept. 2001.

[67] L. L. Baker, S. Rubayi, F. Villar, and S. K. Demuth, "Effect of electrical stimulation waveform on healing of ulcers in human beings with spinal cord injury," Wound Repair and Regeneration, vol. 4, no. 1, pp. 21–28, 1996.

[68] L. C. Kloth and J. A. Feedar, "Acceleration of Wound Healing with High Voltage, Monophasic, Pulsed Current," Physical Therapy, vol. 68, pp. 503–508, Apr. 1988.

[69] J. W. Griffin et al., "Efficacy of High Voltage Pulsed Current for Healing of Pressure Ulcers in Patients with Spinal Cord Injury," Physical Therapy, vol. 71, pp. 433–442, June 1991.

[70] A. Franek, A. Polak, and M. Kucharzewski, "Modern application of high voltage stimulation for enhanced healing of venous crural ulceration," Medical Engineering & Physics, vol. 22, pp. 647–655, Nov. 2000.

[71] E. J. Peters, L. A. Lavery, D. G. Armstrong, and J. G. Fleischli, "Electric stimulation as an adjunct to heal diabetic foot ulcers: A randomized clinical trial," Archives of Physical Medicine and Rehabilitation, vol. 82, pp. 721–725, June 2001.

[72] P. E. Houghton et al., "Electrical Stimulation Therapy Increases Rate of Healing of Pressure Ulcers in Community-Dwelling People With Spinal Cord Injury," Archives of Physical Medicine and Rehabilitation, vol. 91, pp. 669–678, May 2010.

[73] A. Franek et al., "Using High-Voltage Electrical Stimulation in the Treatment of Recalcitrant Pressure Ulcers: Results of a Randomized, Controlled Clinical Study," Ostomy Wound Management, vol. 58, pp. 30–44, Mar. 2012.

[74] S. Ud-Din et al., "Electrical stimulation increases blood flow and haemoglobin levels in acute cutaneous wounds without affecting wound closure time: Evidenced by non-invasive assessment of temporal biopsy wounds in human volunteers," Experimental Dermatology, vol. 21, no. 10, pp. 758–764, 2012.

[75] S. Ud-Din et al., "Angiogenesis Is Induced and Wound Size Is Reduced by Electrical Stimulation in an Acute Wound Healing Model in Human Skin," PLOS ONE, vol. 10, p. e0124502, Apr. 2015.

[76] D. Perry et al., "Treatment of symptomatic abnormal skin scars with electrical stimulation," Journal of Wound Care, vol. 19, pp. 447–453, Oct. 2010.

[77] K. Zhou et al., "Silver-Collagen Dressing and High-voltage, Pulsed-current Therapy for the Treatment of Chronic Full-thickness Wounds: A Case Series," Ostomy/Wound Management, vol. 62, pp. 36–44, Mar. 2016.

[78] B. Kaada and M. Emru, "PROMOTED HEALING OF LEPROUS ULCERS BY TRANSCUTANEOUS NERVE STIMULATION," Acupuncture & Electro-Therapeutics Research, vol. 13, no. 4, pp. 165–176, 1988.

[79] W. Gibson, B. M. Wand, C. Meads, M. J. Catley, and N. E. O'Connell, "Transcutaneous electrical nerve stimulation (TENS) for chronic pain - an overview of Cochrane Reviews," The Cochrane Database of Systematic Reviews, vol. 2019, Apr. 2019.

[80] T. Lundeberg, J. Kjartansson, and U. Samuelsson, "EFFECT OF ELECTRICAL NERVE STIMULATION ON HEALING OF ISCHAEMIC SKIN FLAPS," The Lancet, vol. 332, pp. 712–714, Sept. 1988.

[81] T. Lundeberg, S. Eriksson, and M. Malm, "Electrical Nerve-Stimulation Improves Healing of Diabetic Ulcers," Annals of Plastic Surgery, vol. 29, pp. 328–331, Oct. 1992.

[82] A. Jerčinović et al., "Low frequency pulsed current and pressure ulcer healing," IEEE Transactions on Rehabilitation Engineering, vol. 2, pp. 225–233, Dec. 1994.

[83] D. Lawson and J. S. Petrofsky, "A randomized control study on the effect of biphasic electrical stimulation in a warm room on skin blood flow and healing rates in chronic wounds of patients with and without diabetes," Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, vol. 13, pp. CR258–263, June 2007.

[84] S. Farnia et al., "A randomized controlled study on the effect of two different treatments (FREMS and TENS) in myofascial pain syndrome - ProQuest," Europa Medicophysica, vol. 40, pp. 293–301, Dec. 2004.

[85] E. Bosi et al., "Effectiveness of frequency-modulated electromagnetic neural stimulation in the treatment of painful diabetic neuropathy," Diabetologia, vol. 48, pp. 817–823, May 2005.

[86] E. Bosi et al., "Frequency-modulated electromagnetic neural stimulation (FREMS) as a treatment for symptomatic diabetic neuropathy: Results from a double-blind, randomised, multicentre, long-term, placebo-controlled clinical trial," Diabetologia, vol. 56, pp. 467–475, Mar. 2013.

[87] M. Bevilacqua, L. J. Dominguez, M. Barrella, and M. Barbagallo, "Induction of vascular endothelial growth factor release by transcutaneous frequency modulated neural stimulation in diabetic polyneuropathy," Journal of Endocrinological Investigation, vol. 30, pp. 944–947, Dec. 2007.

[88] A. Janković and I. Binić, "Frequency rhythmic electrical modulation system in the treatment of chronic painful leg ulcers," Archives of Dermatological Research, vol. 300, p. 377, July 2008.

[89] A. Margara, F. Boriani, F. D. Obbialero, and M. A. Bocchiotti, "Frequency rhythmic electrical modulation system in the treatment of diabetic ulcers.," Estratto da Chirugia, vol. 21, no. 6, pp. 311–314, 2008.

[90] A. Santamato et al., "Effectiveness of the Frequency Rhythmic Electrical Modulation System for the Treatment of Chronic and Painful Venous Leg Ulcers in Older Adults," Rejuvenation Research, vol. 15, pp. 281–287, June 2012.

[91] E. M. Ahmed, "Hydrogel: Preparation, characterization, and applications: A review," Journal of Advanced Research, vol. 6, pp. 105–121, Mar. 2015.

[92] K. Yang, C. Freeman, R. Torah, S. Beeby, and J. Tudor, "Screen printed fabric electrode array for wearable functional electrical stimulation," Sensors and Actuators A: Physical, vol. 213, pp. 108–115, July 2014.

[93] L. Wang et al., "Enhanced cell proliferation by electrical stimulation based on electroactive regenerated bacterial cellulose hydrogels," Carbohydrate Polymers, vol. 249, p. 116829, 2020.

[94] M. Liu, S. Beeby, and K. Yang, "Electrode for Wearable Electrotherapy," Proceedings, vol. 32, no. 1, p. 5, 2019.

[95] H. Zhou et al., "Stimulating the Comfort of Textile Electrodes in Wearable Neuromuscular Electrical Stimulation," Sensors (Basel, Switzerland), vol. 15, pp. 17241–17257, July 2015.

[96] J. Petrofsky et al., "Current distribution under electrodes in relation to stimulation current and skin blood flow: Are modern electrodes really providing the current distribution during stimulation we believe they are?," Journal of Medical Engineering & Technology, vol. 30, pp. 368–381, Jan. 2006.

[97] CENELEC, "BS EN 60601-1:2006+A12:2014 Medical Electrical Equiptment. General Requirements for Basic Safety and Essential Performance," Nov. 2006.

[98] J. Petrofsky and E. Schwab, "A re-evaluation of modelling of the current flow between electrodes: Consideration of blood flow and wounds," Journal of Medical Engineering & Technology, vol. 31, pp. 62–74, Jan. 2007.

[99] N. Charkoudian, "Skin Blood Flow in Adult Human Thermoregulation: How It Works, When It Does Not, and Why," Mayo Clinic Proceedings, vol. 78, pp. 603–612, May 2003.

[100] H. Suh et al., "A New Electrode Design to Improve Outcomes in the Treatment of Chronic Non-Healing Wounds in Diabetes," Diabetes Technology & Therapeutics, vol. 11, pp. 315–322, May 2009.

[101] Y.-S. Sun, "Electrical Stimulation for Wound-Healing: Simulation on the Effect of Electrode Configurations," BioMed Research International, vol. 2017, 2017.

[102] K. Yang et al., "Development of User-Friendly Wearable Electronic Textiles for Healthcare Applications," Sensors, vol. 18, p. 2410, Aug. 2018.

[103] G. Paul, R. Torah, S. Beeby, and J. Tudor, "The development of screen printed conductive networks on textiles for biopotential monitoring applications," Sensors and Actuators A: Physical, vol. 206, pp. 35–41, Feb. 2014.

[104] S. Beeby et al., "Energy Harvesting Power Supplies for Electronic Textiles," in 2019 IEEE International Conference on Flexible and Printable Sensors and Systems (FLEPS), pp. 1–3, July 2019.

[105] G. Acar et al., "Wearable and Flexible Textile Electrodes for Biopotential Signal Monitoring: A review," Electronics, vol. 8, p. 479, May 2019.

[106] T. Perera, M. Mohotti, and M. Perera, "Stretchable Conductive Yarn for Electronic Textiles Made Using Hollow Spindle Spinning," in 2018 Moratuwa Engineering Research Conference (MERCon), pp. 544–548, May 2018.

[107] J. Jianming, P. Wei, Y. Shenglin, and L. Guang, "Electrically conductive PANI-DBSA/Co-PAN composite fibers prepared by wet spinning," Synthetic Metals, vol. 149, pp. 181–186, Mar. 2005.

[108] D. Bowman and B. R. Mattes, "Conductive Fibre Prepared From Ultra-High Molecular Weight Polyaniline for Smart Fabric and Interactive Textile Applications," Synthetic Metals, vol. 154, pp. 29–32, Sept. 2005.

[109] J. Foroughi, G. M. Spinks, G. G. Wallace, and P. G. Whitten, "Production of polypyrrole fibres by wet spinning," Synthetic Metals, vol. 158, pp. 104–107, Feb. 2008.

[110] Y. Wang, M. Rouabhia, and Z. Zhang, "PPy-coated PET fabrics and electric pulse-stimulated fibroblasts," Journal of Materials Chemistry B, vol. 1, no. 31, pp. 3789–3796, 2013.

[111] H. Okuzaki, Y. Harashina, and H. Yan, "Highly conductive PEDOT/PSS microfibers fabricated by wet-spinning and dip-treatment in ethylene glycol," European Polymer Journal, vol. 45, pp. 256–261, Jan. 2009.

[112] T. Bashir, M. Skrifvars, and N.-K. Persson, "Surface modification of conductive PEDOT coated textile yarns with silicone resin," Materials Technology, vol. 26, pp. 135–139, July 2011.

[113] Y. Merhi and S. Agarwala, "Direct write of dry electrodes on healthcare textiles," in 2021 IEEE International Conference on Flexible and Printable Sensors and Systems (FLEPS), pp. 1–2, 2021.

[114] B. Ding, X. Wang, and J. Yu, eds., Electrospinning: Nanofabrication and Applications. Elsevier, 2019.

[115] A. Komolafe, H. Nunes-Matos, M. Glanc-Gostkiewicz, and R. Torah, "Influence of textile structure on the wearability of printed e-textiles," in 2020 IEEE International Conference on Flexible and Printable Sensors and Systems (FLEPS), pp. 1–4, Aug. 2020.

[116] G. M. Paul et al., "A Smart Textile Based Facial EMG and EOG Computer Interface," IEEE Sensors Journal, vol. 14, pp. 393–400, Feb. 2014.

[117] T. Kuroda, H. Takahashi, and A. Masuda, "Chapter 3.2 - Woven Electronic Textiles," in Wearable Sensors (E. Sazonov and M. R. Neuman, eds.), pp. 175–198, Oxford: Academic Press, Jan. 2014.

[118] K. Yang, R. Torah, Y. Wei, S. Beeby, and J. Tudor, "Waterproof and durable screen printed silver conductive tracks on textiles," Textile Research Journal, vol. 83, pp. 2023–2031, Nov. 2013.

[119] M. de Vos, R. Torah, and J. Tudor, "A novel pneumatic dispenser fabrication technique for digitally printing electroluminescent lamps on fabric," in 2015 Symposium on Design, Test, Integration and Packaging of MEMS/MOEMS (DTIP), (Montpellier, France), pp. 1–4, IEEE, Apr. 2015.

[120] N. Karim et al., "All inkjet-printed graphene-based conductive patterns for wearable e-textile applications," Journal of Materials Chemistry C, vol. 5, no. 44, pp. 11640–11648, 2017.

[121] C. Goth, S. Putzo, and J. Franke, "Aerosol Jet printing on rapid prototyping materials for fine pitch electronic applications," in 2011 IEEE 61st Electronic Components and Technology Conference (ECTC), pp. 1211–1216, May 2011.

[122] M. G. Honarvar and M. Latifi, "Overview of wearable electronics and smart textiles," The Journal of The Textile Institute, vol. 108, pp. 631–652, Apr. 2017.

[123] Y. Merhi, P. H. Mikkelsen, C. Suetta, J. V. Nygaard, and S. Agarwala, "Mechanical performance of electronically functional smart textiles," Transactions on Additive Manufacturing Meets Medicine, vol. 2, no. 1, 2020.

[124] K. Garbacz, L. Stagun, S. Rotzler, M. Semenec, and M. von Krshiwoblozki, "Modular e-textile toolkit for prototyping and manufacturing," Proceedings, vol. 68, no. 1, 2021.

[125] A. O. Komolafe, R. N. Torah, K. Yang, J. Tudor, and S. P. Beeby, "Durability of screen printed electrical interconnections on woven textiles," in 2015 IEEE 65th Electronic Components and Technology Conference (ECTC), pp. 1142–1147, 2015.

[126] C. Zhu, Y. Li, and X. Liu, "Polymer interface molecular engineering for e-textiles," Polymers, vol. 10, no. 6, 2018.

[127] A. Komolafe et al., "Integrating Flexible Filament Circuits for E-Textile Applications," Advanced Materials Technologies, vol. 4, no. 7, p. 1900176, 2019.

[128] B. Moineau, C. Marquez-Chin, M. Alizadeh-Meghrazi, and M. R. Popovic, "Garments for functional electrical stimulation: Design and proofs of concept," Journal of Rehabilitation and Assistive Technologies Engineering, vol. 6, p. 2055668319854340, Jan. 2019.

[129] M. Catchpole, "E-Textile Seam Crossing with Screen Printed Circuits and Anisotropic Conductive Film," Proceedings, vol. 32, no. 1, p. 16, 2019.

[130] A. Komolafe et al., "E-textile technology review–from materials to application," IEEE Access, vol. 9, pp. 97152–97179, 2021.

[131] M. H. Kim et al., "Thermoelectric energy harvesting electronic skin (e-skin) patch with reconfigurable carbon nanotube clays," Nano Energy, vol. 87, p. 106156, 2021.

[132] Z. Cao, E. Koukharenko, M. Tudor, R. Torah, and S. Beeby, "Flexible screen printed thermoelectric generator with enhanced processes and materials," Sensors and Actuators A: Physical, vol. 238, pp. 196–206, 2016.

[133] M. Bouklachi, M. Biancheri-Astier, A. Diet, and Y. L. Bihan, "Energy harvesting of a nfc flexible patch for medical applications," in 2019 IEEE Wireless Power Transfer Conference (WPTC), pp. 249–252, 2019.

[134] D. Hardy, R. Wickenden, and A. McLaren, "Electronic textile reparability," Journal of Cleaner Production, vol. 276, p. 124328, 2020.

[135] J. Stanley, J. A. Hunt, P. Kunovski, and Y. Wei, "A review of connectors and joining technologies for electronic textiles," Engineering Reports, vol. n/a, no. n/a, p. e12491.

[136] R. Rathinamoorthy and S. Rajendran, "15 - regulatory bodies and their roles associated with medical devices and wound dressings," in Advanced Textiles for Wound Care (Second Edition) (S. Rajendran, ed.), The Textile Institute Book Series, pp. 423–461, Woodhead Publishing, second edition ed., 2019.