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‘Smart Dressings’ for Advanced Woundcare: A Review

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Abstract— [1]**Chronic wounds are a common side effect of diabetes mellitus, obesity, pressure ulcers and age-related vascular diseases, the incidences of which are growing worldwide. The increasing financial burden of chronic wounds on global health services has provoked technological research into improving wound diagnostics and therapeutics via ’smart’ dressings, within which elements such as microelectronic sensors, microprocessors, and wireless communications radios are embedded. This review highlights the progress being made by research groups worldwide in producing ‘smart’ wound device prototypes. Significant advances have been made, e.g. flexible substrates have replaced rigid circuit boards, sensors have been printed on commercial wound dressing materials and wireless communication has been demonstrated. Challenges remain, however, in the areas of power supply, disposability, low profile components, multi-parametric sensing and seamless device integration in commercial wound dressings.**

Keywords— chronic wounds; dressing saturation; smart bandage; wound diagnostics; wound infection; wound monitoring; wound pH;

I. INTRODUCTION

Wounds are often classified as chronic when they show no significant progress towards healing in a timely fashion. In fact chronic wounds may take years to heal, often remaining in an inflammatory phase and unable to transition to subsequent wound-healing phases [1]. Some may never heal, posing considerable challenges for both patients and healthcare systems. For individuals, they are painful and potentially life- and limb-threatening [2]. For healthcare provision, they engender prolonged hospitalisation and indeterminate wound clinic attendance [3]. The economic burden that wounds impose on the NHS in the UK is estimated to be between £5.1 and £4.5 billion [4]. A recent study undertaken by the American Alliance of Wound Care Stakeholders found that wound care costs ranged from $28.1 billion to $31.7 billion annually in the US, and ‘that the prevalence and incidence of chronic wounds is likely to increase - due in part to the increase in average age of population, along with increases in the prevalence of obesity, diabetes and lower extremity disease’ [5]. Other reports put this cost at $50 billion, in the US, annually [4], [6], [7]. Wound healing rates as low as 30.5% have been reported for complicated cases at hospital-based wound clinics [8].

Non-healing wounds, such as pressure ulcers, leg ulcers, diabetic foot ulcers and non-healing surgical wounds arise commonly due to underlying diseases such as age related debility or paralysis, diabetes or peripheral arterial/venous disease, vasculitis, sickle cell anaemia, immunosuppression, renal impairment, autoimmune disease, and dermatological disease [5]. Diabetics and the elderly are particularly predisposed to develop chronic wounds. This predisposition stems from their already compromised general health and vasculatory systems, which radically impair their wound healing ability [9].

Wound healing is complicated or delayed by two types of factors: systemic and local. Systemic factors include age, body type, chronic disease, immunosuppression, nutritional status, radiation therapy and vascular insufficiencies [10]. Local factors, and their causes, include desiccation, infection, abnormal bacterial presence, maceration, necrosis, pressure, trauma and oedema [11]. Currently, clinicians monitor and assess local factors subjectively using visual inspection, and, less commonly in the clinical setting, using lab testing of exudate swabs. These sensing modes for characterisation of wound parameters are summarised in Table 1. Whilst the latter is invasive, both methods of assessment are labour intensive and yield only sporadic updates on wound healing. The continued rising costs and increasing occurrence of chronic wounds demonstrate that this archaic and reactive approach to wound care is ineffective, and that a proactive preventative approach needs to be adopted.

This need can be met by emerging technology which will provide clinicians with non-invasive, quantitative wound data to inform both wound assessment and characterisation through continuous wound monitoring. These ‘smart’ dressings will combine integrated multi-parametric sensing of wound parameters with wireless communication of this data in real time. Two major benefits from this giant leap in wound care will be to reduce wound healing times and to facilitate remote monitoring of patients. The outcomes will be faster healing, reduced complications, shorter inpatient stays, reduction in both public health clinic and

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General Practitioner attendance and the number of required home visits, resulting in overall cost savings for wound care provision. This will result in a decrease in unnecessary expenditure in this field, thereby freeing up much needed health care budgets [4].

This paper reviews current wound care practices and challenges, and assesses how emerging smart electronic technology will assist in addressing wound care needs. Key wound parameters that are the target of current prototype sensing are highlighted. Several wireless wound sensing prototypes are reviewed, followed by a discussion on the potential barriers to clinical implementation.

II. Chronic Wound Challenges

The complexity of chronic wound care is not to be underestimated and the challenges it poses for technology development are daunting. A smart wound dressing has many needs to fulfil in the areas of diagnosis, treatment, monitoring, practical application and sensor functionality. Before reviewing newly developed devices, an understanding of these challenges is necessary.

A. Diagnosis Challenges

When a patient with a chronic wound presents to a clinician, first it is essential to address the underlying cause of the wound and any potential factors which the individual may have which will impact negatively on wound healing. Use of the multidisciplinary clinical team is essential to achieve good clinical outcomes [12]. Following the initial patient assessment, the wound assessment often begins with a categorisation based on the depth of tissue loss. Wounds can vary in depth from superficial to extensive tissue loss with bone and muscle exposure, as outlined in Table 2. A clinician will consider as many wound parameters as possible in order to accurately stage the wound but also to determine an appropriate treatment plan. Wound parameters can be subdivided into 3 types: physical, biological and biochemical. Common wound parameters are outlined in Table 1 along with the current mode of assessment [13]. Physical parameters are currently visually assessed, and whilst this aids speedy diagnoses, the downside is that the process is both subjective and qualitative. For instance, wound exudate may be described by one clinician as yellow, thick and moist, whilst another may deem the same fluid to be green, very thick and moderately moist. As a result, each may diagnose a different wound related problem and/or treatment plan [14]. Alternatively, detection of biological and biochemical parameters requires painful wound swabbing, costly lab testing, and whilst it delivers quantitative and objective data, the lengthy process delays diagnosis and provides only one-off measurements. Of additional concern is the fact that wound swabs currently being taken are not always reliable for infection detection, due to the growth of some bacteria which is not always due to infection [15]. However, where infection is present in a wound, timely treatment is critical [16], [17].

Table 1 Wound Parameters and Sensing Modes

Parameter		Sensing Type	Sensing Mode
Physical	Wound Area	Imaging	Impedance
	Wound Depth	Visual	
	Wound Margin	Visual	
	Oedema	Visual	
	Exudate Colour	Visual	
	Exudate Viscosity	Visual	
	Exudate Volume	Visual	
	Exudate Odour	Olfactory	
	Skin Temperature	Thermocouple	Electrical
	Pressure		Electrical
	Pain	Vocal	
Biological	Microbial Culture (MMP)	Elisa MMP	Electrochemical
		Disposable MMP	Electrochemical & Impedance Spectroscopy
	Wound Histology		
	White Cell Counts		
	Erythrocyte Sedimentation		
	pH	Carbon Fibre	Voltammetry
		Hydrogel pH	Fluorescent Spectroscopy
		Hydrogel pH	Electrochemical
Biochemical	Glucose		
	Haemoglobin		
	Plasma Albumin		
	Lipids		Electrochemical/ Optical
	Urea & Electrolytes	Uric Acid	Electrochemical
		Carbon Fibre	Electrochemical

		Enzymatic	Electrochemical
	HbA1C		
	Rheumatoid Factor		
	CRP		
	Oxygen	Oxygen	Bio-electrical

B. Treatment & Monitoring Challenges

The function of wound dressings is to address specific issues within the wound, for example excess moisture or bioburden, and to promote wound healing [18]. A moist wound environment is key to encouraging the healing process [19]. Maintaining this environment and monitoring any changes in the wound healing pathway are among the primary challenges encountered in current wound care practice. For instance, a spike in peri-wound skin temperature, along with high exudate volume, is most likely an indication of infection [20]. The balanced presence of metalloproteinases (MMP-2) and many other biomarkers is an indicator of good wound healing [21], whilst the lack of oxygen in a wound will prevent tissue growth [22], [23]. Currently, the accepted method of monitoring wound healing is to remove the dressing in order to inspect the wound. This can cause pain for the patient, may disturb the optimal wound environment and can regress healing by up to 12 hours [24], [25]. In general, wound dressings may not need to be changed on a daily basis, with some suitable for once or twice weekly changes depending on the type of dressing. However, overly frequent dressing changes has been identified as a problem in clinical practice, compounding the morbidity associated with wound dressing changes and increasing unnecessary expenditure [26], [27]. By embedding microelectronic sensors and wireless communications into wound monitoring devices or dressings, it is envisaged that clinicians could be provided with a quantitative view into the wound milieu without causing disturbance to it, enabling them to prescribe both optimised and personalised therapy. Currently, however, only a portion of these sensors are suitable for integration into wireless wearable wound monitoring dressings.

Table 2 Wound Staging Characteristics

Stage	Description
I	tissue loss on top layers only
II	tissue loss at epidermis and dermis
III	tissue loss to subcutaneous level
IV	Extensive loss/damage to tissue, muscle & bones.

C. Sensor-specific and Practical Challenges

Sensor-specific challenges include the availability of miniaturised and low-profile components [28], biocompatibility [29], substrate flexibility [30], moisture and bio-fouling resistance [31], [32], dependability [33], calibration [34] and most importantly disposability [35]. Disposability of devices is necessary in order to prevent cross contamination from infected dressings.
Practical challenges lie in both dressing integration and in the clinical use of embedded sensors. These include, but are not limited to: placement of electronic modules and sensors on or in the dressing; ease of use for non-technical users such as the caregiver or patient; the need for minimal assembly or peripheral equipment [36]; the preservation of core dressing functionality [37]; ease of dressing change and disconnection of soiled parts; prevention of infection cross contamination [38]; sterilisation logistics [39]; device tracking and secure integration with patient records [40], connectivity [41]; power and/or recharging requirements [42]–[45].

The following section will identify the specific wound parameters being sensed, outline their role in wound healing and discuss how they are currently measured.

III. Wound Parameters and Sensors

1) Potential Hydrogen (pH)

pH is the universal measurement for acidity and is related to the activity of hydrogen ions in a solution. The pH scale ranges from 0 to 14 [46]. The internal environment of the human body is predominantly neutral at pH 7, whilst the pH of skin ranges from 4-6 [47]. The skin's acidic milieu becomes disturbed when there is a break in the skin's integrity. pH plays a vital role in wound healing, and as such, wound pH measurements could be useful to identify non-healing wounds early in the wound healing

trajectory [48]–[51]. The pH of a wound can be detected from within the wound exudate with different pH values being indicative of the various stages of wound healing [52]. For instance, wound repair mechanisms operate in a slightly acidic environment and so the pH of a healing or acute wound tends to be in the 5-6 range [9], [49], [52]. Chronic wounds (non-healing), however, tend to have a pH in the 7.15 – 8.90 range [48], sometimes rising to pH 10, due in part to the proliferation of bacteria [53] [54] [55] [56]. Large differentials in wound pH can therefore provide an early alert of infection, making pH a key parameter in wound healing and characterisation [57].

Many sensors are currently available with potential to detect the level of pH in wounds [58]. However, limitations of these sensors have to date, prevented their successful integration into wound dressings. These include colour-changing pH-sensitive films that require visual inspection [58], luminescent detectors [59], radio frequency (RF) optical sensors [60] that may be inaccurate due to leaching of dye, matrix inflexibility, and wavelength interference, and both potentiometric and voltammetric electrochemical pH systems [61] that suffer from electrode fouling, biocompatibility, chemical leaching, and calibration issues. The limited availability of wound fluid in dry or healing wounds is a challenge for all these sensors.

2) Moisture

Detection of moisture in chronic wounds can provide key quantitative data for as much as four diagnostic parameters: exudate volume, wound exudation rate, wound dressing saturation and dressing efficacy. A dry or very wet wound hinders wound healing, the solution for which includes a change to moisture retentive dressings that hold moisture around a dry wound, or super absorbent dressings that draw excess moisture away from the wound. In the case of diabetic foot ulcers, it is vitally important that a wet ulcer is offloaded to prevent further maceration of the wound tissue and degradation of the ulcer [62]. Dressing saturation indicators are necessary for timely changing of fully saturated dressings, assessment of dressing efficacy and rate of wound exudation. Currently the amount of wound moisture is detected using methods such as visual inspection, the use of indicators such as Woundsense^{TM} dipsticks, humidity sensors or by electrical impedance moisture mapping [63]. All involve either subjective assessment, some degree of wound disturbance, and/or peripheral equipment, and are particularly unsuited to ambulatory care settings.

3) Temperature

Temperature has an important role to play in the functioning of every system in the body, with all cellular functions affected by temperature [38], [51], [64]. This is also the case in wound healing [65]–[68]. A prolonged temperature increase of over 1.11 °C can be an indicator of bacterial infection [69] and can be detected by palpation of the wound surround. Infection is generally detected by a combination of classic signs like redness, swelling, pain, heat detected by palpation [70] and odour, to name but a few. Non-invasive means of measuring body surface heat include long-wave infrared thermography [70] and infrared cameras [66], but real-time monitoring of wound and/or peri wound temperature is currently not a part of routine clinical practice. If implemented in an unobtrusive manner, continuous wound temperature monitoring could lead to earlier detection of infection.

4) Pressure

Compression therapy improves venous flow which speeds up wound healing [71], [72]. It is typically used to treat venous leg ulcers and requires the application of compression bandages by trained clinicians. The aim is to achieve pressure at the ankle of approximately 40 mmHg, decreasing as it moves up the leg [73]. Without monitoring sub-bandage pressure there is no way of knowing if adequate or excessive pressure is being applied or if pressure is changing over time, and ill-fitting compression bandages may worsen venous insufficiency or cause tissue necrosis [74]. Commercially available piezo-electric [15] and capacitive pressure sensors [35] have been used to detect external bandage pressure, but their integration into wound dressings has yet to be realised. However, optical pressure sensors based on Fiber Bragg Grating (FBG) are currently being developed and their improved sensitivity, accuracy and dimensions render them suitable for medical applications [75].

5) Wound Oxygenation

Oxygen is a key moderator in the healing process of wounds and is required for collagen deposition, epithelialisation, fibroplasia, angiogenesis and infection resistance [22]. In the absence of oxygen, wound healing is impaired [23], [76], with tissue hypoxia being the leading cause of prolonged hospitalisation due to non-healing wounds [77]. According to Schreml *et al*., partial pressure of oxygen in non-healing wound exudate is between 5-20 mmHg, whereas in healthy tissue it is around 30-50 mmHg [76]. Monitoring cutaneous oxygen status requires measurement of both the transcutaneous oxygen pressure (T_cpO_2) on the skin surface [78] in addition to the underlying tissue oxygen tension. Methods to date have included histochemical staining with hypoxia markers, PET imaging of radioactively labelled markers, and point measurements using Clarke electrodes or planar electrodes [79]. These methods have required invasive procedures such as tissue biopsy: needle stick directly in wounds and heating inflamed skin to 44 °C [80]. Non-invasive monitoring includes pulse oximetry based on oxygen-dependant spectral properties of haemoglobin, optical methods using sensing films and 2D luminescence imaging of physiological wound oxygenation [81]. An interesting approach by Li *et al.* is the image capture of phosphorescence emission of paint-on sensing

bandages [79]. This method generates an oxygen map of underlying tissue, albeit non-continuously, and has real potential application in wearable smart wound dressings.

6) Uric Acid

Uric acid (UA) is a key wound biomarker and studies show that elevated uric acid correlates to wound severity and oxidative stress in chronic venous leg ulcers [82]. Uric acid has an inhibitory role in healing by promoting inflammation and is associated with highly reactive superoxide radicals, which can disrupt normal functions of lipids, DNA and proteins in wound healing [82], [83]. Continuous measurement of this biomarker in wound fluid can contribute to clinical assessment of wound chronicity and response to treatment [84]. Current uric acid sensors included commercial meters from companies such as Benecheck Plus™ (General Life Biotechnology Company, Taiwan), Multisure™ (Apex Bio, Taiwan), and Easytouch™ (Bioptik Technology Inc., Taiwan), as well as electrochemical and amperometric sensors [84]–[86]. They are limited by single-use strips and sterile sampling lancets which make them unsuitable for continuous real-time monitoring. The future for low cost, small, portable and disposable sensors lies in screen-printed electrodes, electrochemical biosensors based on nanomaterials and optical based FBG sensors [85], [87], [75].

Section IV will highlight the new wireless prototype devices under development by various research groups, which have addressed some wound care challenges, and which show promising results for wireless wound sensing and communication.

IV. Current Wearable Systems

There are currently no point of care (POC) wireless wound monitoring devices on the market. However, there are a number under development by various university research groups, who have produced device prototypes on which preliminary testing has been carried out on human subjects. The challenges for producing a wireless wearable wound monitoring device are three-fold: technical, wound-specific and practical. The technical challenge is to develop a sensing and communications solution which is miniaturized, transmits data wirelessly, consumes minimal power and is low cost. The wound-specific challenge is to create a solution which is multi-parametric, biocompatible, moisture/biofouling resistant, conformable, low profile and extremely robust. The practical challenge is to produce a clinical product that is easy to use and activate on a patient, disposable, incinerable and interchangeable with a range of commercial wound dressings. The following devices have each addressed some of these challenges and their individual successes are moving the technology collectively closer towards meeting chronic wound care needs.

A team at the University of South Australia has developed a low-power portable telemetric system for wound condition sensing and monitoring [88]. The system aims to monitor wound temperature, sub-bandage pressure and moisture from within a wound dressing. A flexible, 0.15 mm thick, 2-layer, printed circuit board (PCB) contains the device circuitry and components including customised interface circuits, RF transceiver, serial interface, Balun device, 10-bit analog-to-digital converter (ADC) and 2.4 GHz chip antenna**Error! Reference source not found.**. The temperature (CMOS IC), pressure (piezo-resistive, 38 x 38 x 0.5 mm^3) and moisture (piezo-resistive, 10 x 5 x 0.5 mm^3) sensors are located at opposite ends of the board. Biocompatibility issues have been addressed by the application of a coating of polydimethlylsiloxane (PDMS) over the exposed circuit components. The device weighs 9.74 g including an alkaline battery. Maximum power consumption is 17.4 mA and sensing data is transmitted in Zigbee 802.15.4 protocol to a handheld receiver with an LCD screen. See Figure 1. The device is linked to the medical records of a specific patient using the transmission device identification, however unique frequency channels must be allocated to each device where multiple patients are present in proximity, in a hospital ward or wound clinic, for instance. The device is not integrated into a wound dressing but is placed proximal to it so that the moisture and temperature sensors are under the dressing (Figure 1). It appears then that sensing only takes places on a corner of the wound. The moisture sensor output was expressed in % relative humidity (RH), reaching 100% RH when dressing was wet and reducing to 0% RH when dressing fluid was directed away from the sensor. The pressure sensor was placed under 2- and 4-layer compression bandages. Experiments on a human leg demonstrated that postural changes (sitting, standing, lying) resulted in differing pressure outputs, with standing showing the highest sub-bandage pressure (~45 mmHg) and sitting with an elevated leg generating the lowest (~14 mmHg) [73]. The device is intended to be reusable, on a single patient, after sterilisation.

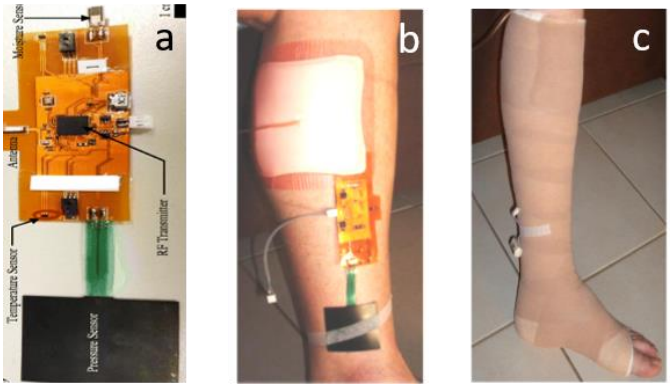

Figure 1 (a) Photo of the wireless sensing system fabricated on a 0.15 mm thick, 2-layer flexible printed circuit board. The diagram shows various parts of the sensing system. (b) Dressing and sensors in place on leg prior to bandage application. (c) Bandaging in place immediately following application.

Mostafalu et al at Harvard Medical School and Massachusetts Institute of Technology (MIT), have also been working on a similar device [89], referred to as a smart bandage for monitoring and treatment of chronic wounds. The parameters sensed and monitored are temperature and pH. This 2-part device comprises a disposable sensor patch (Figure 2) and a reusable electronics component. The former has 2 layers, is 3 mm thick and contains flexible pH and temperature sensors. It also contains thermally activated drug-releasing micro-beads and a micro-heater.
The pH sensor was fabricated on a polyethylene terephthalate (PET) substrate whilst the resistive (20 Ω) microheater was fabricated with 200 nm thick, gold zigzag tracks on a parylene substrate. These two components were then embedded in a layer of alginate hydrogel before being connected to the electronic module (Figure 2).

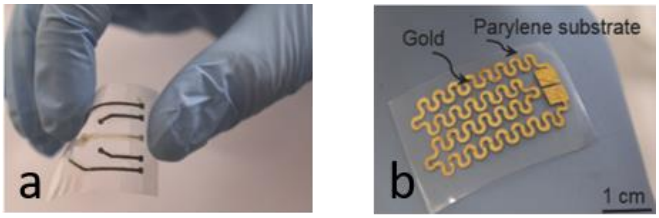

Figure 2 (a) Optical images and design of the fabricated pH sensor on PET film. Carbon/PANI and silver/silver chloride served as working electrode and reference electrodes, respectively. (b) Optical image of the flexible heater fabricated using gold electrodes on a Parylene substrate.

The temperature sensor is a commercially available (Omega, Chart Temperature) and is located beside the heater. A detachable electronics module contains a Bluetooth Low Energy (BLE) module and an Arduino microcontroller, which controls the sensors and triggers the activation of the drug-containing microbeads in response to temperature variation (Figure 3). When tested, the pH sensor displayed a 6 mV drift over a 12-hour period which, for daily dressing changes, would be acceptable. However, remotely monitored dressings can remain unchanged for up to 10 days and if the drift were cumulative this could amount to 120mV which is equivalent to over 5pH. The total expected pH range in chronic wounds is between 7.19 and 8.9 [48].

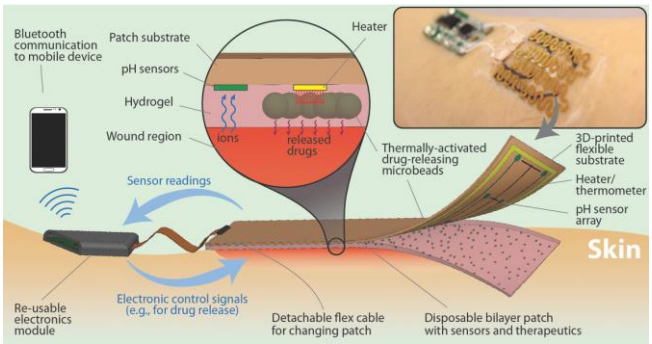

Figure 3 Schematic and conceptual view of the automated smart bandage. The bandage was comprised of an array of flexible pH sensors and a flexible heater to trigger thermo-responsive drug carriers containing antibiotics. Thermo-responsive drug carriers were embedded in a layer of alginate hydrogel which was cast around the pH sensors and on top of the flexible heater. The sensors and heater were connected to an electronic module that could record the sensors' signal and power the heater, if needed. The electronic module could also communication wirelessly to computers and smartphones.

At Tufts University, Mostafalu et al worked on a wireless flexible bandage for continuous monitoring of wound oxygenation [90]. Lack of oxygen in a wound can result in tissue loss and adversely affect healing, therefore monitoring this parameter is key for

chronic wounds. Using off-the-shelf electronic components and a custom oxygen sensor on parylene, a flexible and wireless bandage was developed in a single package. In this instance, a flexible bandage (based on TangoPlus elastomer from Stratasys) was 3D printed, on which the sensors and electronics were mounted as shown in (Figure 4). The hydrogel layer is in direct contact with the wound. Onboard electronics include an Arduino Lilypad microcontroller and an Xbee wireless transmitter, potentiostat, and front-end amplifier. Total package height is 19 mm. An alternative version includes the Light Bean Bluetooth microcontroller and a BLE wireless radio pairing (45.7 x 20.3 x 7.6 mm^3). The device consumes 20 mA in active transmission mode and is powered by a 3 V CR2032 coin cell battery of 225 mAh capacity. The electronic patch is reusable whilst the sensor patch is intended to be disposable.

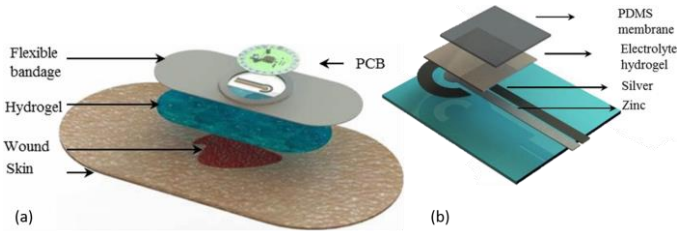

Figure 4 (a) Structure of flexible galvanic oxygen sensor on parylene. (b) 3-dimensional model of smart bandage

Temperature and pH are also monitored by a smart bandage with wireless connectivity for optical monitoring of pH, currently under development by Kassal et al at the University of Zagreb [60] along with Steinberg et al [91]. The 2-part assembly comprises an optoelectronics probe connected to a wireless RFID platform (Figure 5). The RFID platform is fabricated on a 60 x 60 x 10 mm^3 FR4 rigid board and contains an integrated circuit and temperature sensor. The probe assembly includes an LED and photodiode positioned on a separate FR4 rigid board, with a plastic housing to maintain 6 mm distance above the wound dressing. A pH sensitive film (15 x 15 mm^2) is screen printed onto a commercial wound dressing and reversibly changes colour from yellow to purple when the dressing fluid pH changes from acidic to basic. By placing the probe over this film, and emitting light from the LED, the photodiode measures the colour of the reflected light from the pH sensitive film. This data is stored and on request is transmitted wirelessly via RFID to an Android app or PC, where conversion to pH units takes place using a calibration curve. However, the pH indicator dye is not suitable for use directly in non-cellulose materials, so the dye must firstly be covalently immobilised on cellulose particles and then embedded into a hydrogel coating for use in commercial dressings. The sensor demonstrated precision and accuracy above 0.05 pH units and 0.08 pH units respectively, within 6.5 – 8.5 pH range.

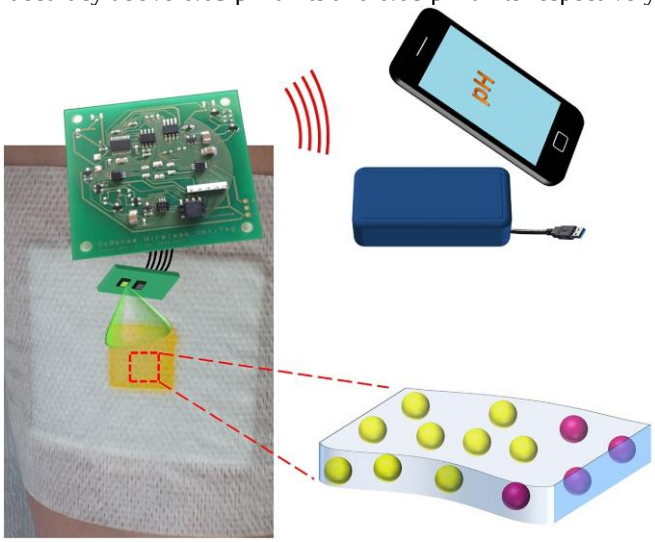

Figure 5. A schematic showing operation of the wireless smart bandage. The pH-induced color change of cellulose particles with covalently linked GJM 534 is measured and sent by contactless readout to a remote unit.

In another project, Kassal and Steinberg *et al.* also looked at uric acid biosensing as an indicator of wound status [86]. It is a key biomarker in wound monitoring as the concentration of uric acid in a wound significantly decreases during bacterial infection. Like the previous smart bandage, this is a bandage-based sensing system with non-contact wireless communication. Prussian blue carbon working and silver/silver chloride (Ag/AgCl) reference electrodes were screen printed onto a commercial dressing, with the uricase enzyme being immobilised onto the carbon electrode (Figure 6). A biocompatible chitosan layer was used to coat the electrodes. A connected potentiostat, similar to that used in [60], measures the current output of the sensor, stores the data and

transmits it wirelessly on request by RFID to a PC or smartphone. The sensor demonstrated sensitivity Relative Standard Deviation (RSD) of 1.85%, Stability RSD of 2.02% and Mechanical Deformation RSD of 5.60%.

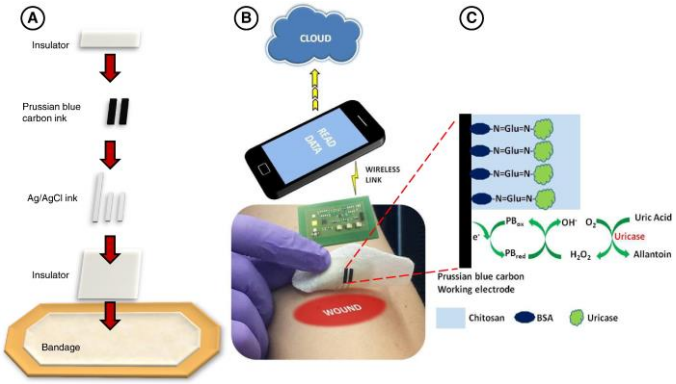

Figure 6 (A) Screen printing the smart bandage, (B) Wearable potentiostat determines UA concentration and wirelessly communicates with a computer or Smartphone, (C) Schematice showing amperometric detection of UA with uricase immobilised on PB working electrode

Pal *et al.* at Purdue University developed an omni phobic paper-based bandage (OPSBs) which wirelessly monitors wound parameters [55]. Sub-bandage pressure is measured using a high precision impedance analyser (AD5933, Analog Devices Inc), whilst wound pH and uric acid levels are quantified electrochemically using a detachable and rechargeable potentiostat (LMP91000, Texas Inst. Inc.), powered by a rechargeable battery. The device is controlled by an Arduino Nano V3.0 microcontroller and wireless communication is through the 2.4 GHz ISM band via an RF transceiver (nRF24L01, Nordic Semiconductors Inc.).
The stencil printed uric acid sensor comprised three electrodes, printed with carbon and Ag/AgCl conductive inks on omni-phobic Whatman #1 paper. See Figure 7. Uricase was the chosen enzyme due to its high selectivity towards uric acid. pH sensor electrodes were printed using Ag/AgCl inks between which a pH-responsive polymeric composite was pipetted and dried. Seven Ag/AgCl electrodes were printed in a hexagonal array for pressure ulcer sensing and coated with conductive hydrogel to improve skin-to-sensor conductivity. Tissue damage is detected by the impedance analyser chip located in the detachable potentiostat, in frequencies ranging from 1-100 kHz. The chemical sensors use low supply currents (<15 mA) and a 3.6 V rechargeable battery lasts 7 days, sampling once every 2 hours.

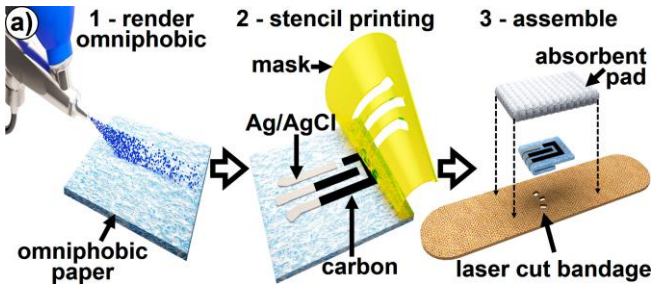

Figure 7 Schematic diagram of the fabrication of OPSBs: 1)Whatman #1 paper is rendered omniphobic; 2) stencil printing is used to pattern flexible conductive electrodes using carbon and Ag/AgCl inks; 3) openings are laser cut on the adhesive layer of the bandage to interface the wearable potentiostat with the paper-based sensors in the OPSB. OPSBs are assembled by placing the paper-based sensors between the adhesive layer and the absorbent pad of the commercial bandages.

Another uric acid sensing device was developed by RoyChoudhury *et al.* at Florida International University [84]. Sensor electrodes are cut from screen-printed conductive graphite paste on an adhesive vinyl sheet and transferred directly onto wound dressing material Figure 8. Conductive Ag/AgCl paste is applied to form the reference electrode with the enzyme uricase (UOx) entrapped, in a polymer, on the working electrode. The UA sensor is interfaced with a LMP91000 potentionstat which is mounted on a two-layer flexible Kapton tape. A low power data processing microcontroller (CC2650) is integrated with a Bluetooth module for wireless data transmission. A 3.7 V lithium ion battery powers the device providing 350 mAh, with an average power consumption of ~56 µW. The UA biosensor demonstrated sensitivity enough to detect sample volumes as low as 0.5 µL. In studies, however, exudate constituents such as electrolytes, lactate, glucose and proteins caused a change in the sensor response. The potential for these elements to occlude and/or limit the sensor are intended to be investigated in future studies.

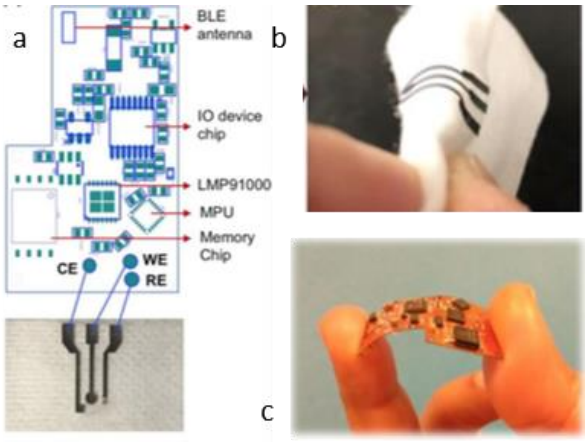

Figure 8 (a) Circuit design of components embedded on the PCB interfaced with the flexible wound sensor. (b) Flexible electrode. (c) Flexible electronics.

A similar bandage-based colorimetric measurement of pH has been developed by Mirani *et al.* at the University of Victoria [92]. This hydrogel-based system, referred to as 'GelDerm', incorporates an array of colour-changing pH sensors based on pH-responsive dye **Error! Reference source not found.**. Each sensor is 12 mm square in size and cumulatively the array provides a map of the pH across a wound area. The image of the sensor colours is captured by a smartphone app (iDerm) as shown in Figure 9; therefore, the sensors must be used in a commercial dressing that has a transparent backing layer. Transparent backed dressings are normally only used for low exuding wounds [37] which may limit the use of this device in wound management. The pH sensing demonstrated ±10% accuracy. In addition to pH sensing, this device can also deliver antibacterial agents to the wound as soon as the dressing is applied to the wound. This is done via drug-eluting (gentamicin) scaffolds, which are located at the centre of the dressing and embedded in the hydrogel with the pH sensors.

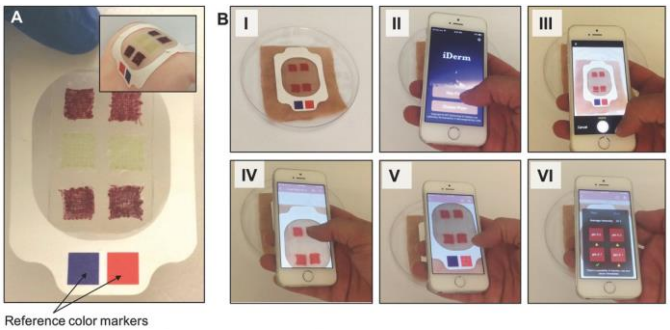

Figure 9 Integration of GelDerm with commercial dressings. A) GelDerm was integrated with Mepitel wound dressing; the red and blue squares on the film are reference colour markers used for correcting the grayscale intensity and eliminating the effect of lighting condition in the environment on the detected pH. Inset show Gelderm/Mepitel placed on a piece of pig skin showing good adhesion to the tissue under bending. B) Image sequences demonstrating image capture and processing using iDerm.

V. Outlook

The devices highlighted here have made significant progress in advancing the development of smart wound dressings. Key wound parameters are being sensed, conformal substrates have been explored and wireless communication has been demonstrated. The authors believe, however, that successful clinical implementation is hindered by the limitations of current device hardware such as detachable and rigid PCBs, non-incinerable and bulky power supplies, the challenges associated with integrating electronic devices with commercial wound dressings, and single parameter sensors. This section discusses each of these limitations and offers some options for ways to meet these challenges. It also discusses the potential of AI and machine learning to change inform an improve wound care management.

A. Detachable and rigid PCBs

A promising advancement observed with the sensors in this review [55], [60], [84], [86], [89], [90] has been the achievement of conformality and flexibility, which is clearly a prerequisite for components in close contact with painful wounds. Whilst conformality has been demonstrated in these sensors, the electronic circuitry, with its surface-mounted components, is primarily a

rigid construction. For that reason most of the prototype devices reviewed in this paper were 2-part assemblies, primarily for comfort and the economics associated with reusability [60], [86], [89], [90]. However, in practical terms the greatest threat to a wound is infection [16]. By introducing reusable hardware into a routinely-applied wound product, the risk of infection rises significantly [93]. Additionally, requiring that an electronic part be detached from an often soiled and infected dressing further increases the risk of cross contamination as well as the workload of the caregiver. By firstly making the electronic hardware soft, flexible and low-cost, engineers will be better placed to fully integrate this hardware into a dressing system. Some potentially significant developments have been made in this regard, for example, Xu *et al.* have managed to connect rigid components with flexible serpentine connecting wire and embedded them in a dielectric gel with an elastomeric pouch [94]. Transient electronics, which dissolve after a period of time without releasing harmful by-products, have emerged as a potential diagnostic/therapeutic tool in wound care [95]. Whilst historically electronics have been kept away from the body, the biocompatibility of new sensor substrates means that there is now a possibility of placing sensors directly on the wound or embedding them within the wound dressing. The theranostic possibilities for this scenario are immense for wound care.

B. Power Supplies

A major challenge for all wearable technology has been that of energy consumption and lifetime of the power source [96]. Practical solutions have reduced the power demand by developing simpler electronic designs, duty cycle sampling, limiting communications power requirements through local processing, designing flexible batteries and harvesting power either remotely or from the human body [44], [97]. There is a constant trade-off between delivering sufficient power to medical devices whilst maintaining a flexible and incinerable battery housing [40]. Kim et al have recently produced zinc-ion batteries in the shapes of letters, rings and circles, making them ideally suited for wearable devices [44]. These batteries and flexible circuitry could be integrated into wound dressing borders, making the wound area very accessible whilst not obstructing the core functions of the dressing. Any batteries used in clinical environment will need to be incinerable in order to meet hospital disposability protocols [98]. Many printed batteries are incinerable and almost as flexible as wound dressing individual layers [99]. The battery surface area, however, tends to be correlated to power and capacity and, when sized appropriately for wearable wound dressings, tends to fall short on device power requirements [100]. It follows that energy harvesting must be considered as a power supply option, provided it does not require more hardware and real estate than a simple battery [42], [43], [45].

C. Device/dressing integration perspective.

The evolution of modern dressings began in 1962 [101] and their continued development has sought to achieve the ‘ideal dressing’ [102]. Dressings are chosen based on the condition of the wound bed, the amount of wound fluid, bioburden and overall objectives of the wound management plan, so there is no ‘one size fits all’ dressing [24], [69]. Advanced dressings fulfil different functions such as exudate management [103], debridement [104], pain, odour or infection control, and promotion of granulation or epithelialisation [105]. They are made from a wide range of materials including hydrocolloids, hydrogels, foams and films[106]. Following correction of the underlying aetiological factors, wound dressings are the primary treatment in wound care [18] and if technology is to supplement this long-standing solution, then engineers must be cognisant of their role and function and not impede the primary function of the dressing, i.e. wound control and exudate management, in any way. Collaboration between the medical device industry, clinicians, materials and biomedical engineers is required in order to solve the challenges that still surround the successful integration of user-friendly wound dressings with functioning electronics. It is the authors’ opinion that the practical implementation and uptake by clinical users of these devices is dependent on the seamless integration of electronic hardware with fully disposable dressing systems.

D. Single parameter sensors

Detection of a single parameter in a non-healing wound is insufficient for a complete clinical diagnosis, as the challenge for clinicians is to correlate a myriad of components that contribute to wound chronicity [20]. In order to improve the wound diagnosis and subsequent treatment strategy, technology needs to deliver a multi-parametric sensing solution that detects cellular, molecular, electrochemical and physical wound parameters [71]. Integrating numerous sensors onto a wearable device may make it unwieldy and power hungry, and therefore multi-parametric sensors are essential if the technology is to progress. By examining emerging technologies across broader disciplines, multi-parametric sensor solutions may be found, albeit many remain at concept or early stage development. For instance, Slomovic *et al.* are working on advanced synthetic molecular networks for wound diagnostics [107]. The potential suitability of these networks is due mainly to their ability to simultaneously report on ‘wound infection, inflammation, protease balance, epidermal and dermal signal transduction pathways that regulate cell migration, proliferation and wound healing angiogenesis.’ Slomovic notes that synthetic biology devices, “such as engineered gene circuits, bring new capabilities to molecular diagnostics, expanding the molecular detection palette, creating dynamic sensors, and untethering reactions from laboratory equipment”. Additionally, thread-based microfluidics have made advances in the field of diagnostic applications and given their flexibility and similarities to dressing materials, could prove ideal for integration in wound

care dressings [108]. All have a common goal of a future when wearable wound care devices will look, feel and behave more like skin.

E. Artificial Intelligence and Machine Learning in Woundcare

As far back as 1960's, the potential for AI and machine learning to revolutionise healthcare, was predicted by Schwartz [109]. '*it seems probable that in the not too distant future the physician and the computer will engage in frequent dialogue, the computer continuously taking note of history, physical findings, laboratory data, and the like, alerting the physician to the most probable diagnoses and suggesting the appropriate, safest course of action. One may hope that the computer, well equipped to store large volumes of information and ingeniously programmed to assist in decision making'.* The subjective nature of wound care diagnosis and the qualitative notetaking make wound care the ideal target for AI implementation and where it can surely make the biggest impact. Machine learning and deep learning learn best from large amounts of data and learn from it by finding data patterns from which they can make predictions. Smart devices integrated into wound dressings can record multiparametric data in real-time, store this data for learning, and together with patients' systemic factors, predict more 'probable' diagnoses and make more informed treatment decisions. Additionally, smart dressings can identify potential issues with compliance, proficiency of wound care management and validate functionality of commercial dressings.

VI. Conclusion

There is significant potential for emerging smart connected wound monitoring devices to inform optimal wound care treatment programmes, leading to better clinical outcomes, whilst facilitating efficiencies in resource utilisation for management of patients with chronic wounds, including reduced personnel and materials. However, these benefits can only be realised once key technical issues are sufficiently resolved.

- Flexible, low power and low cost electronics which can be deployed as a conformal layer within the dressing.
- Batteries are required which are flexible, compatible with incineration and sufficiently powerful to last for the duration of the active life of the dressing. Some of the battery power requirement could be mitigated if suitable energy harvesting solutions become available.
- Multiparameter sensors or combinations of sensors are required, which are self-calibrating and where performance is not impacted by biofouling. These sensors should measure selected physical, chemical and biochemical parameters of the dressing, the wound exudate, the surrounding tissues and the patient.
- Smart dressings should be able to connect seamlessly either directly or via a gateway device, to the patient electronic medical record system, and provide appropriate user interfaces for the patient, the carer and the clinician as applicable. This interface could include feedback on quality aspects related to the application of the dressing.

Emerging solutions for each of the above technical challenges are creating opportunities for a new generation of smart wound monitoring technologies. These will likely disrupt the wound care market, by enabling the introduction of value based reimbursement for treatment of patients with chronic wounds. By enabling objective measurement of treatment programmes, providers can move from a product centric business model to an efficient service based model.

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