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D1.1 State-of-the-art study report

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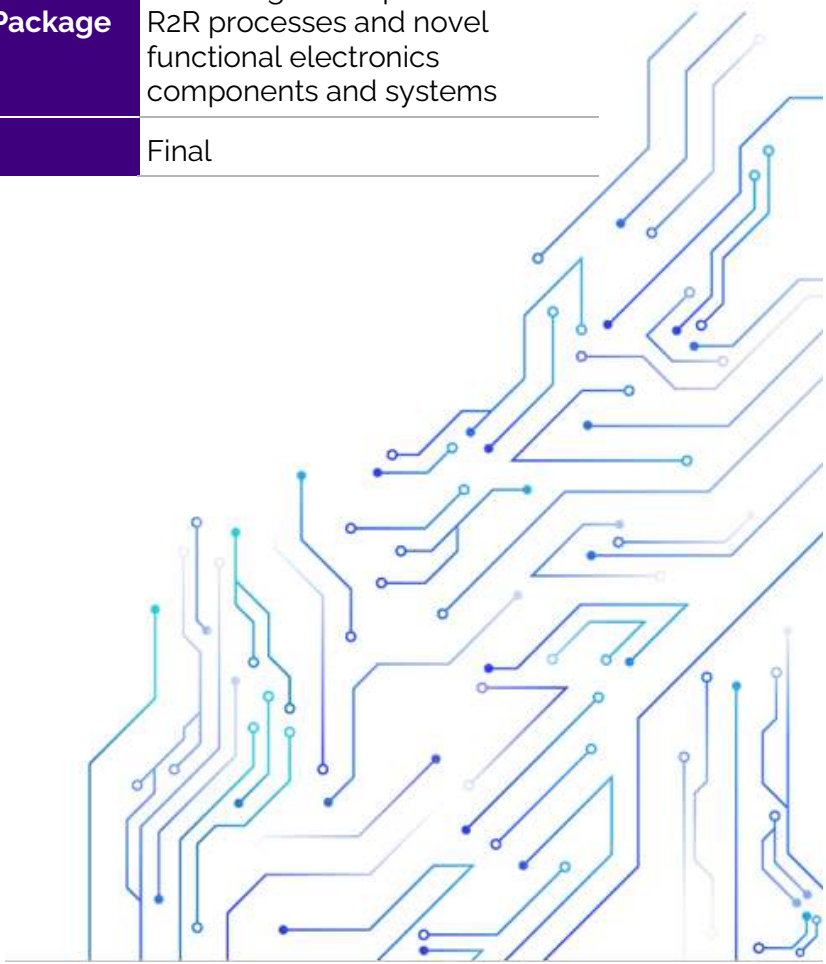

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Abstract

Functional electronics will allow the creation of more functional, lower cost and higher volume diagnostic devices that are more sustainable. We describe the use of roll-to-roll processing for manufacture of electronics systems on flexible film substrates and use of cold atmospheric plasma for immobilization of bioreceptor on a transducer interface. The utility of this approach is described for applications in point-of-care diagnostics, wearables, wound monitoring and blood self-sampling.

Statement of originality

This deliverable contains original unpublished work except where clearly indicated otherwise. Acknowledgement of previously published material and of the work of others has been made through appropriate citation, quotation or both.

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1 Introduction

Long and healthy lives are important for societal well-being and there is a continuing need to promote good public health and improve protection from health threats. Although there has been significant governmental and private expenditure on healthcare there is a challenge of increasing healthcare costs because of an ageing population in many industrialised countries or a lack of resources within Low and Medium Countries (LMICs). There is a need to move healthcare away from symptomatic treatment of diseases by blockbuster drugs and towards a more predictive, preventive and personalized medicine. Identifying individuals at the earliest stage of their disease will completely change the therapeutic paradigm and transform the way that healthcare is delivered so that it is more focused on sustaining health rather than treating late stage-patients with symptomatic disease. For most chronic disorders – such as cancer, metabolic disease, cardiovascular disease, diabetes, dementia - the disease process starts decades earlier before it appears symptomatically. In other disease conditions, such as cardiometabolic and infectious diseases, there is often a need for rapid diagnosis. There is therefore a need for disruptive innovation which can improve health outcomes, lower costs and improve access.

Wearable and point-of-care (PoC) diagnostic devices along with digital health technologies are allowing continuous, longitudinal monitoring of health within clinics, home as well as in resource-limited field setting. Information can be provided about mechanical, physiological, and biochemical parameters and be used for tracking gait, as well as for cardiovascular and metabolic biomarkers [1]; [2] [3] [4] [5]. PoC and wearable devices that can provide either rapid or continuous data collection with actionable health insights therefore have the potential to revolutionise care within a variety of settings.

Electronics manufacturing has largely been carried out using rigid printed circuit board (PCB) technology with advantages of reliability and low cost but nonetheless this approach is resource intensive, creates hazardous waste and is difficult to reuse. There is therefore an increasing trend to go from bulky rigid PCBs to flexible stretchable and structurally integrated systems on flexible (plastic/paper) substrates. This offers opportunities for development of diagnostic systems with wireless communication which will require consideration of design and material selection, manufacturing process development as well as the verification and testing of devices.

Integration of electronic functions can be based on a variety of printed materials and functional components which can have advantages of functionality, performance, reliability, and power requirements. Carbon based materials can offer advantages such as conformability and biocompatibility which is important for wearables that need to be worn on the skin or incorporated into clothing. Moreover, 2D carbon-based materials, such as graphene, offer excellent electrical, thermal, optical and mechanical properties that can be used for sensing of chemical, biological and physical parameters [6]. It's also important to consider that the global consumption of material resources is expected to more than double between 2015-2050 and with an increase of electronic waste production there is a need for end-of-life solutions that reduce the carbon footprint and increase the potential for use of abundant materials.

The global market for flexible electronics is already large, estimated at +6 Billion € in 2021 and a planned annual growth rate of more than 13% for the time period 2021- 2027. Flexible electronics components such as capacitors, sensors and transistors will be even more integrated into devices used for healthcare. Sensing capacities is expected to expand and to be increasingly more robust. Flexible electronics prototypes or commercial products have already been reported for temperature, pressure, metabolites such as glucose monitoring features. There are a number of key challenges that need to be addressed

including: (1) functional integration in flexible substrates (2) scalable manufacturing of flexible form factors (3) power sources/energy scavenging (4) durability of the sensing capacities (e.g. for cases with direct and prolonged contact with human tissues such as skin) (5) accuracy and robustness of the measurements to support large clinical adoption (6) multiplexing of sensing elements (7) cost of goods and sustainability of the electronic products.

2 Technology Components

2.1 Flexible Integrated Circuits

Active electronics devices, also known as Integrated Circuits (ICs), are at the heart of an increasing number of products that we all use in our daily lives. Some of the main functionalities of the ICs include interfacing with sensors, processing data, communications as well as driving external devices / systems. The current (traditional) ICs are manufactured in plants costing, up to several Billion $USD, using a lot of energy, and water, as well as generating a large amount of CO2 emissions. These traditional ICs are typically 100 mm thick, are also rigid and brittle, as processed on glass substrate at high temperatures. Due to the complexity of processing, the ICs can take 3 to 6 months to manufacture with a minimum cost per IC that cannot go low enough, to address many high-volume low-cost applications.

PragmatIC's proprietary Flexible Integrated Circuits (FlexICs), manufactured within a proprietary FlexLogIC line, improve many of the traditional ICs and related manufacturing limitations. The FlexICs are: 30 mm thin and flexible and are 10 to 20 times cheaper than traditional ICs. For a given function FlexICs are 5 to 10 times cheaper to design, with same EDA tools, compared to traditional ICs. They are also 10 to 20 times faster to manufacture (days versus months). A FlexLogIC manufacturing plant being 100 times cheaper than a traditional ICs' manufacturing plant, millions of $USD instead of billions for similar capacity, with a 30 times smaller in footprint and with 40 times fewer people to operate. to a traditional ICs' manufacturing plant. The FlexLogIC manufacturing plant uses approximately 100 times less energy than a traditional ICs' manufacturing plant as well as approximately 100 times less water and 1000 times less CO2 emissions. FlexICs and the related manufacturing plant FlexLogIC, open up application with price points and form factors, not possible with traditional electronics ICs.

An important part of a FlexIC based system, that needs attention, is integration at high speed, to keep cost low. One of the approaches that has been validated and is now in volume production, is the use of traditional Pick and Place equipment (P&P), with Anisotropic Conductive Paste (ACP) dispensing and curing. Any existing P&P machine, only requires a custom pick head to be able to pick FlexICs. The custom pick head is simple and low cost and several generic ACPs have been validated and are in use.

2.2 Power Storage

Portable and wearable devices can provide excellent opportunities to improve quality of life through point-of-care diagnostics and patient monitoring. However, such devices typically need an energy source to provide measurements and their analytics, as well as data read-off via indicators, displays, or wireless connectivity.

Today, the status quo is to use coin or button cell batteries that are predominantly based on alkaline, lithium, silver, and zinc chemistries. Such cells are widely available and provided in a range of sizes. However, these cells typically introduce major challenges in device disposal and recycling. These miniature batteries are complex, expensive, and often unecological to first collect, process, and then recycle. As a consequence, an estimated 97% of miniature batteries end up in landfill, or are incinerated.

With the emergence of flexible electronics, there is now a growing trend to provide micro and flexible batteries that conform with the desired form factor. For lithium-based chemistries this can create even greater risks than their cylindrical counterparts due to

autoignition from puncturing the cell. Printed zinc-air batteries are interesting from an ecological and safety standpoint, but suffer from exponential decay of the available current density as the oxide continues to grow at the air-breathing cathode (exasperated by its high surface to volume ratio in printed form). They are highly suited for very low discharge currents.

Paper-based biofuel cells offer an interesting opportunity to utilise eco-friendly and organic materials (papers and carbon) by exploiting the use of biological catalysts (enzymes) to convert biofuels such as glucose and oxygen into electricity. Performance of biofuel cells have been increasing to several milliwatts per square centimeter due to improved enzyme engineering and development of the enzyme immobilisation. Furthermore, industrial enzyme manufacturing driven by the beverage, food, and textile markets has made the technology economically interesting. Another key point is that the structure of a biofuel cell intrinsically provides super capacitive behaviour, making it ideal for delivering short bursts of energy, such as when wirelessly communicating data. In summary, biofuel cells offer an interesting compromise between sustainability and power density for microelectronic applications.

The main challenge for printed biofuel cells is that the complex behaviour of the biofuel cell must be optimised to the electronic load. Specifically, the enzymes should be protected from irreversible damage by avoiding prolonged high-current discharges and by ensuring suitable recovery periods. Furthermore, the enzymes naturally provide improved performance at body temperature, and reduced performance at cold temperatures. These factors must therefore be taken into consideration (and ideally tested) to adequately design the required biofuel cell.

2.3 Cold Atmospheric Plasma for Joining and Receptor Immobilisation

Immobilisation of a bioreceptor on a transducer for creation of biosensor elements within diagnostics is a particular challenge for R2R processing since this typically involves a large number of wet chemical processes and with requirement for considerable incubation time intervals between each step. The quality of the biosensor is dependent on how well the bioreceptor adheres to the substrate or sensor transducer. There are a number of immobilization methods that can be used but these are not useable in R2R processes since they are complex, multi-step, wet chemical processes which are time consuming. Cold atmospheric plasma technology is an exciting new approach that can allow the introduction of biomolecules (dispersed an aqueous solution which is atomised) into the plasma beam (Figure 1). The technology uses minimum power so that the epitope integrity of the molecules is not destroyed. This has been demonstrated to create a fast, single-step, high density substrate coverage deposition technique that can be applied to a wide range of substrates and has significant potential for R2R processing [7].

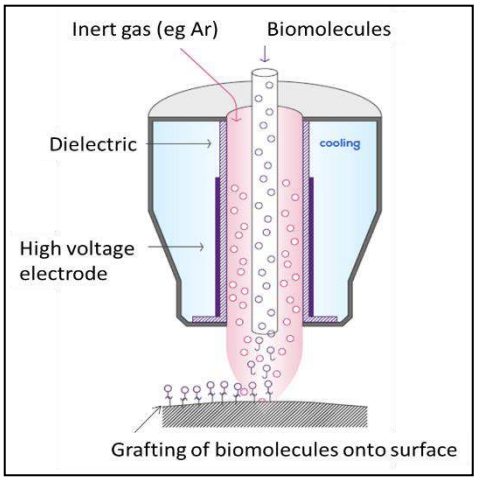

Figure 1 Cold atmospheric plasma for deposition of bioreceptors

The key challenge for the wider use of R2R processes is the integration of different electronic components into a single system in R2R process

which include the need for accurate printing methods for use with new sustainable / biodegradable / recyclable plastic, polymer or paper substrates which are lightweight and can be large area or stretchable.

3 Roll-to-Roll Processing

3.1 Mass-production

3.1.1 Manufacturing methods

Roll-to-Roll (R2R) manufacturing (Figure 2) [8] has been widely used for the high volume and low-cost manufacture of Radio Frequency IDentification (RFID) tags. RFID tags represent an ideal use case for R2R processes since the coil antenna is larger in size than other integrated circuit (IC) chips - with an associated requirement for low-cost substrate and the IC itself only requires two electrical interconnects with little need for high precision bonding or high-resolution metal wire interconnects.

Wiring patterns on film substrates are mainly prepared by a) screen printing or b) lithographically defined and etched copper layers. The screen-printing approach offers quick and sustainable (because of minimized use of metals and chemicals) manufacture, however, with limited capabilities in line resolution (typically above 80 µm). The lithographic approach offers high resolution copper patterns, down to 20 µm line / space geometries. This enables highly sensitive micro-electrodes as well as the opportunity for direct integration of micro-controller IC devices. In general, etched, or electro-plated copper lines show much higher performance in terms of electrical conductivity and high frequency signal transmission in comparison to screen printed silver lines.

Mass-manufactured structures are becoming smaller whilst at the same time the manufacturing scale is becoming larger. Microscale structures have the benefit of decreased material costs. Demonstration of volume production of microfluidic structures is, however, still very limited and there is a need to show the viability of such processes and devices. Specifically, there is a need to show that small structures can be manufactured accurately, flexibly and in a cost-efficient manner. Microfluidic manufacturing can be subtractive (removal of material, e.g., milling or laser ablation), additive (addition of material, e.g., 3D printing) or moulding (formation of the existing material, e.g., thermal imprinting). The different manufacturing methods are typically classified as either low or high-volume production. Low-volume production techniques such as laser ablation and 3D printing allows production of tens of devices in an hour. High-volume production techniques such as hot-embossing or injection moulding enables manufacturing of thousands of devices in the same period of time [9].

3.1.2 Material selection

The variety of materials that are available for use within roll-to-roll processing continues each year to expand and provide more functions, structures, and possibilities. Materials for microfluidics used in point-of-care (PoC) diagnostics or lab-on-a-chip (LoC) devices are typically organized into three main categories of inorganic, polymeric, and paper but hydrogels and composite materials also play an increasingly important role. Inorganic materials refer to silicon-, glass or ceramic-based microfluidics. Polymers are commonly classified as either (i) elastomers (e.g., polydimethylsiloxane PDMS or thermoset polyester TPE); or (ii) thermoplastic polymers (polystyrene PS; polycarbonate PC; poly-methyl methacrylate PMMA; poly-ethylene glycol diacrylate PEGDA; polyurethane PU; or perfluorinated compounds, also known as teflons, such as fluorinated ethylenepropylene FEP, perfluoroalkoxy PFA, or polyfluoropolyether diol methacrylate PFPE-DMA).

Hydrogels are distributed as organic-, inorganic, polymeric- or paper-based materials. Composite materials vary from cyclic olefin polymers (COP) to hybrids/combinations of inorganic-, polymeric- and/or paper-based materials. COPs are a class of polymers formed from cyclic olefin monomers and ethene, typically they are made of multiple monomers and thus are also referred to as cyclic-olefin copolymer (COC). The list of available materials for microfluidic devices is very extensive but within this report our focus is around paper- or other bio-based or sustainable substrates.

Paper as fabrication material has a number of advantages. It (i) is low cost, (ii) comes in variety of thicknesses, lengths and porosities, (iii) is made of bio-degradable polymer cellulose or blends of it, (iv) can be modified chemically in a variety of ways to incorporate different functional groups or reagents, (v) provides light background for colorimetric tests, (vi) passively transports aqueous solutions without active pumping, (vii) flexible as thin, (viii) is already used in wound dressings, and (ix) has been used for decades as a platform for microfluidics, analytical chemistry and diagnostics [10].

There are several ways to create microfluidic paper-based analytical devices (μPADs) such as: wax printing, inkjet printing, photolithography, flexographic printing, plasma treatment, laser treatment, wet etching, screen printing, and wax-screen printing [11]. Multi-layered structures can be bonded together by wax bonding [12], laser welding, adhesives, solvent lamination, hot-embossing or ultrasonic welding. Of course, some of these methods are for smaller batches and others are more environmentally friendlier than others.

Manufacturing μPADs enables cost-efficient, more sustainable and simpler production. However, it is not always possible to use paper for R2R manufacturing. Thicker paper substrates may crack under tensions and rollers, they also have huge autofluorescence for a variety of wavelengths limiting the detection capabilities used to read out the result from the assay. In addition, precise flow control is the biggest problem in the field of μPADs [13]. Thus, other polymers such as bio-based polyimides or polyimines are also being explored because they have particular properties that exceed those of paper [14].

As in the case of other bio-based materials, autofluorescence is considerable issue and so electrochemical (EC) or colorimetric read-outs offer better detection options than fluorescence-based techniques. Among these are chemiluminescence (CL), photoelectrochemical (PEC) and electrochemiluminescence (ECL) sensing [13; 11].

The transition of paper-based microfluidic devices from the laboratory into the users' hands will be highly dependent on ensuring that effective fluid flow control is achieved by use of paper of substrate. Recent developments in this area have shown significant progress, nevertheless paper-based microfluidic devices lack a rapid and easy way of manufacturing and industrial implementation. Therefore, developing simple and low-cost μPADs with integrated flow control methods which are applicable in existing mass production and fabrication facilities is a pre-requisite for successful commercialisation of these type of devices [13].

Paper based microfluidic devices have been largely limited for research applications with only a few considered for commercialization due to high manufacturing costs because of complexity, reliability, long-shelf life and other systems needed for their operation [15]. With increasing demand for cost-effective microfluidic devices, a number of smart designs of paper-based microfluidic devices have been reported [16; 10; 17]. Nevertheless, the most important factor for correct material selection is that it is suitable for the purpose and that it offers enough advantages than disadvantages for the targeted applications.

R2R processes have potential for wearable and flexible electronics for diagnostic applications. The potential of semi-additive R2R processing (Figure 2A) to create a

patterned copper electrode layer as part of an impedimetric point-of-care diagnostic cartridge (Figure 2B) has been demonstrated. The process incorporates lamination of dry film photoresist, photolithography, development, etching, stripping of photoresist and laser dicing. The point-of-care cartridge comprises an electrode layer using PEN substrate, a hot embossed fluidic layer and with both layers joined using PSA tape that is laser-structured to open selected areas of the electrode layer [18; 9].

The R2R process flows, akin to microfabrication process flows, can be very complex and consist of tens of steps. Most often, a roll of material is transferred from one R2R tool to another for various processing steps. Some tools can perform multiple process steps at once. However, because of the yield considerations a single multi-step tool for the entire process flow is usually a poor choice. Optimizing, synchronizing, and fine-tuning various process steps and, therefore, tools for specific process flows and novel materials is the biggest challenge in R2R manufacturing. Processing may include the use of lasers for cutting and/or ablation, installation of different parts (e.g., circuits, resistors, etc.) by SMT (surface mount technology) pick-and-place machines (P&Ps), dispensing or spotting of different synthetic or biological materials (e.g., antibodies, primers, adhesives). A key challenge is the need for accurate printing methods with use of plastic or paper substrates which can be large area or stretchable.

3.2 Lithographic patterning of metal layers by roll-to-roll processing

Lithographic patterning enables high resolution metal patterns and circuits. This is widely used in semiconductor industry and printed circuit board (PCB) manufacture. Transferring lithographic processes to roll-to-roll (R2R) manufacture requires film substrates in roll format, metal deposition (e. g. sputtering) on the film and the lamination of dry film photoresist on the metalised film roll [8]. UV exposure of the projected metal pattern can be done either via standard glass photomasks or via direct writing of an UV light beam. For the mask-based lithography process a large area (up to 30 cm x 30 cm) is exposed by one UV light shot. This is quick but not very flexible in terms of variation or combination of designs. In contrast, digital writing is mask-less and therefore allows for “endless” patterns on the film roll. This can be achieved by “stitching” of segmented patterns in the direction of transport of the film roll.

UV exposure is done by large area UV lamps for the mask-based process. Commercially available equipment for the direct write process use either an UV laser beam or an optically focused beam from UV light emitting LED arrays. The following figures show the roll-to-roll direct write system at Fraunhofer EMFT and the tool for the lamination of dry film photoresist.

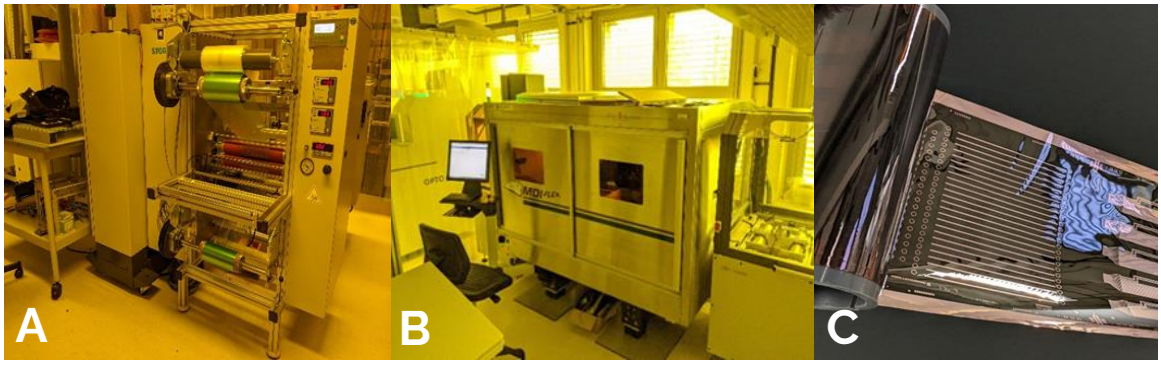

Figure 2 Equipment for R2R lithography at Fraunhofer EMFT; (A): lamination of photoresist; (B): direct write R2R UV-lithography; (C): sample with copper patterns on Polyimide film roll

Patterning of copper layers can be done in various ways. The standard manufacture process uses polymeric film substrates (Polyimide or PET) on which a thin copper film (thickness 9 µm, 18 µm or 36 µm) is laminated by a thin adhesive layer (e. g. epoxy). After UV exposure and development of the photoresist the film substrate is moved through a copper etching bath. Copper areas that are not covered by the patterned resist are etched and removed. Then the resist layer is stripped, and the pattern is ready for further integration steps.

An alternative way is the application of the so-called "semi-additive" process. Here a very thin (100 nm to 300 nm) sputtered seed layer of copper (and eventually an adhesion layer of Chromium) is first deposited on the film. Then the photoresist is laminated, exposed to UV-light and developed. In a subsequent step the web enters an electroplating bath. Copper grows in the open resist channels from the bottom copper seed layer to the projected thickness (typically 5 to 10 µm). After this plating process the resist is stripped, and the thin seed layer is etched off. The several micrometers thick copper patterns remain on the film roll. This process sequence shows advantages in terms of sustainability as only the amount of copper that is required for the line patterns is deposited.

The industrialisation of roll-to-roll lithographic patterning of copper layers is at an early stage. This represents a valuable chance for the development of new "greener" process sequences as they could be adapted very well in time to planned new production sites in Europe.

4 Applications

4.1 Point-of-care diagnostics

Traditionally diagnostic tests have been performed in centralized laboratories by trained personnel with specialised equipment because of their complexity. PoC diagnostics offers the potential to automate and miniaturise these tests so that they can be used in more locations, e.g., by the patient bedside, within the community, at home or as wearable or implantable device. PoC diagnostics will therefore be carried out by a wider range of people and address unserved markets. This has the potential to be disruptive in several testing markets, as an example within infectious disease the testing pathway within a centralized from an initial appointment with a clinician to the test result and treatment can take four days. This contrasts sharply with an analysis time which can be less than 30 minutes for PoC diagnostics.

A POC diagnostic typically incorporates an assay that is contained within a cartridge and hardware for detection of the assay endpoint. The assay comprises the biochemical components that carry out the identification of the chemical or biological analyte whilst the combination of cartridge and hardware are used to automate the biochemical protocols. The most widely used commercially available POC diagnostic devices are the Lateral Flow Tests (LFTs) or Lateral Flow Assays (LFAs), which are membrane/paper-based cartridges where a composite assay strip is flanked by a reagent/sample pad at one end and an absorption pad at the other. The strip contains two or more lines striped into the nitrocellulose membrane, one or more test line(s) consist of a disease-specific antigen or antibody receptor and one line is used as a control. LFTs/LFAs are ordinarily used for simple Yes/No answers - such as testing pregnancy or drug abuse - in a qualitative or semi-quantitative manner and in which case a "visual" readout is sufficient. Bioassays that require quantification typically need defined handling in terms of applied volumes as well as incubation time and defined analysis of the generated signal which is not possible by the user alone. To allow quantification of the signal, readout devices are used to compensate for user-induced handling variations and the bioassays are implemented into so called “Lab-on-a-chip” systems (LoC), which contain internal standards, control elements and pre-stored biochemicals. LoC systems are envisioned to provide “sample in – answer out” with a minimum of handling steps, ease of use and a maximum of robustness and reliability. The most common readouts for LoC systems use either optical (absorption, fluorescence, luminescence) or electrochemical detection. There is considerable potential to use flexible electronics for the development of highly functional, low cost and high volume PoC diagnostics. As the COVID-19 pandemic has shown us, the demand of highly specialised materials for PoC diagnostics, such as plastic tubes for polymerase chain reaction (PCR) or nitrocellulose membranes for LFTs/LFAs, have increased and there has been and still remains very long delays due to an increased demand and lack of supply. An approach that does not make use of these materials is therefore greatly preferred. The possibility of a further pandemic0 will not diminish today or in the nearby future.

In 2003, the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR) published criteria for an ideal diagnostic test. These criteria are known by the acronym ASSURED and have become widely accepted as the benchmark for an ideal test that can be used at the POC. During these years, it has developed to REASSURED criteria. This stands for real-time connectivity, ease of specimen collection, affordability, sensitivity, specificity, user-friendliness, rapidness and robustness, equipment-free and environmental-friendliness, and deliverability to end-

users. Currently and most likely there will not be a perfect test, PoC tests are typically trade-offs between accuracy, accessibility, and affordability [19; 10; 20].

LFTs/LFAs have been used in rapid diagnostics over a number of decades. Despite becoming lower cost as well as being easier to develop and use, they lack good sensitivity and multiplexing capacities. The limitations of multiplexing capabilities of LFTs/LFAs (two to three types of biomarkers at best on short paper strip) are due to technical and operation-wise challenges, such as cross-reactivity and selection of appropriate diluents. Quantitative results from colorimetric-based LFTs/LFAs are also very difficult to obtain without external optical reader. However, these disadvantages could be mitigated by using more quantitative detection methods such as fluorescence or electrochemical detection and creation of multi-chambered microfluidic device for multiplexed reaction.

Paper-based diagnostic devices for multi-step assays can be separated into three techniques: (i) fluidic creation [13, 21, 22], (ii) sensing [23], and (iii) fluid manipulation [13; 24].

An inexpensive platform called omniphobic paper-based smart bandages (OPSBs) for measuring multiple parameters to perform real-time monitoring of chronic wounds (both open wounds and pressure ulcers) have been previously demonstrated [25]. However, their mass-manufacturability and sustainability has not demonstrated, and they have limited sensing capabilities – additionally, removal of these adhesive bandages may lead to secondary damage to wound tissues.

4.2 Wearables and wound monitoring

People with underlying health conditions - e.g. elderly, obese individuals or those with diabetes and/or cardiovascular diseases - can have significant shifts in their physiological response from normal day-to-day activities. Heart rate (HR) and Blood Pressure (BP), are two important vital signs that can dynamically and directly reflect the physiological status of the body. These cardiovascular parameters can be affected by fluctuations of various biomarker concentrations from activities including movement, stress or the intake of food, drinks and drugs that can lead to sudden and occasionally lethal alterations. As a consequence wearables that allows tracking of metabolites and haemodynamic parameters can provide more personalised monitoring of a patient to avoid dangerous events and save lives. Wearables have considerable potential for individuals with hypoglycaemia- or hyperglycaemia-induced hypotension or hypertension, which increase the risk of stroke, cardiac diseases, retinopathy and nephropathy in patients with diabetes [26].

It is estimated that nearly 50 million people suffer from hard-to-heal wounds, globally, including an estimated 2–4.5 million people affected in the US alone. Wound treatment is complex and varies across a broad continuum of care. Non-healing wounds significantly deteriorate the patients' quality of life and can cause serious medical events such as limb amputations or premature death. An aging population along with increasing prevalence of diseases such as cancer and diabetes will mean that this market will continue to increase. Additionally, an increasing number of older adults are undergoing surgery and are at risk of wound complications. The global market for chronic wound therapeutics was worth +10 billion € in 2020. The market is expected to grow over 15 billion € at a CAGR of +6 % during the next few years, leaving room for the development of even more advanced therapeutics for the most complex cases.

Chronic wounds have diverse etiologies with diverse signatures but can be divided into three main categories: venous leg ulcers (VLUs), diabetic foot ulcers (DFUs) or pressure ulcers (PUs). Dressings are developed based on different types of wound conditions such

as dry, exuding, superficial or deep and clean or infected. The main wound dressings include those targeting: chronic ulcers; lower infected acute wounds; and large full-thickness burns. Wound dressings are mainly designed to keep the injury site sealed and protected with some that release drugs or compounds to prevent infection and help with faster healing. These wound dressings are not able to provide information of the wound bed and cannot recognise the different stages of wound healing and consequently the healing rate. Monitoring of the healing process requires the dressing to be removed with associated pain and compromising the healing process by inducing unnecessary inflammation reaction. This also adds to the cost of the treatment which can include travel for patients in less densely populated areas. There is a need for smart dressings that can provide diagnostic information to combat infection, through detection of early stage of microbial (bacteria or fungi) infections, as well reducing the number of bandage dressing changes, laboratory blood analysis and guide the application of therapeutics. This would allow better wound management and improve clinical outcomes as well as reduce costs for patients and healthcare systems.

Biomarkers that would provide useful information as part of smart dressing include those for vascularisation, inflammation and infection. If an infection is not treated at an early stage and a biofilm is established within necrotic tissue then there could be requirement for limb amputation, infected DFUs are the main cause of non-traumatic lower limb amputation. Some of the key biomarkers for wound dressings include those for moisture, oxygen, temperature, pH, pressure, and strain sensors. Uric acid sensors have also been incorporated in some dressing prototypes to provide information on the risk of wound infection development [27; 28]. Very commonly, smart dressings from the recent literature are based on flexible electronics approaches [28]. More precise monitoring of wound healing can be provided by multimodal sensing bandages. For example, a dressing has been reported equipped with temperature, pH, and uric acid sensors with on-demand release of antibiotics to wound site.

Skin is naturally acidic (pH 4-6) to support proliferation of fibroblasts, promote angiogenesis and epithelialisation, release oxygen from oxyhemoglobin and control bacterial colonisation. The pH of the tissue underlying skin is more neutral (pH 7.4) and so wounding would expose the underlying tissue and change the acidic environment. Chronic wounds suffer from cycles of ischemia-reperfusion injury leading to higher pH than that of regular healing wounds. Wounds are typically colonised with environmental pathogens and have a higher pH of up to 10 to optimise bacterial growth, 80% of chronic wounds have an elevated pH. Different types of pH sensors have been fabricated for wound care applications including conducting polymer sensors, ion-selective electrodes and ion-selective field effect transistors. A low-cost stretchable sensor with Nernstian response to pH was created by spraying conductive inks and polymers on an Ecoflex substrate that could form and maintain conformal contact with curved surfaces. Colorimetric sensors have also been used for the development for smart bandages these have the advantage of having a visual readout with no requirement for integrated electronics but can have a problem of leaching of colorimetric dye into the skin. This has been in part been addressed through incorporation of pH-responsive dyes in mesoporous silica particles, to prevent leakage, and introducing into flexible hydrogel fibers fabricated through microfluidic spinning. The fibers were attached to transparent medical table for long term monitoring of cutaneous wounds.

Temperature can provide information about healing through indication of adequate blood flow, presence of infection and oxygenation. PUs with high temperatures have found to heal more slowly than low-temperature ulcers where the higher temperatures indicate the presence of higher colonisation. Extreme hypothermia has also been correlated with unsuccessful wound healing and increased wound infection. The most common type of

flexible temperature sensors uses metallic resistive sensing. An array of microfabricated temperature sensors, using conductive ink, on a conformal wound dressing have been used for skin temperature mapping of a cutaneous wounds. The drawback can be that mechanical strain can change the electrical resistance and impact on the accuracy of the temperature sensors. Separately, the accuracy is often typically dependent on conformal contact. These issues can be addressed through use of suitable porous substrates and octopus-mimicking surfaces. Carbon nanotube-based sensors have been developed as low cost and highly sensitive devices but their use could be limited because of their potential toxicity.

Chronic wounds have insufficient wound oxygenation due to inefficient vascularisation. Oxygen is required to support the wound bed with cell proliferation, angiogenesis, collagen synthesis and bacterial defense. Acute hypoxia in a chronic wound could be detrimental to the wound healing process and result in unnecessary tissue loss. Some studies have suggested a minimum tissue oxygen tension of 20mmHg to promote wound healing whilst others have shown much lower values for non-healing wounds. Monitoring of tissue oxygenation would provide useful information about would healing. A flexible and wireless smart bandage with oxygen sensor was structured using an electrochemical galvanic cell, with silver and electroplated zinc electrodes for respectively the cathode and anode, on a flexible parylene C substrate.

Inflammation from injury enhances capillary permeability and leakage of fluid from blood vessels. The exudate is mainly produced during the inflammation and proliferative stages of wound healing but the production rate depends on the stage of healing and wound characteristics. Wound healing in a moist environment has a greater rate of revascularisation and dry wounds have slower progression in the remodelling phase of wound healing. Separately, some bacterial species grow better in a moist environment so excessive wound fluid may increase the risk of bacterial infection. Measuring the moisture level in the wound environment can be used for monitoring the wound status as well as interventions to manage the exudate and moisture levels. Electrochemical sensors for monitoring moisture as part of a dressing showed that 40% of time dressing changes occurred before the optimal time.

Currently, the number of markers that are being monitored are limited and the majority of these are nonspecific. VeCare is an example of a complex smart dressing, including a passive microfluidic collection of exudate fluid, an array of sensors analyzing temperature, pH and a collection of biological markers (TNF-α, interleukin-6, interleukin-8, and transforming growth factor-β1), Staphylococcus aureus) and a low power Bluetooth enabled data transmission system. The cytokines are measured by aptamer-electrochemical sensing technology [28]. Lou et al. have reported a Band-Aid equipped with a temperature sensor, tracking and reporting the main stages of wound healing (e.g. inflammatory cell infiltration, angiogenesis, and healing) and early phase of infection, by relying on a customized smart phone application [29]. There remains, however, a need to identify more suitable markers that can be integrated into a multiple sensor format.

Delivery of drugs to the wound bed can be used to modulate physiological processes involved in tissue healing. This could include release of antimicrobials if biomarkers that are indicative of an infection are detected. Drug delivery can be through passive, semi-passive or active means. Passive methods involve release of predesigned dosages of the drug and are relatively easy to integrate within the dressing. Semi-passive drug delivery systems use materials that are able to respond to changes in the wound pH, temperature and enzyme level but do not allow active control of the drug release profile. Active drug delivery systems combine on-demand induction based on either external stimuli (e.g., temperature, electrical signal, light, etc.) or through integrating information from one or more biomarker sensors [28] as well as providing a precise control of the temporal or

spatial release profile. Drug delivery can be achieved through various means including wearable mechanical and piezoelectric pumping, thermo-responsive and iontophoretic systems. Thermally actuating systems use an external heater to heat up a thermo-responsive material and release the drug into the environment. In iontophoresis, ions move across a membrane through an externally applied electrical potential difference. Smart gelatin-based hydrogels including organic semiconductor Poly(3,4-ethylenedioxythiophene)-poly(styrenesulfonate) (PEDOT:PSS) and multiwall carbon nano tubes (MWCNTs) have been used for active wound dressing systems. The gels can both monitor the motion activities of the wound area and enhance the healing by electrical stimulation. Moreover, they are self-healable [30]. A smart skin-inspired hydrogel was designed by integrating cellulose nanofibers (CNF) into a polyamethacrylate (PMA) network. The CNFs have been coated with tannins to confer antimicrobial properties. The gel has shown remarkable properties, high stretchability, and toughness, complying well to the range of motion of the wound itself and potentially to protect the wound against external damages. The piezoresistive response of the gel can be used to track motions, such as bending, nodding [31].

A key limitation of existing smart dressings is the robustness of the sensor systems within the wound environment which is moist and concentrated with various proteins and can limit the sensitivity of the sensors over a short period of time. There is also a need for greater consideration of the sustainability of the materials used with smart wound dressings.

4.3 Home sampling of blood

Laboratory analysis of body fluids such as blood and plasma are essential tools in diagnosis and medical decision making. The global blood testing market size is expected to reach USD 140.3 billion by 2028 [32]. Traditionally, blood is sampled through venepuncture, where a trained phlebotomist obtains about 5-10 ml of blood into a collection tube and sends the sample to a laboratory for analysis. This process requires trained personnel, cold chain transportation and travelling of patients to health care centre. Venepuncture sampling is consequently associated with high costs, and inconvenience for low-mobility patients as well as patients living remotely or in low-resource settings. The alternatives are novel patient centric microsampling solutions allowing for samples to be taken without trained personnel in the patient's home. Such devices generally sample below a few hundreds of microliters of blood and preserves it in either liquid or dry state. Generally, the microsampling device market can be divided into two groups based on the mode of sampling i.e., so called upper-arm devices and finger-prick devices. Upper arm-devices, typically represented by companies such as Tasso Inc, YourBio Health, Drawbridge Health and Loop Medical, are based on a plastic-cup like device which is attached to the upper arm of the patient whereby microneedles penetrate the skin and the under-pressure in the device sucks blood into it. Different adaptors are available for storing liquid blood that is further pipetted into specific volumes at the laboratory or adaptors for dried sample collection.

Finger prick devices collect capillary blood from a finger on the patient. Blood flow is induced by punctuating the fingertip with a lancet which can be done by the patient themselves or with the aid of a care giver or relative. Most systems take advantage of storing the sample in a dried format. In dried blood spot (DBS) technology, which was introduced by Robert Guthrie in the 1960s for PKU (phenylketonuria) screening in new-borns, the blood sample is applied on a paper and allowed to dry. Through the drying, a biohazard–free and cold transport–independent blood sample is created that can be delivered to the laboratory for analysis via ordinary mail service. So far, around 2000

different analytes ranging from metals and small molecules to DNA and proteins have been analysed on DBS [33]. Despite its many advantages and wide range of applications, its full introduction in clinical use have been hampered by the difficulty of enabling accurate quantitative analysis using DBS as there is no volume control in the applied sample on a DBS paper. The issue with lack of volume control has been recognized by a handful of companies devoted to volumetric DBS where DBS Systems SA, Capitainer AB, Trajan Scientific and Medical Pty Ltd. are the main players on the market. Table 1 lists the companies with respective websites.

Table 1a: Upper arm volumetric sampling systems

Upper arm devices	
Tasso Inc	https://www.tassoinc.com/
YourBiohealth Inc	https://yourbiohealth.com/
Drawbridge health Inc	https://www.drawbridgehealth.com/
Loop Medical SA	https://www.loop-medical.com/

Table 1b: Finger prick volumetric sampling systems

Finger prick devices	
DBS system SA	https://hemaxis.com/
Capitainer AB	https://capitainer.se/
Trajan Scientific and Medical Pty Ltd	https://www.trajanscimed.com/

In addition to the volumetric sampling systems described above, there are other products that have a lower focus on volume precision and accuracy are available such as those provided by Spot on Science, and Weavr Health. Solutions for collecting capillary blood in regular microtubes are also available.

The ability to control sample volume and easily enable quantitative analysis opens up new opportunities for research studies as well as in clinical applications. From a cost perspective, switching to DBS home sampling has been demonstrated to be associated with a cost reduction of 43% for hemato-oncology patients (€277 to €158) and 61% for nephrology patients (€259 to €102) from a societal perspective (total costs) per blood draw [34]. This has the potential of reducing clinical trial costs and consequently self-sampling or remote sampling has gained interest by the pharma industry as well [35; 36].

4.3.1 Therapeutic drug monitoring

Therapeutic Drug Monitoring (TDM) is the clinical practice of measuring drug concentration in body fluids such as blood or plasma and then use it to adjust the drug dosing regimen by targeting a predefined concentration or exposure interval, called a therapeutic range. This involves competencies in pharmaceutics, pharmacokinetics, and pharmacodynamics. A critical input parameter in the process is based on the relation in time between the concentration of specific drug in a blood sample and when the dose of that drug was administered. The goal of TDM originally is to individualize therapeutic regimens for optimal patient benefit but the indications for drug monitoring have widened

to include efficacy, compliance, drug-drug interactions, toxicity avoidance, and therapy cessation monitoring [37]. Clinical TDM currently targets various drugs, including anticonvulsants (phenytoin, carbamazepine, phenobarbital, primidone, valproic acid, clonazepam), cardioactive drugs (digoxin, procainamide, quinidine), respiratory-acting drugs (theophylline, caffeine), psychotropic medications (clozapine), mood active drugs (lithium, nortriptyline, doxepin), immunosuppressants (cyclosporine, tacrolimus, mycophenolate, sirolimus, everolimus), antineoplastic (methotrexate), and anti-infective (amikacin, gentamicin, tobramycin, vancomycin, piperacillin, cefuroxime, voriconazole, ganciclovir, meropenem, flucloxacillin) [38].

With traditional venepuncture sampling, the time of sampling is registered by the sampling nurse. Moving to remote sampling by the patient themselves in their homes, calls for alternative solutions for registering the time. There are a variety of integrated solutions where both sampling and measurement is performed on site [39]. Although these point-of-care type solutions are today mainly at an academic proof-of-principle level, Merck Inc have presented a patient centric TDM solution as part of their smart-trial concept applying so called smart packaging or electronic adherence monitoring [40]. Here, traditional DBS was used and the time and date of drug administration and blood sampling was self-reported by the study participants themselves. The authors states that Merck plans to develop a sampling system that automatically captures time and date of the sampling. To our knowledge there are still no such devices that are commercially available. What can be found in published literature is a patent application by Neoteryx on integrated electrodes in their Mitra sampling device for resistive detection of blood sampling and Merck presenting a modified Tasso device with integrated electronics for time stamp management.

5 Conclusion

Functional electronics offers huge potential for the creation of more functional diagnostic devices - including PoC, wearables, wound monitoring and blood self-sampling – that are more sustainable and at lower cost and higher volume. This is underpinned by the use of volume manufacturing approaches such as roll-to-roll processing for the manufacturing of electronic systems as well as novel approaches for incorporation of digital and analogue circuitry and power sources on flexible film substrates. The right choice of technology will depend on the sensor and system requirements of the target application. The generally higher cost for lithographic patterning of copper layers can be strongly reduced when roll-to-roll processing is introduced. One bottleneck is the immobilisation of biological receptor on a transducer interface at high volume within a R2R process may be addressed by the use of cold atmospheric plasma deposition. There remains a considerable gap for these early efforts to be translated into products on the market with a variety of issues that need to be addressed including the durability and reliability of device functionality.

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