



Université catholique de Louvain  
École polytechnique de Louvain  
ICTEAM

# **Wearable nano-engineered systems: Towards real-time health monitoring for remote places**

Dissertation présentée en vue de l'obtention du grade de  
Docteur en Sciences de l'ingénieur  
par  
**Darwin Rodolfo CAINA AYSABUCHA**

**Promoteur :**  
**Dr. Sorin Melinte**

**2022**







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**Membres du jury :**

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**Prof. Sabine Szunerits**

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**2022**



# Abstract

In the coming years preventive medicine and medical treatment will strongly rely on wearable and implantable biomedical devices. Advances in manufacturing, energy harvesting systems, and information technologies are contributing to a transformation in the mobile health era in terms of healthcare management and real-time, personalised tracking of the health status. Thus, the demand of wearable devices for monitoring and treatment of chronic diseases such as diabetes in remote places is expected to drastically increase. Specifically, the design and development of next-generation wearable devices for the diabetes treatment involves multi-disciplinary fields such as transdermal drug delivery, radio-frequency energy harvesting, and embedded, low-power electronics. In this thesis, we present the integration of various concepts from these areas relevant for wearable healthcare technologies to progress towards wearable devices for monitoring and treatment of diabetic patients in remote places.

First, our efforts have been focused on the design, simulation, and fabrication of planar, small and flexible antennas for both radio-frequency energy harvesting and wireless communication purposes, focusing on the unlicensed band of 2.45 GHz. Next, a novel painless patch design is presented as a transdermal insulin delivery system. The patch is based on the integration of nano-engineered heating elements - gold nanomesh thin layers - on polyimide substrates for transdermal insulin therapy by wireless, electrothermal actuation. A thin film of reduced graphene oxide integrated onto the nanoheater provides the drug reservoir. Numerical computations to analyse the Joule heating of the patch in contact with the human skin were performed. Finally, the architecture and the design of the wearable electronic system to control the electrothermal patch with a smart phone are described, considering that the transdermal patch is powered via batteries and radio-frequency energy harvesting.



# Acknowledgements

There are no words to express my gratitude to many people, who helped and supported me during this long journey, which has been a special period of my life. First of all I would like to thank God and my family. I would like to thank *L'Académie de recherche et d'enseignement supérieur* (ARES) and *Universidad Central del Ecuador* (UCE) for the financial support of my PhD program. This unique experience will be fruitful for my academic career in Ecuador. I would like to express my gratitude to my supervisor, Dr. Sorin Melinte. His mentorship, encouragement and guidance made this thesis possible. I had the opportunity to learn from him many things from both scientific and personal perspectives. I would like to acknowledge all the members of my PhD thesis advisory committee Prof. Christophe Craeye, Prof. Benoît Hackens, Dr. Radu Popa, and Prof. Sabine Szunerits for their guidance and comments to improve my manuscript. I would also like to acknowledge my colleagues Hamid Oubaha and Georgiana Sandu for their recommendations and comments to my manuscript, as well as for their help with writing reports during the doctoral training program. My time at ICTEAM would not have been the same without a number of great colleagues - Hamid Oubaha, Georgiana Sandu, Ran Ye, Ionel Avram, Wenhao Du, Qiang Ma, Jonathan Avila Osses, Yanping Li (+), and the young fellows from Ecuador - Diego, Alexander and José. In addition, I would also like to take this opportunity to thank the administrative and technical staff at ICTEAM - Viviane Sauvage, Anne Gillet, Brigitte Dupont, Isabelle Dargent, Christel Derzelle, Pascal Simon, Souley Djadjandi, Benoît Hubert, and Maxime Drouguet, who kindly helped and answered to my numerous requests during my stays at the Institute.

*Agradezco a Dios, a mis padres Jorge y Magdalena por su inagotable esfuerzo y sacrificio para que pueda cumplir mis metas profesionales. A toda mi familia, ya que su apoyo y sacrificio ha sido fundamental a lo largo de este camino, especialmente a Lourdes, Sebastián, Sofia, Jorge,*

*Jenny, William y Suellen. Una dedicación profunda a María Sebastiana una persona ejemplar e inolvidable. También un agradecimiento especial a la Fundación Hanns Seidel por su ayuda para mi formación en la Escuela Politécnica Nacional, en especial al señor Armin Schlegl (+) quien nunca dejo de creer en mi.*

*Ich danke der Baden-Württemberg-Stiftung für die Unterstützung meines Aufenthaltes an der Hochschule Mannheim. Besonderer Dank gilt der Hanns-Seidel-Stiftung für die Unterstützung meiner Ausbildung sowohl in Ecuador als auch in Deutschland mit seinem Motto "Im Dienst von Demokratie, Frieden und Entwicklung".*

*J'aimerais remercier le directeur de la Résidence Bauloy Francisco Gimeno, ainsi que tous les membres, spécialement Michel García, Jacques Bernis, Vincent Delannoy, l'Abbé Gottigny, l'Abbé Dalleur, et l'Abbé Arévalo, pour leur amitié et leur soutien. Je tiens également à remercier les résidents pour leur accueil et leur hospitalité lors de mes séjours à Louvain-la-Neuve.*

*Je n'oublierai pas non plus de remercier tous mes collègues d'ICTEAM pour les bons moments passés ensemble dans l'Institut.*

*Quito, le 24 novembre 2021.*

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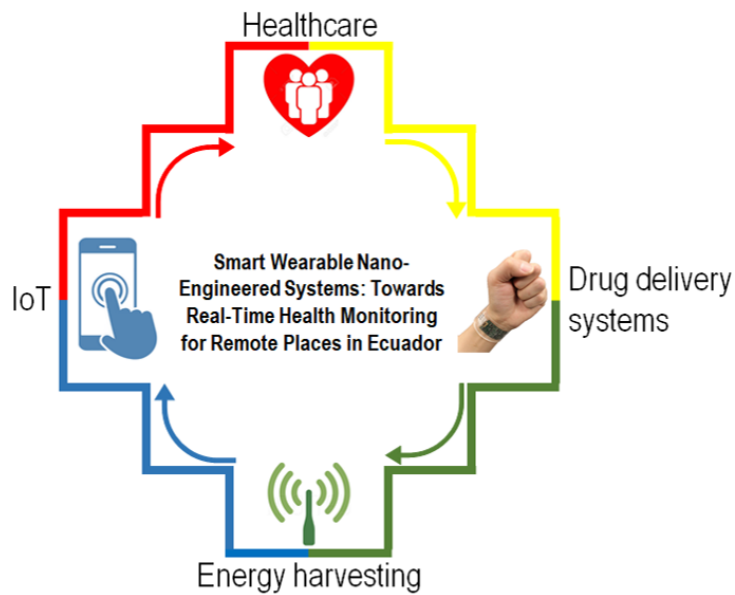


# Preface

Before I came here I was confused about this subject. Having listened to your lecture I am still confused. But on a higher level.

---

Enrico Fermi



*Chakana* summarizing this thesis framework: Sustainable wearable devices - exemplified by drug delivery systems, boosted by smart energy harvesting - exemplified by flexible antennas, and Internet-of-Things (IoT) - exemplified by emerging smart phone technologies, for applications in healthcare.

Wearable technology is one of the most promising avenues for the healthcare sector. In the coming years preventive medicine and medical treatment will heavily rely on wearable and implantable biomedical devices for health monitoring, drug delivery and many more purposes. We consider it as a promising technology for developing countries as well, where the healthcare systems face many problems such as lack of infrastructure, specialist medical doctors, and difficult-to-solve economical and social issues. People in remote places have a wide range of healthcare needs like the monitoring of the health status in order to detect in early stages the diseases as well as treatment of normal or chronic diseases. Nowadays, the need for a fast and accurate diagnosis has become crucial at the first level of health systems, as the COVID-19 pandemic has showed it.

To summarize our research, we first overview the main scientific and technological advances for wearables in the healthcare field in the last years. Based on this input, we define the actions of our initiative as presented in the *Chakana* or *Inka cross*, a symbol of the ancient Andean cultures. The four arms in the *Chakana* represent the four life elements: earth, air, fire, and water. This PhD work is linking this symbol with four main areas relevant for wearable healthcare technologies: the networked patients providing the basic medical information - detailed and accurate, the intelligent drug delivery systems, the smart energy harvesting for availability anywhere of the medical services, and the Internet-of-Things offering the *modus operandi* for real-time health monitoring.

Chapter 1 reviews these outstanding engineering topics at the heart of wearable technologies impacting in the healthcare field. The focus is on drug delivery systems for diabetes, radio-frequency (RF) energy harvesting, and artificial intelligence-driven Internet-of-Things. A natural link to these topics is the emerging field of flexible electronics, encompassing ultra-low-power electronics and computing textiles, which is also discussed. We capture the state-of-the-art for the selected topics, and in each section we highlight some of the most promising avenues for the healthcare field in the short and long terms. The Chapter ends with a conclusion for the hypotheses underlying the present work.

In Chapter 2, we tackle the topic of wearable antennas for both energy harvesting and wireless communication purposes. This segment of work is potentially helpful from an engineering perspective and provides valuable information for researchers working in the energy harvesting area. Focusing on the unlicensed band of 2.45 GHz and on energy harvesting, we present novel designs for antennas on flexible substrates, namely Kapton, together with the basic implementation of the required

electronic modules for a complete wearable RF energy harvesting system. These parts are mechanically flexible, due to the presence of Kapton, but they are also designed to be sewable for easy integration in textiles.

Chapter 3 presents the design of a novel drug delivery system. The novel patch for insulin delivery was implemented via the integration of nano-engineering heating elements on polyimide substrates for electrothermal transdermal therapy. In the first part of Chapter 3, we present how we use colloidal lithography and graphene technology to develop the first generation of such transdermal patches for automated insulin delivery. In the second part of Chapter 3 we present the theoretical background supporting our approach. The numerical modeling effort uses COMSOL ([www.comsol.com](http://www.comsol.com)) to analyze the Joule heating in an illustrative version of the patch in contact with the epidermis.

Several Appendices detail the fabrication and the architecture of the wearable electronic system that provides assistance for reproducible patch operation. This segment of work involves the work performed for transmitting and receiving information between a smart phone and the transdermal patch.

The thesis ends with the general conclusions and a discussion about future perspectives of wearable technologies for the healthcare field. We also underline how science and technology can support the healthcare system in Ecuador, and therefore improve people's quality of life. We comment on ARES (Académie de Recherche et d'Enseignement Supérieur) cooperation which is partly funding this thesis. Finally, the main scientific outcomes of this work are summarised and a list of publications generated by this thesis is given.



# Chapter 1

## Wearable technology

It does not matter how slowly you go as long as you do not stop.

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Confucius

### 1.1 Healthcare wearable devices

In the coming years preventive medicine and medical treatment will rely on healthcare wearable and implantable devices. [1–3] A healthcare wearable device (HWD) refers to an electronic device intended to be used on the human body for healthcare purposes. [4] Such devices are already widely applicable in health monitoring, diagnosis, and drug delivery. In the last years, on the one hand, the development and advances of wearable devices has changed drastically the healthcare sector, taking major challenges in monitoring and treatment of normal and chronic diseases like diabetes for instance. On the other hand, pediatric patients and elderly patients have benefited a lot from this technology. [5] Moreover, the arrival of mobile devices such as smartphones and tablets has been key, because HWDs have been integrated into the cloud. [6] This has allowed to greatly extend the functionality of HWDs and to get continuously improved devices for healthcare applications for the networked patients. [7]

Healthcare systems through telehealth can take advantage of on-demand monitoring of patients, for diagnosis and treatment of diseases in real-time either locally or remotely. At the same time, the advantage of disease monitoring at earlier stages cuts healthcare expenditures, reducing time and money for both the patient and the healthcare provider. Clearly, the improvement of the medical ecosystem can be achieved by

means of prediction and prevention of diseases using the modern technologies that are part of HWDs. Wearable technology is thus expected to play a tremendous role in the healthcare systems in the coming years, specially in developing countries. [8] There is a well-known deficiency of infrastructure in the healthcare systems around the world, recently evidenced with COVID-19 pandemic. For instance, people in Ecuador have limited access to specialist medical doctors or to good quality healthcare services. The new challenges in the healthcare sector demand of delivering higher quality and personalized medical services to all patients. We can understand why renewed and massive efforts in science and technology are needed to support the healthcare field. [9]

The fulfillment of novel HWDs is a great challenge. Modern HWDs with integrated mechanically flexible and stretchable materials exhibit unique characteristics compared to the traditional rigid and bulk electronic devices, improving wearability and offering more friendly operation. Shi *et al.* emphasized that in order to improve the human-device interaction in the case of wearable devices, three aspects should be considered: i) reducing the thickness of rigid layers, ii) transferring rigid electronic blocks on soft substrates with stretchable interconnectors, and iii) using intrinsically, mechanically flexible materials. [2] Novel materials in nanoscale range have received wide attention for this purpose, due to their remarkable properties and perspectives in healthcare. Moreover, advances in computing science and biotechnology are contributing to the development of remarkable modern and sophisticated wearable devices for monitoring, diagnosis, and drug delivery. However, in the coming years, one expects that the research in the wearables field will be focused more on urgent clinical trials than into healthcare materials, nanomedicine and biosensors like witnessed by the last years. [10]

HWDs are placed usually on the epidermis of patients, incorporated on garments, or accessories. Most of the devices are operating on the skin for measuring electrophysiological or biochemical signals, and to manage the delivery of drugs. For that reason, HWDs need to satisfy medical and ergonomic requirements for long-term monitoring and treatment, avoiding injuries to the patient. The devices should be mechanically flexible, stretchable, with micro or small dimensions, nontoxic and comfortable. [3] An overview of the main electronic components of a typical HWD is shown in Fig. 1.1.a (see discussion below).

### 1.1.1 Biosensors for wearables

Biosensors are a key component in healthcare monitoring and biosen-

sors market is growing rapidly. The first successful attempt dates back to 1962 with the invention of a glucose biosensor based on an oxygen electrode by Leland C. Clark Jr. and Champ Lyons. [11] Today, biosensors are frequently included in portable analytical devices that measure biological or chemical reactions by generating electrical signals proportional to the concentration of an analyte. [12] Figure 1.1.b shows the parts of a typical biosensing system. [13] Biosensors can detect a wide range of biological elements such as viruses, bacteria, antibodies, enzymes, and nucleic acids. Biosensors can be classified according to the signal transduction such as electrochemical (amperometric, impedimetric, potentiometric), optical, thermal and electro-mechanic (mass-sensitive). [14] Biosensors can be embedded into electronic patches, wristbands and all sort of accessories, textiles, tattoos, and prosthetics. Importantly, they can read the physico-chemical status of the human epidermal surface to collect health data for real-time therapeutics.

Skin-mountable HWDs show great promise for biosensing and drug delivery, in such a way that these modern devices can offer a noninvasive monitoring as an alternative to blood monitoring biomedical devices. They offer the capability to readily sample epidermal biofluids. [15] The noninvasive analysis can be done through transdermal approaches and/or via various biofluids such as sweat, tear, saliva or interstitial fluid (ISF), all representing milestones in clinical diagnostics (Fig. 1.1.c).

There are many efforts underway for building superior biosensors. Kim *et al.* reported a sweat-based fully integrated wearable sensor array for multiplexed *in situ* perspiration analysis. It measures sweat metabolites (glucose, lactate) and electrolytes (sodium ions, potassium ions), as well as the skin temperature (Fig. 1.2.a). [13] Bandodkar *et al.* demonstrated skin-worn, tattoo-based iontophoresis-sensor platforms for minimally invasive glucose monitoring (Fig. 1.2.b). [16] Arakawa and co-workers developed a biosensor for real-time monitoring of saliva glucose. [17] The glucose biosensors remained over the years on top of the most avant-garde, minimally invasive and noninvasive sensing technologies and this evolving scientific know-how is heavily used nowadays for diagnosis and treatment of diabetes. [9, 18, 19]

Electrochemical biosensors are among the most suitable for healthcare applications, as they offer mechanical flexibility, an important requirement in order to allow attachment to the human body. [21] In this way, the coupled fields of flexible electronics and electrochemistry are addressing the future needs of low weight, low cost, and mechanically flexible electronic devices compatible with non-invasive body-size biosensing platforms, electronic skin, and human-integrated adaptive electronics. [22]

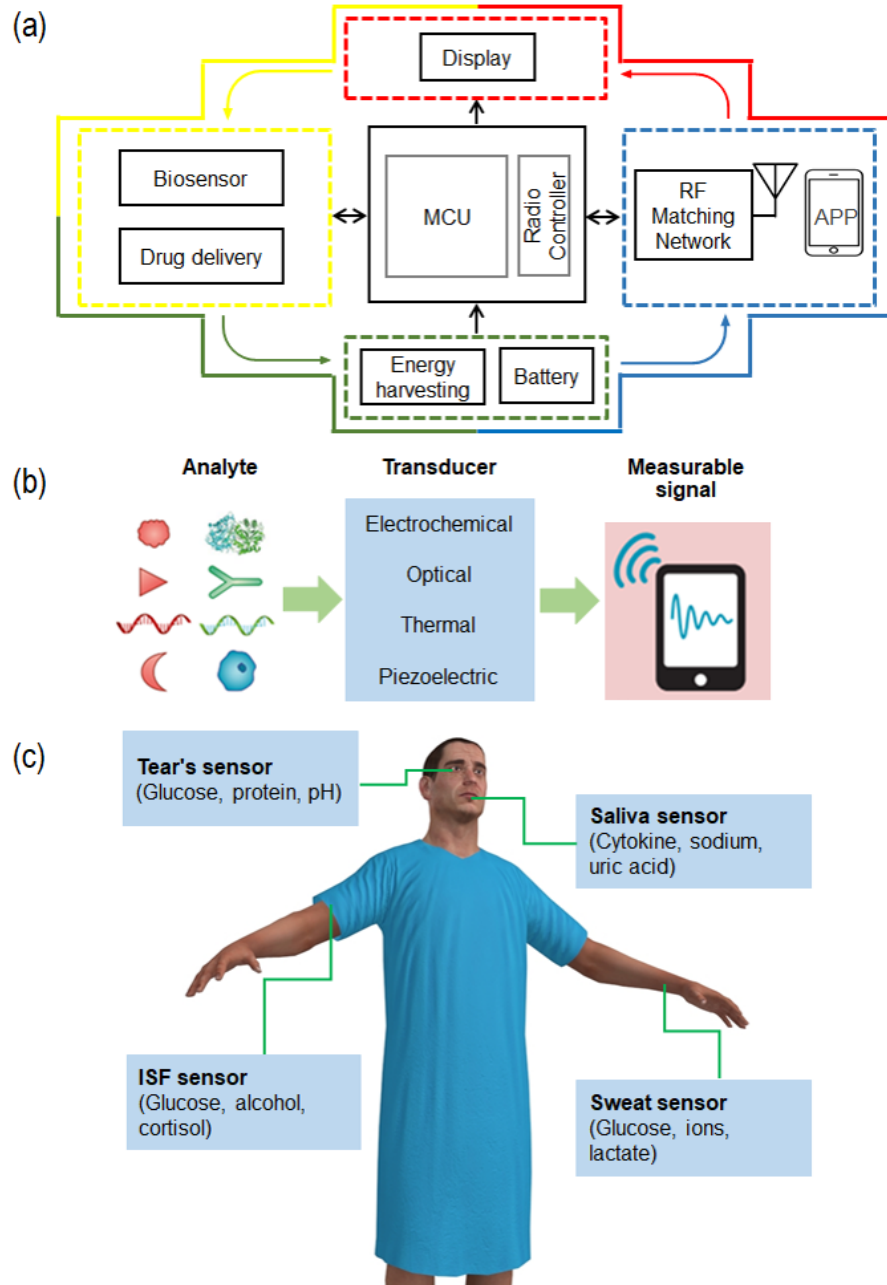


Figure 1.1: (a) Architecture for a healthcare wearable device. (b) Biosensor components: analytes/bio-receptors, transducer, electronic system. [13] (c) Types of biofluids for sensing: tear, saliva, sweat, interstitial fluid. [15]



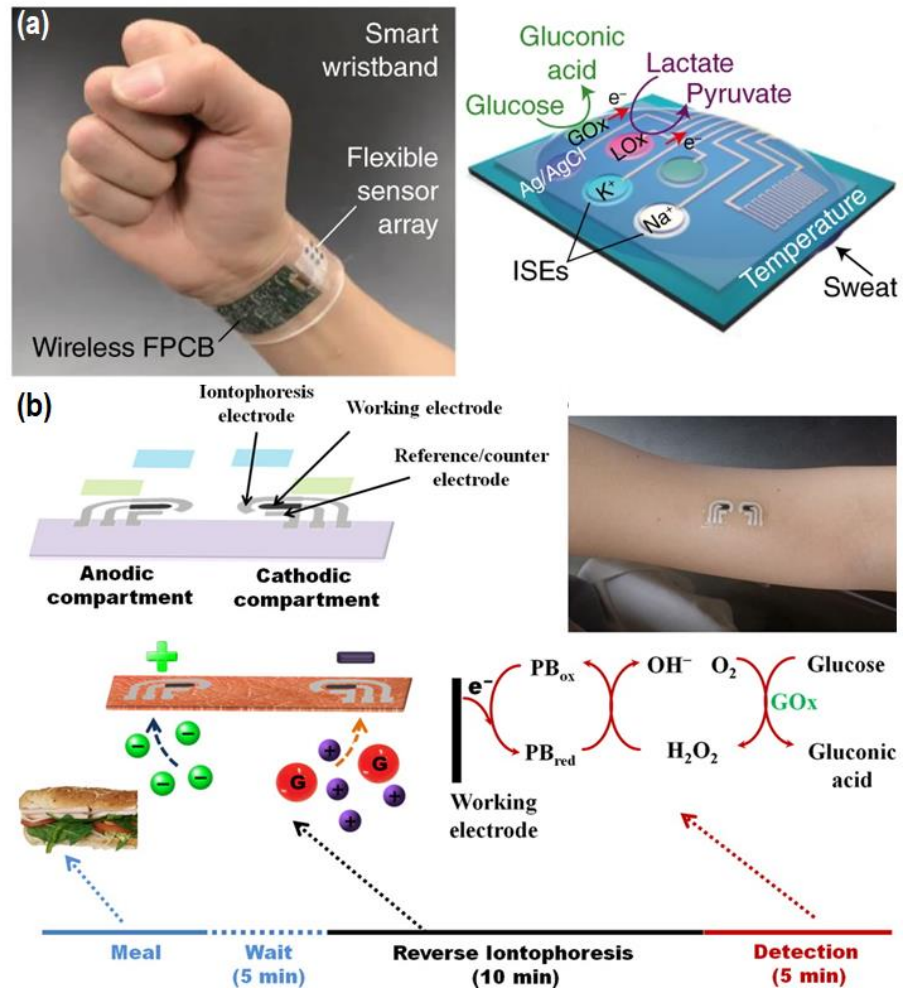


Figure 1.2: Biosensors and applications in wearable technology. (a) Exercise-based sweat biosensor. [13,20] (b) Iontophoresis-based biosensor. [16]

**Materials for biosensors.** Biosensors for *in vivo* applications need exemplary materials both for substrates and active elements. These materials should meet various requirements such as mechanical flexibility, stretchability, non-toxicity, lightweight, and with the new age of circular economy, they have to be even recyclable and biodegradable.<sup>1</sup> Certainly, polymers are among the mostly suitable materials for substrates, displaying unique electrical and mechanical properties. They must be selected according to the targeted applications due to the various existing types and the plethora of methods for obtaining thin films. In the past, the most common materials for substrates were polydimethylsiloxane (PDMS), polyethylene terephthalate (PET), polyethersulfone, polymer-based hydrogels, and polyimide (PI) films. Today, the progress in sustainable manufacturing puts natural biomaterials, like silk fibroin, in the forefront of the biomedical field.

Efforts in the developing novel biosensors with high sensitivity and selectivity asked for new functional materials. Nanomaterials provide big opportunities for a new generation of biosensors for healthcare. Comparing with bulk materials, nanomaterials offer improved mechanical, electrical, optical, chemical properties for developing the next generation of HWDs. Nanomaterials can have chemical and physical properties tuned according to the application, by controlling their size, shape and chemical constitution. For instance, carbon materials designed for wearable electronics [23], like carbon nanotubes and graphene, are also auspicious materials for emerging technologies targeting *in vivo* sensing. [24, 25] Certainly, when it comes to the shape of nanomaterials, nanowires have a special place in this nanobiotechnology area. As an example, Si nanowires can be used to probe protein complexes inside living cells [26] and ZnO nanowires can be used for next generation of vaccines [27].

**Fabrication techniques for biosensors.** For mechanically flexible electrochemical biosensors many techniques are available such as sputtering, various types of lithography, micro-machining, printing, electrospinning, and electro-deposition, to name a few. Sputtering is suitable for working with some nanomaterials in vacuum conditions avoiding contamination. [28] This technique was used for the fabrication of a me-

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<sup>1</sup>It is impossible to systematize materials used for prototyping of biosensors as the involved stakeholders - patient, the hospitals, the government, and the manufacturers have different priorities in terms of safety, usability or cost. The landscape is so complex as the biosensor market segmentation is still analyzed by technology, application and regions and not by materials. In a basic ranking, in terms of mechanical properties, copper foils, thin polymer films as well as graphene and its derivatives are certainly frontrunners.

chanically flexible electrochemical glucose biosensor with 10 nM limit of detection. [29] Nano-imprint lithography has been using for biosensors fabrication due its resolution down to  $\sim 10$  nm; Jiang *et al.* used it for a surface plasmon resonance biosensor chip [30] and Ahn *et al.* for the fabrication of pyrrole-based electrochemical biosensors [31]. Contact-printing has been used to design a glucose sensor with a limit of detection of 35  $\mu$ M. [32] Zhao *et al.* fabricated a nanoribbon biosensor by chemical lift-off lithography. [33] Electrospinning is a scaffold fabrication technique having the capability of producing nanofiber webs; Kim *et al.* demonstrated the fabrication of a novel glucose-responsive, micro- and nanofiber hydrogel-based biosensor with 1 mM limit of detection. [34] Electrodeposition is a straightforward fabrication technique of metal nanostructures on the electrode surface because of its stability and simplicity. For example, Lu *et al.* used it in the fabrication of a biosensor based on gold nanoflowers [35] and Fallatah and co-workers employed it for depositing  $\text{CeO}_2$  shaped-controlled nanomaterials on carbon cloth for biosensors achieving 1 nM limit of detection for glucose [36]. A very brief summary of electrochemical biosensors for enzymatic detection of glucose is shown in Table 1.1.

The conventional manufacturing of products use additive or subtractive techniques, but many are not suitable for intricate and complex designs which are required for medical applications. In subtractive manufacturing, exemplified by etching techniques, objects are producing by removing unnecessary materials from a solid block of material, to create a desired geometry. This process has low utilization rate of materials, sometimes long production cycle, and the process can generate mechanical stress deteriorating the final product. A typical example is the production of Si nanowires by metal-assisted chemical etching. The rise of additive manufacturing, rapid prototyping and three-dimensional printing is of great help as these procedures work by adding layer-upon-layer of material, complementing the standard deposition techniques used in micro-electronics. While the materials could be plastic, metal, nanomaterials, and even human tissue, today, the domain of additive manufacturing encompasses solid, powder and liquid-based methods. Of course, the best of both worlds in terms of fabrication, *i.e.* additive and subtractive manufacturing, can be achieved with hierarchical approaches, where cycles of additive-subtractive steps are interlinked to produce new architectures for biosensing.

| Biosensor | Application         | Substrate                              | Active element          | Fabrication method | Limit of detection | Ref. |
|-----------|---------------------|----------------------------------------|-------------------------|--------------------|--------------------|------|
| Enzymatic | Glucose             | Kapton                                 | Au/MoS <sub>2</sub> /Au | Sputtering         | 10 nM              | [29] |
| Enzymatic | Glucose             | Hydrogel                               | Au nanoparticles        | Electrospinning    | 1 mM               | [34] |
| Enzymatic | Glucose             | Carbon cloth                           | CeO <sub>2</sub>        | Electrodeposition  | 1 nM               | [36] |
| Enzymatic | Glucose and lactate | Polyethersulfone and polyethyleneimine | Carbon nano-tubes       | Contact printing   | 35 $\mu$ M         | [32] |

Table 1.1: Electrochemical biosensors for enzymatic detection of glucose. As explained in the text, the limit of detection varies orders of magnitude, depending on fabrication technology.

### 1.1.2 Drug delivery systems

Beyond the monitoring and diagnostics of patients through wearable technology, treatment and control of diseases are also important. Over the past years drug delivery systems were built for various medical conditions. They are able to deliver drugs to desired tissues, organs, cells and subcellular organs through a variety of drug carriers. Significant progress has been achieved lately in this field by major advances in pharmaceutical and bioengineering sciences. [37] New materials and techniques are enhancing constantly drug delivery systems, [38, 39] and even creating new routes for drug delivery as depicted in Fig. 1.3. Conventional ways to deliver therapeutics compounds are injections (intravenous, intramuscular, subcutaneous), oral, pulmonary (i.e. inhalation), surgical implantation, ocular (topical and injections), mucosal routes (vaginal, nasal, bucal), and transdermal. In particular, transdermal drug delivery is a prospective method that enables modern and painless drug delivery systems. The use of microneedles (minimally invasive) and controlled delivery by electrothermal wearable devices (non-invasive) are two major advances towards real-time monitoring of diabetes. [40]

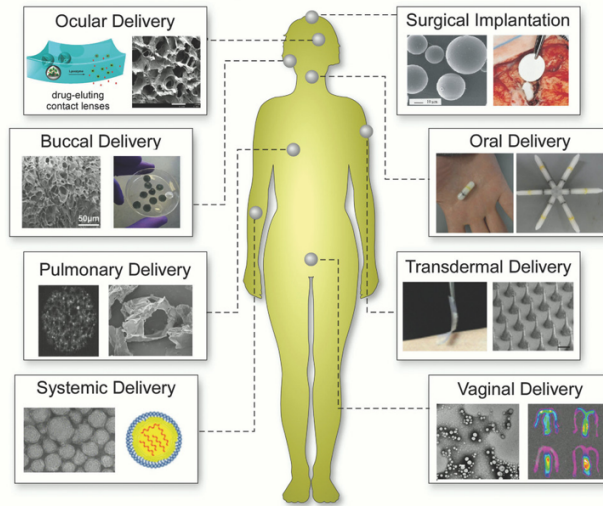


Figure 1.3: Routes of drug delivery (reproduced from Ref. [38]).

**Transdermal drug delivery (TDD)** has many advantages over the previous and old methods. Indeed, TDD systems as parts of HWDs have lately drawn tremendous attention for the advantages over conventional drug delivery methods as they are noninvasive and offer on-

demand delivery of therapeutic compounds. Amjadi *et al.* categorizes the wearable transdermal drug delivery systems in four categories: (i) mechano-responsive transdermal drug delivery systems, (ii) electrically-activated transdermal drug delivery patches, (iii) light-responsive skin patches, and (iv) bio-responsive skin patches. Figure 1.4 shows the four categories. [41]

Currently, about 20 drugs have been approved by U.S. Food and Drug Administration for transdermal delivery, sharing several characteristics such as low molecular weight, lipophilicity and relatively low dose supply requirements. [42] The highest selling transdermal patch remains the nicotine patch, but the transdermal delivery industry is growing worldwide. [43] From a physicochemical point of view, an ideal transdermal drug candidate has to meet a number of requirements: (i) low molecular weight, (ii) lipophilic character, and (iii) low dose administration. Insulin is not an ideal transdermal drug candidate due to this large molecular weight, restricting its passive transdermal delivery. A number of different innovative approaches have been explored over the years to modify the barrier properties of the *stratum corneum* (SC), translating from passive to active methodologies (Fig. 1.5.a). The simplest active approach relies on the use of chemical penetration enhancers, which increase the drug partitioning into the barrier domains of the SC without long-term skin damage. Other active modes of skin permeabilization are associated with physical methods based on the formation of microcavities into the skin *via* mechanical or thermal approaches (Fig. 1.5.b). [9]

Iontophoresis (ITP) is a promising technique that uses an electrical current for enhancing transdermal administration of charged drugs into tissues.<sup>2</sup> Iontophoretic skin patches, using physiological acceptable electrical currents (0.1-1 mA/cm<sup>2</sup>) applied for minutes to hours via externally placed electrodes, facilitate the drug delivery across the SC. However, conventional iontophoresis is not sufficient for effective delivery of large, hydrophilic, or electrically neutral molecules. Almost ten years ago Chen *et al.* reported on the use of unilamellar nanovesicles with membrane thickness of 3-5 nm with entrapment efficiency of 89% of insulin for insulin delivery through microneedle-induced skin microchannels using in addition iontophoresis for enhancing transdermal delivery. [44] The permeation rates of insulin from nanovesicles driven by iontophoresis through skins with microneedle-induced microchannels were cca. 700 times higher than rates observed for passive diffusion.

<sup>2</sup>The electrode containing the drug is applied to the area that needs to be treated. The second electrode, without the medication, is positioned in the proximity of the first electrode. The electrical stimulation delivers the ionized drug at the chosen location through the skin.

*In vivo* studies revealed that the blood glucose levels of diabetic rats induced by the insulin release from nanovesicles driven by iontophoresis through skins with microneedle-induced microchannels were 33.3% and 28.3% of the initial levels at 4 and 6 h, which are comparable to those induced by subcutaneous injection of insulin. A comparable approach was used by Kajimoto *et al.* [45] employing a current density of  $0.45 \text{ mA/cm}^2$ , a duration 1 h, and liposomes encapsulating insulin (INS-lipo) in a rat model of type I diabetes. Interestingly, iontophoresis of INS-lipo resulted in a gradual decrease in blood glucose levels, with levels reaching 20% of initial values at 18 h after administration. These lower blood glucose levels were maintained for up to 24 h and significant amount of insulin were also detected in plasma 18 h after iontophoresis of INS-lipo.

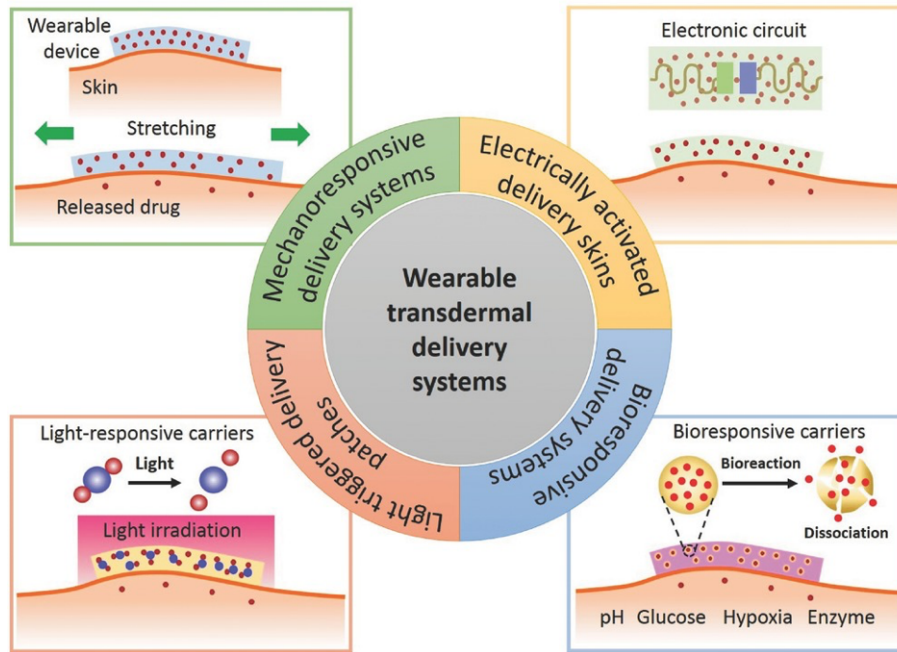


Figure 1.4: Types of wearable transdermal drug delivery. [41]

The combination of skin barrier impairment using microneedles (MNs) coupled with iontophoresis has been pursued by the team of Donnelly [46], who reported on the release of insulin from polymeric MNs based on poly(methylvinylether-*co*-maleic acid) (PMVE-*co*-MA) formed in laser-engineered silicon templates. One of the main advantages of MNs is that a wide variety of drugs can be successfully delivered transdermally and intradermally. [47–50] Since the first proof-of-concept of



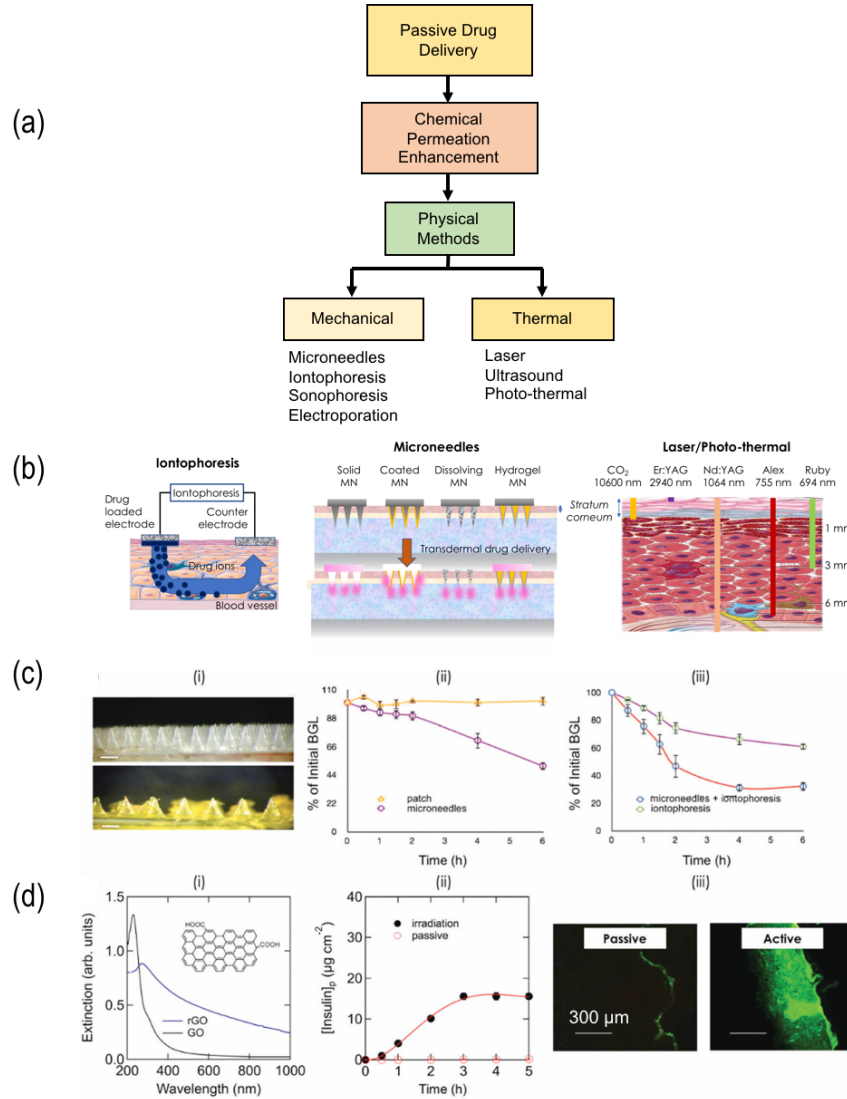


Figure 1.5: (a) Technology evolution from passive to active transdermal delivery. (b) Different physical enhancement methods for transdermal drug delivery. (c) Microneedle (MN) arrays for insulin delivery. (d) Photothermal insulin delivery. (a, b) Adapted from Fig. 17 in Ref. [9]. (c, d) Adapted from Fig. 18 in Ref. [9].



such a device for enhanced drug delivery into the skin, [51] a growing body of literature has investigated various microfabrication technologies for arrays of MNs, including materials other than silicon, like metals, polymers and hydrogels.

Hydrogel MN arrays based on PMVE-*co*-MA and poly(ethyleneglycol), 15% and 7.5% weight and crosslinked at 80° C for 24 h have been first described by Donnelly *et al.* (Fig. 1.5.c) for insulin delivery. Through the attachment of insulin-loaded patches to the base of the MN array a drug reservoir could be created. Upon application onto the skin, water diffuses into the MN array, resulting in swelling of the hydrogel and liberation of insulin without destruction of the MN array. The transdermal drug delivery can be easily controlled by modulating the crosslink density of the hydrogel matrix. This indicates that drug delivery can be tailored on a case-by-case basis to meet the requirements of different drugs with different therapeutic windows. [50] A similar concept was validated by Yamamoto and coworkers [52] using MN arrays based on hyaluronic acid loaded with insulin. The length of the MNs was 800 microns with a base diameter of 160 microns and a tip diameter of 40 microns, maintaining the skin piercing ability for 1 h even at elevated humidity of 75 %.

Thermal ablation, based on the selective removal of the SC by localized microsecond heat pulses, is another promising alternative to increase the permeability of the skin's outer barrier layer while sparing deeper living tissue. [53, 54] The creation of local heat leads to cell ablation and transient creation of microchannels or pores typically 50-100 microns in diameter. This technology enables the transdermal delivery of a wide range of drugs including macromolecules. Laser-based thermal ablation needs wavelength considerations for using the right laser. Visible light (400-700 nm) is readily absorbed by blood and the skin surface components, thereby limiting its tissue penetration with low heating effects and no skin ablation. By contrast, the near-infrared (NIR) wavelengths of the erbium-yttrium-aluminum-garnet (Er:YAG) laser as well as those of the CO<sub>2</sub> laser, located above 9000 nm in the far-infrared, induce heating and microporation of the skin through water excitation and explosive evaporation of the epidermis. The Er:YAG laser is preferentially used as its light is strongly absorbed by water, which results in about 15 times better light absorption by the skin, highly favoured for enhanced transdermal drug delivery when compared to the CO<sub>2</sub> laser. [55] The Er:YAG laser was used to study the transdermal delivery of insulin, [56] a research effort that concluded that Er:YAG laser treatment can be effective for transdermal delivery of macromolecules and hydrophilic compounds such as peptides and protein-based drugs.

The advances made in the synthesis of nanomaterials proved to be beneficial for recent advancements in transdermal drug delivery approaches (Fig. 1.5.d). Photo-thermal active materials such as reduced graphene oxide (rGO) [57] have shown to be beneficial for a photothermal based skin ablation and insulin delivery. The strong optical absorption across the NIR spectrum of water soluble rGO coupled with its high chemical and thermal stability allows rapid temperature rise and insulin delivery *via* the skin. [58] For this purpose, a photo-thermal active hydrogel patch was developed. The 3D structure of the hydrogel was favorable for the integration of insulin due to interaction with the porous hydrophilic network of the PEG-based hydrogel network. The temperature reached in the patches upon light illumination was high enough to interfere with the affinity between human insulin and rGO, resulting in its release. Using such insulin loaded photothermal active hydrogels (Fig. 1.5.d), it was demonstrated that the affinity of insulin inside the hydrogel can be modulated upon NIR irradiation with a permeation of insulin taking place at a flux of  $5.8 \pm 0.2 \mu\text{g}/\text{h}\cdot\text{cm}^2$  in a relatively short time scale (0-3 h), significantly higher than passive diffusion.

Further insight into the technology of TDD systems will be provided in Chapter 3, especially from the perspective of electrothermal actuation of such wearables. Certainly, no matter the active method employed for drug delivery, one major direction of work in TDD systems are closed-loop architectures for sensing and treatment, operating with the required clinical accuracy. [59]

## 1.2 Internet of Things: Artificial intelligence

Internet of Things (IoT) is the connection of things or everyday devices, like personal smart phones, into a global data network. It is part of the emerging industrial revolution, the so-called industry 4.0. The next generation of HWDs are developing rapidly for integrating to the IoT network and adding artificial intelligence (AI) capabilities to achieve higher levels of connectivity and functionality. [2] In particular, wearable devices oriented to arthritis management have been successfully linked with smart phones. Such HWDs are already taking advantage of the opportunities that offer the IoT network. [7] The IoT vision for healthcare is driven by emerging technologies such as nanobioelectronics, ultra-low-power electronics, smart energy harvesting, state-of-the-art communication technologies, edge and cloud computing, and AI.

Each patient has a particular health profile, while the devices used to measure health status are (becoming) standard. Traditionally, the

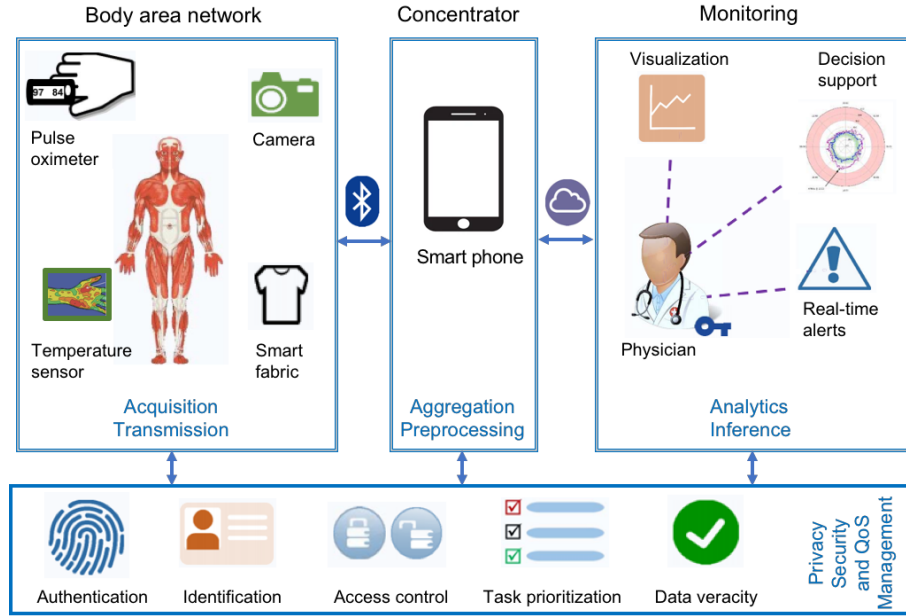


Figure 1.6: Components of IoT infrastructure for healthcare applications. Adapted from Ref. [3]

monitoring and diagnosing of vital signs together with the collection of biological samples need to be executed by trained staff. These samples most of the time must be transported to specialized laboratories in the big cities, which could delay the obtention of the results. The medical procedure can be optimised by integrating healthcare wearable devices to the IoT network. In short, the IoT ecosystem is composed by three major components [60] things, data (processing), people, with (i) things referring to physical devices like biosensors, (ii) data indicating the amount of collected information from devices, that will be further stored and analyzed, and (iii) people providing the data and benefiting of outcomes. The data management process can include automation of data and AI support of human decision making.

Therefore, the general architecture of IoT for healthcare applications is shown in Fig. 1.6. The first area contains the sensing and treatment devices - the things making up a body area network centered on the patient. This body area network can transmit the health data to the Internet through different technologies, like Bluetooth, Wi-Fi, or 5G connections (see Table 1.2). The second area includes the data concentrators, used to gather the data from the body area network. Usual

concentrators are smart phones, tablets and others. They will send and receive health datasets to the cloud and monitoring centers - communicating with physicians or health providers. In this architecture, the data will be analyzed by a specialist physician, who will make a diagnosis based on the available data, while the interaction with the patient is remote. The effort in developing such architecture is also going into addressing issues about privacy, security of the data and quality of service (QoS) management. While in the above case, the things are operated by the networked patient, it is obvious that the IoT network also encompasses specialised clinical devices. Habibzadeh *et al.* consider healthcare IoT devices of two types, personal and clinical. Personal devices are designed for non-invasive self monitoring such as heart-rate trackers embedded in smart clothes. The clinical devices are designed for health monitoring under guidance of a physician or a caregiver, such as specific (closed-loop) drug delivery systems. All devices for *in-vivo* applications should have clinical validation before wearing. [1]

| Network   | Rate           | Band           | Distance    | Power (mW) |
|-----------|----------------|----------------|-------------|------------|
| Bluetooth | 2.1 Mbps       | 2.4 GHz        | 0.1 - 400 m | 0.5 - 100  |
| RFID      | 106 - 424 Kbps | 13.56 MHz      | 0.1 - 1 m   | <1         |
| Wi-Fi     | 1 - 300 Mbps   | 2.4 GHz        | 0.1 - 100 m | >1000      |
| UWB       | 53 - 480 Mbps  | 3.1 - 10.6 GHz | 0.1 - 10 m  | <1         |

Table 1.2: Types of short-distance radio communication technologies. For personal wireless area networks, Bluetooth is the short-range standard technology. Wi-Fi and Bluetooth are in some sense complementary in their applications and usage. For the radio-frequency identification (RFID) technology, the industrial, scientific and medical (ISM) band with a low data speed is indicated, but other bands are in use as well. The ISM bands are portions of the radio spectrum reserved internationally for ISM purposes, excluding applications in telecommunications. The ultra-wideband (UWB) is a short-range technology for transmitting information across a wide bandwidth (> 500 MHz); for example, Series 6 of Apple Watch uses it. Wi-Fi represents a family of wireless network protocols used for local area networks as its wired counterpart Ethernet; thus, Wi-Fi enabled devices can network to each other through wireless access points as well as to Internet and wired devices.

State-of-the art wearable prototypes for IoT-driven healthcare rely

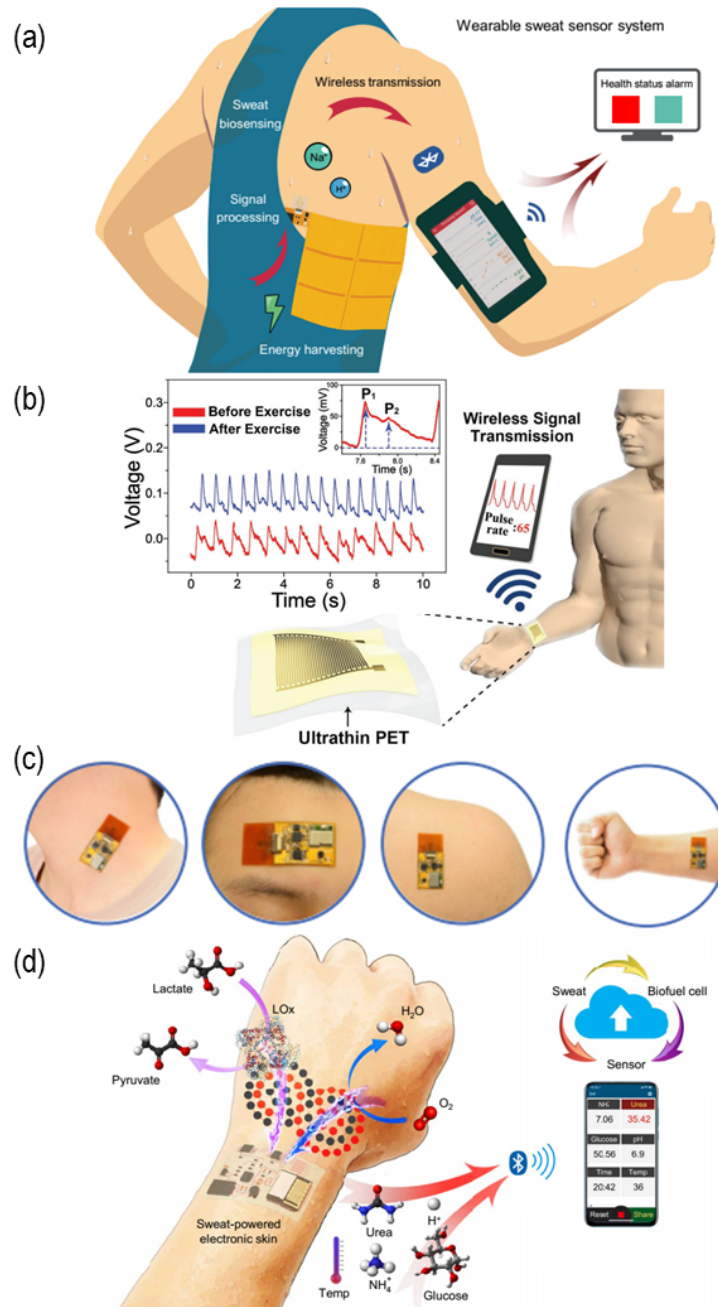


Figure 1.7: Bluetooth: The workhorse of IoT for healthcare applications. (a) Battery free, wearable sweat sensor-based system with wireless communication. [61] (b) Self-powered piezoelectric pulse sensor to enable measurement of radial/carotid pulse signals in near-surface arteries. [62] (c) Wearable device for continuous detection of temperature, respiration rate and low concentrations of uric acid and tyrosine. [63] (d) Integrated electronic skin for multiplexed metabolic sensing *in situ* with wireless data transmission capabilities. [64]

mainly on Bluetooth technology. For instance, Song *et al.* reported a battery-free driven system that was able to power multiplexed sweat biosensors and wirelessly transmit data to the user interfaces through Bluetooth during on-body human trials. This is a battery-free wearable platform that efficiently extracts power from body motion through a triboelectric nanogenerator, whose power output is  $\sim 416 \text{ mW/m}^2$  (Fig. 1.7.a). [61] Park *et al.* demonstrated a self-powered piezoelectric pulse sensor to enable *in vivo* measurement of radial/carotid pulse signals in near-surface arteries. The inorganic piezoelectric sensor on an ultrathin plastic achieves conformal contact with the complex texture of the rugged skin, which allows to respond to the tiny pulse changes arising on the surface of epidermis. Wireless transmission by Bluetooth of detected arterial pressure signals to a smart phone demonstrated the possibility of self-powered and real-time pulse monitoring system (Fig. 1.7.b). [62] Yang *et al.* demonstrated a continuous detection by wearables of temperature, respiration rate and low concentrations of uric acid and tyrosine, analytes associated with diseases such as gout and metabolic disorders (Fig. 1.7.c). [63] The communication with the smart phone is ensured by Bluetooth-based protocols. Yu *et al.* reported perspiration-powered integrated electronic skin for multiplexed metabolic sensing *in situ*. It contains multimodal sensors and displays a very stable performance during a 60-hour continuous operation. It selectively monitored key metabolic analytes (e.g. urea,  $\text{NH}_4^+$ , glucose, and pH) and the skin temperature during prolonged physical activities and wirelessly transmitted the data to the user interface using Bluetooth (Fig. 1.7.d). [64] Lee *et al.* reported that graphene doped with gold and combined with a gold mesh has improved electrochemical activity over bare graphene, sufficient to form a wearable patch for sweat-based diabetes monitoring and feedback therapy. The patch consists of a heater combined with temperature, humidity, glucose and pH sensors and polymeric microneedles that can be thermally activated to deliver drugs transcutaneously. [65] The setup includes an external controller for providing the electrical power and acquiring the data; it further transmits data by Bluetooth to a smart phone.

**Artificial intelligence.** The healthcare sector is taking advantage of the AI development, in both diagnosis and treatment, and implementation of preventive and therapeutic measures are multiplying nowadays. [66, 67] Clearly, AI and HWDs are changing the vision of healthcare sector, because the digital ecosystem of patients, caregivers and physicians will be able to make data-driven decisions for treatment or therapeutic procedures. In fact, AI is deeply associated with the development of computer algorithms to mimic the human intelligence, for

instance, the diagnosis abilities of physicians, or to enhance the ability of humans to provide healthcare. The goal in both cases is to assist clinical decision-making for the healthcare sector.

Undeniably, AI has advantages over some traditional techniques used in clinic laboratories, allowing a better diagnostic, effective treatment and better patient results. The aggregated clinical data can come from different sources such as biosensors, medical notes, electronic health records (EHRs) from medical devices, laboratory images, physical examinations, and so on. Besides single-payer healthcare, AI can also support more general tasks for the population health management (e.g. integration of information technology into existing clinical workflows and training aspects to physicians and caregivers), as well as administration (e.g. maintenance of the healthcare platforms and updating patient databases), and regulation in the healthcare field (e.g. data standardization). Figure 1.8 shows the applications of AI in healthcare. Some barriers for a rapid adoption of AI are related to privacy and data integrity concerns. Therefore, He *et al.* highlighted key issues to be considered in the implementations for the coming years, such as data sharing and data security, as well as patient safety - related with enhanced control for algorithm quality and clear responsibilities for an adverse event while using AI-based technology. [68]

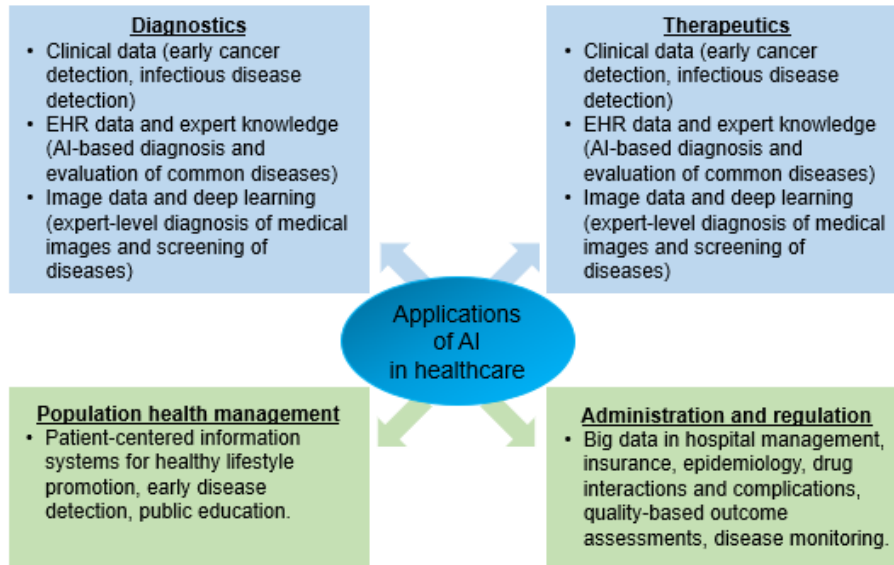


Figure 1.8: Applications of AI in healthcare. [68]

For example, Jim *et al.* (Fig. 1.9) proposed an architecture for AI-wearable devices with three components: (i) collection of information



from different sources for the patient, (ii) signal conversion and adaptation to be sent to the cloud, (iii) performing data processing and AI algorithms. [69]. Asharafian *et al.* proposed that AI can support three pillars for healthcare applications: (i) diagnostics and prognostics, (ii) decision making, and (iii) robots and robotic surgery. [70]

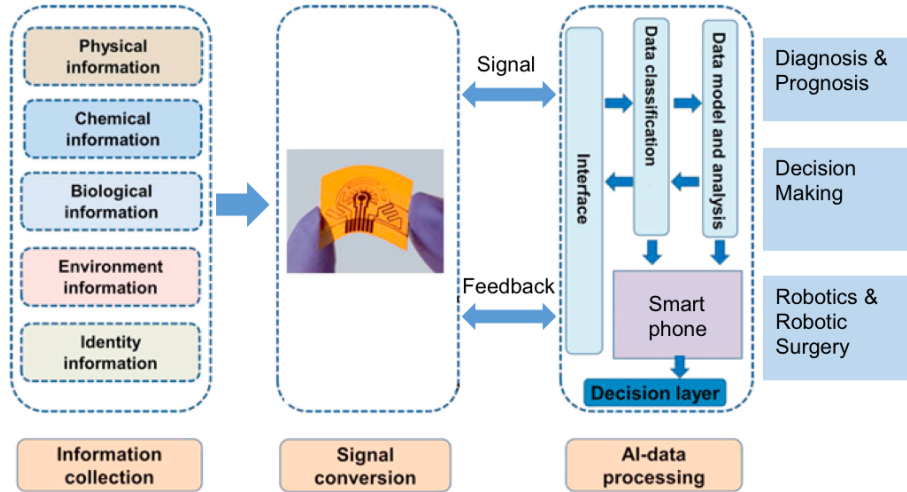


Figure 1.9: Architecture of AI-enhanced wearable devices for healthcare applications (adapted from [69, 70]).

Machine learning (ML) refers how a system can learn and make forecast based on data, without requiring programming. Accordingly, ML is one of the most used form of AI used in healthcare, which could take data and diagnostic the health status of the patient. It can help to clinical decision, support human judgement and increase treatment efficiency. It can support the development of novel therapies and therapeutics for patients, and also can track diseases to better understand the evolution of it.

ML methods are mainly categorized into three approaches such as supervised, unsupervised and reinforcement learning. Figure 1.10 shows the supervised and unsupervised methods. [60] However, sometimes supervised and unsupervised are combined to form semi-supervised methods such as deep neural networks and convolutional neural networks. [71]

Supervised learning uses a preprocessed training set of sample to define labels and to build a model. Some of the supervised approaches in healthcare are support vector machines,  $k$ -nearest neighbors, and bayesian models. Unsupervised learning do not have in advance the training set and no labels are given to the learning algorithm. They find hidden patterns or trends in data. They include gaussian mixture



models and  $k$ -means clustering algorithms. [72] One key aspect before selecting the method is the quality of the data. In many cases some issues need to be solved, such as increasing the quality of the training data, data should be representative according to the target population taking into account for example, demographics, identifying the source of the data, guaranteeing noise-free datasets to avoid wrong training model. The results are still difficult to interpret by unassisted humans. [66]

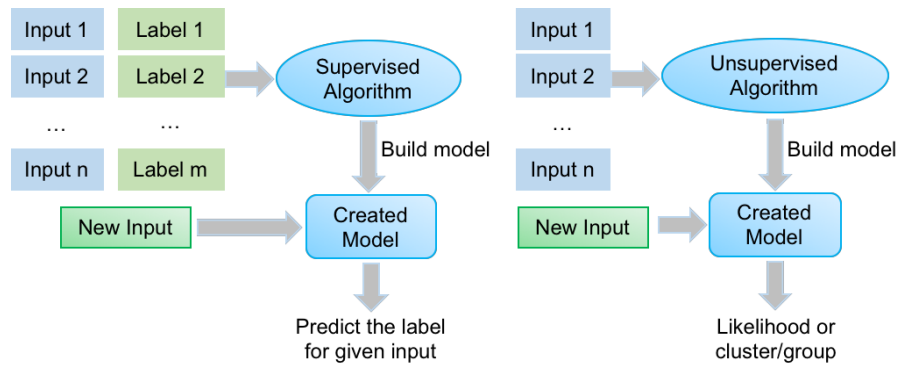


Figure 1.10: Supervised and unsupervised ML approaches. [60]

Many efforts show the potential of AI in the healthcare field. Yu *et al.* highlighted automated image diagnosis as one the most successful domain of medical AI applications, for instance, in dermatology. [66] More medical AI applications are revealed in Table 1.3.

Table 1.3: A brief overview of artificial intelligence tools and their applications in healthcare (adapted from ref. [73]); the focus is on diabetes.

| Tool                    | Description                                                                                                                                                                                                                                                                                     | Applications                                                                                                                                                                                                                                                                                                                        | Ref.      |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Hierarchical clustering | Unsupervised algorithm for grouping similar objects into clusters, by sequentially merging elementary units (agglomerative) or sequentially splitting sets of units starting from the whole sample (divisive).                                                                                  | Unsupervised hierarchical clustering separated samples (over hundred microarray data from 16 different skin conditions) by disease and common cellular and molecular pathways. This is an example of cross-disease analysis of molecular profiles from multiple skin diseases (using frozen robust multi-array analysis algorithm). | Ref. [74] |
| Decision tree           | Supervised method in which the data are sequentially split (throughout the branches) according to several input thresholds to obtain final groups (represented in the leaves) that are informative about the target value.                                                                      | Decision tree algorithms can prognosticate the likelihood of diabetes in patients with high accuracy (70% or higher).                                                                                                                                                                                                               | Ref. [75] |
| Random forest           | Multitude of decision trees (forest) trained by taking random decisions about the samples and the variables to include each time (for reducing overfitting), and outputting predictions based on the mode (classification) or the mean (regression) of the predictions of the individual trees. | Random forest approaches can predict diabetes mellitus.                                                                                                                                                                                                                                                                             | Ref. [76] |
| Continued on next page  |                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                     |           |

Table 1.3 – continued from previous page

| Tool                  | Description                                                                                                                                                                                                         | Applications                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Reference |
|-----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| $k$ -means clustering | Unsupervised algorithm aiming to partition observations into ( $k$ ) clusters, so that each observation will belong to the cluster with the nearest mean (cluster centroid), serving as a prototype of the cluster. | The performance of any skin detection system depends on assessment of two components: feature extraction and detection method. Skin color is a robust cue used for human skin detection. However, the performance of color-based detection methods is constrained by the overlapping color spaces of skin and non-skin pixels. To increase the accuracy of skin detection, texture features can be exploited as additional cues. Based on the fact that the skin region of an image is a group(s) of homogenous connected pixels, texture information can be used to describe skin regions. | Ref. [77] |
| Factor analysis       | Unsupervised method used to describe the variability among several observed, correlated variables, in terms of a potentially lower number of unobserved variables called factors.                                   | Factor analysis can provide insights into the pathophysiology of the insulin resistance syndrome.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Ref. [78] |
| Logistic regression   | Supervised approach used to model the probability of a certain class or event to occur as a function of explanatory variables.                                                                                      | Baseline tobacco and alcohol consumptions can be used in predicting lowered insulin sensitivity.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            | Ref. [79] |

### 1.3 Energy harvesting: Radio-frequency energy harvesting

Most of the wearable devices are powered by batteries. Batteries, although being a primary power source, have some limitations such as lifespan and size and are not free of the risk associated with leaking toxic hazardous substances. They also require periodic replacements for continuous operation of devices. To extend the lifetime of wearables, energy harvesting and energy storage are considered in the design of the systems from the beginning. Technically, we can extend the lifetime by both minimizing the power consumption of electronic components and by increasing the power generation with high-efficiency power converters. Recent advances in new materials, nanofabrication and recent IoT technologies have allowed to build ultra-low-power devices and to increase the efficiency of energy harvesting devices, typically in the milliwatt range useful for wearable applications. Figure 1.11 presents the power consumption spectrum of common electrical devices. A summary of power densities of common available sources is shown as well.

For healthcare applications, RF energy harvesting (RFEH) sources are suitable as a secondary power source, because patients usually stay at home or even on the bed with limited movement, or without movement for long periods of time. Usually, these sources are small and intermittent, so a boost converter and a regulator of voltage should be included.<sup>3</sup> Moreover, a charge controller is also needed if the system has a rechargeable battery.

Today, RFEH is a growing field due to the broad deployment of wireless technologies everywhere. It converts electromagnetic radiation, captured from sources such as Wi-Fi devices, Bluetooth, TV and radio broadcast stations, mobile communications (2G to 5G, etc), and the ISM band into electricity. Indeed, electromagnetic radiation is abundant indoors and outdoors and can be harvested at any time, and without intervention of the patient for healthcare applications. Due to the fact that the power consumption of wearable devices is continuously decreasing, ambient RFEH is becoming an interesting secondary power source. Figure 1.12 shows a conceptual schema of a RF energy harvesting system.

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<sup>3</sup>Buck or step-down converter is a DC/DC converter that reduces the input voltage from an unregulated DC source to a constant or steady output voltage. Boost or step-up converter is a DC/DC converter that increases the input voltage from an unregulated DC source to a constant or steady output voltage. Depending of the application boost converters or buck converters are needed.

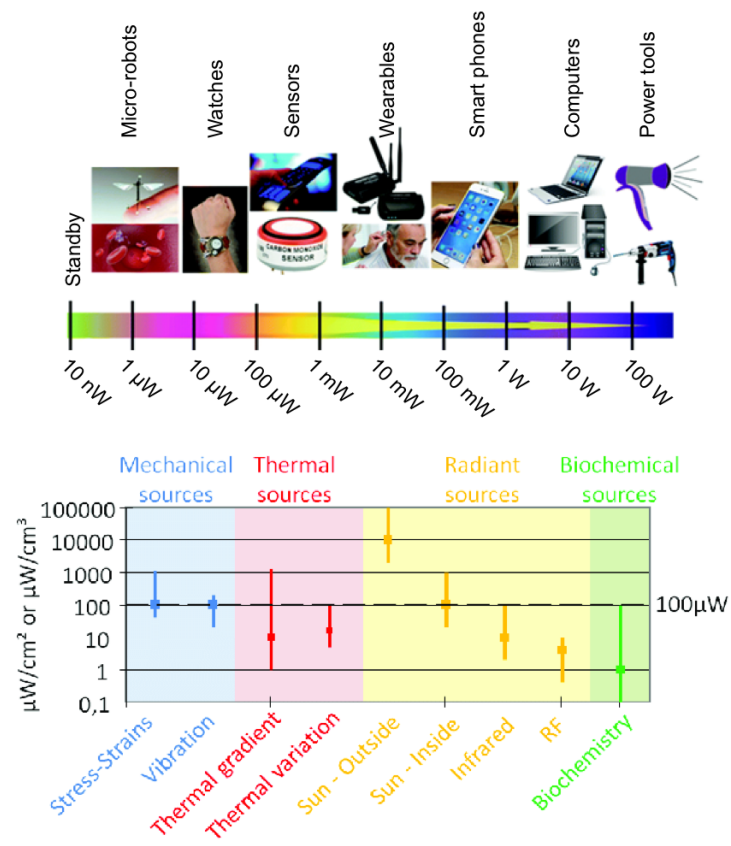


Figure 1.11: Power consumption spectrum of electrical devices and power densities of common available sources. [80]

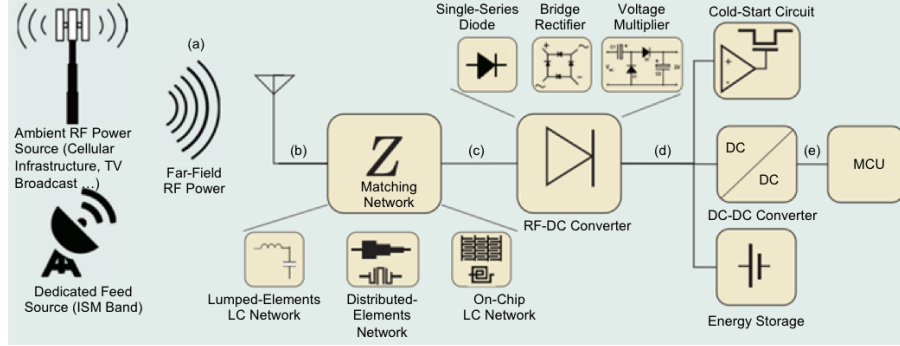


Figure 1.12: Conceptual diagram of a RFEH node, revealing the power sources and conversion stages, as well as commonly reported implementations (adapted from [81]).

Recent efforts validated the use of electromagnetic radiation as an alternative to generate DC voltage to supply power to HWDs. Certainly, it is recommendable to take into account for healthcare applications the radiation exposure to avoid negative health effects in the patient. For example, over 10 GHz electromagnetic fields are blocked by the skin, and the skin burns if the energy density is above  $1000 \text{ W/m}^2$ . [82] Tran *et al.* proposed several metrics in the design of such energy harvesting systems such as (i) conversion efficiency, (ii) sensitivity, (iii) operational range, and (iv) output power. [82] The power conversion efficiency is calculated as the ratio of power delivered to the load to the harvested power  $\eta_{P_{out}/P_{in}}$ . Sensitivity is defined as the minimum needed power to trigger the circuit. The operational range is related to the frequency of the electromagnetic radiation being harvested. The output power is obtained as DC power, obtaining DC voltage and DC current depending of the targeted applications.

The total efficiency of a system depends of the individual efficiency of each module. Each module has power losses such as the output power is much smaller than the input power ( $\eta$ ). Figure 1.13.a shows the involved blocks in the RFEH and the losses along the RFEH system. [83] Definitely, the first stage of the RFEH system is one of the most important, because an efficient antenna that captures the maximum amount of available electromagnetic energy in the space is needed. The antenna design needs novel single/multiband/wideband radiation geometries including linearly/circularly polarisation, but also, efficient matching networks and rectifying circuits. [84]

Antennas for healthcare monitoring should be integrated in HWDs, so that they should not affect the regular habits of the patient, mean-

ing antennas must be comfortable, noninvasive, and unobtrusive. For instance, Corchia *et al.* reported two highly embeddable antennas, the first one based on non-woven conductive fabrics with a size of 44 mm x 19 mm working at the frequency of 2.53 GHz, and the second one based on the embroidery of conductive threads with a size of 60 mm x 50 mm at the frequency of 2.22 GHz. [85] Mandal *et al.* fabricated a compact miniaturized wearable antenna with the appearance of a button on clothing. [86] We note that many groups started efforts to design implantable antennas; in this case, the specific absorption rate has to be taken into account for safety reasons [87].

Rectifying antennas (rectennas)<sup>4</sup> [88, 89] have matured as the cornerstone of RFEH. Wagih *et al.* present multiple rectenna topologies for RFEH emphasizing multiband operation due to the low power spectral density in single band as depicted in Fig. 1.13.b.c.d [81] Antenna properties (e.g. lobe directivity and polarization) heavily impact onto the amount of harvested power. The reception antenna is an essential part of a rectenna system and rectennas are becoming a reliable and efficient solution for supplying power to modern HWDs. Although first rectennas were built almost half a century ago via etched copper circuits supported on Kapton, rectennas can be built today with different materials, like two-dimensional nanomaterials, as reported by Zhang *et al.* [89] These authors demonstrated a thin and flexible rectenna based on MoS<sub>2</sub> heterojunctions with a cut-off frequency of 10 GHz.

In addition to the antennas, it is also highly important to consider matching networks and rectifiers stages. [82] They are also critical for the global efficiency of the RFEH system. It is well known that a good impedance matching network ensures the maximum power transfer between the antenna and the load. There are mainly three matching network configurations called L, T and  $\pi$ . Rectifiers are used to convert AC to DC current, because received signals in the antenna have a sinusoidal waveform. Common topologies for rectifiers are half-wave or full-wave. Many circuit implementations are available; the voltage multiplier is a frequently used type of rectifier that converts and boosts AC to DC power. Some common configurations are Cockcroft-Walton, Greinacher, Dickson charge pump, and the differential drive voltage multiplier.

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<sup>4</sup>Rectenna describes an antenna connected to a rectifier for harvesting RF power.

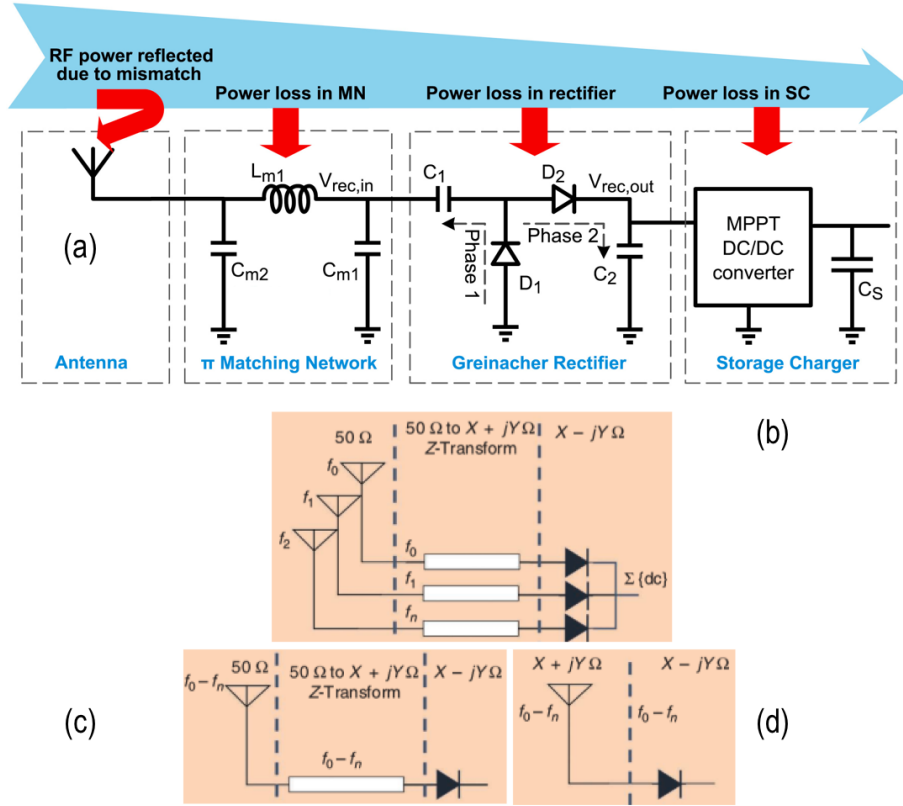


Figure 1.13: (a) Representation of power losses at different stages of a RFEH system (reproduced from [83]). (b, c, d) Rectenna topologies for RFEH (reproduced from [81]). (b) A multiband rectenna: it contains three single band antennas with  $50 \Omega$  impedance each one. Each single antenna has a working frequency  $f_0$ ,  $f_1$ ,  $f_2$ . Therefore, each antenna has its own matching network to transform the impedance value of the antenna from  $Z = 50 \Omega$  to  $Z = X + jY \Omega$ . This impedance matches the conjugate impedance of the rectifier  $Z = X - jY \Omega$ . (c) A broadband rectenna: it contains a broadband antenna with  $50 \Omega$  impedance for frequencies  $f_0 - f_n$ , describing the frequency band. It has a broadband matching network to transform the impedance value of the antenna from  $Z = 50 \Omega$  to  $Z = X + jY \Omega$ . This impedance matches the conjugate impedance of the rectifier  $Z = X - jY \Omega$ . (d) A broadband rectenna: it contains a broadband antenna with complex impedance for frequencies  $f_0 - f_n$ . However, this impedance has to match the conjugate impedance of the rectifier  $Z = X - jY \Omega$ . This rectenna does not have a matching network. The dashed lines represent the measurement planes where the impedance bandwidth needs to be maintained (i.e. reflected power is less than 10%).



Due to the fact that HWDs should be as much small as possible to get wearability and portability features, it is not possible to attach one antenna for each functionality into a RFEH system. For instance, a single antenna can be used for both transmission and reception of tasks. Some efforts have been done in that direction. Xu *et al.* proposed a simultaneous wireless information and power transfer (SWIPT) to supply IoT smart sensors at a frequency of 2.45 GHz. [90] Zhu *et al.* fabricated a flexible and stretchable wideband rectenna. In this prototype, a NFC coil was designed for data transmission and the rectenna for RF energy harvesting and enabled self-powering devices for remote sensing (Fig. 1.14.a). [91] In Fig. 1.14.b [92] a flexible, right handed circularly polarized antenna on a silicone wristband is shown.

Going one step further, ML is also being implemented in the energy harvesting systems, in order to improve the harvesting energy. For instance Ye *et al.* studied different ML algorithms to model RF energy harvesting systems and improve their efficiency. [93]

## 1.4 Flexible electronics

The increasing importance of flexible electronics for the healthcare field draws massive engineering efforts worldwide. Conventional electronics is rigid, while flexible electronics bears the promise to adapt to any shape because it presents bendable, twistable and stretchable capabilities. Such mechanically flexible electronic devices can be built in two ways. The first one is by using a mechanically flexible substrate with conventional electronic components. The second one, pursues the integration of all electronic components as mechanically flexible devices. Therefore, many advances in new materials, fabrication techniques, low-power computing, power sources have contributed to bring many of the conceived products into practical applications for the healthcare field.

There are several types of substrates for building flexible electronic devices such as glass, metal, polymers, and lately paper. Paper presents great opportunities for flexible electronics, due to remarkable features like a porous structure for good adhesion of active materials, but there are still challenges and hurdles to be solved for rational use of paper in this field. [94] On the one hand, metal foils are costly and not easy to deal in the fabrication. On the other hand, when laminated to thin polymer layers or integrated to flexible glass they become extremely interesting for processing circuitry. Polymers are mostly flexible materials and must be selected according to the applications due to many

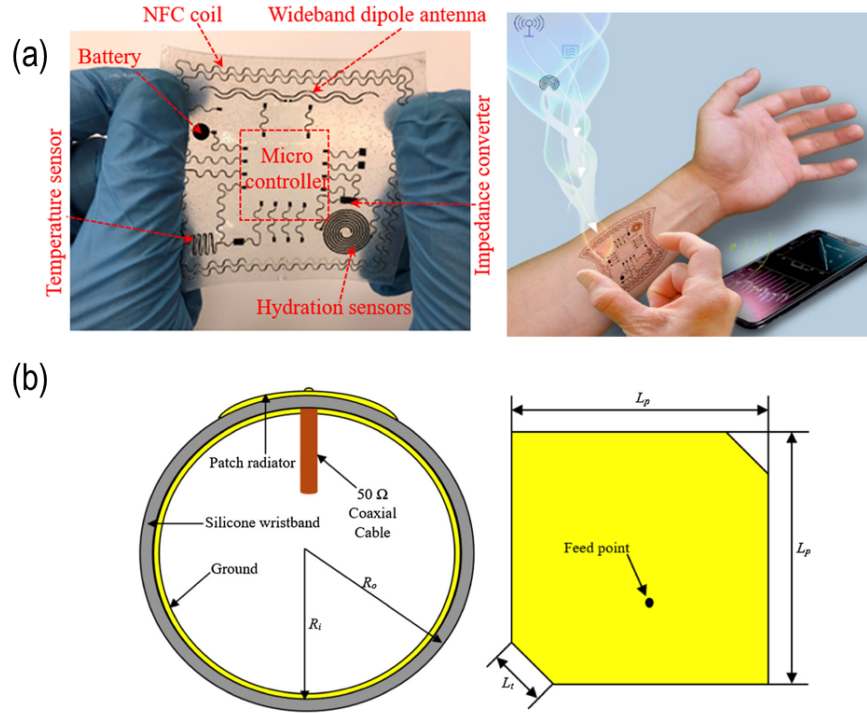


Figure 1.14: (a) (Left) The optical image shows a wearable platform including a near-field communication (NFC) coil for short-range communication, a wideband dipole antenna for RF long-range communication, sensing units (i.e., temperature sensor, hydration sensor, and electrodes for electrophysiological signal monitoring), as well as the pins to connect commercially off-the-shelf chips (not illustrated, for clarity purposes). (Right) The flexible wideband antenna behaves differently according to the part of the body where is attached (arm - shown here, head or abdomen). [91] (b) A wristband antenna compatible with flexible electronics is shown: left (side view) and right (radiator). The values in mm for the geometrical parameters are outer radius  $R_o = 35$ , inner radius  $R_i = 33$ , patch length  $L_p = 34$  and truncated length  $L_t = 3.85$ . [92]

existing types. Some of the polymers proposed as flexible substrates are: polyimide, polyethylene terephthalate, polycarbonate, and thermoplastic polyurethane. Our group, in collaboration with Lille University, France, reported on many devices based on Kapton substrates [19,95,96], including prototypes for healthcare applications. We consider Kapton one of the most remarkable substrates nowadays for flexible electronics.

Kapton is used in flexible electronics as substrate mainly due to a Young's modulus of a few GPa. Kapton is a polyimide film developed by DuPont, and has excellent mechanical, physical, and dielectric properties over a wide range of temperatures. [97] It can withstand temperatures of up to 400° C. The drawback of Kapton is that the surface needs chemical treatment before printing or manufacturing for certain applications [98–101] Figure 1.15 summarizes some Kapton-based systems for flexible electronics.

A wearable system for electrocardiography (ECG) was reported, using a hybrid solution where soft and hard electronics are combined. The electrodes provided 1 mV signal at 4.7 cm electrode spacing; a printed nickel oxide thermistor was used for measuring skin temperature. The sensors were directly printed on a Kapton substrate. The Kapton supports also the components to process and compute the signal coming from sensors, as well as the components for transmitting the data to the cloud (Fig. 1.15.a). [102]

Wang *et al.* developed a Kapton-based adaptive fully soft robot (Fig. 1.15.b). [99] It is capable of sophisticated shape adaptation and two-way locomotion in a programmable and adaptive sensing-actuating manner. Carbon black nanoparticles (2% weight) doped a liquid crystal elastomer to enhance its thermal conductivity. The soft robot was built using a Kapton film (50  $\mu\text{m}$  thick), a patterned 500  $\mu\text{m}$  thick composite layer, and an ultrathin Au heater.

Figure 1.15.b presents a fabricated flexible patch using Kapton as substrate, for treatment of subcutaneous wound infections via photothermal irradiation, allowing the local healing of infected skin wounds at early stage. This can be done by placing Kapton/AuNHs - rGO (Kapton/gold nanoholes - reduced graphene oxide) patch over the wound and irradiating for 5 minutes with 940 nm light with a light emitting diode array of 10 W and  $6 \times 6 \text{ mm}^2$  in size. [96]

Valentine *et al.* reported a hybrid printing method for manufacturing soft electronics, enabling surface mount electrical components to be integrated onto printed soft circuits. Such printing approaches have enormous potential for soft robotics and healthcare wearable devices. [103–105]

Besides actuators and sensors and other components of drug delivery

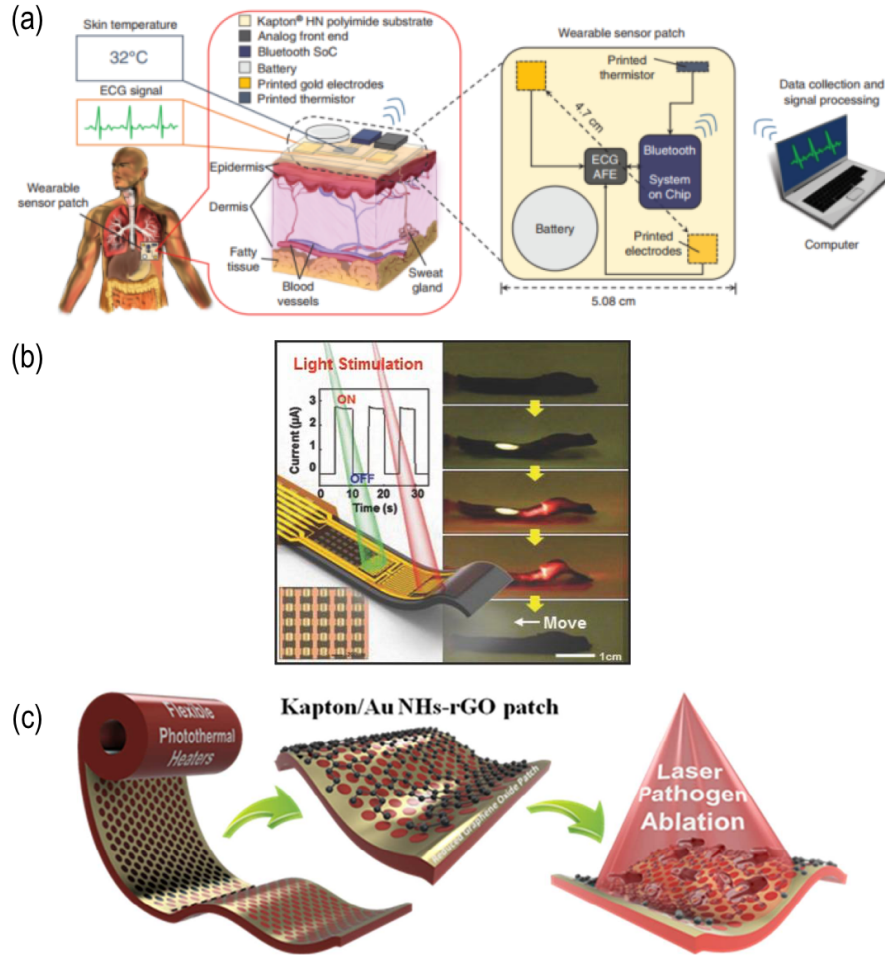


Figure 1.15: (a) Wearable system for ECG and skin temperature monitoring. [102] (b) Adaptive crawling locomotion can be realized through the conjugation of sensing and actuation, where the sensors sense the environment and actuators respond correspondingly to control the locomotion autonomously. [99] (c) Flexible patch for antibiotic-free treatments of skin infections. [96]

systems, there are numerous efforts to print power sources on mechanically flexible substrates, Kapton being one of them. However, this topic falls somehow outside the main focus of this PhD work and it will not be reviewed in length. Kapton is also widely employed as substrate for fabricating flexible antennas and various components for energy harvesting circuits. Inkjet-printed multiband antennas for integration in wearables are very popular [101] and this topic will be further detailed in Chapter 2. Copper laminated on Kapton substrates are used in Chapter 3 for the engineering of the electrothermal drug delivery system and are discussed extensively later.

#### 1.4.1 Ultra-low-power computing

Ultra-low-power HWDs should offer a long autonomy to enable a truly continuous monitoring and treatment for long periods of time. Such HWDs are based on the well-known embedded system architecture shown in Fig. 1.16.<sup>5</sup> The software is the abstract part of the system; it includes the programs or code that indicate the sequence in which the hardware components operate. It is stored in the non-volatile memory. The hardware contains all the electronic components needed to operate the device. The design is using a real-time operating system. The central processor unit (CPU) which executes software instructions and the input/output ports allow the interaction between the embedded system and the external world. Sensors communicate with analog-to-digital converters (ADCs), while actuators are interfaced with digital-to-analog converters (DACs). Dedicated subsystems can be implemented as application-specific integrated circuits (ASICs) or field-programmable gate arrays (FPGAs) which typically can be reconfigured. Power consumption is a major design constraint for modern embedded systems, especially for low power applications such as wearables. The number of components to be connected in an embedded system is increasing and the demand for ultra-low-power computing is increasing. The tradeoff between the embedded system required by wearables with architectures including both energy harvesting and drug delivery systems favours Kapton as substrate for flexible printed circuit boards.

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<sup>5</sup>Typically, ultra-low power microcontrollers use less than 100  $\mu\text{A}/\text{MHz}$  in active mode and 10 nA in sleep mode with full memory retention. The Embedded Microprocessor Benchmark Consortium has developed ultra-low power benchmarks (<https://www.eembc.org/products/>) to quantify energy efficiency.

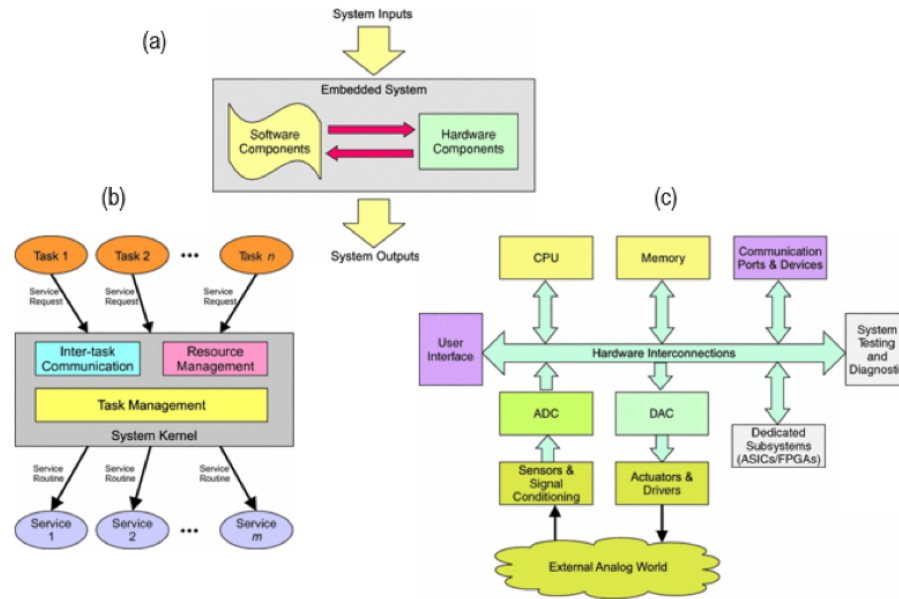


Figure 1.16: (a) General view of an embedded system. (b) Software elements in an embedded system. (c) Hardware structure in an embedded system. [106]

#### 1.4.2 Computing fabrics

The next generation of wearable devices will be conveniently worn on textiles with electronic functionalities. [107] Electronic textiles are nowadays understood as the convergence of electronics and textiles into computing fabrics. On the one hand, textiles can be combined with classical electronics devices such as integrated circuits, passive and active components, and conventional power sources. On the other hand, textiles can be fabricated directly with electronic functionalities. Nowadays, computing fabrics are even considered as a kind of skin, because they can be in direct contact with the human body, offering a platform for monitoring and treatment. Textile-embedded sensors and actuators, are already in the market.

Figure 1.17 shows the traditional manufacturing processes of textile, starting with the fiber, coil, and yarn. [108] Textiles can be classified in three main series: woven, knitted (weft and warp knits), and non-woven fabrics (Fig. 1.17). [109]

Textiles applications for healthcare applications are multiplying with the arrival of novel techniques of fabrication. The common techniques for the fabrication of textiles are categorized into physical and chemical

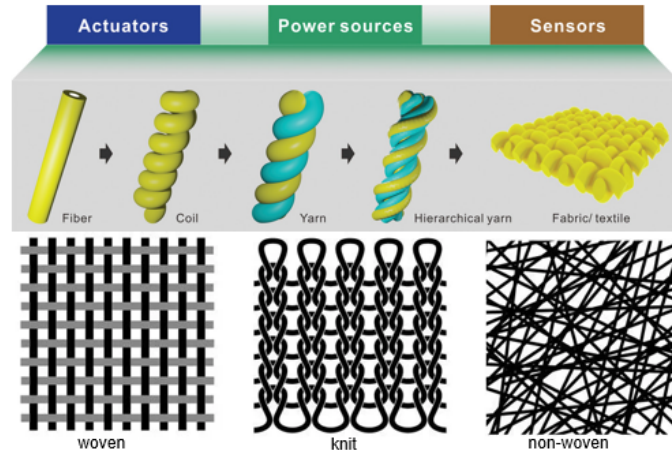


Figure 1.17: (Top) Textiles for healthcare applications should be lightweight, conformable, and breathable. By adding computing and communications capabilities, besides power sources, sensors and actuators, they could be integrated to the IoT network. (Bottom) Types of textiles. [109]

methods. Physical methods most commonly used are printing, spinning, coating, physical vapor deposition. Chemical methods include chemical vapor deposition, plating, and carbonization. [110] The 3D printing method is one of the most used nowadays, because of low temperature, low cost, non-vacuum operation, and compatibility with a large amount of materials. It allows to obtain smart textiles and some attributes such as bending, twisting, corrugation, and elongation can be tuned. Thus, 3D printing offers customizable textiles to meet the requirements for healthcare applications. An example for non-woven fabrics is shown in Fig. 1.18 with polylactic acid processing. [111]

Healthcare demands unique features for textiles for seamless integration of sensors, actuators, and power sources as well as data storage components, like on Kapton. We remind that for the energy harvesting module the literature covers work on textile substrates and hybrid approaches using both Kapton and fabrics. [81] In particular, health monitoring and disease treatment ask for power supplies with high capacity to ensure long-time autonomous operation. While a continuous improvement of rechargeable battery energy density is required, textiles are suitable for electrical power storage with mechanically flexible batteries and supercapacitors. Indeed, textile-integrated energy storage devices can be an option to replace the bulky and uncomfortable traditional batteries incorporated in garments. [112]



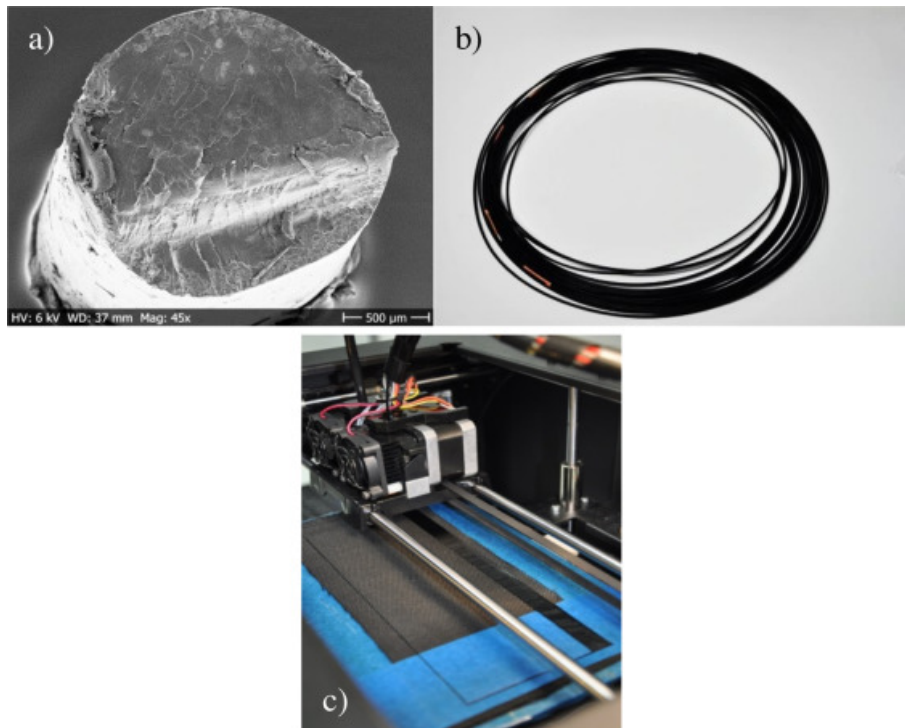


Figure 1.18: 3D printing of polylactic acid. [111] (a, b) Views of 2% carbon nanotube polylactic acid 3D filament. (c) Printing polylactic acid on polylactic acid fabric. In order to ensure adhesion, the printed and substrate polymers have to be integrated in the ‘flow’ state of matter and not in the ‘glassy’ state, so that molecular chains are mobile.



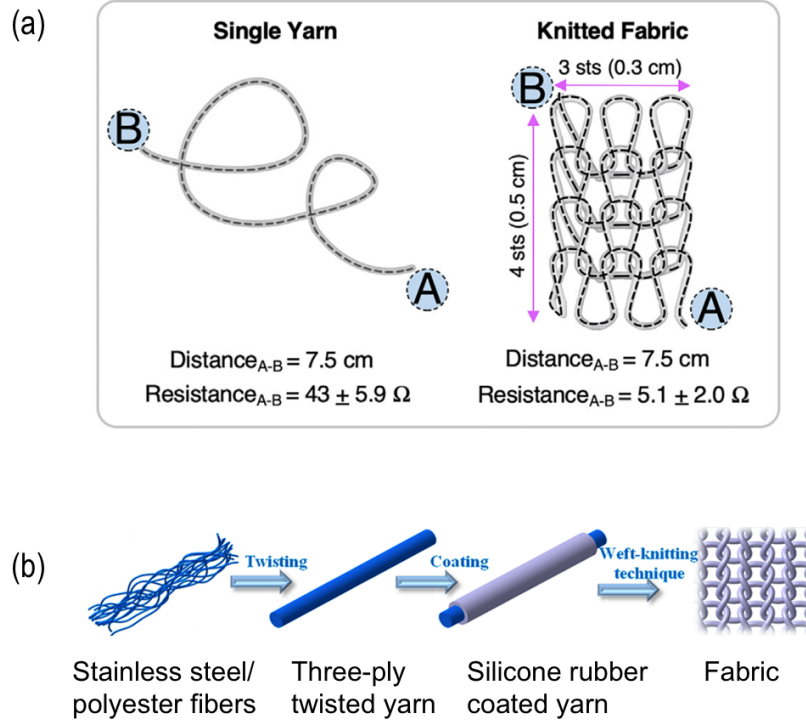


Figure 1.19: (a) Knitted electrodes are a promising architecture for textile energy storage devices because yarns can be manipulated into interconnected loops, allowing charges to move through the path of least resistance, rather than following the geometric path of the yarn through the knit structure. While short segments of fiber and yarn devices (typically less than 4 cm) have demonstrated high capacitance and energy density, they often suffer from high resistance at longer lengths, leading to reduced electrochemical performance (sts = stitches). [113] (b) Fabrication of self-charging knitted textile [114].

Fiber- and yarn-based supercapacitors meet these requirements owing to their excellent electrochemical performance according Levitt *et al.* (Fig. 1.19a). These authors demonstrated 3D knitted energy storage textiles devices with high capacitance up to 707 mF/cm<sup>2</sup> and 519 mF/cm<sup>2</sup> at 2 mV/s, with excellent cycling stability over 10000 cycles, in 1M phosphoric acid and polyvinyl alcohol-phosphoric acid gel electrolytes, respectively. [113]

Dong *et al.* reported a highly stretchable and washable all-yarn based self-charging textile, as shown in Fig. 1.19b. A knitted triboelectrical nanogenerator offered a power density of 85 mW/m<sup>2</sup>. A commercial purchased three-ply twisted stainless steel/polyester fiber blended yarn was employed as conductive electrode together with silicone rubber as dielectric. It was observed that the yarn can maintain ~70% capacitance after 60000 stretching cycles. [114]

Sundriyal *et al.* demonstrated a battery-supercapacitor hybrid device using inkjet printing techniques with different metal oxide inks over fabric substrates. The MnO<sub>2</sub>-NiCo<sub>2</sub>O<sub>4</sub> was used as a positive electrode, and reduced graphene oxide as a negative electrode. It showed a stable performance in the 0-1.6 V range with a maximum power density of 2500 mW/cm<sup>3</sup>, and 92% of capacitance retention after 5000 cycles. [115]

Lund *et al.* reported a fully textile piezoelectric generator that operates under wet conditions. A 2.5 × 20 cm<sup>2</sup> of piece of the textile produced a continuous output of 4 μW. The design is based on melt-spun microfibres with a core-sheath structure. One electrode, in form of a conducting yarn, is wrapped around yarns of bicomponent microfibres by weaving. The conducting core of the biocomponent fibers consists of 10% wt carbon black in a polymer matrix and the core is surrounded by poly(vinylidene fluoride). [116]

Dong *et al.* demonstrated a stretchable yarn-based triboelectric nanogenerator with coaxial core-sheath morphology. A silver-coated nylon yarn of diameter 180 μm acts as one electrode material and silicone rubber acts as the dielectric material. Due to the spring-like winding structure, the yarn exhibits stretchability up 200% tensile strain. At a fixed frequency of 3 Hz, the maximum average power densities of a single yarn-based triboelectric nanogenerator can reach 11 and 0.88 W/m<sup>3</sup> under compressing state and stretching state, respectively. [117].

Virtual reality (VR) pain management is made possible today by wearables with major effort from global technology actors like Google and Samsung. While VR has proven efficient in addressing acute pain through diversion, the use of the technology to address chronic pain is new, and in this area computing fabrics will play a key role.

## 1.5 Conclusion: Choice of the present work

At the end of this section, we conclude that new technologies are maturing and are more and more used in healthcare applications, expanding the sector in the short-term. Some of these promising technologies, besides novel drug delivery systems, are the IoT, artificial intelligence, and the RF energy harvesting. New wearables are strongly based on computing systems using Kapton substrates and textiles, both promoting functional electronics for green and circular economy.

The development of wearable technology takes huge importance in developing countries. Within the objectives of the funding agency supporting this work, an immediate application appeared to be in diabetes: 9.5% of Ecuadorians have a high level of glucose.<sup>6</sup>

Science and engineering could help people in Ecuador to deal with this major health problem. [9] Therefore, based on the-state-of-art, we have chosen to develop insulin delivery systems to be integrated on Kapton and textiles, and to be further developed as autonomous wearable systems. Such systems have the advantages of being bendable and easier to be manufactured with a high throughput. We also have chosen to address several components of such wearables, to understand better the challenges in each module, for example, in terms of standardisation, certification and regulation compliance.

The required biosensing module is out of the scope of this work, the focus being on the therapeutic aspects of the platform and on the drug delivery module - presented in Chapter 3. For the RF energy harvesting module, presented in Chapter 2, we focused on new antenna concepts, miniaturized design and integration on Kapton and textiles. We were interested in decreasing the use of resources by reducing the level of power consumption in the overall architecture of the electronic system. Similarly, having the same target of low-power consumption, the insulin delivery module is to be achieved by combining the reduced graphene oxide as drug reservoir with Kapton-based electrothermal actuators. Animal experiments carried out by our collaborators at Lille University, France, in the group of Prof. S. Szunerits were decisive on our technological choices and to develop the prototypes included in the present thesis.

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<sup>6</sup>According to International Diabetes Federation (<https://www.diabetesatlas.org/en/>), diabetes prevalence refers to the percentage of people aged 20-79 years who have type 1 or type 2 diabetes: this indicator fluctuates from 5 to 6% from 2010 to 2045. The age-adjusted comparative prevalence of impaired glucose tolerance is 9.5% (2019) and it is expected to increase to 10.4% (2045).

By studying the state-of-the-art, before COVID-19 pandemics, we understood that it will not be possible to address the improvement of the entire system characteristics (e.g. performance, robustness, reliability). For example, dealing with integration of primary power sources, we have opted for a traditional and effective integration of thin film batteries on Kapton and textile by soldering. In fact, even this rudimentary integration, as described in the Annexes, poses a series of challenges for the newcomer.

More importantly, the work to develop the RF energy harvesting module and the electronic board for wireless communication with the electrothermal patches for insulin delivery, involves serious logistic resources, available only in Belgium, and the effective research stay in Belgium was  $2\frac{1}{2}$  years over the entire thesis. Therefore, while the Chapter 3 detailing on the insulin delivery module seems more accomplished, it is not the case for the Chapter 2 focused on RF energy harvesting. For the sake of the clarity, in the Chapter 2 dedicated to the RF energy harvesting, we have not included all incipient work on thermal energy harvesting, although we have devoted some efforts to this topic as well. In the conclusion of the Chapter 2 and in the perspectives of the thesis, we will point out this preliminary work.

## 1.6 List of abbreviations

|            |                                          |           |                                                      |
|------------|------------------------------------------|-----------|------------------------------------------------------|
| ADC        | :Analog-to-digital converter             | MCU :     | Microcontroller unit                                 |
| AI         | :Artificial intelligence                 | ML :      | Machine learning                                     |
| ASIC       | :Application-specific integrated circuit | MN :      | Microneedle                                          |
| AuNHs      | :Gold nanoholes                          | MPPT :    | Maximum power point tracking                         |
| CPU        | :Central processing unit                 | NIR :     | Near-infrared                                        |
| DAC        | :Digital-to-analog converter             | NFC :     | Near-field communication                             |
| DL         | :Deep learning                           | PB :      | Prussian blue                                        |
| ECG        | :Electrocardiogram                       | PDMS :    | Polydimethylsiloxane                                 |
| EHR        | :Electronic health record                | PEG :     | Polyethylene glycol                                  |
| Er : YAG   | :Erbium-doped yttrium aluminium garnet   | PET :     | Polyethylene terephthalate                           |
| FPCBs      | :Flexible printed circuit boards         | PI :      | Polyimide                                            |
| FPGA       | :Field programmable gate array           | PMVE :    | Poly(methylvinylether)                               |
| GOx        | :Glucose oxidase                         | QoS :     | Quality of service                                   |
| HWDs       | :Healthcare wearable devices             | RF :      | Radio frequency                                      |
| INS – lipo | :Liposome encapsulated insulin           | RFEH :    | Radio frequency energy harvesting                    |
| IoT        | :Internet of Things                      | RFID :    | Radio frequency energy identification                |
| ISEs       | :Ion sensing electrodes                  | rGO :     | Reduced graphene oxide                               |
| ISF        | :Interstitial fluid                      | SC :      | <i>Stratum corneum</i>                               |
| ISM        | :Industrial, scientific and medical      | SWIPT :   | Simultaneous wireless information and power transfer |
| ITP        | :Iontophoresis                           | TDD :     | Transdermal drug delivery                            |
| HWDs       | :Healthcare wearable devices             | UWB :     | Ultra-wide band                                      |
| LOx        | :Lactate oxidase                         | VR :      | Virtual reality                                      |
| MA         | :Maleic acid                             | Wi – Fi : | Wireless fidelity                                    |

3D

:Three dimensional

5G :

Fifth generation technology standard for broadband cellular networks

## Chapter 2

# Radio-frequency energy harvesting

One scientific epoch ended and another began  
with James Clerk Maxwell.

---

Albert Einstein

### 2.1 Introduction

Radio-frequency energy harvesting (RFEH) consists in the collection of small amounts of ambient electromagnetic energy for converting it into electrical energy. It attracts great attention as a very promising technology to enable low-power devices for wireless sensor networks (WSNs). [118, 119] Indeed, RF sources are ubiquitous due to the large deployment of wireless communication infrastructures in almost all economic sectors. The amount of power harvested from the ambient air for RFEH is low [120] and typically varies between  $0.2 \text{ nW/cm}^2$  and  $1 \text{ }\mu\text{W/cm}^2$ . Nevertheless, considerable improvements have been observed in the RFEH technology in the recent years, which could facilitate novel communication services in many fields, including healthcare. [82] Accordingly, Internet-of Things (IoT)-based healthcare wearable devices are adopting this type of green renewable energy, because such modern devices have low-power requirements. While this technology can be used alone to power electronic devices or recharge secondary batteries, in most of the cases it is used as an addition to complement other energy harvesting technologies or power sources. [89]

The figure of merit for RFEH is the overall conversion power efficiency. It depends on the performance of each component of the whole

system. The antenna is one of the most important components and plays a significant role in the RFEH system; it is located at the beginning of the system. In this context, one of the challenges for the next-generation healthcare wearable devices is the design of planar, miniaturized, and flexible antennas. They should be able to integrate easily with small and compact wearable devices and they should display a suitable frequency range. [121] For healthcare applications the industrial, scientific, and medical (ISM) band (915 MHz, 2.45 GHz, and 5.8 GHz) is the most desirable.

The patch antenna is one of the most common antennas for healthcare products. It is well known for its characteristics, mainly because it can be attached to the human body. [122] This stems from the fact that the patch antenna has an outward radiation pattern from the human body, minimizing the absorption of radiation by various human tissues. The rectangular patch antenna is the most used for operating at 2.4 GHz. [123–125] Patch antennas are also of interest to be integrated into textiles and to be used in implantable medical devices. [126] Exploiting flexible substrates such as polymers, textiles, and even paper is a promising avenue to obtain mechanical flexibility for antennas. Nanomaterials and new designs are also nowadays promising to get novel flexible and portable antennas, truly comfortable to the patient.

In the literature many approaches for these kind of antennas were reported. For instance, Ahmed *et al.* proposed a flexible inkjet-printed multiband antenna, printed on a Kapton polyimide-based flexible substrate. [101] The triangular monopole design allows to get multiband operation. The antenna resonates at 1.2, 2, 2.6, and 3.4 GHz, as depicted in Figure 2.1.a. [101] This multiband antenna has 2.1 dBi gain in the 2.5 - 2.7 GHz band. The resonance frequency shifts 3% in concave bending, but there is no change in convex bending. Cylindrical geometries were chosen with radii of 59 and 78 mm for bending studies. For convex bending, an increase by 0.2 and 0.4 dBi in gain is observed at 2.6 GHz for 78 and 59 mm configurations, respectively. For concave bending, an increase by 0.1 dBi in gain is observed only at 2.6 GHz for the 59 mm configuration. Yan *et al.* reported a flexible, dual-band textile antenna for WLAN applications. The textile-based antenna is shown in Figure 2.1.b. [127] The dual-band antenna has a -1.4 and 5.20 dB gain measured under bending conditions, respectively, for the 2.4 and 5.4 GHz bands.<sup>1</sup> Song *et al.* demonstrated a microstrip patch antenna with composite based on silver nanowires (AgNWs) and polydimethyl-

<sup>1</sup>Note that a negative gain means that the antenna is not radiating properly in a certain direction. While a poor antenna efficiency can be due to internal losses, here the negative gain arises from direct contact with lossy materials (textiles).



siloxane (PDMS). [128] The thickness of the AgNWs/PDMS layer is close to 0.5 mm. Two types of antennas were fabricated, a single patch at 3 GHz, and a 2-element array at 6 GHz. Figure 2.1.c shows the single patch, which is stretchable, tunable and deformable. [128] The gain for the single antenna is 0.37 dBi, whereas for the 2-element array it is 4.90 dBi.

Common antennas also include the inverted-F antenna (IFA), used in the ISM band for IoT-based healthcare wearable devices. [129] The planar IFA version is actually a variant of the patch antenna. This type of antenna is used for both communication and energy harvesting and even implantable biomedical applications. Basically, it consists of a  $\lambda/4$  monopole antenna that runs parallel to a ground plane, as depicted Figure 2.1.d.

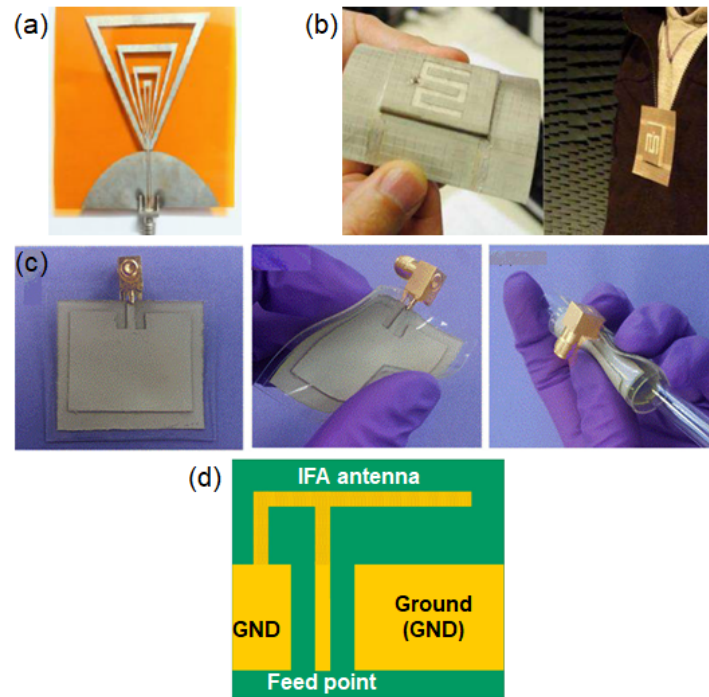


Figure 2.1: (a) Kapton-based flexible antenna. [101] (b) Textile-based antenna. [127] (c) AgNW/PDMS-based antenna. [128] (d) IFA antenna. [129]

The amount of harvested energy with just a single antenna is small. To maximize the power output, the use of multiple antennas or of an array of antennas is required [130], yet it increases the device size and

brings other operation issues. Nevertheless, there are nowadays many methods to improve RFEH such as novel technologies, new geometries, and smart materials. In particular, in the last decade metamaterial-based antennas were presented as a good option for enhancing the performance of RFEH systems. [131]

We show here efforts carried out on the design, fabrication and characterization of antennas for energy harvesting. A patch antenna is proposed at 2.4 GHz. Next, a Yagi Uda antenna is fabricated in a flexible manner on Kapton.<sup>2</sup> Finally, the proof of concept of RF energy harvesting is demonstrated at 2.4 GHz and 915 MHz frequencies, which correspond to ISM bands.

## 2.2 Flexible substrates

The increasing importance of flexible electronics (FE) for healthcare applications requires a lot of efforts in the industrial design and engineering fronts. Conventional electronics modules are rigid and bulk, because conventional electronics uses rigid substrates, such as FR4<sup>3</sup>. The goal of FE is to develop devices able to adapt to any shape and to present bendable, twistable and stretchable features according to the final application. Flexible devices can be built in two ways: using a flexible substrate with conventional electronic components or integrating all electronic components as flexible items. Therefore, advances in new materials and fabrication techniques have appeared recently to bring many of the conceived products into practical applications of adaptive electronics, especially for healthcare. [94, 132, 133]

To date, RF applications were mainly addressed using rigid substrates such as Rogers and FR4. [134] Therefore, antennas have been fabricated on rigid substrates, with macroscopic dimensions and conventional materials. Flexible antennas for healthcare applications could allow conformable patches on different parts of the patient's body. Moreover, they can grant fully-integrated IoT devices for monitoring and treating patients remotely. [135]

Substrate materials for flexible antennas require minimal dielectric losses, low relative permittivities, low coefficients of thermal expansion, and high thermal conductivities.<sup>4</sup> They should have a large dielectric

---

<sup>2</sup>An IFA antenna has been integrated to an embedded system to build a wireless portable electronic system to manage an electrothermal patch, which is discussed further in the thesis. This antenna is presented in Appendix A and Appendix B.

<sup>3</sup>FR4 is a standard defined by the National Electrical Manufacturers Association for a laminated glass-reinforced epoxy resin.

<sup>4</sup>Note that the effective permittivity depends on the antenna nature. For a patch

constant for warranting small size antennas and a large beamwidth. [136] There are several types of substrates for flexible antennas such as thin glass, metal foils, polymer substrates, textiles, and paper. However, polymers are the most used substrates for flexible antennas, because glass has poor flexibility, while metal foil is costly and not easy to deal with in the fabrication. On the one hand, the integration of antennas in textiles is sought as a potential breakthrough in this field. [137] On the other hand, paper is also an interesting flexible substrate sharing with the textiles some unique features. For example, paper has ability to absorb liquids. This can be used to change the dielectric constant of the substrate for some biosensing applications (e.g. detection of salt (electrolyte) concentration or other health-related biomarkers present in sweat). [138] This remarkable feature of paper, shared with some textiles and polymers, namely the porous structure, can be used in designing antennas using liquid metals.

Polymers are flexible materials and must be selected according to the target applications. Notable examples include polyimide (PI), PDMS, and elastomers. Kapton is one of the most used materials as a substrate in flexible electronics. Kapton is a polyimide film developed by DuPont. It has excellent mechanical, physical, and dielectric properties ( $\epsilon_r = 3.4$ ) over a wide range of temperatures. [97] It can withstand temperatures of up to 400°C. Due to a Young's modulus of a few GPa, Kapton is used in FE applications. The drawback of Kapton is that its surface requires a treatment before printing or manufacturing for certain applications. [98, 139] Our group has been reporting on many devices based on Kapton substrates [19, 95, 96]; some prototypes, under development, are included in Appendix B.

## 2.3 Rigid patch antenna

### 2.3.1 Design of a patch antenna

Parameters for the microstrip patch antenna design are as follows: the working frequency is  $f_r = 2.45$  GHz, the thickness of the FR4 substrate is  $h = 1.55$  mm, and the relative permittivity of the dielectric substrate is  $\epsilon_r = 4.3$ . The dimensions of the patch antenna are determined by the following equations [140]

$$\epsilon_{eff} = \frac{\epsilon_r + 1}{2} + \frac{\epsilon_r - 1}{2} \left( 1 + 12 \frac{h}{W} \right)^{-1/2}, \quad (2.1)$$

antenna, decreasing permittivity leads to an increase in gain (effective area of the patch) at fixed frequency. Size is a key metrics for flexible antennas.

$$W = \frac{c}{\sqrt{2}f_r} \sqrt{\frac{1}{\epsilon_r + 1}}, \quad (2.2)$$

$$L_{eff} = 2\Delta L + L, \quad (2.3)$$

$$L_{eff} = \frac{c}{2f_r\sqrt{\epsilon_{reff}}}, \quad (2.4)$$

$$\Delta L = 0.412 \times h \times \frac{(\epsilon_{reff} + 0.3)(\frac{W}{h} + 0.264)}{(\epsilon_{reff} - 0.258)(\frac{W}{h} + 0.8)}, \quad (2.5)$$

where  $c = 3 \times 10^8$  m/s is the speed of light,  $\epsilon_{reff}$  is the effective dielectric constant,  $f_r$  is the resonance frequency,  $W$  is the width of the patch,  $L$  is the length of the patch,  $L_{eff}$  is the electrical length, and  $\Delta L$  is the fringing length. From the above equations [140] the dimensions of the patch antenna were calculated as shown in Figure 2.2.a and e, whereas the fabricated patch antenna is shown in Figure 2.2.b.

First of all, the patch antenna was simulated using the CST Studio Suite commercial software (<http://www.cst.com>), that uses the finite difference time domain (FDTD) method to solve the corresponding Maxwell's equations. More precisely, it uses the finite integration technique (FIT), which may be viewed as a variation of FDTD. This simulation was performed to know in advance the behavior of the patch antenna according to the calculated dimensions. The defined parameters for the numerical simulation were as defined above, while the electrical conductivity of the Cu was assumed to be  $5.8 \times 10^7$  S/m.

During the simulation, the inset feed depth dimensions were manipulated to obtain the target values for the resonance frequency and the impedance at the edge of the feeder, whose value should be around 50  $\Omega$ . From the numerical simulation results displayed in Figure 2.2.c, we can see that the return loss ( $S_{11}$ ) is around -24 dB at the resonance frequency of 2.44 GHz. Figure 2.2.d presents the simulation values for the impedance. The real part of the impedance ( $Z$ ) at the resonant frequency is around 50  $\Omega$  and the imaginary part is small ( $Z = 50.6 - j6.67$  [ $\Omega$ ]). The resonance frequency close to 2.44 GHz shows that the patch antenna is operating in the ISM band.

After the simulation, the antenna was designed for fabrication using the DipTrace software. The gerber files <sup>5</sup> were obtained from the software and sent to the manufacturer. The antenna was fabricated by

<sup>5</sup>The gerber format is an open ASCII vector format for printed circuit board (PCB) designs ([www.wikipedia.org](http://www.wikipedia.org)).

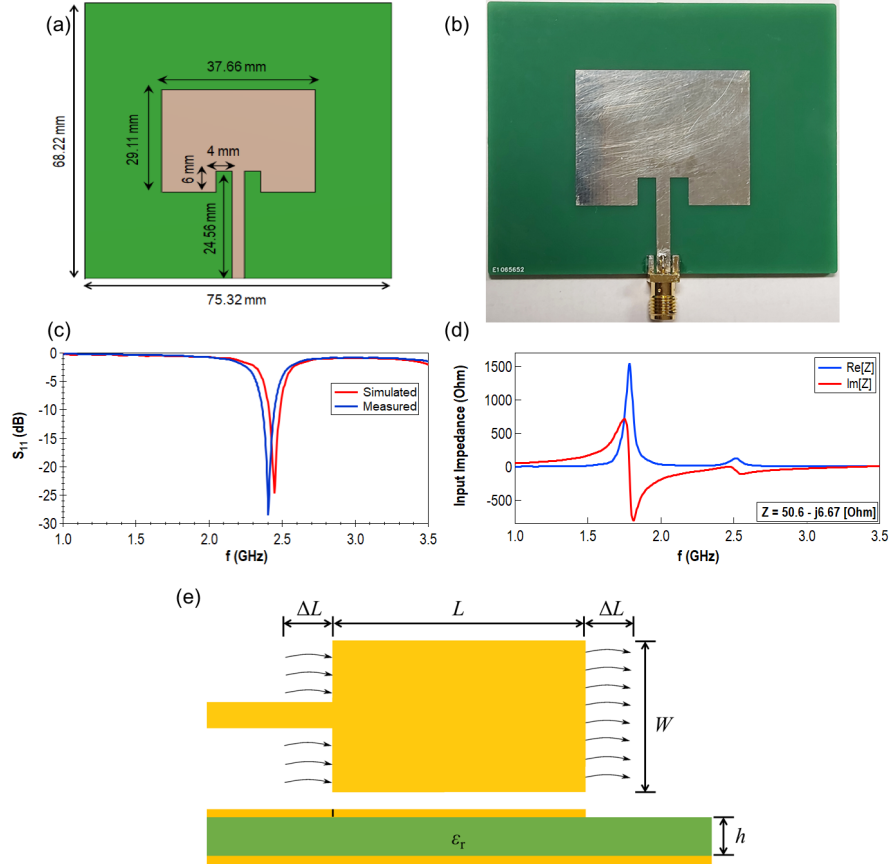


Figure 2.2: (a) Layout of a patch antenna with dimensions. (b) Fabricated patch antenna with a soldered SMA connector. (c)  $S_{11}$  parameter measured as a function of frequency (blue curve) and numerically computed for the patch antenna with a resonance frequency at 2.44 GHz (red curve). (d) Numerically computed input impedance (real and imaginary parts) as a function of frequency. (e) Schematics of the patch antenna.

Eurocircuits according to the information and defined parameters in the gerber files. The antenna fabrication was done using a standard printed circuit board (PCB) technique. The top layer was made of copper  $35 \mu\text{m}$  thick as well as the bottom layer - acting as a ground plane. The length and width of the patch area were 29.11 mm and 37.66 mm, respectively. The dimensions of the dielectric substrate layer were 68.22 mm length and 75.32 mm width. We recall here that the thickness of the FR4 dielectric layer is 1.55 mm.

The characterization of the patch antenna was performed in the Wel-

come platform of UCLouvain. First of all, an SMA connector of  $50\ \Omega$  was attached at the edge of the microstrip feeding of the patch antenna. Two types of measurements were carried out to evaluate the antenna performance. The Anritsu MS4644B Vector Network Analyzer, with maximum frequency of 40 GHz was used to measure the reflection coefficient ( $S_{11}$  parameter) *vs* frequency as depicted in Figure 2.2.c. The anechoic chamber was used to get the radiation pattern as shown in Figure 2.3.a, where the numerically computed and the measured radiation pattern are presented. They are also consistent with the 3D view of the radiation pattern obtained from the numerical computation, as depicted in Figure 2.3.c. Figure 2.3.b shows the patch antenna mounted on a holder and on the turntable platform inside the anechoic chamber. A holder was home-made by 3D printing with dimensions shown in Figure 2.3.d. The holder dimensions were defined according to the specifications of the 2 axes turntable platform.<sup>6</sup>

To obtain the radiation pattern in the anechoic chamber a transmitting antenna was used (SATIMO QH800 reference antenna). It has a frequency range from 0.8 to 12 GHz, average gain of 5 to 15 dBi, dual linear polarization,  $50\ \Omega$  impedance, is made of Al, and with dimensions of  $264\text{ mm} \times 264\text{ mm} \times 245\text{ mm}$ . The patch antenna was mounted as a receiving antenna on the turntable platform.

As expected in our design, the patch antenna radiates only in one direction because a ground plane is placed on its back side, which fulfils the basic requirement for attaching the antenna on the human body. It could be concluded that the results between the numerical simulation and the fabricated antenna were quite similar and the CST Studio Suite software is a powerful tool to design antennas oriented towards energy harvesting and healthcare applications.

### 2.3.2 Simulation on the human body

Antennas are an adverse environment for the human body, and vice versa. When an antenna operates in contact with the human body, the antenna's performance is affected. [135] For example, Hall *et al.* reported the performance evaluation of an antenna at 2.45 GHz due to different antenna placements on the human body. [141] As a consequence, numerical modeling of antennas to be attached on the human body faces challenges for improving as much as possible the antennas design and performance, especially for healthcare applications.

<sup>6</sup>The antenna measurements in Welcome facility at UCLouvain were supported by the antenna group at ICTEAM lead by Prof. C. Craeye, especially by Sumit Karki and Khaldoun Alkhalifeh.

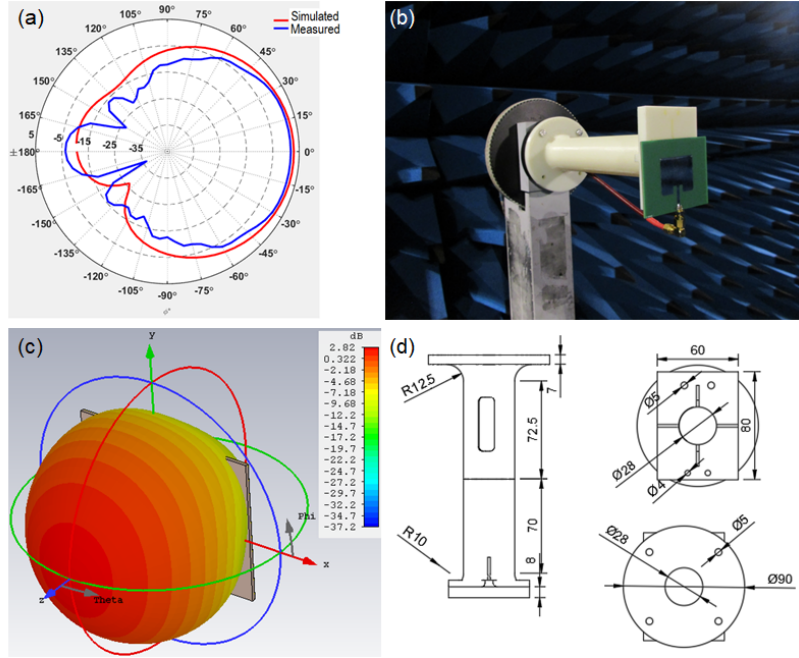


Figure 2.3: (a) Comparison between numerical results and measurement for the radiation pattern. (b) Antenna measurement in the anechoic chamber. (c) Numerically computed 3D view of the radiation pattern. (d) Holder design for the patch antenna with dimensions.

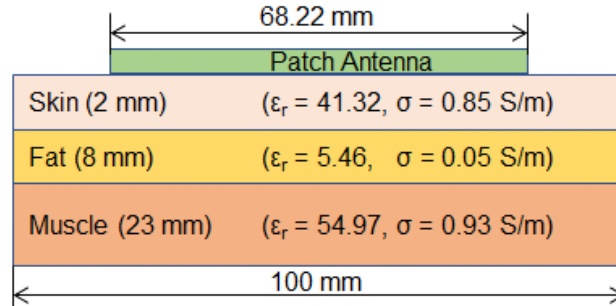


Figure 2.4: Layers of one of the Phantom models (see Table 2.1) considered to perform the numerical simulation. [142] The electrical resistance per square of the top skin layer is around  $600 \Omega/\square$ . As presented in the next chapter, this value is over two orders of magnitude higher than the corresponding resistance of the electrothermal patch, and the leakage current in the skin is minimal provided also the high contact resistance of the skin ( $1000 \Omega$  or higher, depending on the condition of the skin). Note that iontophoresis employs electrical current densities of around  $1 \text{ mA}/\text{cm}^2$ .

In general, to test the performance of an antenna on the human body, the use of a synthetic platform is recommended. It can emulate the human skin, in particular, with appropriate electrical and physiological properties. The Phantom model is commonly used to evaluate antennas operating on the human body. The Phantom models for our analysis consist of 3 homogeneous layers (in the  $z$ -direction): a skin layer of 1.2 - 2 mm, a fat layer of 2.4 - 10.5 mm, and a muscle layer of 3.6 - 40 mm. The reference values for simulation of the Phantom models are shown in Figure 2.4 and Table 2.1. The  $x - y$  shape of the Phantom models is a square with dimensions 100 mm  $\times$  100 mm.

| Layers           | $\epsilon_r$ | $\sigma$ (S/m) | h (mm) | f <sub>r</sub> (GHz) | S <sub>11</sub> (dB) | Ref.  |
|------------------|--------------|----------------|--------|----------------------|----------------------|-------|
| Phantom model #1 |              |                |        |                      |                      |       |
| Skin             | 41.32        | 0.85           | 2      | 2.43                 | -37.29               | [142] |
| Fat              | 5.46         | 0.05           | 8      |                      |                      |       |
| Muscle           | 54.97        | 0.93           | 23     |                      |                      |       |
| Phantom model #2 |              |                |        |                      |                      |       |
| Skin             | 38.00        | 1.46           | 1.5    | 2.43                 | -36.98               | [143] |
| Fat              | 5.28         | 0.10           | 10.5   |                      |                      |       |
| Muscle           | 52.73        | 1.74           | 40     |                      |                      |       |
| Phantom model #3 |              |                |        |                      |                      |       |
| Skin             | 41.32        | 0.85           | 1.2    | 2.43                 | -39.83               | [144] |
| Fat              | 5.46         | 0.05           | 2.4    |                      |                      |       |
| Muscle           | 52.70        | 1.76           | 3.6    |                      |                      |       |
| Phantom model #4 |              |                |        |                      |                      |       |
| Skin             | 38.00        | 1.46           | 1.3    | 2.43                 | -36.46               | [145] |
| Fat              | 10.8         | 0.27           | 10.5   |                      |                      |       |
| Muscle           | 52.70        | 1.74           | 20.0   |                      |                      |       |

Table 2.1: Evaluation of the patch antenna performance carried on different Phantom models.

Physical parameters of human tissues such as density, heat capacity, thermal conductivity, and basal metabolic rate are summarised in Table 2.2. These values were defined in the CST Studio Suite software for the Phantom models.

The patch antenna from Section 2.3.1 was used on the Phantom models for its performance evaluation. As shown before (Figure 2.3), the measured results displayed a reasonable agreement with the numerical simulated ones. [146] For example, Ali *et al.* reported the design and evaluation of a flexible dual-band meander line monopole antenna for on- and off-body healthcare applications.



| Tissue Poperties                         | Skin  | Fat   | Muscle | Unit              |
|------------------------------------------|-------|-------|--------|-------------------|
| Density ( $\rho_x$ )                     | 1109  | 911   | 1090   | kg/m <sup>3</sup> |
| Heat capacity ( $C_x$ )                  | 3.391 | 2.348 | 3.421  | kJ/K/kg           |
| Thermal conductivity ( $\kappa_x$ )      | 0.37  | 0.21  | 0.49   | W/K/m             |
| Basal metabolic rate (BMR <sub>x</sub> ) | 1620  | 300   | 480    | W/m <sup>3</sup>  |

Table 2.2: Parameters of human tissues, where  $x$  is skin, fat and muscle.

Therefore, taking advantage of the available simulation tool, we evaluated numerically the performance of the antenna in different realistic situations. Figure 2.5a shows the reflection coefficients ( $S_{11}$  parameters) for the patch antenna in both free space and on the Phantom model displayed in Figure 2.4. The plot allows one to know the amount of power radiated or reflected by the antenna in both scenarios. A slight downshift of the resonance frequency is observed for the case of an antenna operating on the human body. This shift is present for all the considered Phantoms (Figure 2.5b and Table 2.1).

Due to the fact that the patch antenna is to be placed on the human body, it is also important to evaluate the impact of (convex) bending on its performance. The cylindrical geometry was selected for the bending study (Figure 2.6a) and the 3D view of the bent antenna is shown in Figure 2.6b. Three values of the cylinder radius were considered to evaluate the antenna performance for convex deformation: 100, 150, and 200 mm. The Figure 2.6c shows the results obtained for  $S_{11}$  in comparison with the flat geometry of the antenna placed on Phantom 1.

Apart from the intrinsic performance of the antenna on the human body, the negative effects of electromagnetic fields on human organisms and tissues have been discussed in the literature.<sup>7</sup> Therefore, it is important to quantify such effects in terms of the specific absorption rate (SAR), a measure of how transmitted RF energy is absorbed by a defined human tissue. This parameter (measured in W/kg) can be defined as  $SAR = \frac{\sigma E^2}{\rho}$ , where the biological tissue is characterised by its the electrical conductivity  $\sigma$  in S/m, mass density  $\rho$  in kg/m<sup>3</sup>, and *rms* value of the electric field strength  $E$  in V/m. Interestingly, an estimation of SAR can be obtained using CST Studio Suite software as

<sup>7</sup>IEEE Standard for Safety Levels with Respect to Human Exposure to Radio Frequency Electromagnetic Fields, 3 kHz to 300 GHz. IEEE Std. C951-2005 Revis. IEEE Std. C951-1991, <https://doi.org/10.1109/IEEESTD.2006.99501> (2006); IEEE Standard for Safety Levels With Respect to Human Exposure to Electromagnetic Fields, 0–3 kHz. IEEE Std. C956-2002, <https://doi.org/10.1109/IEEESTD.2002.94143> (2002).

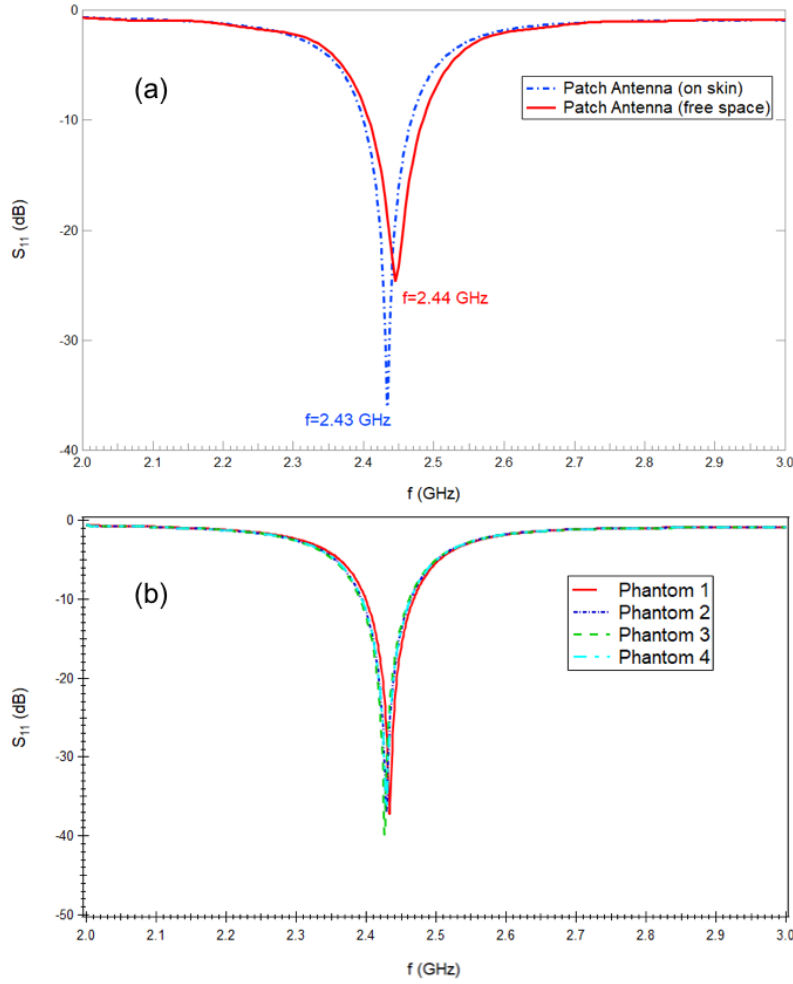


Figure 2.5: (a) Comparison of computed  $S_{11}$  as a function of frequency for the patch antenna in free space and on the human body (Phantom 1). (b) Comparison of computed  $S_{11}$  vs frequency plots of patch antenna for the four analyzed models.

well. Both International Commission on Non-Ionizing Radiation Protection and Institute of Electrical and Electronics Engineers (IEEE) have proposed acceptable SAR values. The former recommends 1.6 W/kg averaged over 1 gram of human tissue and the latter recommends 2 W/kg averaged over 10 grams. [147, 148].

The SAR values were generated by simulation when the antenna is mounted on the Phantom model defined in Figure 2.4. The SAR value for 1 gram of tissue is shown in Figure 2.7.a and for 10 grams of tissues

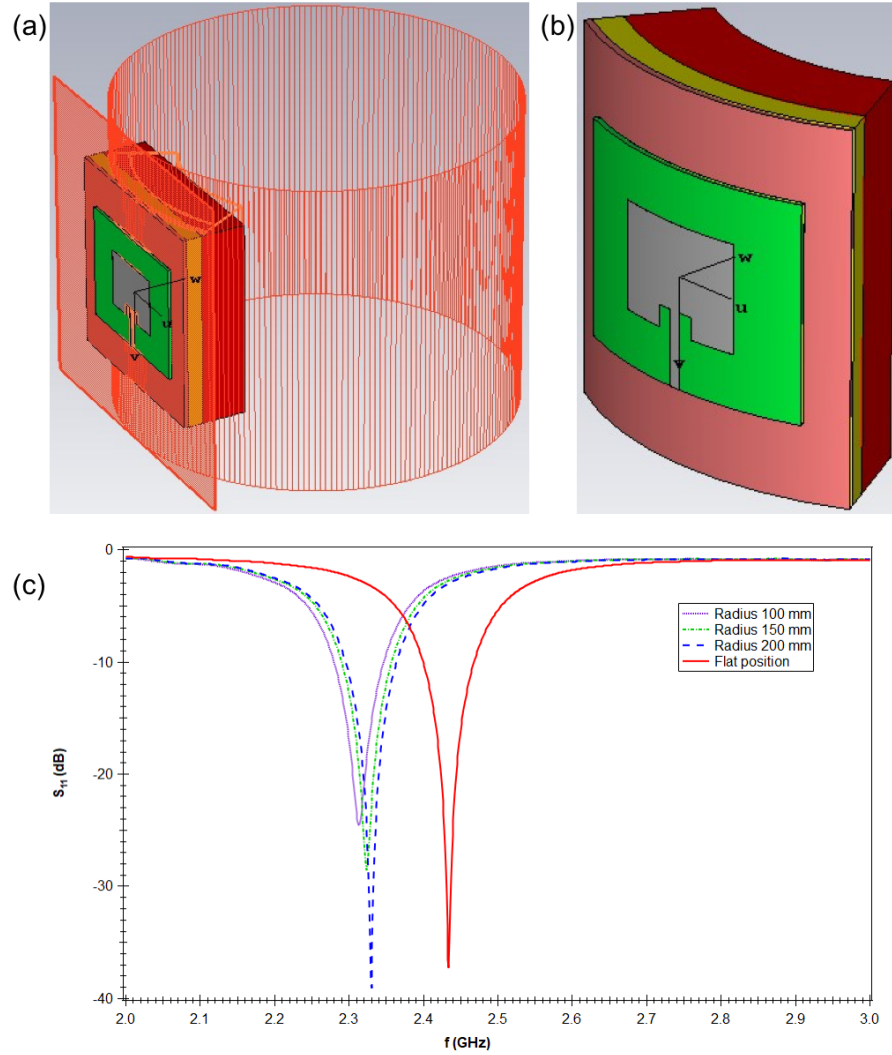


Figure 2.6: (a) Sketch of a patch antenna placed on Phantom 1 and deformed on a cylinder with radius of 100 mm. (b) A 3D view of the simulated bent antenna with Phantom 1. (c)  $S_{11}$  vs frequency numerical results for the patch antenna on Phantom 1 under three bending conditions: radius of 100 mm, 150 mm, and 200 mm. The curve corresponding to the flat position is the same to the blue curve displayed in Figure 2.5a. The frequency and gain are: 2.31 GHz and -24.51 dB for radius of 100 mm, 2.32 GHz and -28.53 dB for radius of 150 mm, 2.33 GHz and -39.09 dB for radius of 200 mm, 2.43 GHz and -37.29 dB for flat position.

is shown in Figure 2.7.b.

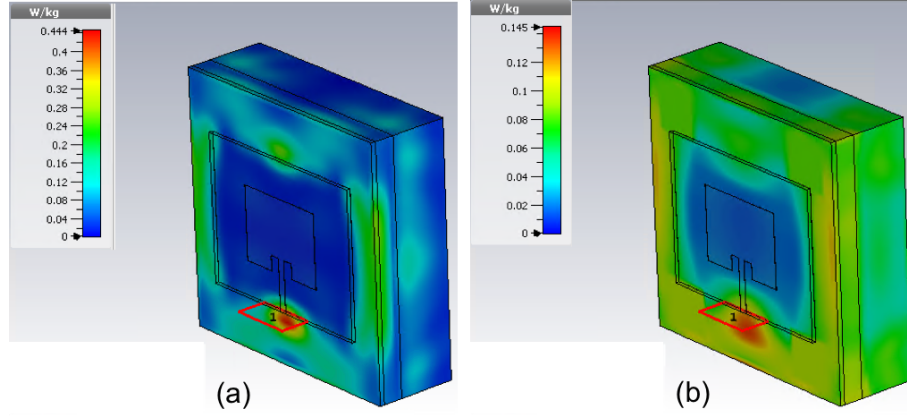


Figure 2.7: (a) Estimation of SAR relating to 1 g. (b) Estimation of SAR relating to 10 grams.

The SAR analysis is becoming critical to properly evaluate and design modern antennas for healthcare applications. From the simulations, the patch antenna introduced in Section 2.3.1 provides a SAR of 0.444 W/kg for 1 gram and 0.145 W/kg for 10 grams of tissue. As a reference, for example, the iPhone 6 Plus model A1524 has SAR values for body of 1.19 W/kg for 1 gram and 1.00 W/kg for 10 grams. In conclusion, the low values of SAR demonstrate as well that the proposed antenna is suitable for healthcare applications.

## 2.4 Textile patch antenna

Antennas for healthcare can be integrated on textiles. [137,149] They can facilitate the implementation of on-body wearable devices devoted to the ubiquitous monitoring of the health status of the patient. Many efforts have been done recently in this direction. For example, Hertleer *et al.* studied the use of textiles in the design of antennas at 2.45 GHz. [137] These authors found that the antenna on textiles have an efficiency of around 75 %. [137] Scarpello *et al.* demonstrated a wearable and washable antenna. They recommended to use conductive ink instead of an electrotexile for the conductive layer (patch and ground plane): the ink antenna suffers less deterioration than the electrotexile after several washing cycles. [150] Table 2.3 shows the basic description of some reported antennas on textiles in the literature. Antennas on textiles need conductive textiles for the patch and the ground plane and non-

conductive textiles for the substrate. [149] Textiles as substrates are thus a good choice to fully integrate antennas into garments since conductive layers can be printed or embroidered with conductive inks or metallic yarns.<sup>8</sup>

| Application     | Conductive material            | Dielectric material |          |              | Performance | Ref.  |
|-----------------|--------------------------------|---------------------|----------|--------------|-------------|-------|
|                 |                                | Material            | $h$ (mm) | $\epsilon_r$ |             |       |
| WLAN (2.45 GHz) | Copper                         | Fleece fabric       | 3.5      | 1.1          | -           | [151] |
| WLAN (2.45 GHz) | Electron, Shieldit Super, Zelt | Fleece fabric       |          |              | 75%         | [137] |
| ISM (2.45 GHz)  | Electron, Conductive ink       | Cotton / Polyester  | 2.808    | 1.6          | 43%         | [150] |

Table 2.3: Some antennas on textile materials reported in recent literature. In Ref. [151] the radiation efficiency was not reported. The gain in the 2.45 GHz band is 8 dBi. Note that textiles have usually a low dielectric constant.

In this Section, some simulations are presented to evaluate the behavior of antennas on textiles. For this purpose the geometry of the antenna from Section 2.3.1 is considered for the numerical analysis. For numerical computation purposes, the Table 2.4 shows the dielectric properties for four of the most common fabrics (cotton, jeans, viscose and Lycra<sup>®</sup>):  $\epsilon_r$  and the dissipation factor value ( $\tan \delta$ ).

| Fabric  | $\epsilon_r$ | $\tan(\delta)$ |
|---------|--------------|----------------|
| Cotton  | 1.58         | 0.02           |
| Jeans   | 1.62         | 0.018          |
| Viscose | 1.64         | 0.016          |
| Lycra   | 1.68         | 0.008          |

Table 2.4: Dielectric properties of the studied fabrics. [152]

The CST Studio Suite software was used to evaluate the patch an-

<sup>8</sup>A typical metallic yarn is made of copper wires (12 or more filaments) of 30 microns diameter or higher from providers like Elektrisola, Switzerland, and a core yarn like Lenzing Profilen<sup>®</sup> polytetrafluoroethylene monofilament, Lenzing Plastics GmbH, Austria. The core yarn is used to support the very thin copper wires to improve the processability. Moreover, polyester multifilaments are used as a cover layer to protect copper wires and aid their movement through the needle and embroidery process.

tenna behaviour on these four types of textiles, also in conjunction with the Phantom 1. Figure 2.8 shows the  $S_{11}$  parameters computed for each of the four textiles studied.

It is observed that with the decrease of the dielectric constant the resonance frequency shifts upwards. The resonance frequency of the patch antenna with textile substrates is above 3.7 GHz compared to the one with the FR4 substrate from Section 2.3.1 at 2.44 GHz. When the patch antennas are placed on the human body (Phantom model 1), however, a resonance frequency upshift is observed in all cases, contrary to the FR4 substrate. The resonance frequency shift is 9 MHz for the cotton, 9 MHz for the jeans, 7 MHz for the viscose, and 9 MHz for the Lycra, making thus difficult to rationalise the frequency shift, for example, as a function of the dielectric constant.

## 2.5 Split ring resonator-based antenna

The patch antenna proposed in Section 2.3.1 has several advantages for usage in healthcare applications as previously described. However, it has a series of disadvantages such as narrow bandwidth, low efficiency, and low gain. Current and future healthcare applications are looking for novel antennas with flexibility, size reduction, bandwidth enhancement and so on. The split ring resonator (SRR) design could be suitable to improve the antenna performance. [153] For example, Zhao *et al.* reported the use of the SRR design for reducing the size of a patch antenna, achieving a diminution of 29.3% and also shifting the resonance frequency from 6.6 to 4.67 GHz. [154] Liu *et al.* proposed a patch antenna working with a SRR to achieve higher directionality and gain. [155]

The SRR resonance characteristics are of interest for the antenna design. They have enormous potential for enhancing the antenna performance for energy harvesting applications. [156] Indeed, the SRR behaves as a resonant LC circuit. The condition of resonance in this circuit is defined as  $f_r = (2\pi\sqrt{LC})^{-1}$ , where L depends on the current path on the SRR structure, and C depends on the gap dimensions between the SRR elements.<sup>9</sup> One can combine a patch antenna with SRR elements in order to improve the antenna gain. Mishra *et al.* reported a SSR-embedded patch antenna, achieving the increase in gain with better efficiency and displaying a shift in the resonant frequency. [157] Figure 2.9 shows patch antennas co-integrated with SRR elements. Table 2.5 compares the SRR-based microstrip patch antennas from Figure 2.9.

<sup>9</sup>Split ring resonators are metamaterial structures which are also used to generate a negative dielectric constant (a negative magnetic permeability).

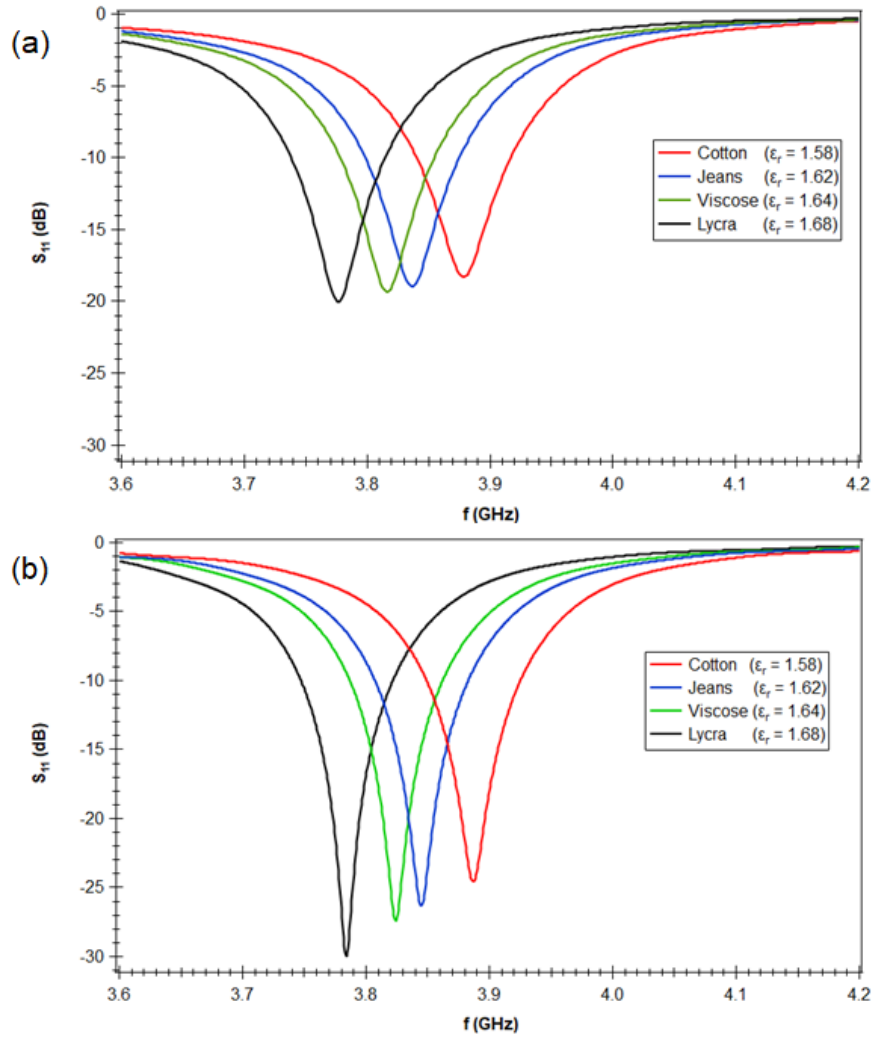


Figure 2.8:  $S_{11}$  parameter as a function of frequency for the patch antenna of Section 2.3.1 with four different types of textiles (cotton, jeans, viscose, Lycra). The textile replaces in each case the FR4 substrate for the same thickness. The numerical computation was performed for the flat position in free space (a) and on Phantom 1 (b).

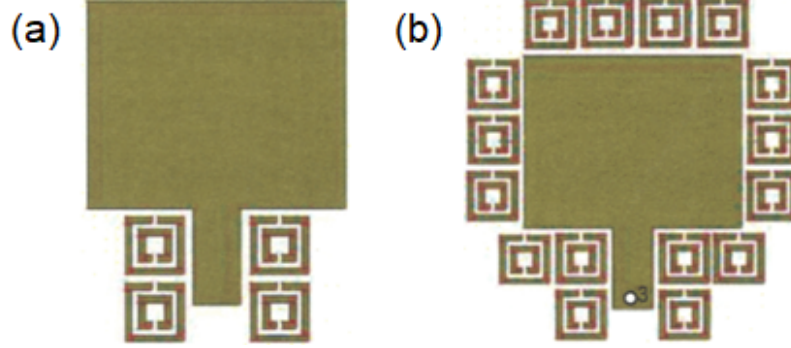


Figure 2.9: (a) SRRs along the feed of the patch. (b) SRRs around edges of the patch. [157]

| Antenna                       | $f_r$ (GHz) | $S_{11}$ (dB) | Gain (dBi) | BW(%) | $\eta$ (%) |
|-------------------------------|-------------|---------------|------------|-------|------------|
| Patch                         | 8.8         | -21.74        | 5.11       | 6.2   | 75         |
| SRR along the feed of patch   | 8.9         | -41.25        | 5.32       | 5.6   | 81         |
| SRR around edges of the patch | 8.5         | -25.48        | 5.51       | 5.2   | 83         |

Table 2.5: Comparison of the SRR-based patch antennas. [157]

We present here a Yagi Uda antenna design that incorporates SRR elements. This antenna is composed of one dipole and multiple square SRRs. The Yagi Uda antenna is a common type of antenna used for TV reception and has good performance features such as high gain and directivity. [158] This novel configuration of antenna aims at increasing the performance of a Yagi Uda antenna by adding SRRs elements.<sup>10</sup> The layout of proposed SRR-based Yagi Uda antenna is shown in Figure 2.10.a. It consists of one dipole of 12 mm each leg with 0.5 mm width. There is one multiple SRR at each side of the dipole. Each SSR is composed of an outer square of 10 mm and an inner square of 8.1 mm. The width of the SRR elements is 0.4 mm. The pattern design of the SSR-based Yagi Uda antenna, obtained via the commercial Layout Editor software, is depicted in Figure 2.10.b. The antenna was numerically simulated and fabricated on a flexible substrate with the following characteristics:

<sup>10</sup>Herraiz-Martinez *et al.* reported on a similar approach with a dipole loaded with split ring resonators. [159]



- Supplier: Goodfellow Cambridge Limited
- Product: DuPont™ Kapton® HN
- Dimension: 100 mm × 100 mm
- Thickness: 0.16 mm
- Kapton thickness: 0.075 mm
- Copper thickness: 0.070 mm

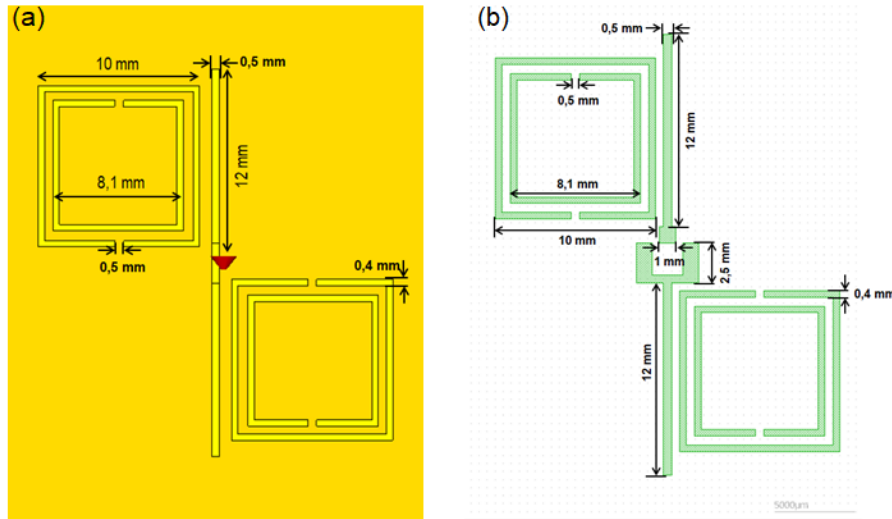


Figure 2.10: (a) Layout (with the Kapton support of 26 mm × 32 mm) of the proposed SRR-based Yagi Uda antenna. (b) Design of the proposed antenna for fabrication onto Kapton laminated Cu substrate. This antenna has a bi-directionnal radiation pattern and radiates equally above and below. It is sometimes an advantage, but most of the times it is a drawback, because it is difficult to say where (i.e. on which substrate) the antenna will be placed. In particular, its matching will degrade.

Photolithography was used to transfer the pattern design from the mask (Figure 2.10.b) into the copper side of the Kapton laminated copper substrate. The different steps of the photolithography process are described in the Table 2.6.

Table 2.6: Summary of the photolithography process for SRR-based Yagi Uda antenna fabrication on Kapton laminated copper.

| No.                    | Step name                    | Description                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                      | Substrate preparation        | <ul style="list-style-type: none"> <li>• Cut the Kapton laminated copper substrate into a 3-inch round shape.</li> <li>• Clean the laminated Kapton substrate with acetone and isopropanol in an ultrasonication bath for 5 min each and blow dry it with N<sub>2</sub>.</li> <li>• Fix the substrate to a silicon wafer using double sided scotch tape (copper side facing up) to facilitate the manipulation of the substrate.</li> </ul> |
| 2                      | Hexamethyldisilazane coating | <ul style="list-style-type: none"> <li>• Coat the copper side of the substrate with hexamethyldisilazane (HMDS) in the LP-III oven.</li> <li>• Parameters: Hexamethyldisilazane coating at 120 °C.</li> </ul>                                                                                                                                                                                                                               |
| 3                      | Photoresist coating          | <ul style="list-style-type: none"> <li>• Machine: Suss Gamma Microtech.</li> <li>• Spin coat manually the S1818 photoresist (~5 ml) on the copper side of the substrate.</li> <li>• Parameters: 3000 rpm at 1000 rpm/s for 60 s.</li> </ul>                                                                                                                                                                                                 |
| 4                      | Soft bake                    | <ul style="list-style-type: none"> <li>• Soft bake of the substrate in the Suss Gamma oven.</li> <li>• Parameters: 110°C for 60 s.</li> </ul>                                                                                                                                                                                                                                                                                               |
| Continued on next page |                              |                                                                                                                                                                                                                                                                                                                                                                                                                                             |

Table 2.6 – continued from previous page

| No.                    | Step name   | Step description                                                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5                      | Exposure    | <ul style="list-style-type: none"> <li>• Machine: MA6/BA6.</li> <li>• Mask name: Kapton laminated Yagi Uda.</li> <li>• Exposure of the substrate.</li> <li>• Parameters: 365 nm, dose 220 mJ/cm<sup>2</sup>, flood exposure, exposure time 7.3 s.</li> </ul> <b>Recipe:</b> NocontactGS.                                                                                                                                                       |
| 6                      | Development | <ul style="list-style-type: none"> <li>• Photoresist development in the hood after post exposure bake in the Suss Gamma oven at 110 °C for 2 min.</li> <li>• Parameters: Remove the substrate from the Si wafer. Soak the Kapton laminate copper substrate in AZ 726 MIF developer for 60 s without shaking, then move it in fresh developer for another 20 s, then rinse with de-ionised water and dry it with N<sub>2</sub> flow.</li> </ul> |
| 7                      | Hard bake   | <ul style="list-style-type: none"> <li>• Hard bake of the developed substrate in the Suss Gamma oven.</li> <li>• Parameters: 120 °C for 2 min.</li> </ul>                                                                                                                                                                                                                                                                                      |
| 8                      | Cu etching  | <ul style="list-style-type: none"> <li>• Cu etching.</li> <li>• Parameters: Soak the laminated Kapton substrate into the FeCl<sub>3</sub> solution (CIF-AR 43) for ~ 1 h with shaking.</li> </ul>                                                                                                                                                                                                                                              |
| Continued on next page |             |                                                                                                                                                                                                                                                                                                                                                                                                                                                |

Table 2.6 – continued from previous page

| No. | Step name | Step description                                                                                                                                                                                                                                                                                      |
|-----|-----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 9   | Cleaning  | <ul style="list-style-type: none"> <li>• Cleaning of photo-patterned laminated Kapton substrate.</li> <li>• Parameters: Soak the sample into DI-water for 30 min, soak the sample into acetone for 15 min, rinse the sample with isopropanol, blow dry the sample with N<sub>2</sub> flow.</li> </ul> |

Once the fabrication process was finished, an uFL connector <sup>11</sup> was attached at the center of the dipole antenna in order to perform the measurements. The fabricated antenna together with the connector are shown in Figure 2.11.a. Figure 2.11.b shows a scanning electron microscope image of the dipole antenna width. We can see that there is a small reduction of the dipole width of around 30  $\mu\text{m}$  (from the nominal width of 500  $\mu\text{m}$ ) due to the fabrication process. This aspect can be easily corrected by adjusting the etching time for the Cu patterns and has a minimal influence on the performance, as we will show below.

The antenna was simulated using the CST Studio Suite software and the characterization was performed in the Welcome platform, UCLouvain. Measurements of the  $S_{11}$  parameter with an Anritsu MS4644B Vector Network Analyzer 40 GHz were carried out to evaluate the performance of the antenna. Figure 2.12 shows the return loss for both numerically computed and measured data, which are in reasonable agreement.

From the results we can see that the resonance frequency  $f_r$  is at 2.55 GHz and the return loss is around -14.71 dB. The resonance frequency is not truly located within the 2.45 GHz ISM band, which extends from 2.4 to 2.5 GHz. However, there are many techniques to shift the resonance frequency towards the left or right side. On the one hand, in fabrication there are two basic forms: by changing the dimensions of the antenna [160] or by using substrates with different dielectric constants. [138] On the other hand, the fabricated antenna can be tuned with a matching network which contains passive elements that are placed just before the antenna input. Figure 2.13 shows the shift to left of the resonance frequency by introducing passive elements. Reaching the target frequency at 2.45 GHz implies adding an inductor of 10 nH in series and a capacitor of 2 pF in parallel. Note that adding passive elements it is not a preferred approach for the integration of the antenna with a RF electronic circuit, as these elements could introduce losses, inductor losses being sometimes higher than capacitor losses. From this point of view, changing the antenna design is more appropriate.

The current density distribution of the antenna is shown in Figure 2.14. The maximum value is 235 A/m. It reveals that the resonance frequency is defined mainly by the outer SRR elements due to a stronger current density distribution on the far apart edges of the SRR elements.

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<sup>11</sup>It is an ultra-small surface-mount coaxial connector with 50  $\Omega$  impedance.

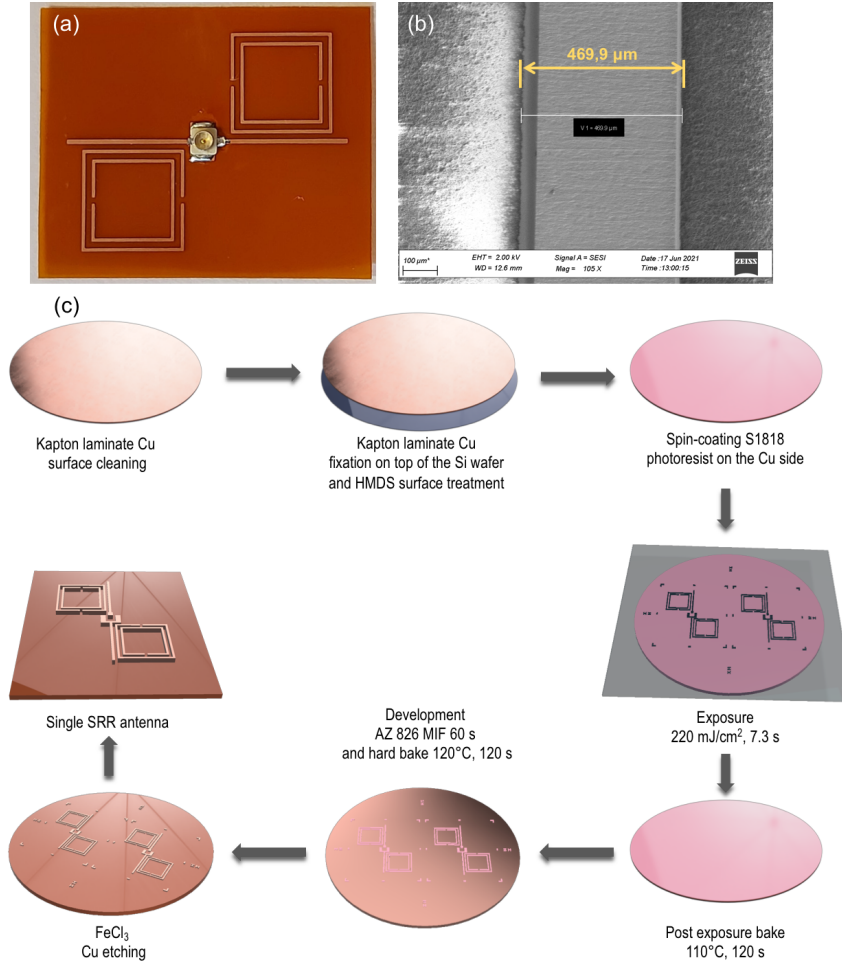


Figure 2.11: Fabricated SRR-based antenna. (a) Fabricated antenna on Kapton with uFL connector. It is important to consider a balun (balanced-to-unbalanced) circuit to connect the coaxial cable (unbalanced line) with the dipole (balanced load) to achieve the best performance. (b) SEM image of the dipole antenna width. (c) Schematics of the fabrication sequence. The SSRs are used to reduce size and to improve gain, directivity, and bandwidth of the antenna.

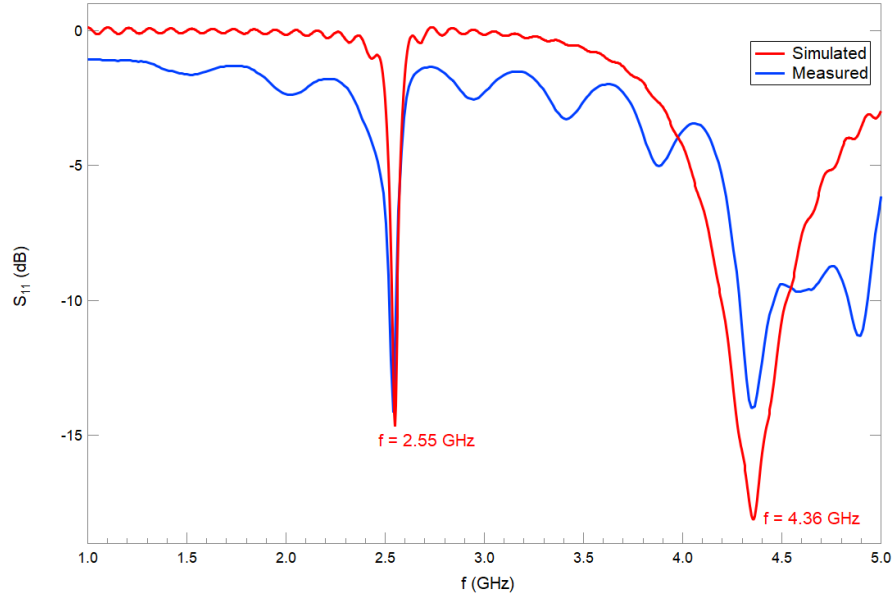


Figure 2.12: Return loss of the SRR-based Yagi Uda antenna: numerically computed and measured.

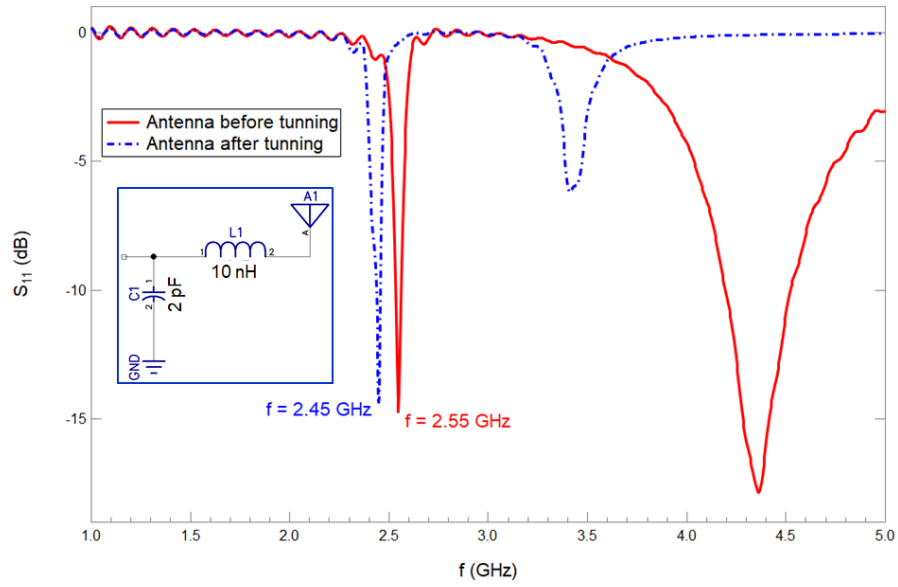


Figure 2.13: SRR-based Yagi Uda antenna tuning at 2.45 GHz by introducing passive elements  $L = 10$  nH and  $C = 2$  pF.

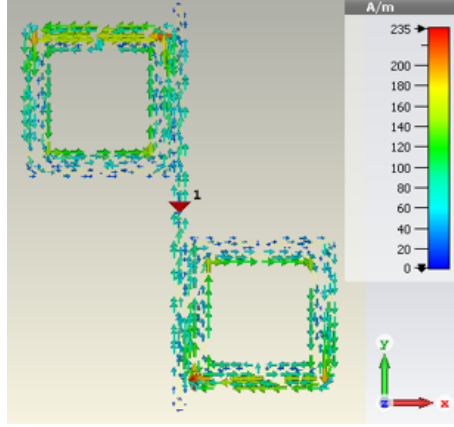


Figure 2.14: Numerically computed result of current density distribution of the SRR-based Yagi Uda antenna.

The estimated 3D gain at the resonance frequency is shown in Figure 2.15. The antenna shows a gain of 0.779 dB in the elevation direction with the Phi angle of 200 degrees.

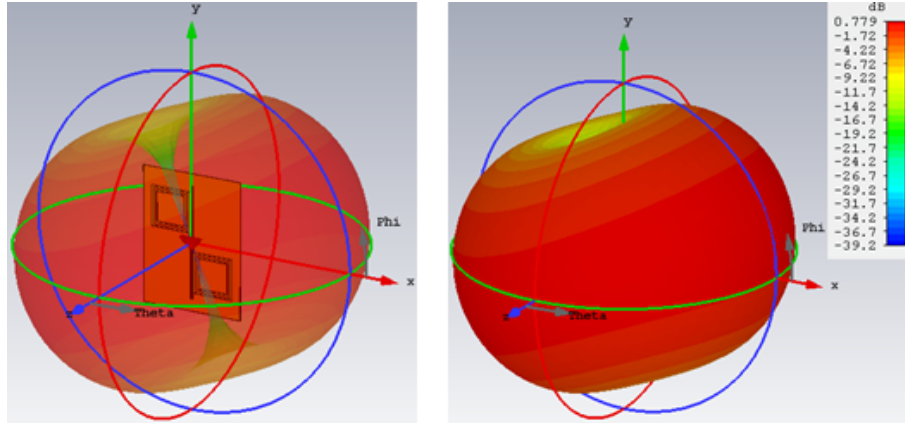


Figure 2.15: Numerically computed result of 3D gain of the SRR-based Yagi Uda antenna.

## 2.6 RF energy harvesting at 2.4 GHz

An RF energy harvesting demonstrator at 2.4 GHz is presented in this Section as a proof-of-concept. The designed antenna from Section 2.3.1 is used here as a receiving antenna to harvest RF energy. A conceptual block diagram for this purpose is shown in Figure 2.16.a.



On the transmission side, an Anritsu continuous wave generator 68377C is used as signal source. It has a broad frequency coverage from 10 MHz to 50 GHz. For transmitting, the Rohde & Schwarz HL024A1/S1 crossed log-periodic antenna is used. This kind of antenna is designed for simultaneous reception of horizontally and vertically polarized waves. It operates in the frequency range from 1 to 18 GHz with a gain of 7 dBi. On the reception side, as mentioned above, the first element is the patch antenna. The received energy goes to an RF-DC circuit.<sup>12</sup>

Figure 2.16.b, shows the output voltage of the RF-DC circuit as a function of the different power levels generated on the transmission side and of the distance between the transmitting and the receiving antennas. To estimate the performance of the proposed patch antenna, a commercial one-quarter wavelength monopole is also used as receiving antenna. It provides an omni-directional radiation pattern at 2.4 GHz and has a gain of 2 dBi. The red curves represent the output voltage of both patch and monopole antennas at a distance of 0.5 m between transmitting and receiving antennas. The blue curve represents the output voltage for the patch antenna at a distance of 1 m. We can see that our proposed patch antenna has a better performance for RF energy harvesting than the commercial monopole antenna.

The output voltage from the RF-DC circuit varies according to the input power level, as shown above. However, it is necessary to get a fixed voltage value to operate standard electronics. Most of the prototypes developed in this PhD thesis operate at 3.3 V. To obtain this value, a DC-DC converter circuit right after the RF-DC circuit is needed. Other DC power outputs (for instance, provided by Li-ion batteries) can be accommodated between the RF-DC circuit and the DC-DC converter. Such an architecture is displayed in Figure 2.17.

The bill of materials for the microcontroller-based flexible PCB is shown in Table 2.7 and the bill of materials for the flexible PCB of the DC-DC circuit is shown in Table 2.8.

## 2.7 RF energy harvesting at 915 MHz

A second demonstrator for RFEH is presented here at 915 MHz. This frequency is also part of the ISM band. A conceptual block diagram for RFEH at 915 MHz is shown in Figure 2.18.a. The RF energy harvesting system is mainly composed of commercial products by Powercast. The

<sup>12</sup>The RF-DC circuit was provided for the purpose of this test by Prof. David Bol (UCLouvain).

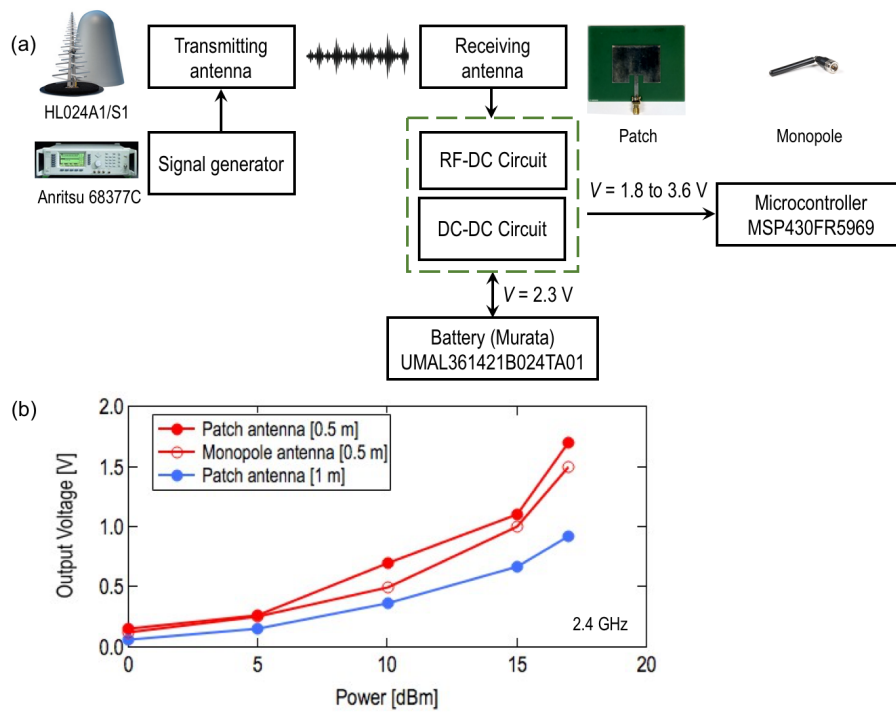


Figure 2.16: (a) Conceptual block diagram for RFEH at 2.4 GHz. (b) Output DC voltage obtained with both patch antenna and monopole antenna.

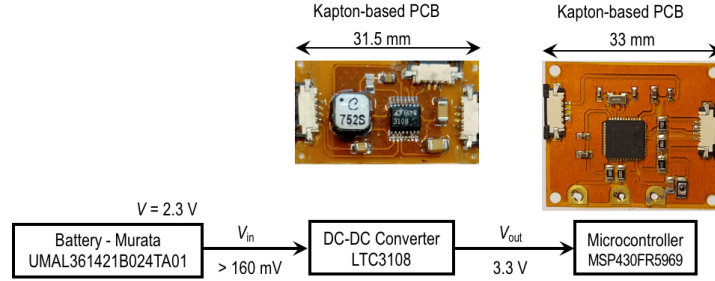


Figure 2.17: The DC-DC circuit shown here is based on a LTC3108 integrated circuit by Analog Devices, requiring a minimum input DC voltage of 160 mV. It is an ultra-low voltage step-up converter and power manager. Here, it is used to supply constant voltage to a microcontroller-based flexible PCB by using the output of a rechargeable battery (2.3 V). The microcontroller is a MSP430FR5969 by Texas Instruments.

| Component | Value or Part Number  |
|-----------|-----------------------|
| C1        | 22 pF                 |
| C2        | 22 pF                 |
| C3        | 0.1 $\mu$ F           |
| C4        | 1 $\mu$ F             |
| C5        | 0.1 $\mu$ F           |
| C6        | 1 $\mu$ F             |
| C10       | 1 nF                  |
| R1        | 4.75 K $\Omega$       |
| R2        | 4.75 K $\Omega$       |
| R3        | 10 $\Omega$           |
| R4        | 10 $\Omega$           |
| R5        | 47.5 K $\Omega$       |
| ES1       | Switch                |
| Y1        | Crystal 32.768 KHz    |
| U1        | MSP430FR5969          |
| Vin       | Flat connector 4 pins |
| I2C       | Flat connector 4 pins |

Table 2.7: Bill of materials (i.e. list of components) for MSP430-based flexible PCB for energy harvesting at 2.4 GHz.

goal is to demonstrate how the integrated electronic board described in Appendix B can work with harvested energy from RF sources.

On the transmission side, the RF wireless power transmitter TX91503

| Component | Value or Part Number  |
|-----------|-----------------------|
| C1        | 1 nF                  |
| C2        | 330 pF                |
| C3        | 1 $\mu$ F             |
| C5        | 220 $\mu$ F           |
| C7        | 220 $\mu$ F           |
| L1        | LPR6235               |
| U1        | LTC3108               |
| FPC-Vin   | Flat connector 4 pins |
| FPC-Vo    | Flat connector 4 pins |
| FPC-Batt  | Flat connector 4 pins |

Table 2.8: Bill of materials (i.e. list of components) for LTC3108-based circuit.

from Powercast was used to generate and transmit a signal at 915 MHz with an output power of 3 W. On the reception side, a dipole antenna DA-915-01 by Powercast was used as a receiving antenna. It has an omni-directional radiation pattern and a frequency range from 902 - 928 MHz. The antenna impedance is 50  $\Omega$  and has an SMA port. The energy received by the antenna goes to a module based on the P2110B integrated circuit from Powercast. The P2110B circuit has built-in RF-DC and DC-DC converters. Therefore, the module is able to provide an output voltage of 3.3 V. The designed flexible printed circuit board has also a flat connector to connect a rechargeable battery as an additional input power source. We observed that placing the antenna at 15 cm from the transmitter is good enough to get a voltage of 3.3 V. When the RF source is not available, the battery can supply power to the electronic board (2.3 V).<sup>13</sup> Figure 2.18.b shows a mechanically flexible prototype for the control board of the electrothermal patch connected to the RF energy harvesting module and the rechargeable battery. More details about this demonstrator are provided in Appendix B. These electronic boards are mechanically flexible, due to the presence of Kapton, but they are also designed to be sewable for easy integration in textiles (see the hole-type connectors in Figure 2.17) as they have circuitry only on one side.

<sup>13</sup>The next logical step of the prototyping implies the presence of the LTC3108 integrated circuit on the P2110B-based flexible printed circuit board, to obtain regulated 3.3 V from the battery, when the RF source is not available. Charging the battery from RF energy harvesting is also possible. The development on this direction, however, was made difficult by the COVID-19 lockdown and the availability of the electronic components.

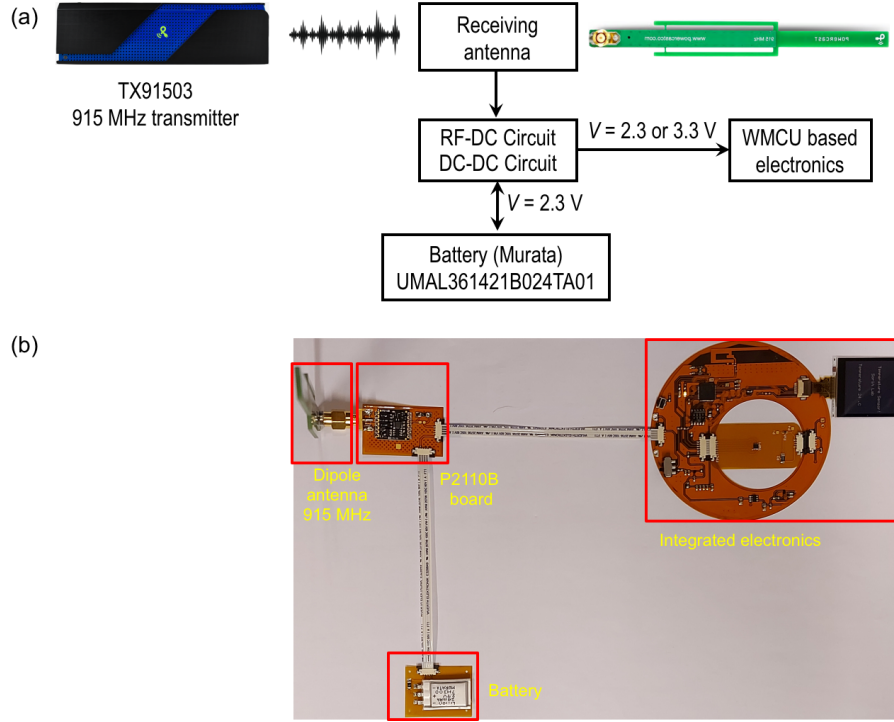


Figure 2.18: a) Conceptual block diagram for RFEH at 915 MHz. (b) Control board and electrothermal patch powered by RFEH at 915 MHz.

## 2.8 Conclusion

Batteries are still the main power source for electronic appliances such as IoT devices for healthcare, which grew rapidly over the last few years. But a battery, rechargeable or not, needs to be replaced from time to time, causing a detrimental environmental footprint. Thus, new energy sources can support the sustainability of future digital technologies. In this sense, RFEH has a promising future for ultra-low-power IoT-based devices for healthcare, since RF sources are ubiquitous due to the large deployment of wireless communication infrastructures for different services.

Due to the low power density incident on the RFEH system, each of its stages must be carefully designed so as not to affect the overall RFEH performance. The antenna is one key component for this purpose. It should be planar, small, and flexible in order to integrate easily with small and compact wearable devices on the human body. Given these demands, we presented in this Chapter the simulation, design and

fabrication of two antennas. The first one is a patch antenna which is planar and small. It was used as a receiving antenna at 2.4 GHz for harvesting RF energy. The patch antenna shows good performance compared to a commercial monopole antenna. The second antenna is an SRR-based Yagi Uda antenna. The purpose of the second antenna was to explore new techniques to enhance its performance, such as the addition of SRR elements. Moreover, the fabrication process for a flexible antenna on Kapton was defined and calibrated. In both cases, the advantage of the numerical computation has been used to evaluate the antenna performance in advance.

Apart from Kapton, textiles are also important materials in wearable technologies. Research institutions in Belgium, such as Ghent University, and worldwide have built up their own laboratories to develop smart textiles, namely fabrics enabling various functional components such as antennas to be embedded in them. The idea of incorporating Kapton-based antennas in between textile sheets where the devices can be hidden, while maintaining the flexibility and comfort of the textile is very promising. Moreover, wearing clothes integrated with antennas and sensors defined by embroidery will allow parameters describing our physical condition to be continuously passed on to specialised medical staff.

In conclusion, the presented antenna designs are the starting point to fabricate planar, small and flexible antennas to be integrated with wearable devices and to contribute in achieving self-powered systems using RFEH. Two RFEH systems working at 915 MHz and at 2.4 GHz bands were presented as a proof of concept to supply power to low-power electronic devices. The two demonstrators can be integrated into a single platform to achieve multiband operation and to increase the amount of harvested RF energy. In that sense, e-peas, a UCLouvain-born company, already offers integrated circuits for RFEH at 915 MHz and 2.4 GHz. These products can be integrated with the proposed antennas and with other antennas operating in the ISM bands.



## 2.9 List of abbreviations

|           |                                    |                    |                                              |
|-----------|------------------------------------|--------------------|----------------------------------------------|
| AgNWs     | :Silver nanowires                  | $\tan\delta$ :     | Dissipation factor                           |
| BMR       | :Basal metabolic rate              | $W$ :              | Width of the patch                           |
| BW        | :Bandwidth                         | WLAN :             | Wireless local area network                  |
| $c$       | :Speed of the light                | WMCU :             | Wireless microcontroller unit                |
| C         | :Capacitance                       | WSN :              | Wireless sensor network                      |
| $C$       | :Heat capacity                     | $Z$ :              | Impedance                                    |
| CST       | :Computer simulation technology    | $\Delta L$ :       | Fringing length                              |
| DC        | :Direct current                    | $\epsilon_{ref}$ : | Effective dielectric constant                |
| $E$       | :Electric field strength           | $\epsilon_r$ :     | Relative permittivity                        |
| FE        | :Flexible electronics              | $\eta$ :           | Efficiency                                   |
| $f_r$     | :Resonance frequency               | $\kappa$ :         | Thermal conductivity                         |
| $h$       | :Thickness of the substrate        | $\lambda$ :        | Wavelength                                   |
| IFA       | :Inverted-F antenna                | $\rho$ :           | Mass density of biological tissue            |
| IOT       | :Internet-of-Things                | $\sigma$ :         | Electrical conductivity of biological tissue |
| L         | :Inductance                        |                    |                                              |
| $L$       | :Length of the patch               |                    |                                              |
| $L_{eff}$ | :Electrical length                 |                    |                                              |
| PCB       | :Printed circuit board             |                    |                                              |
| PDMS      | :Polydimethylsiloxane              |                    |                                              |
| PI        | :Polyimide                         |                    |                                              |
| RFEH      | :Radio-frequency energy harvesting |                    |                                              |
| SAR       | :Specific absorption rate          |                    |                                              |
| SRR       | :Split ring resonator              |                    |                                              |
| $S_{11}$  | :Return loss                       |                    |                                              |



## Chapter 3

# Electrothermal patches driving the transdermal delivery of insulin

El sabio ignora lo trágico de la pasión y el temor a la muerte, de la misma manera que desconoce la fuerza y el riesgo, el heroísmo bárbaro, grotesco o sublime.

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Emil Cioran

### 3.1 Introduction

Transdermal skin patches represent key products from research in materials science. The medical impact of transdermal drug delivery as non-invasive and painless system is constantly highlighted when compared to intravenous drug delivery routes. The potential to maintain steady-state drug levels in blood after topical application, with the amounts being varied by changing the drug concentration and components in the patch has been put forward in favor over oral drug delivery [13, 161–164]. The first transdermal patches consisted of a combination of a reservoir containing the drug and a rate-controlling membrane [165]. Uncontrolled drug delivery and potential drug overdose are the major limitations of these passive transdermal skin patches. A key technology advancement to achieve efficient and controlled delivery of therapeutics is the development of on-demand dosage transdermal skin patches [166–171] with no liquid reservoir, where drug delivery is initiated upon an external stimulus from the drug-incorporated matrix.

A catalogue of different transdermal patches is currently developed for actively delivering various therapeutic agents including lipophilic, low-molecular weight to water-soluble macromolecules such as peptides and proteins, which have limited transport across the outermost layer of the epidermis the *stratum corneum* [47, 163, 164, 170, 172, 173].

The use of on-demand transdermal patches is clearly a key medical challenge for chronic diseases such as diabetes. Diabetes is one of the leading causes of early mortality worldwide [174], mainly caused by cardiovascular diseases.<sup>1</sup>

Diabetes complications often ensue because of the long-term uncontrolled blood glucose levels despite the current treatments. All oral antidiabetics are unable to achieve a long-term glycemic control, leading clinicians to finally prescribe insulin administration [175]. So far, insulin is delivered by numerous daily subcutaneous needle injections through pen or catheters connected to pumps. Unfortunately, these methods are both painful and inconvenient, as the invasive multiple injections significantly deteriorate the life quality of patients [176]. The discomfort associated with this type of administration often leads diabetic patients to neglect or even give up the therapy and thereby induces variable glycemic control, as well as the development of complications. Efficient and non-invasive dosing of insulin remains an important challenge with different technical achievements reported over the last years. The reported methods comprise along to inhaling approaches (*e.g.* rapid-acting inhaled insulin - ExuberaR) and nasal delivery (under phase 2 and 3 clinical trials) [177], transdermal delivery protocols [58, 163, 172, 178–181].

Besides of the work of Prausnitz and co-workers, who demonstrated that the removal of full epidermis by microdermabrasion significantly increases insulin skin at levels sufficient to reduce blood glucose level [182, 183], insulin delivery using microneedles is certainly one of the most promising transdermal delivery approach [47, 179, 180]. The first generation of polymer-based microneedles, dissolved during the contact with the skin, are currently replaced by hydrogel-based microneedles [179]. The latter enable to release hydrophilic drugs by swelling in the dermis layer and to be withdrawn from the skin owing to their toughness [47]. Application of a hydrogel-based microneedle patch carrying 62 insulin

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<sup>1</sup> The diabetes prevalence in Latin America is around 9.2% of population aged 20 to 79 years, while Ecuador shows a lower value of 5.5%. According to the National Institute of Statistics and Census (INEC), diabetes was the second cause of death in Ecuador. In 2018, 6507 deaths were recorded for diabetes, representing cca. 10% of the total deaths. The number of diabetes deaths were around of 4,890 deaths in 2019. Mortality caused by diabetes mellitus is typically higher in the provinces of Guayas, Los Ríos and Manabí, located on the Pacific coast.

units ( $1 \text{ IU} = 35 \mu\text{g}$ ) has lowered the glucose level of a diabetic rat by 10% after 2 h and by 63% after 12 h point administration. Yet, to achieve sufficient insulin delivery iontophoresis-assistance was necessary. In line with this effort, alginate-based microneedle array-engineered patches loaded with Exendin 4 and glucose oxidase have been recently proposed by Chen and co-workers for type 2 diabetes therapy [162]. While skin iontophoresis principle generated commercial platforms in the past [184], electrode complexity and corrosion upon storage, as well as stringent requirements on drug formulation to diminish the role of competing ions involved in the process hamper the progress and the hybridization of the technology with other techniques that modulate the *stratum corneum* to facilitate specific paths for insulin.

Different to the microneedle and iontophoresis systems, heat-assisted microporation enhances transdermal delivery of insulin. Direct laser-based heating is limited to the use of Er:YAG, whose light output is strongly absorbed by water, which results in about 15 times better light absorption by the skin and favored transdermal insulin delivery [185]. While the light of near-infrared (NIR) lasers is not readily absorbed by the skin and heating effects are minor, the combination with NIR absorbing materials was proven to be beneficial for insulin permeation through the skin [177]. The main current limitation of this approach is the integration of powerful laser diodes into the patches. The state-of-the-art of different developed systems for controlled insulin delivery via skin is summarised in Figure 3.1.

Here, we engineer a transdermal patch for insulin delivery using standard components in wearable systems. **The key novel aspect of this system is the use of an electrothermal protocol for on-demand release of insulin with enhanced dose delivery through the skin together with the possibility of drug reloading after release.** Our results unveil that nano-perforated gold thin layers, generated onto Kapton sheets (50 - 125  $\mu\text{m}$  in thickness) using colloidal lithography, present outstanding electrothermal capabilities. These platforms can be further loaded with biological molecules by post-coating the layer of gold nanoholes (Au NHs) with a micrometer-thick reduced graphene oxide (rGO) drug reservoir.

The reliability of rGO in electrothermal applications [186] together with good insulin loading capacity [58, 187] and insulin release ability, owing to the formation of a thermal gradient weakening non-covalent insulin interactions with rGO, suggest it as an ideal transdermal drug release matrix in connection with electrothermal patches.<sup>2</sup> By using *in*

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<sup>2</sup>Besides being water soluble, offering both powder or solution formulation capa-

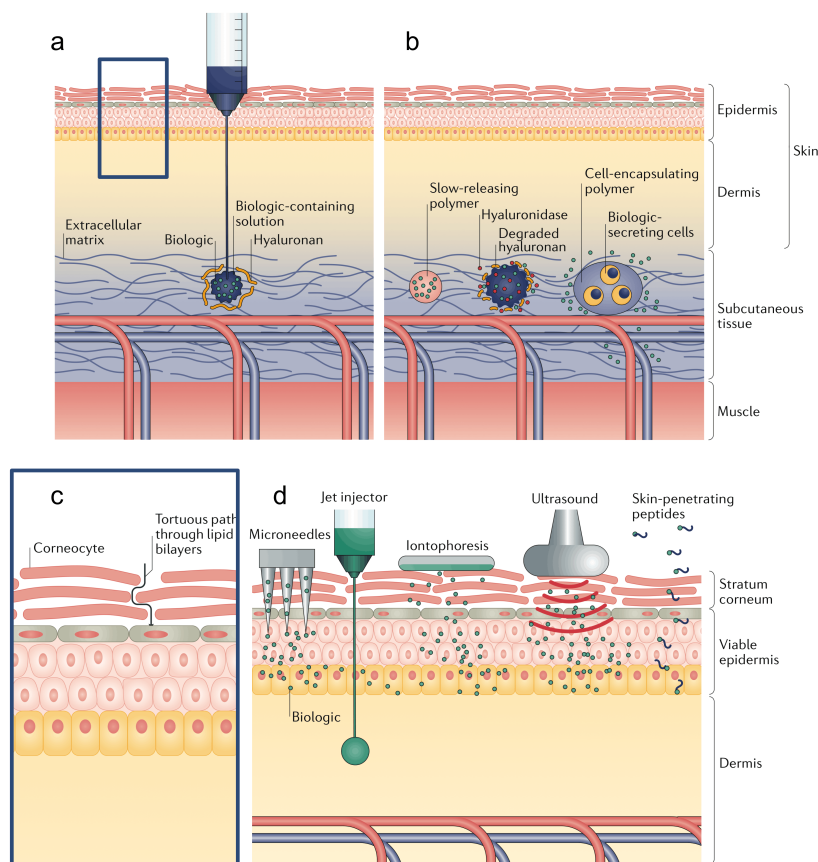


Figure 3.1: State-of-the-art in skin delivery of therapeutic agents summarising the challenges with the involved barriers [(a) - subcutaneous route) and [(c) - transdermal route] and envisaged solutions [(b) - dispersion and diffusion of drugs] and [(d) - transport of drugs across epidermis]. Controlled-release techniques are used for tackling issues with the extracellular matrix proteins. Matured technologies for transport through *stratum corneum* include microneedles, jet injectors, iontophoresis and ultrasound skin patches as well as epidermis-penetrating peptides. Adapted from Ref. [161]. The real thickness of the skin layers is not scaled in the drawing. The epidermis layer is cca 60  $\mu\text{m}$  thick and the dermis layer thickness is cca 500  $\mu\text{m}$ . The subcutaneous tissue thickness in males is larger than 1.5 mm, and typically it is higher than 2.5 mm in females. These parameters were taken into account in the numerical work presented in this PhD thesis. For persons with significant body mass index the subcutaneous layer can be 10 times thicker.

bilities, and facilitating thus the mixing with drugs, it has angiogenesis properties of inducing the intracellular formation of reactive oxygen species and reactive nitrogen species. The chemical functionalization can enhance easily the afore-mentioned advantages. Thus, there is still optimism in the nanotechnology community regarding modern chemically engineered graphene oxide as a completely safe and useful material for drug delivery.

*vitro* and *in vivo* experiments, the efficiency of the designed rGO-based electrothermal insulin delivery patch is assessed. The electrothermal system achieves highly-controlled insulin delivery and enables efficient management of blood glucose concentrations without pain and stress.

The patch configuration requires an electrical power density below  $250 \text{ mW/cm}^2$  to reach a steady state temperature of  $50^\circ\text{C}$  in a few seconds. The resulting electrothermal properties are similar to the state-of-the art of graphene aerogels for efficient Joule heating up to  $50^\circ\text{C}$  using  $50 \text{ mW/cm}^3$  [188], free-standing rGO films, attaining  $90^\circ\text{C}$  at  $236 \text{ mW/cm}^2$  power density [189], chemical vapor deposited graphene on Cu foils [190],  $\text{AuCl}_3$  doped and embedded in polyethylene-terephthalate, requiring  $200 \text{ mW/cm}^2$  to reach a steady state temperature of  $100^\circ\text{C}$ , or rGO thin films on polyimide substrates reaching  $50^\circ\text{C}$  steady-state temperature at an input power density of  $250 \text{ mW/cm}^2$  [191].

## 3.2 Materials and methods

### 3.2.1 Fabrication of gold nanoholey thin films on Kapton substrates

Kapton HN polyimide foils (thickness of 50, 75 and  $125 \mu\text{m}$ ) were obtained from DuPont. Rectangular  $20 \times 10 \text{ mm}^2$  and circular pieces with 20 mm diameter were cleaned with acetone in an ultrasonic water bath for 30 minutes, followed with isopropanol for 10 minutes and then dried under a nitrogen flow. A monolayer of 980 nm polystyrene beads (Microparticles GmbH) was first deposited in the middle of the Kapton surface with an area of  $8 \times 10$  or  $11 \times 11 \text{ mm}^2$  by self-assembly. To reduce the size of the particles, plasma etching was employed (see Table 3.1 for further details). The samples were coated with 2 nm Ti followed by 40 nm Au at a constant deposition rate of 0.1 nm/s using physical vapor deposition. The polystyrene beads on top of the Kapton were removed by dissolution in chloroform (overnight). To facilitate the application of the bias voltage, 2 nm Ti and 40 nm Au contacts were further deposited on the K/Au NHs patches and connected on the back side of the devices with flat flexible connectors (FFCs) and flat flexible cables.

Figure 3.2 includes scanning electron microscopy (SEM) images of structures of different gold nanoholes arrays deposited on Kapton formed by colloidal lithography by changing the etching time and an optical image of the active side of a disc type unpatterned device. Scanning electron microscopy images were obtained using an electron microscope ULTRA 55 (Zeiss) equipped with a thermal field emission emitter and three different detectors (Energy selective Backscattered Detector with filter

grid, high efficiency In-lens Secondary Electron Detector and Everhart-Thornley Secondary Electron Detector).

In Table 3.1 we present different structural parameters of the fabricated devices. The etching time corresponds to the following conditions (UCLouvain) power of 30 W, 30 sccm O<sub>2</sub>, 1 sccm SF<sub>6</sub>, pressure of 6 mTorr,  $T = 15^{\circ}\text{C}$  (sample), and DC bias voltage of 163 V.

We used standard Kapton films (thickness of 50 microns) for the integration of electrothermal skin patches, that can be powered via rechargeable Li-ion batteries. Temperature recording was verified by a thermal camera to ensure that the patch induces a homogenous distribution of the temperature across the active surface without the presence of any hot spots. Maps of temperature changes were captured by an infrared camera (Thermovision A40) and treated using ThermoCam Researcher Pro 2.9 software. The temperature was also controlled by a packaged sensor TMP116, integrated on the backside of the device as presented in Appendix A and Appendix B.

### **3.2.2 Post-coating of gold nanoholey thin films on Kapton substrates with reduced graphene oxide**

Graphene oxide (GO) powder (D10) was purchased from Graphenea. The rGO was formed by adding hydrazine hydrate (0.50 ml, 32.1 mM) to 5 ml GO aqueous suspension (0.5 mg/ml) in a round bottom flask and heated in an oil bath at  $100^{\circ}\text{C}$  for 24 h. During this time, the reduced GO gradually precipitates out of the solution. The product was isolated by filtration over a polyvinylidene difluoride membrane with a  $0.45\text{ }\mu\text{m}$  pore size, washed copiously with water ( $5 \times 20\text{ ml}$ ) and methanol ( $5 \times 20\text{ ml}$ ), and dried in an oven at  $60^{\circ}\text{C}$  for 6 h. An aqueous suspension of rGO (1 mg/ml,  $5\text{ }\mu\text{l}$ ) was drop-casted three times onto K/Au NHs and allowed to dry over night at  $70^{\circ}\text{C}$ . This resulted in a rGO film of about 5 to  $25\text{ }\mu\text{m}$  thickness. Typical electrical conductivity of the rGO is 200 S/m, providing thus a resistance per square of about 200 to  $1000\text{ }\Omega$ . This resistive drug reservoir is integrated into a nanoporous heater; thus, the numerical modeling of the resistance network provided by the Au and rGO layers is not straightforward. We have not worked out the details of this electrical aspect of the composite Au-rGO heater. The devices are calibrated as displayed in Figure 3.5. In the thermal model, detailed in the sequel, this rGO layer is not taken physically into account. However, since the rGO drug reservoir is in contact with the skin, the thermal model includes a heat transfer parameter (i.e. the thermal conductance coefficient) for the coupled Au-rGO-skin system that varies three orders of magnitude.

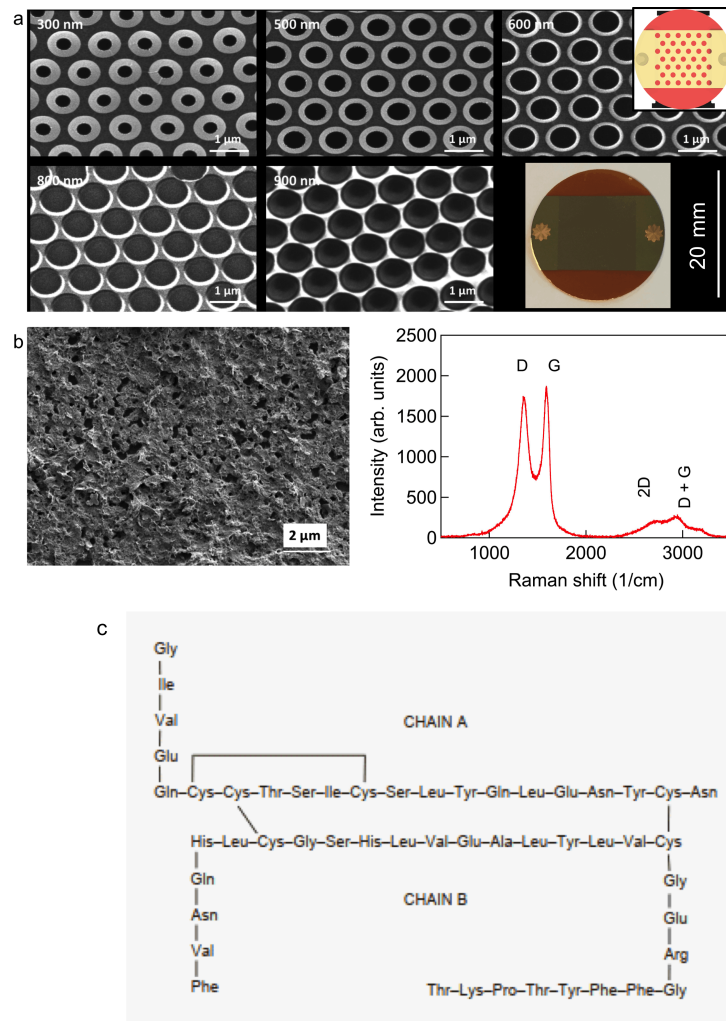


Figure 3.2: (a) SEM images of K/Au NHs devices and optical image of the heater design in the skin patches. The inset is a sketch, but the optical image shows the top side of a real device where the Au layer is continuous. A real device, optically imaged from the back, is shown in Appendix A. (b) SEM and Raman analysis of K/Au NHs-rGO devices. (c) Schematic structure of insulin<sup>a</sup>.

<sup>a</sup>Insulin is a peptide hormone produced by the pancreatic islets. The human insulin protein is composed of 51 amino acids, and has a molecular mass of 5808 Da. Insulin is composed of two peptide chains, labeled A and B, linked by two disulfide bonds - enabled by the thiol side chain of cysteine, and a third disulfide bond is formed within the A chain, among two cysteine units. Typically, the A chain consists of 21 amino acids and the B chain of 30 amino acids, as illustrated. These dimers, in the presence of zinc ions, associate into hexamers. Monomers and dimers diffuse fast into blood, whereas hexamers diffuse slowly. Insulin was the first protein to be fully sequenced.

|             | Etching time    | Hole diameter   | Format             | Resistance ( $\Omega/\square$ ) |
|-------------|-----------------|-----------------|--------------------|---------------------------------|
| K/Au NHs300 | 17 minutes 30 s | $300 \pm 30$ nm | Disk and Rectangle | $3.2 \pm 0.2$                   |
| K/Au NHs500 | 15 minutes 10 s | $520 \pm 30$ nm | Disk and Rectangle | $4.2 \pm 0.2$                   |
| K/Au NHs800 | 7 minutes       | $800 \pm 30$ nm | Disk and Rectangle | $8.4 \pm 0.2$                   |
| K/Au NHs900 | 5 minutes       | $920 \pm 30$ nm | Disk and Rectangle | $22.3 \pm 1.3$                  |

Table 3.1: Etching times for colloidal masks with corresponding hole diameters, substrate format and electrical resistance values for the designed electrothermal patches. Please note that also Oxford Plasmalab 80 Plus, located at IEMN, Lille, France, has been used for this step. The following conditions were employed: 30 sccm  $O_2$ , 2 sccm  $SF_6$ , pressure: 10 mTorr, power: 70 W, DC bias voltage: 130 V,  $T = 17^\circ C$  (sample). Accordingly, the etching duration and the particle size were: 3 minutes (950 nm), 6 minutes (830 nm), 8 minutes (700 nm), 9 minutes (550 nm), 11 minutes (270 nm).



Micro-Raman spectroscopy measurements were performed on a high resolution system (Horiba Jobin Yvon) combined with a 473 nm (1 mW) laser diode as excitation source. Visible light is focused by a 100 $\times$  objective. The scattered light is collected by the same objective in backscattering configuration and detected by a CCD camera. A typical Raman spectrum of rGO-coated gold nanoholey electrothermal patches is presented in Figure 3.2.<sup>3</sup>

### 3.2.3 Insulin loading onto the electrothermal patches

Glycerin, human insulin and fluorescein isothiocyanate-labeled insulin (FITC-insulin) were purchased from Sigma-Aldrich. The human insulin ELISA kit was from Invitrogen and shows an analytical sensitivity of 0.17  $\mu$ IU/ml and an assay range of 0.1 - 250  $\mu$ IU/ml.

To load the patches, 30  $\mu$ l of insulin (100  $\mu$ g/ml in water) was dropped onto the electrothermal patch and kept for 2 h at 4°C. Then the patch was washed three times with water to remove any unbound insulin. The concentration of insulin loaded onto the rGO coating of the patch was determined using high-performance liquid chromatography (HPLC). A standard human insulin calibration curve was generated beforehand from a series of insulin solutions ranging from 1 to 100  $\mu$ g/ml as shown in Figure 3.3. The concentration of insulin in the patch was determined according to  $[\text{insulin}]_{\text{rGO}} = [\text{insulin}]_{\text{initial}} - [\text{insulin}]_{\text{supernatant}}$ , with  $[\text{insulin}]_{\text{rGO}}$  the concentration of insulin on the rGO matrix ( $\mu$ g/ml),  $[\text{insulin}]_{\text{initial}}$  the concentration of insulin in solution (100  $\mu$ g/ml) and  $[\text{insulin}]_{\text{supernatant}}$  the concentration of insulin in supernatant ( $\mu$ g/ml).

High-performance liquid chromatography analysis was performed with a LC2010-HT (Shimadzu) using a C4 QS Uptisphere® column (30 nm, 250  $\times$  4.6 mm) heated at 40°C. The mobile phase is trifluoroacetic acid (0.05%) in water and the eluent is trifluoroacetic acid (0.045%) in acetonitrile (1 ml/minute). The flux was 100% mobile phase for 5 minutes, a linear gradient from 0 - 80% of fluent for 15 minutes, then 80% fluent for 5 minutes. The detector wavelength used was 215 nm.

### 3.2.4 Electrothermal release of insulin into solution

Release experiments were performed into 1 ml deionized water. Different bias voltages (and dc electrical currents) were applied to the electrothermal patches for various time intervals (1 - 10 minutes). The

<sup>3</sup>The D (1350  $\text{cm}^{-1}$ ) and G (1580  $\text{cm}^{-1}$ ) bands are assigned to the local defects/disorder and the  $\text{sp}^2$  graphitized structure of rGO. [D. Graf *et al.*, Nano Lett. 7, 238 (2007).]

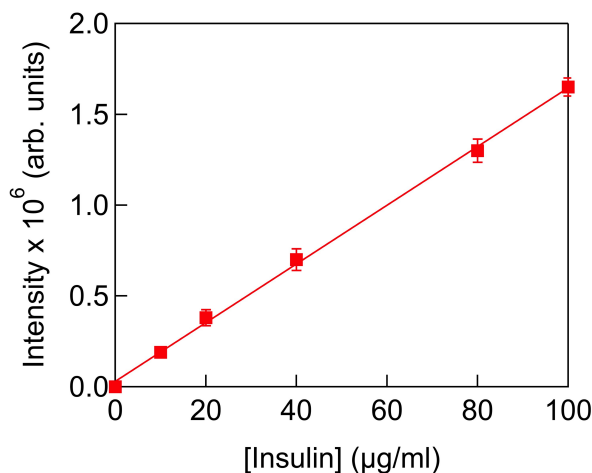


Figure 3.3: Calibration curve of insulin determined by HPLC and linear fit to the data.

quantity of released insulin was determined by assessment of insulin concentration in the supernatant, after electrothermal activation, by HPLC.

### 3.2.5 Characterization of electrothermal patches

Absorption spectra were recorded using a Perkin Elmer Lambda UV-Vis 950 spectrophotometer in a 1 cm quartz cuvette. The wavelength range was 200 - 1100 nm.

### 3.2.6 Determination of insulin activity

The activity of electrothermal released insulin was evaluated *in vitro* on a human hepatic HepG2 cell line model using native insulin as a positive control and the same culture without insulin as a negative control. After overnight culture in a serum-free and glucose-free culture medium, HepG2 cells were incubated for 1 h without insulin (negative control), with native insulin (positive control) and with electrothermally released insulin at a physiological active concentration of 200 nM. After 1 h of incubation, cells were lysed and proteins were collected. Expression of p-Akt and Akt proteins was evaluated by Western blotting analysis. For Western blotting experiments, 40 μg of total proteins of each condition were loaded and separated onto a polyacrylamide gel, then transferred on a nitrocellulose membrane. Immunoblotting for p-Akt and Akt was performed using anti p-Akt specific antibody (Thr-308,

Cell signaling), anti Akt specific antibody (sc-8312, Santa Cruz) and fluorescence-coupled secondary antibodies against both mouse and rabbit primary antibodies. Analysis of the Western blot was performed using Odyssey revelation process and ImageJ quantification technique. A one-way ANOVA test was carried out. Fluorescence images were acquired on a TS 100 Eclipse Nikon microscope equipped with a green fluorescent protein filter cube (excitation 469/35 and emission 525/39) and 10× and 40× objectives.

### 3.2.7 *In vitro* skin permeation experiments

Skin permeation studies were performed using fresh mice skin. For this, mice C57BL/6 were anaesthetized with isoflurane, shaved with an electric shaver (Philips Series 7000) and further treated with a depilatory cream (Veet) for 1.5 minutes. Then mice were killed by cervical dislocation and the skin from the back of the mice was cut into pieces of at least 20 mm in diameter and preserved in Dulbecco's modified Eagle medium (DMEM) supplemented with gentamicin (0.4%). The thickness of the skin was determined with a digimatic micrometer (Mitutoyo) and was  $600 \pm 5 \mu\text{m}$ . A special designed static Franz diffusion cell exhibiting an effective area of  $0.78 \text{ cm}^2$  was adapted for electrothermally-initiated permeability tests. After filling the receptor compartment with degassed phosphate buffer saline (PBS) with pH 7.4, the solution was maintained at  $32^\circ\text{C}$  using a circulating bath (Julabo) and stirred with a magnetic stirring bar at around 500 rpm. The mouse skin was carefully clamped between the donor and the receptor compartment (8 ml). Pre-incubation in the receptor compartment medium for 20 minutes was performed before the electrothermal patch was applied to the skin previously wetted with  $30 \mu\text{l}$  of a glycerin solution (50%) to insure contact between the patch and the skin. Electrothermal patches loaded with 2.8 IU were used for the permeation studies. Electrothermal activation was performed upon continuous application of  $250 \text{ mW/cm}^2$  electrical power density for 1 minute (corresponding to cca.  $52^\circ\text{C}$ ). At determined time intervals,  $300 \mu\text{l}$  aliquots of diffused solution were removed from the receptor compartment and analysed using HPLC. After each sampling, an equal volume of fresh diffusion medium was added to the receptor compartment to maintain a constant volume. All experiments were performed in triplicates.

The release and permeation profiles were determined by plotting the cumulative amount of insulin in the receptor compartment ( $Q_{exp}$ ) against time,  $Q_{exp} = c_n^{insulin} \times V_{insulin} + \sum_{i=1}^{n-1} c_i^{insulin} \times V_{insulin}$ , with  $Q_{exp}$  the cumulative amount of insulin diffused through the skin ( $\mu\text{g}$ ),

$c_n^{insulin}$  the amount of insulin ( $\mu\text{g}$ ) determined at the  $n^{th}$  sampling interval, and  $V_{insulin}$  the volume of the acceptor phase (receptor compartment) (ml). The insulin flux ( $J_{insulin}$ ) was determined according to  $J_{insulin} = A_{insulin}/S_{insulin}$ , with  $J_{insulin}$  is the flux of insulin through the skin ( $\mu\text{g}/(\text{cm}^2\text{h})$ ),  $A_{insulin}$  the linear slope of the cumulative amount versus time curves in equilibrium conditions ( $\mu\text{g}/\text{h}$ ), and  $S_{insulin}$  the surface of the membrane of the Franz cell. To estimate the amount of insulin trapped in the skin, the skin was added into water/ice mixture for 10 minutes and sonicated in the presence of  $\text{ZnO}_2$  beads (4 mm in diameter), before being centrifuged for 30 minutes at 13500 rpm using an ultracentrifuge (Midi Scanfuge ORIGIO). The liquid phase was collected and filtrated through a  $0.1 \mu\text{m}$  Nylon filter (Whatman Puradisc 13 mm) and the amount of insulin was determined.

The Franz cell used for transdermal insulin delivery experiments comprises two parts and it is shown in Figure 3.4. The bottom part consists of a carved disc of 35 mm in outer diameter (7 mm in thickness) and of 19.5 mm inner diameter (6 mm in thickness). The piece is pierced at its center with a hole of 1 cm in diameter. Two 6 mm thick sculpted zones of  $13.0 \times 4.7 \text{ mm}^2$  and  $11.0 \times 3.9 \text{ mm}^2$  are accommodated into the disc to facilitate the electrical connections to instrumentation.

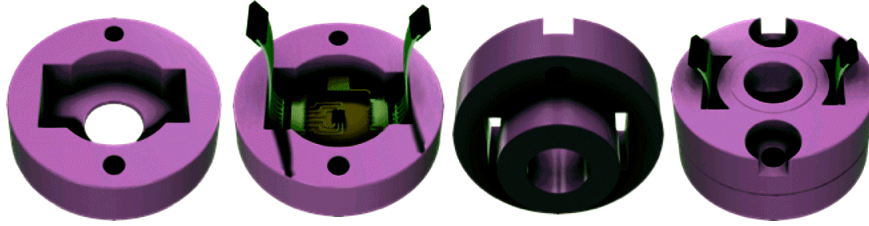


Figure 3.4: Schematics of the Franz cell used for transdermal insulin delivery experiments.

At the outer part, there are two tapped holes having 3.3 mm in diameter for connection to the top part. The top part (35 mm in diameter, 9 mm in thickness) continues with a cylinder of 19.5 mm in diameter, 6 mm in thickness. Two exits having the same dimensions as that of the sculpted zones in the bottom part are carved for accessing the electrical contacts of the patch. Two 4 mm in diameter holes are drilled on the outer part for accommodating the fixation screws.

### 3.2.8 *In vivo* studies

Delivery of insulin from the electrothermal patch was investigated in C57BL/6 mice as model. Before the experiment, the back of the

mouse was shaved (Philips Series 7000). The shaved area was further treated with a depilatory cream (Veet) for 1.5 minute to eliminate all the remaining hair. The next day the mice fastened for 4 h and the blood glucose level was determined using a glucometer. Before application of the electrothermal patch, the mice are anesthetized with isoflurane for 2 minutes (level 2, 1 l/minute air) and the blood glucose level was determined again. Then, the electrothermal patches loaded with 6 IU (210  $\mu$ g insulin) were applied to the shaved area and fixed with the help of adhesive tape (Sparadrap Micropore, 2133). The patch was activated for 10 minutes at 250 mW/cm<sup>2</sup> electrical power density under anesthesia and then removed. Blood glucose level values determined by a glucometer were plotted against time to obtain the blood glucose level-time profiles.

After C57BL/6 mice were subjected to electrothermal treatment, their skin was excised and immersed into formaldehyde (4% in PBS) for 24 h, followed by dehydration (STP120, Leica) through a graded series of alcohols each for 2 h [70% (2 times), 90% (2 times), 100% (3 times)]. Then, the skin was immersed into xylene (2 times for 2 h) followed by immersion into a paraffin bath of 60°C (2 times for 2 h). A skin section of 5  $\mu$ m thickness was cut from the sample (RM2143, Leica) and stained for microscopic examination. Giemsa staining was achieved through the immersion of the skin into: acetone (3 minutes, 2 times), ethanol (90%, 2 minutes), ethanol (70%, 2 minutes), ethanol (50%, 2 minutes), ethanol (30%, 2 minutes), water (2 minutes), PBS (pH 6.8, 0.3 M, 5 minutes), Giemsa (1/10 in PBS, 45 minutes), PBS (pH 6.8, 0.3 M, 2 minutes), acetic acid (0.15%, 20 s), water (2 minutes).

All animal experiments throughout this study were conducted according to the policy of the Federation of European Laboratory Animal Science Association and the European Convention for the protection of vertebrate animals used for experimental and other scientific purposes, with implementation of the principle of the 3Rs (replacement, reduction, refinement).

### 3.3 Results

As explained above, the architecture of the electrothermal skin patch is illustrated in Figure 3.5 and it is based on Kapton, a polymer with a glass transition between 360 and 410°C highly suitable for electrothermal systems [192]. Based on experiments and numerical calculations (Section 3.4), the best performing K/Au NHs electrothermal interface has 300 nm diameter holes. Unless otherwise specified, this was the

diameter of the gold holes in the electrothermal patch. An applied voltage of 1.0 V was sufficient to raise the temperature to a steady state value of 40°C in about 10 s (Figure 3.5). Transdermal drug delivery systems are typically occlusive patches, yet the core of the device is a nanoporous metallic layer. Thus, it is mechanically compatible with both nanomesh electronic interfaces, offering air and moisture permeability, and with nanopatterned additive slabs for drug encapsulation generated with cost-effective procedures [193,194]. For practical utility, note that polyimide may be sterilized with standard methods.

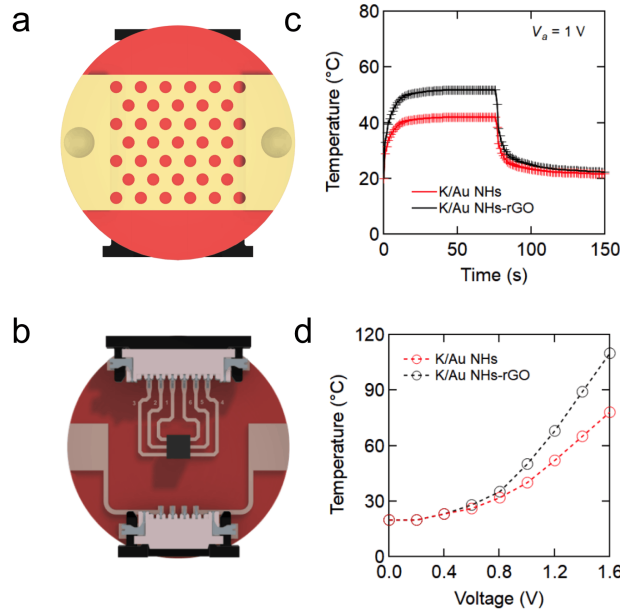


Figure 3.5: (a) Schematics of the active side based on nano-perforated gold layers formed by colloidal lithography on polyimide substrates. (b) Schematics of the passive back side with integrated electronics for temperature control and electrical biasing. (c) Temperature profile over time upon the application of 1.0 V for 75 s for K/Au NHs and K/Au NHs-rGO patches. (d) Steady-state temperature of K/Au NHs and K/Au NHs-rGO patches as a function of applied voltage. Here, the probed patches are far away from the skin.

For the controlled release of therapeutics, chemically-derived rGO was post-coated on the K/Au NHs devices due to its excellent drug loading capacity. Moreover, rGO thickness is a straightforward parameter to control the electrical resistance of the coupled metal-rGO system and thus the magnitude of the dc electrical power required to drive the

K/Au NHs-rGO patches to a defined temperature (Figure 3.5). Insulin loading was achieved by dropping insulin (100  $\mu\text{g}$ ) onto the rGO coating layer of the electrothermal patch. Non-covalent interactions through H-bonding, electrostatic interactions, and  $\pi - \pi$  stacking have been put forward as coupling mechanisms between rGO and insulin. The loading capacity of the rGO coating of the electrothermal device for human insulin (Figure 3.6) was determined as reported previously for insulin loaded hydrogels [58]. Here it was about 95%, which correlates to about 95  $\mu\text{g}$  (2.7 IU). Generally, to correct high concentrations of blood sugar in humans, 0.3 - 1.0 IU/kg insulin is needed to decrease the blood glucose by 50 mg/dl.

Figure 3.6 shows the cumulative *in vitro* release profile of insulin from the electrothermal patch into PBS (pH 7.4) maintained at 37°C upon the application of a dc electrical bias.

To test the biological active of the electrothermally released insulin, human hepatic HepG2 cells were cultivated in the presence of native or electrothermally released insulin. Insulin acts on HepG2 through its receptor, which after binding induces a signaling cascade leading to protein kinase B phosphorylation (p-Akt). This well-characterized key regulator of hepatic glucose metabolism is used here as a marker for assessing the metabolic activity of insulin.

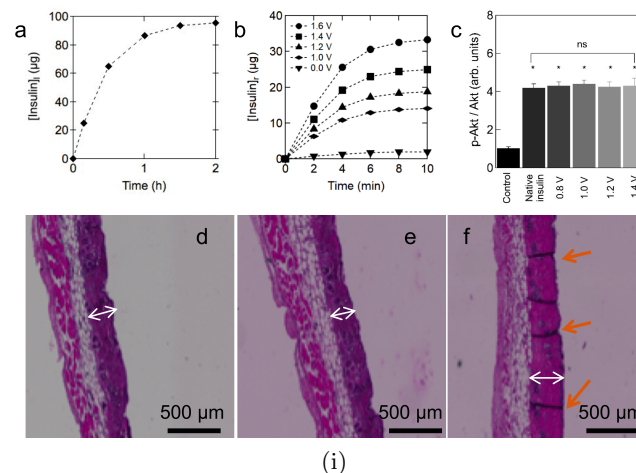


Figure 3.6: (a) Human insulin loading on the electrothermal patch. (b) Cumulative *in vitro* release profile of insulin from the patch in PBS (pH 7.4) maintained at 37°C upon application of different heating ramps determined by HPLC. (c) Analysis of Akt phosphorylation in HepG2 cells exposed to insulin released from the electrothermal patch at the indicated applied voltages. All data points represent the average  $\pm$  standard deviation of at least four different measured samples. Phosphorylation of Akt (p-Akt) over total Akt (Akt) was measured by Western Blotting using rabbit polyclonal antibodies. All the samples( were compared to cells treated with vehicle only, dimethyl sulfoxide (negative control). The results are expressed as the mean  $\pm$  standard deviation of at least 3 independent samples for each group (one-way ANOVA test, ns means not significant, \* represents a significant difference at  $P \leq 0.05$ ). Haematoxylin and eosin staining showing the histological changes of skin after heating for 10 minutes: (d) 52°C (1.0 V), (e) 55°C (1.05 V), (f) 60°C (1.1 V). The white arrows indicate the thickness of the epidermis and the red arrows indicate the canals formed.



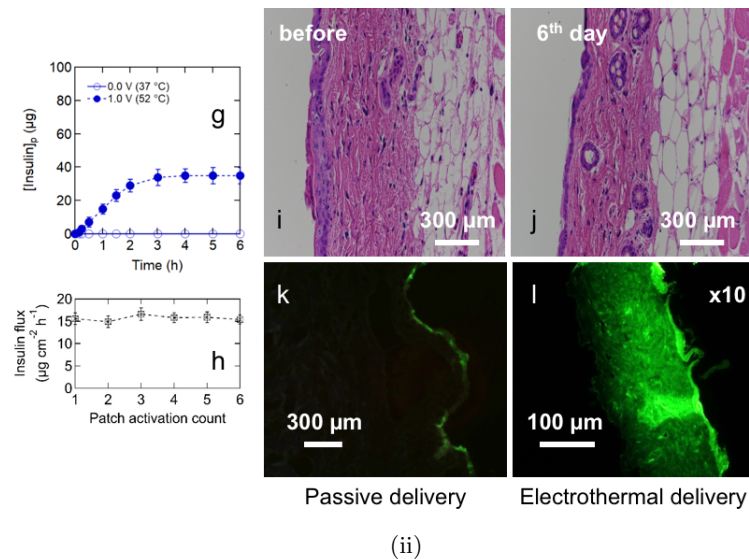


Figure 3.6: (g) *In vitro* cumulative permeation of insulin delivered from an electrothermal patch loaded with 100  $\mu\text{g}$  (2.8 IU) insulin across mouse skin upon continuous application of 1.0 V bias voltage for 10 minutes (closed symbols) as well as passive delivery (open symbols). (h) Reusability experiments were performed by patch reloading with 2.8 IU followed by application of a 1.0 V bias voltage for 10 minutes and determination of the insulin flux for 2 h. Histology results for long term insulin delivery are illustrated by haematoxylin and eosin staining of mice skin before (i) and after (j) stimulation every day for 10 minutes at 52°C. All data points represent the average  $\pm$  standard deviation of at least four different measured samples. *In vitro* cumulative permeation (2 h) of FITC-insulin delivered from an electrothermal patch loaded with 100  $\mu\text{g}$  (2.8 IU) insulin across mouse skin upon passive delivery (k) and upon continuous application for 10 minutes at 52°C (l).

Figure 3.6 displays insulin activity (p-Akt/Akt ratio), which increases when HepG2 cells were treated with insulin in comparison to non-treated cells. Applied voltages up to 1.6 V have no effect on the biological insulin activity, which was as active as native insulin. For transdermal delivery, the skin temperature at which threshold pain occurs is around 52°C (1.0 V), indicating that the biological activity of the insulin electrothermally released from the engineered patch is preserved.

Next, we tested the potential damage on the skin caused by heating. Damages on skin tissue are caused upon exposure for a prolonged time at temperatures above the physiological limit. Typical haematoxylin and eosin stained images of skin tissue upon heating exhibit the attributive characteristics of normal *dermis stratum*, as shown in Figure 3.6. No visible tissue damage is observed for both epidermis and dermis until 55°C (1.05 V), while at 60°C (1.1 V) thickening of the epidermis and skin disruption were observed. No long-lasting effects on skin integrity, evaluated by staining mouse skin with haematoxylin and eosin after application of electrothermal pulses of 1.0 V for 10 minutes for 6 days (Figure 3.6), were observed.

Figure 3.6 shows a standard permeation profile of insulin from patches loaded with 100  $\mu\text{g}$  insulin. The high molecular weight and hydrophilic character of insulin restrict passive skin permeation and no skin permeation of insulin is detected without electrothermal activation. When a mouse skin is subjected to a 10 minutes heating at 1.0 V (52°C), after a lag time of about 20 minutes, sustained transdermal transport of insulin occurs over a time period of 2 h. The total amount of permeated insulin after 2 h equals to  $23 \pm 3 \mu\text{g}$ , outperforming reported permeation percentages for integrated microneedles [47], which correspond to an insulin flux of  $15.6 \pm 1.3 \mu\text{g}/(\text{cm}^2\text{h})$  ( $2.0 \pm 0.4 \mu\text{M}/(\text{cm}^2\text{h})$ ), comparable the results of Pillai *et al.* addressing insulin delivery from poloxamer-407 gels using transdermal iontophoresis in the presence of menthone as skin enhancer [195]. The patch can be reused several times without any apparent loss of performance (Figure 3.6).

To get a better understanding of the mechanism underlying the electrothermal delivery of insulin, *in vitro* permeation studies using FITC-insulin were performed. From the fluorescence images taken after 2 h permeation one can notice that a larger amount of insulin is delivered through micrometer-sized pores (Figure 3.6). However, smaller pores might have been created temporally as fluorescence insulin is observed in the entire skin.

The efficiency of the electrothermal patch to deliver therapeutic insulin quantities was tested by four standard experiments on mice. These groups include (a) no insulin treatment (negative control), (b) subcu-

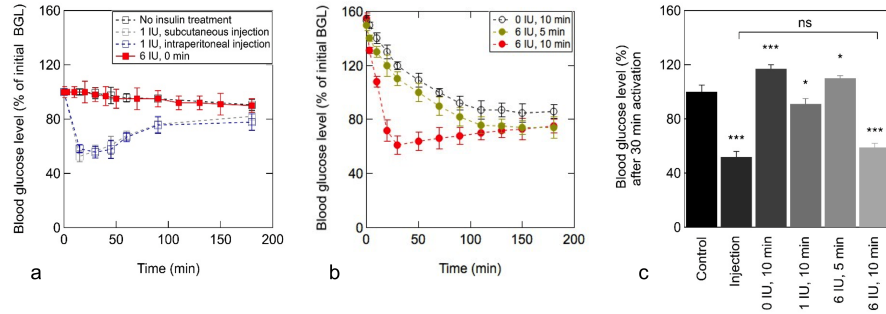


Figure 3.7: (a) Change in BGL (% of basal BGL) with time on four different mice groups: (i) no insulin treatment (negative control group, black), (ii) subcutaneous injection, 1 IU (grey), (iii) intraperitoneal injection, 1 IU (blue) and (iv) application of skin patches loaded with insulin (6 IU) but not activated (red). (b) Change in BGL (% of basal BGL) with time on different mice groups upon electrothermal activation: (i) negative control group with insulin-free patches applied and activated (1.0 V, 10 minutes) (black), (ii) group with insulin-loaded electrothermal patches (6 IU) and activated (1.0 V, 5 minutes) (green) and (iii) group with insulin-loaded electrothermal patches (6 IU) and activated (1.0 V, 10 minutes) (red). (c) BGL (%) determined after 30 minutes activation using different treatments: negative control group (no insulin treatment), subcutaneous injection of 1 IU (positive control group), group with insulin-free patches applied and activated (1.0 V, 10 minutes) and groups with insulin-loaded electrothermal patches and activated as indicated. All data points represent the average  $\pm$  standard deviation of measurements in at least four different mice. The statistical method used is a Mann-Whitney nonparametric test with a confidence interval of 95%. The data were analyzed using GraphPad Prism by comparisons between groups (ns means not significant, \* implies a significant difference at  $P \leq 0.1$ , \*\*\* represents a significant difference at  $P \leq 0.001$ ).

taneous injection (1 IU/kg) as first positive control, (c) intraperitoneal injection (1 IU/kg) as second positive control and (d) electrothermal delivery of insulin from patches loaded with 6 IU. Prior to drug administration, the basal blood insulin of each mouse was monitored, followed by the attachment of the electrothermal patch to estimate the insulin baseline. In mice with an insulin shot via subcutaneous and intraperitoneal injection (Figure 3.7), the blood glucose level (BGL) declined immediately and reached a minimum at 15 and 30 minutes, respec-

tively. Control mice (no insulin treatment) showed a negligible change in the BGL over the determined period (Figure 3.7). The same was true for the transdermal skin patch loaded with insulin without activation, confirming that no passive insulin delivery takes place in vivo.

The BGLs on mice stimulated with the electrothermal insulin patches are depicted in Figure 3.7. In the case of insulin-free patches, an increased BGL was determined after electrothermal activation at 1.0 V for 10 minutes. This is due to experimental constraints generated by the anaesthesia process, necessary to guarantee the patch adhesion during the stimulation and provoking stress and increase of blood glucose. Application of insulin-loaded patches (6 IU) induces a comparable BGL to the insulin-free ones after treatment. Significantly different to the insulin-free patches, the BGL declined steady with a minimum at about 30 minutes after treatment, in line with the time profile of subcutaneous and intraperitoneal injections (Figure 3.7). Activation of 10 minutes was the required time to reach a therapeutic effect (Figure 3.7), as shorter activation times did not show a rapid drop of the BGL. Among the mice that received insulin via electrothermal patches, those given doses with 6 IU displayed BGLs comparable to those treated by injection (Figure 3.7).

### 3.4 Numerical calculations

Joule heating calculations of a Kapton<sup>®</sup> tape covered with a gold thin film heated by an applied electrical current are carried out numerically, considering a periodic array of nano-sized holes patterned in the gold layer, and obtaining thus their overall effect on the thermal and electric conductivities of the system. Effective parameters are obtained and then used in a macroscopic calculation, revealing the dependence of maximum attainable temperature and electrical current on the hole size. The highest temperatures are obtained without holes, but in that case, the electrical current increases to several amperes due to the low resistance of the gold thin film. Then, suitable hole diameters and film thicknesses are analysed such that temperatures  $< 50^\circ\text{C}$  and electrical currents  $< 1\text{ A}$  are expected in heating gold thin films of  $\sim 1\text{ cm} \times 1\text{ cm}$  at applied voltages of  $\sim 1.5\text{ V}$ .

The propagation of heat with a Joule heating source  $\mathbf{j} \cdot \mathbf{E}$  is modelled by the equation [196]:

$$\rho \bar{c} \frac{\partial T}{\partial t} = \nabla \cdot \kappa \nabla T + \mathbf{j} \cdot \mathbf{E}, \quad (3.1)$$

where  $\bar{c}$  is the unit mass heat capacity,  $\rho$  the mass density,  $\kappa$  the thermal

conductivity,  $T$  the temperature,  $t$  the time,  $\mathbf{j}$  the electric current density and  $\mathbf{E}$  the electric field. Heat sinks at temperature  $T_{ref}$  can also be included in the volume or as boundary conditions.

The electric current density and the electric field are obtained from the electric potential  $\phi$  whose distribution is ruled by the equation  $\nabla \cdot \sigma \mathbf{E} = 0$  with suitable boundary conditions. The electric field is given by  $\mathbf{E} = -\nabla \phi$  and  $\mathbf{j} = \sigma \mathbf{E}$ , with  $\sigma$  being the electrical conductivity of the material. The current complies with  $\mathbf{j} \cdot \hat{n} = 0$  at non-conducting boundaries. No radiative heat loss was considered.

### 3.4.1 Simplified periodic geometry

First, we consider the properties of the system at the scale comparable to the diameter of holes patterned in the heating gold thin film, with periodic boundary conditions. The domain considered is a rectangular vertical section of the system of lateral span  $0 < x < L$  and  $0 < y < w$ , with  $L = 3.92 \times 10^{-6}$  m and  $w = 3.3948 \times 10^{-6}$  m. Given the thickness of the Kapton as  $t_K = 1.25 \times 10^{-4}$  m, the thickness of the gold film  $t_h = 40 \times 10^{-9}$  m, the total height of the vertical section is  $t_K + t_h$ . Triangular arrays of holes of diameters from 50 to 900 nm are considered for the gold thin film, with a separation  $a = 980$  nm. Some details of the discretization used in the numerical computations can be seen in Fig. 3.8.

### 3.4.2 Boundary conditions

Periodic boundary conditions for the temperature are considered at  $x$  and  $y$  faces, namely:  $T(x=0) = T(x=L)$  and  $T(y=0) = T(y=w)$ . Flux boundary conditions are considered at the top and bottom faces,  $\kappa \hat{n} \cdot \nabla T = -h(T - T_{ref})$ , with  $h = 250$  W/(m<sup>2</sup>K) and  $T_{ref} = 293.15$  K, where  $\hat{n}$  is the exterior unitary normal to the boundary.

For the electric potential, periodic boundary conditions are established between the  $y$  faces,  $\phi(y=0) = \phi(y=w)$ . The electrical ground is at  $x=L$  and a voltage  $\delta V_a = V_a \cdot L/1$  cm is applied at  $x=0$ , where  $V_a$  is the voltage applied in the 1 cm macroscopic sample.

### 3.4.3 Physical parameters

Temperature dependent electrical conductivity, thermal conductivity and constant specific heat were considered for gold, and temperature dependent specific heat and thermal conductivity were considered for Kapton, with fits in the range 250 - 400 K [197–200]:

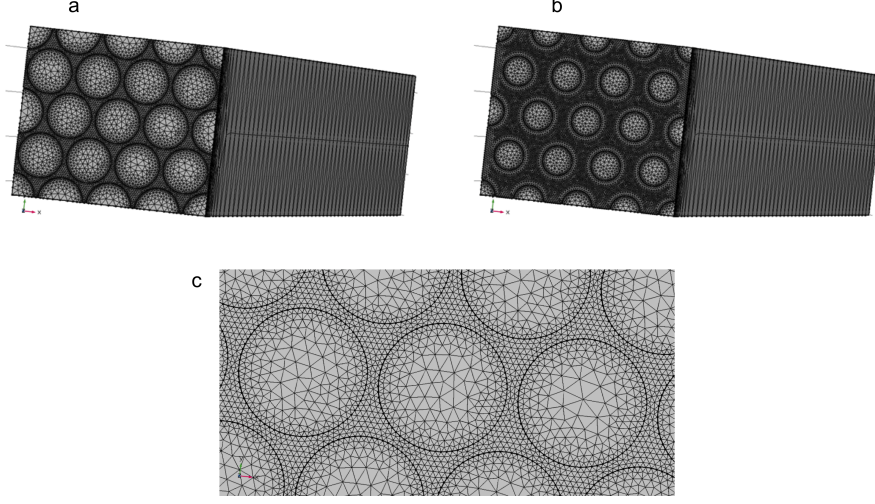


Figure 3.8: (a) Discretization used for the K/Au system with 600 nm diameter holes. (b) Discretization used for the K/Au system with 900 nm diameter holes. (c) Zoom into the mesh generation for the K/Au system with 900 nm diameter holes.

$$\begin{aligned}
\rho_{eAu}/[10^{-8}\Omega\text{ m}] &= -2.53 \times 10^{-1} \pm 2 \times 10^{-2} \\
&\quad + (8.37 \times 10^{-3} \pm 6 \times 10^{-5})T/[K] \\
k_{Au}/[\text{W}/(\text{K m})] &= 301.8 \pm 1.5 \\
&\quad + (-40.32 \pm 18)/(1 + (-0.0129 \pm 0.003)T/[K]) \\
\bar{c}_{Au}/[\text{J}/(\text{kg K})] &= 129 \pm 1.5 \\
\rho_{Au}/[\text{kg}/\text{m}^3] &= 19320 \\
k_K/[\text{W}/(\text{K m})] &= (5.24 \pm 0.32) \times 10^{-3}(T/[K])^{1.02 \pm 0.02} \\
\bar{c}_K/[\text{J}/(\text{kg K})] &= (1.65 \pm 0.2) \times 10^2 + (2.85 \pm 0.2)T/[K] \\
&\quad - (2.87 \pm 0.4) \times 10^{-3}T^2/[K^2] \\
\rho_K/[\text{kg}/\text{m}^3] &= 1420.
\end{aligned}$$

### 3.4.4 Results

The electric current density in the patterned gold thin film shows pronounced variations due to the presence of holes. The temperature is, however, almost constant due to the high thermal conductivity of the K/Au system and the periodic boundary conditions (Fig. 3.9). The maximum temperature depends on the free parameter  $h$ , chosen here to

match the experimental curves. The temperature rises monotonically as a function of time and calculations are stopped arbitrarily at time  $t = 1$  s, near steady state. A plot of the maximum temperature vs. applied voltage is shown in Fig. 3.10.

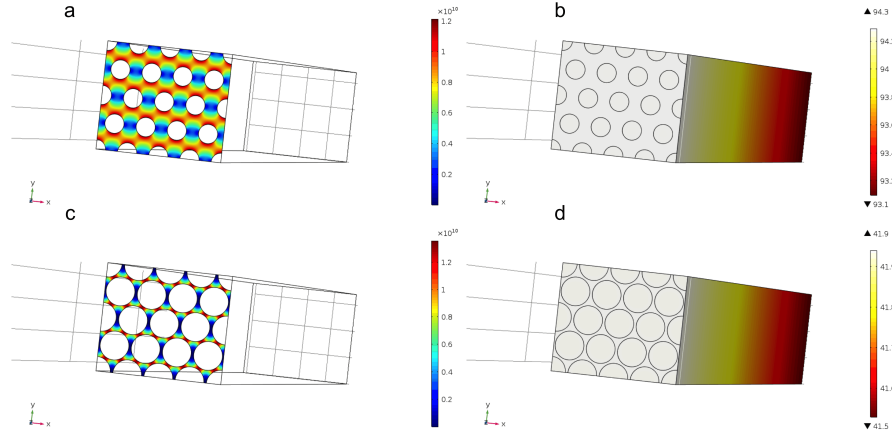


Figure 3.9: (a) Current density ( $\text{A/m}^2$ ) and (b) temperature ( $^\circ\text{C}$ ) for a K/Au system with 600 nm diameter holes and a 40 nm thickness for the gold layer at  $V_a = 2.35$  V. (c) Current density ( $\text{A/m}^2$ ) and (d) temperature ( $^\circ\text{C}$ ) for a K/Au system with 900 nm diameter holes and a 40 nm thickness for the gold layer at  $V_a = 2.35$  V. Note that the maximum current density is around  $10^3$  mA/cm<sup>2</sup>. As discussed previously (Figure 2.4), the expected current density in the skin is lower than 1 mA/cm<sup>2</sup>, the typical value for iontophoresis.

The computed temperature versus voltage curves follow a quadratic shape, as expected for the Joule dissipation of an ohmic element. The result depends on the flux boundary conditions, and thus on the  $h$  parameter, that could also vary with temperature, but was considered here constant. The periodic calculation is the basis for an equivalent model of the macroscopic sample, for which small geometrical details can not be assessed.

### 3.4.5 Large sample extension

In the case of a large sample, effective parameters must be used to take into account the presence of holes in the gold thin film. The mass density can be easily scaled by the volume filling. The electrical and heat conductivities must also be modified by geometric factors. To determine the geometrical dependence of the heat conductivity  $\kappa$ , two



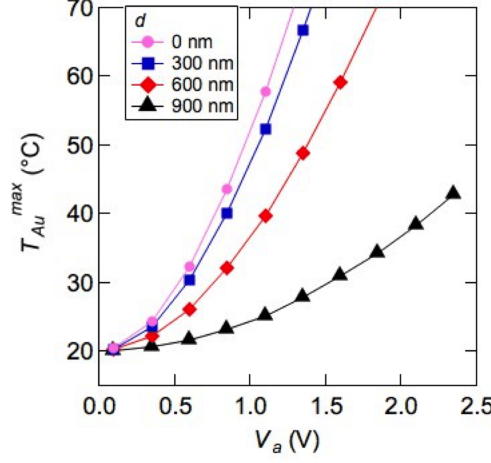


Figure 3.10: Numerical results of the maximum temperature on the gold side of the Kapton tape as a function of the applied voltage  $V_a$ , for indicated hole diameters, at  $t = 1$  s. The thickness of the gold layer is 40 nm.

sides of the holey gold thin film considered previously were put at fixed temperatures with a difference of 0.1 K, namely  $T(x = 0) = 20.1^\circ\text{C}$  and  $T(x = L) = 20^\circ\text{C}$ , keeping the periodic conditions in the  $y$  direction. The heat flux  $\mathbf{q} = -\kappa\nabla T$  was then numerically calculated in the steady state condition and integrated for the boundary  $x = L$  to obtain the heat current  $H_c = \int_{x=L} \mathbf{q} \cdot d\mathbf{S}$ .

We deduce from Fig. 3.11 that the geometrical factor for the in-plane thermal conductivity is  $f_c = 1 - a_2 d^2 / (1 + d a_3)$ , with  $a_2 = 2.7602 \times 10^{12} \text{ m}^{-2}$  and  $a_3 = 1.658 \times 10^6 \text{ m}^{-1}$ . The same factor is valid for the in-plane electrical conductivity  $\sigma^p = 1/\rho_{eAu}^p$ , as the heat flow  $\mathbf{q}$  and the electric current density  $\mathbf{j}$  satisfy the same equation in steady state conditions with non-conducting boundaries, namely  $\nabla \cdot \mathbf{j} = 0$  and  $\nabla \cdot \mathbf{q} = 0$ .

The mass density is modified by the volume fraction. In a triangular lattice the unit cell has an area of  $\sqrt{3}a/2$ , therefore the volume fraction is  $f_v = 1 - 2\pi(d/2)^2/\sqrt{3}a^2$ . This factor modifies also the out-of-plane thermal conductivity  $\kappa_{Au}^s$ . In summary, we obtain:

$$\kappa_{Au}^p = \kappa_{Au} f_c, \quad (3.2)$$

$$\kappa_{Au}^s = \kappa_{Au} f_v, \quad (3.3)$$

$$\rho_{Au}^{eff} = \rho_{Au} f_v, \quad (3.4)$$

$$\rho_{eAu}^p = \rho_{eAu} / f_c. \quad (3.5)$$



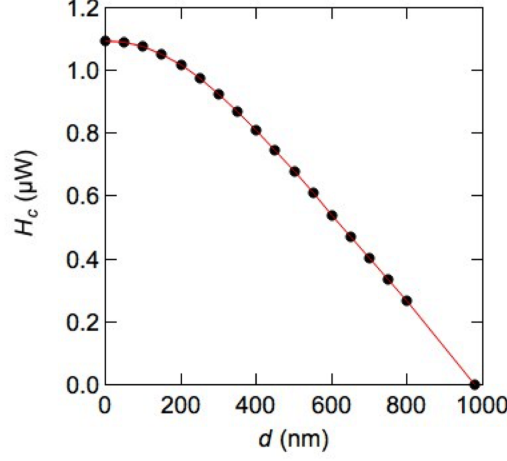


Figure 3.11: Heat current computed for different hole diameters (black symbols) and fit with quadratic-linear function (red curve)  $H_c = a_1(1 - a_2 d^2 / (1 + d a_3))$ , where  $H_c$  is the heat current and  $d$  is the hole diameter, with parameters  $a_1 = 1.0957 \times 10^{-6}$  W (given),  $a_2 = 2.7602 \times 10^{12} \pm 8.9 \times 10^{10}$  1/m<sup>2</sup> and  $a_3 = 1.658 \times 10^6 \pm 9.7 \times 10^4$  1/m.

### 3.4.6 Steady-state temperature of the electrothermal patch

The temperature evolution of the system under a constant current  $I$  heating can be analysed as follows. First, we neglect the vertical variations of temperature in the metal film, and consider only the convective heat lost at the top and bottom boundaries. Then the temperature gradients can be neglected and the convective heat loss can be directly incorporated into the heat equation as:

$$\rho \bar{c} \frac{\partial T}{\partial t} = \mathbf{j} \cdot \mathbf{E} - h_{eff}(T - T_0)/t_h, \quad (3.6)$$

where  $h_{eff}$  is the effective convective heat loss parameter. At equilibrium, the time derivative of the temperature is zero, and the equilibrium temperature  $T_{eq}$  can be found algebraically by solving:

$$\mathbf{j} \cdot \mathbf{E} = h_{eff}(T_{eq} - T_0)/t_h. \quad (3.7)$$

Let's consider the first the case of total, constant electrical current  $I$  heating. Given the cross section  $\tilde{A}$  of the sample, Eq. (3.7) can be

written as:

$$\rho_{eAu}^p \frac{I^2}{\tilde{A}^2} = h_{eff}(T_{eq} - T_0)/t_h, \quad (3.8)$$

$$\frac{\rho_{eAu}}{f_c} \frac{I^2}{\tilde{A}^2} = h_{eff}(T_{eq} - T_0)/t_h, \quad (3.9)$$

$$\rho_{eAu} = \frac{f_c h_{eff} \tilde{A}^2}{t_h I^2} (T_{eq} - T_0). \quad (3.10)$$

Then we use the parametrization of the resistivity  $\rho_{eAu}(T) = u_0 + u_1 T$  (see Subsection **Physical parameters**):

$$u_0 + u_1 T_{eq} = \frac{f_c h_{eff} \tilde{A}^2}{t_h I^2} (T_{eq} - T_0). \quad (3.11)$$

Let's call  $v = \frac{f_c h_{eff} \tilde{A}^2}{t_h I^2}$ , then:

$$T_{eq} = \frac{u_0 + v T_0}{v - u_1}, \quad (3.12)$$

$$T_{eq} = \frac{\frac{u_0 t_h I^2}{f_c h_{eff} \tilde{A}^2} + T_0}{1 - \frac{u_1 t_h I^2}{f_c h_{eff} \tilde{A}^2}}. \quad (3.13)$$

In the case of constant voltage  $V_a$  heating, for a sample of length  $L$ , we get the following equation from Eq. (3.7):

$$0 = u_1 T_{eq}^2 + (u_0 - u_1 T_0) T_{eq} - u_0 T_0 - \frac{V_a^2}{L^2} \frac{t_h f_c}{h_{eff}}. \quad (3.14)$$

By calling  $r = u_0 T_0 + \frac{V_a^2}{L^2} \frac{t_h f_c}{h_{eff}}$ , we get:

$$T_e = \frac{(-u_0 + u T_0)}{2u} + \frac{\sqrt{(u_0 - u T_0)^2 + 4ur}}{2u}. \quad (3.15)$$

The following factors  $h_{eff}$ ,  $f_c$ ,  $u_0$  and  $u_1$  are assumed independent of  $d$  and  $T$  and an estimate for  $h_{eff}$  at fixed  $t_h$  can be obtained. By using Eqs. (3.13) and (3.15), the steady-state temperatures for each  $d$  can be inferred by taking *ad hoc* values  $h_{eff} = 2h = 500 \text{ W/(m}^2\text{K)}$  [Figure 3.12, panels (a) and (b)] and  $h_{eff} = 2h = 200 \text{ W/(m}^2\text{K)}$  [Figure 3.12, panels (c) and (d)] as well as the experimental values for the sample width and length.

We experimentally determined the steady-state temperature as a function of the applied voltage in the fabricated patches. In Fig. 3.13, the

result for the unpatterned sample ( $d = 0$  nm) is shown. The electrical resistivity of the metallic thin layer was measured as a function of the temperature:  $\rho^{exp}(T) = u_0^{exp} + u_1^{exp}T$ , with  $u_0^{exp} = 1.515 \times 10^{-08} \pm 2 \times 10^{-10}$   $\Omega$  m and  $u_1^{exp} = 1.316 \times 10^{-10} \pm 7 \times 10^{-13}$   $\Omega$  m/K. Accordingly, by fitting the Eq. (3.15) to the data of Fig. 3.13, we estimate  $h = 91.6 \pm 0.3$  W/(m<sup>2</sup>K).

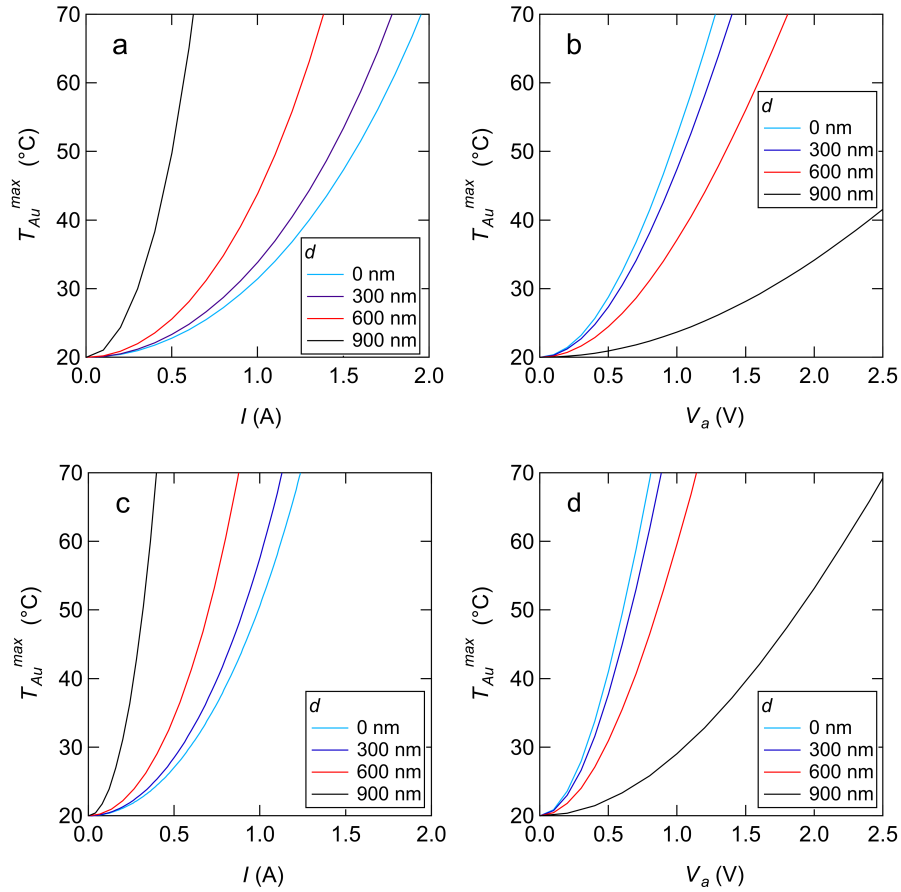


Figure 3.12: Calculated steady-state temperature  $T_{Au}^{max}$  as a function of constant current  $I$  and applied voltage  $V_a$ , respectively, at indicated  $d$  for [(a), (b)]  $h_{eff} = 2h = 500$  W/(m<sup>2</sup>K) and [(c),(d)]  $h_{eff} = 2h = 200$  W/(m<sup>2</sup>K).

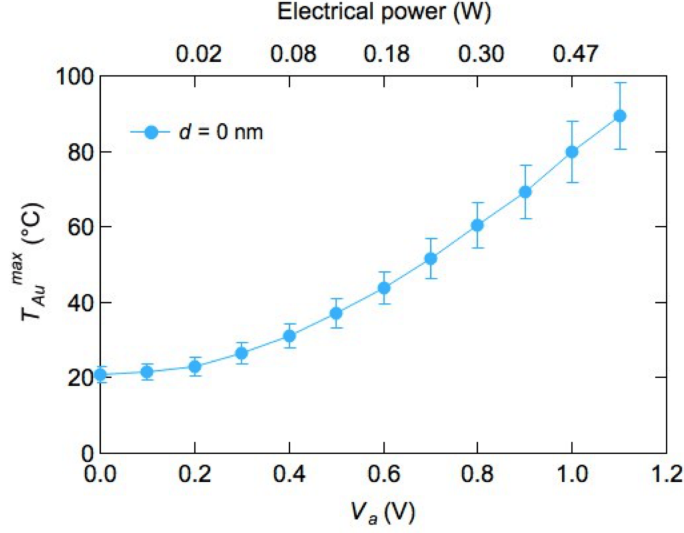


Figure 3.13: The experimentally determined dependence of the steady-state temperature  $T_{Au}^{max}$  as a function of the applied voltage  $V_a$  for unpatterned samples.

### 3.4.7 Macroscopic model

By placing the above effective parameters in a three-dimensional model, we can obtain the temperature distribution in the patch as shown in Fig. 3.14. It consists of a Kapton disc with the central area covered with the heating gold thin film, with thicker gold areas in the borders, and two contacts in these borders, to account for the heat flow into the external leads.

The maximum temperature  $T_{Au}^{max}$  is attained at the center of the system. This temperature was calculated for different hole diameters  $d$ , that can be seen in Fig. 3.15, and also for different  $t_h$  film thicknesses. The total electric current was also calculated and it is shown in Fig. 3.15. Very high electrical current values are obtained for small holes, especially for metallic films thicker than 75 nm, far from typical consumer power supplies. That would require in particular thick electrical power leads. Such electrical power leads are incompatible with the Kapton disc dimensions and the contacts  $C_1$  (Fig. 3.16).

From Fig. 3.17 and Fig. 3.18, two sets of parameters were chosen,  $S1 : \{d = 320 \text{ nm}, t_h = 40 \text{ nm}\}$  and  $S2 : \{d = 850 \text{ nm}, t_h = 100 \text{ nm}\}$ , and the realistic application of the patch was considered.

Through holes at the contacts  $C_1$  (Fig. 3.16) filled with conduc-

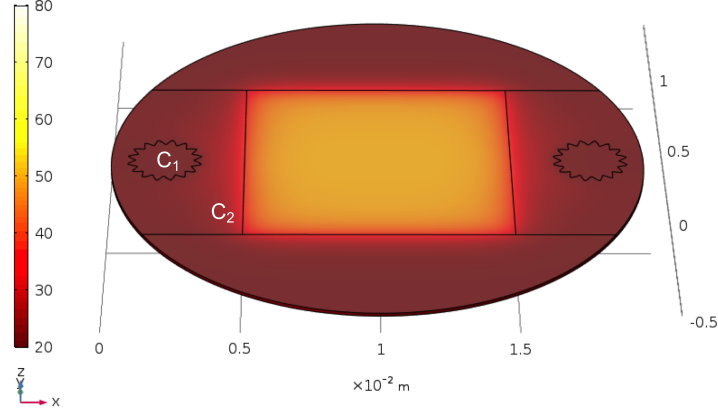


Figure 3.14: Top face temperature distribution of the patch ( $^{\circ}\text{C}$ ) after 60 s with 1.5 V applied voltage in contacts  $C_1$ . The heating gold film has  $h = 250 \text{ W}/(\text{m}^2\text{K})$  on all parts, except on contacts  $C_1$  where  $h = 10000 \text{ W}/(\text{m}^2\text{K})$ . Here  $T_{ref} = 20^{\circ}\text{C}$ . Dimensions of the Kapton disc are 1 cm radius and 0.125 mm thickness. The heating gold film is 100 nm thick, has 850 nm diameter holes, and measures  $1 \text{ cm} \times 1 \text{ cm}$ . The lateral contact gold areas  $C_2$  are 2 times thicker than the central area ( $t_c = 2t_h$ ), *i.e.* 80 nm, and have 1 cm width. The contacts  $C_1$  are 2.5 mm diameter with border ripples for enhanced mechanical properties. The parametrization for the contacts  $C_1$  border is  $(x, y) = ((0.00125 + 0.00015\cos(10s - \pi))\cos(s), (0.00125 + 0.00015\cos(10s - \pi))\sin(s))$ , with  $s$  between 0 and  $2\pi$ . The center-to-center separation of contacts  $C_1$  is 16 mm.

tive epoxy EPO TEK<sup>®</sup> H20E were considered as macroscopic electrical contacts. Due to their small dimensions, the electrically conducting elements of the patch were included in the COMSOL model as a shell of zero thickness with corresponding electrical and thermal properties. An epidermis layer of 60  $\mu\text{m}$  with a dermis layer of 500  $\mu\text{m}$  [201] have been taken into account, in perfect thermal contact with the heating side of the disc, with physical properties [201, 202]:

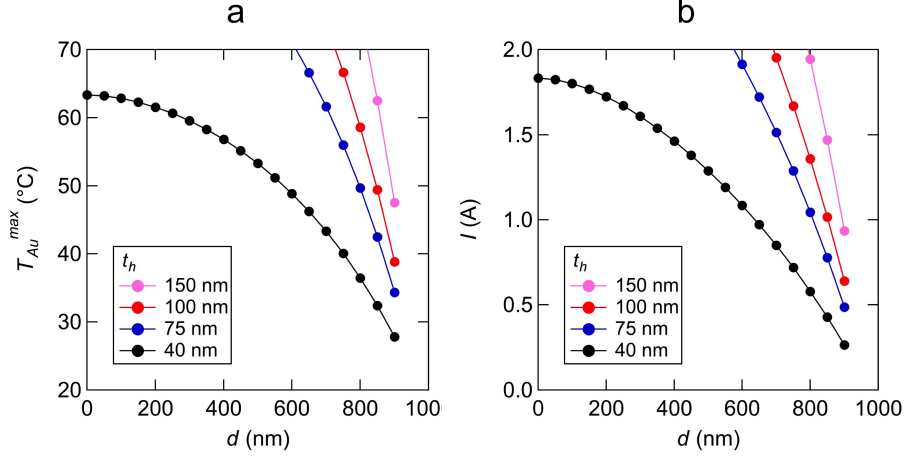


Figure 3.15: (a) Maximum top face temperature  $T_{Au}^{max}$  as a function of the hole diameter for different thicknesses of the heating film at  $V_a = 1.5$  V. (b) Total electrical current in the patch as a function of the hole diameter for different thicknesses of the heating gold film at  $V_a = 1.5$  V. These two quantities were calculated at 60 s heating time.

$$\begin{aligned}
 k_{\text{H}_2\text{O}_2} / [\text{W}/(\text{m K})] &= 29 \\
 \bar{c}_{\text{H}_2\text{O}_2} / [\text{J}/(\text{kg K})] &= 233 \\
 \rho_{\text{H}_2\text{O}_2} / [\text{kg}/\text{m}^3] &= 2600 \\
 k_{\text{epidermis}} / [\text{W}/(\text{m K})] &= 0.26 \\
 \bar{c}_{\text{epidermis}} / [\text{J}/(\text{kg K})] &= 3600 \\
 \rho_{\text{epidermis}} / [\text{kg}/\text{m}^3] &= 1200 \\
 k_{\text{dermis}} / [\text{W}/(\text{m K})] &= 0.53 \\
 \bar{c}_{\text{dermis}} / [\text{J}/(\text{kg K})] &= 3600 \\
 \rho_{\text{dermis}} / [\text{kg}/\text{m}^3] &= 1200.
 \end{aligned}$$

For the dermis, four heat transfer parameters were considered, namely  $h_b = 10, 10^2, 10^3, 10^4$  W/(m<sup>2</sup>K), with  $T_{ref} = 36.5^\circ\text{C}$ . On the top external face of the Kapton, a heat transfer parameter of 250 W/(m<sup>2</sup>K), and  $T_{ref} = 20^\circ\text{C}$  were used, while on the E20H EPO TEK contacts a heat transfer parameter of  $10^4$  W/(m<sup>2</sup>K), and  $T_{ref} = 20^\circ\text{C}$  were taken. Initial temperature was  $36.5^\circ\text{C}$  everywhere.

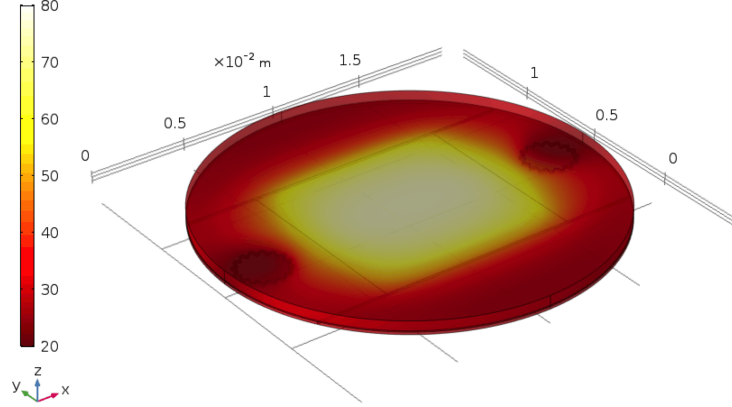


Figure 3.16: Temperature distribution ( $^{\circ}\text{C}$ ) within the electrothermal patches attached to the skin [ $d = 320 \text{ nm}$ ,  $t_h = 40 \text{ nm}$ ,  $60 \text{ s}$ , and  $h_b = 100 \text{ W}/(\text{m}^2\text{K})$  with  $1.5 \text{ V}$  applied voltage].

The temperature distribution within the heating devices attached to the skin is shown in Fig. 3.16 and the temperature as a function of the depth in the skin, for a line passing through the axis of the system between  $0$  and  $560 \text{ }\mu\text{m}$ , *i.e.* center of the tape in the direction of skin, can be seen in Fig. 3.17 (set  $S1$ ) and Fig. 3.18 (Set  $S2$ ) for different values of  $h_b$ .

### 3.4.8 Copper back contact devices

Two copper back contacts of  $3.5 \text{ mm} \times 3.5 \text{ mm}$  centered at the star shaped through contacts were added in the calculation to the electrothermal system considered previously. The nano-patterned area is now  $11 \text{ mm} \times 11 \text{ mm}$ . The thickness of the Kapton is  $75 \text{ }\mu\text{m}$ , and the thickness of the copper layer is  $70 \text{ }\mu\text{m}$ . All other parameters are kept the same. The performance of the new electrothermal system is shown in Fig. 3.19.

The behaviour of the device on the skin is shown in Fig. 3.20, using the set  $S1 : \{d = 320 \text{ nm}, t_h = 40 \text{ nm}\}$ .

The behaviour is qualitatively similar to the devices without copper back contacts, with temperature profiles evolving slightly below the simpler design devices.

The electrical resistance of the gold thin films without holes is negligible, so very high electrical currents result when an electrical voltage is applied. In a practical system, this is a nuisance as it would require

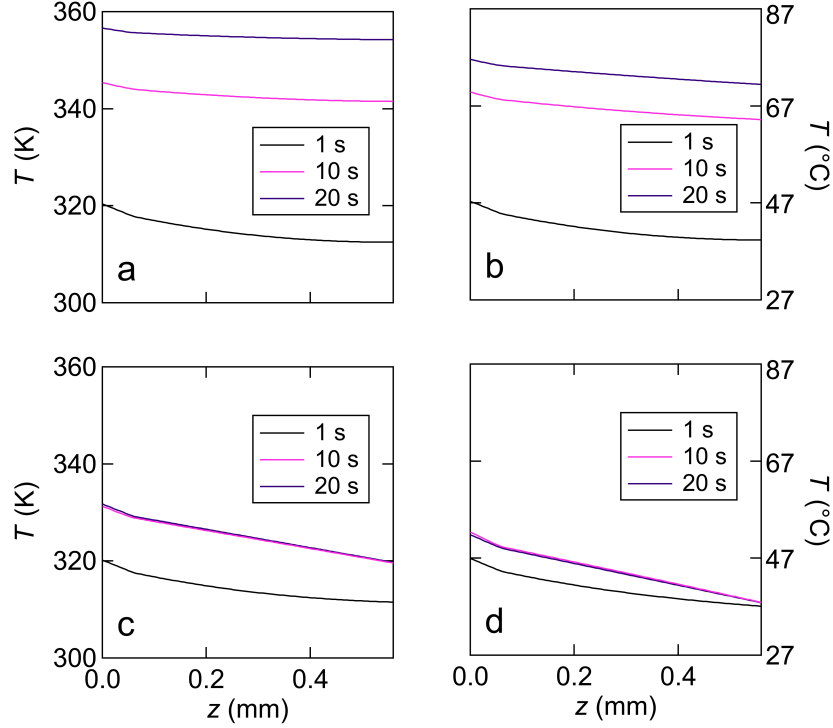


Figure 3.17: *S1*. (a) Temperature distribution inside the skin layer with  $h_b = 10$  W/(m<sup>2</sup>K) at different indicated times. (b) Temperature distribution inside the skin layer with  $h_b = 10^2$  W/(m<sup>2</sup>K) at different indicated times. (c) Temperature distribution inside the skin layer with  $h_b = 10^3$  W/(m<sup>2</sup>K) at different indicated times. (d) Temperature distribution inside the skin layer with  $h_b = 10^4$  W/(m<sup>2</sup>K) at different indicated times.

high power electrical cords and supplies. The presence of holes (besides allowing integration of the electrically resistive drug reservoir with optimal contact area for efficient heat transfer) increases the electrical resistance of the gold thin film and decreases the electrical current.<sup>4</sup> This electrical current can not be very low as it would decrease in turn the Joule dissipation. As a simple rule, electrical currents of 1 A at voltages of 1 V will result in 1 W of electrical power dissipation. This level

<sup>4</sup>Such nanomesh (nanoporous) interfaces can be extremely useful to digitally probe skins as complex ecosystems of micro-organisms. For instance, thinking at nanopore sequencing and single-molecule sensing, information about the bacteria present within the microbiome can be extracted and correlated to different skin types - oily, dry, sensitive or aging.



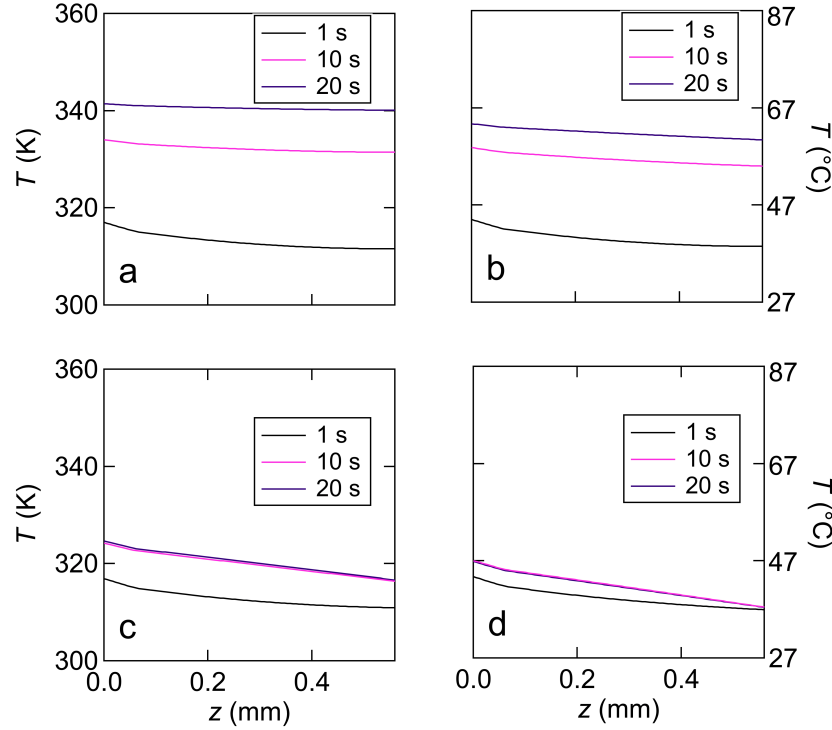


Figure 3.18: *S2*. (a) Temperature distribution inside the skin layer with  $h_b = 10 \text{ W}/(\text{m}^2\text{K})$  at different indicated times. (b) Temperature distribution inside the skin layer with  $h_b = 10^2 \text{ W}/(\text{m}^2\text{K})$  at different indicated times. (c) Temperature distribution inside the skin layer with  $h_b = 10^3 \text{ W}/(\text{m}^2\text{K})$  at different indicated times. (d) Temperature distribution inside the skin layer with  $h_b = 10^4 \text{ W}/(\text{m}^2\text{K})$  at different indicated times.

of dissipation can easily heat small circuit elements to temperatures of  $100^\circ\text{C}$  under typical thermal resistances encountered in electronic circuit boards. This is true for the electrothermal patches considered here. Concerning the heating of the skin, the heat transfer parameter of the deeper skin is not known precisely, therefore, several values were tried. At low  $h_b$  values, 10 or  $100 \text{ W}/(\text{m}^2\text{K})$ , the temperature profile changes fast in a time window of 10 s, with temperatures situated above  $55^\circ\text{C}$ . For high values of  $h_b = 10^4 \text{ W}/(\text{m}^2\text{K})$ , the temperature in the deeper dermis stays constant and a uniform gradient develops, meaning that heat is transferred at a constant rate. The temperature profile settles in a time window of 10 s. Any imperfections in the thermal contact between the patch and the skin will lead to a lower heat transfer towards

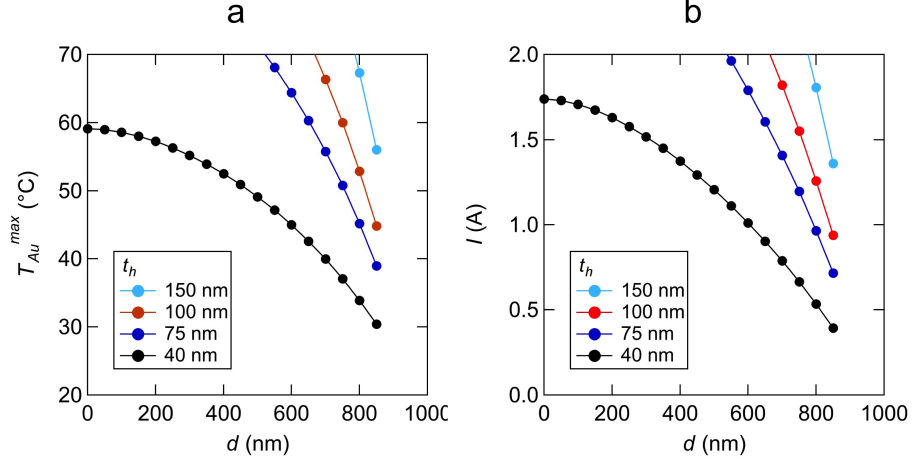


Figure 3.19: (a) Maximum top face temperature  $T_{Au}^{max}$  as a function of the hole diameter for different thicknesses of the heating film at  $V_a = 1.5$  V. (b) Total electrical current in the patch vs hole diameter at constant applied voltage  $V_a = 1.5$  V. These two quantities were calculated at 60 s heating time.

the skin. Humidity of the skin could also lead to some electrical current loss, depending on the ion content of the water. To minimize this effect, pre-cleaning followed by the application of a non-aqueous isolating layer on the skin before contact with the patch would likely be beneficial.

Calculations were performed to obtain the effect of patterned holes in a heating gold thin film deposited on a structured Kapton disc. From these calculations, hole diameters and film thicknesses were chosen such as to produce temperatures around 50°C without using very high electrical currents for heating. Results were also obtained for the temperature distribution in the skin for different heat transfer parameters.

### 3.5 Conclusion

In conclusion, the integration of thin film, nano-patterned heaters into patches loaded with insulin enables efficient transdermal release, capable to reduce the blood glucose level in mice in a comparable manner to insulin injection. The core of our device is a nanoporous metallic layer, which is highly mechanically compatible with both nanomesh interfaces for portable data analysis, offering air and moisture permeability, and micro-patterned additive slabs for drug encapsulation, like

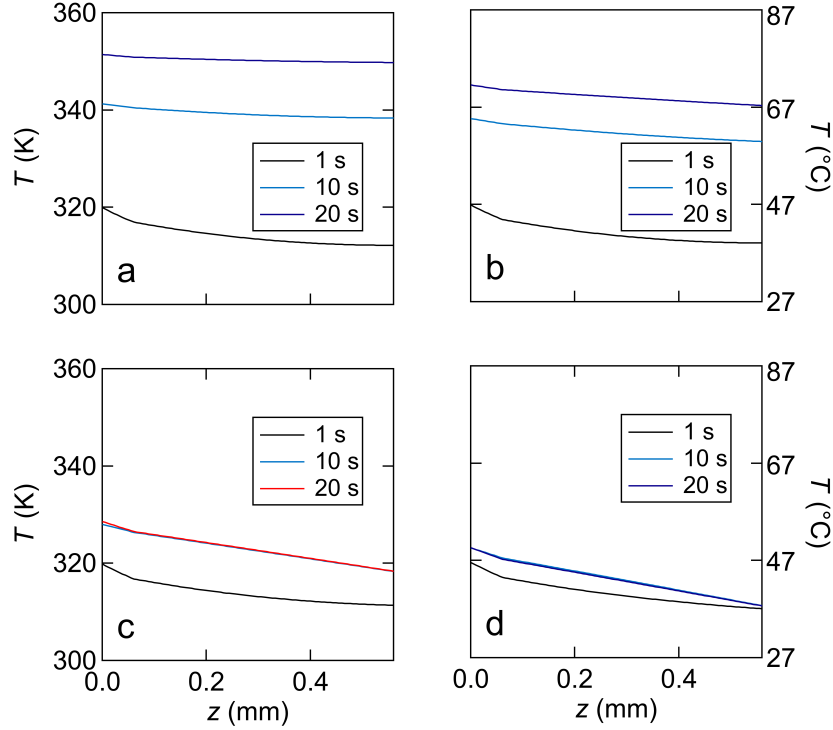


Figure 3.20:  $S1$  with copper back contacts. (a) Temperature distribution inside the skin layer with  $h_b = 10$  W/(m²K) at different indicated times. (b) Temperature distribution inside the skin layer with  $h_b = 10^2$  W/(m²K) at different indicated times. (c) Temperature distribution inside the skin layer with  $h_b = 10^3$  W/(m²K) at different indicated times. (d) Temperature distribution inside the skin layer with  $h_b = 10^4$  W/(m²K) at different indicated times.

hydrogels. With the need of power densities below 250 mW/cm² to reach steady state temperatures of 52°C in few seconds, the designed transdermal drug delivery device is adapted for wearables using next generation energy harvesting units and miniaturised batteries.

We thus provided the proof of concept of a newly engineered transdermal patch with electrothermal control for the delivery of therapeutic agents via incorporation into reduced graphene oxide. For practical utility, we note that polyimide can be sterilized via gamma, electron-beam, and hydrogen peroxide plasma sterilization methods, among others, offering a solid starting point for prototyping more complex drug delivery systems. Our findings do join the worldwide efforts devoted

to expand the portfolio of nano-engineered materials for soft electronics and biotechnology. This new patch could answer the promise for wearable on-demand drug delivery to enhance therapy efficacy and to better manage chronic disease such as diabetes.

### 3.6 List of abbreviations

|              |                                                     |                                    |                                                          |
|--------------|-----------------------------------------------------|------------------------------------|----------------------------------------------------------|
| $x, y, z$    | :coordinates in cartesian coordinate system         | $\rho_{Au}$                        | mass density of gold                                     |
| $\rho$       | :mass density                                       | $\rho_{eAu}$                       | electrical resistivity of gold                           |
| $\rho_e$     | :electrical resistivity                             | $\kappa_{Au}$                      | heat conductivity of gold                                |
| $\bar{c}$    | :unit mass heat capacity                            | $c_{Au}$                           | unit mass heat capacity of gold                          |
| $\kappa$     | :heat conductivity                                  | $\rho_K$                           | mass density of Kapton                                   |
| $T$          | :temperature                                        | $\kappa_K$                         | heat conductivity of Kapton                              |
| $\mathbf{j}$ | :electric current density                           | $c_K$                              | unit mass heat capacity of Kapton                        |
| $\mathbf{E}$ | :electric field                                     | $f_c$                              | geometrical factor effective conductivity                |
| $\phi$       | :electric potential                                 | $f_v$                              | geometrical factor effective volume                      |
| $T_{ref}$    | :reference temperature of environment               | $\mathbf{q}$                       | heat flow                                                |
| $h$          | :heat transfer parameter                            | $\kappa_{Au}^p$                    | effective in plane $\kappa$ of holey gold film           |
| $\sigma$     | :electrical conductivity                            | $\kappa_{Au}^s$                    | effective out of plane $\kappa$ of holey gold film       |
| $\hat{n}$    | :external normal to boundary                        | $\rho_{eAu}^p$                     | effective in plane $\rho_e$ of holey gold film           |
| $t_K$        | :thickness of Kapton tape                           | $\rho_{Au}^{eff}$                  | effective $\rho$ of holey gold film                      |
| $t_h$        | :thickness of holey gold film                       | $H_c$                              | heat current, $\mathbf{q}$ integrated on surface         |
| $t_c$        | :thickness of lateral gold contacts                 | $I_c$                              | electrical current, $\mathbf{j}$ integrated on surface   |
| $L$          | :length of periodic section along $x$ axis          | $\rho_x, \rho_{ex}, c_x, \kappa_x$ | $\rho, \rho_e, c, \kappa$ of $x$ substance, respectively |
| $w$          | :length of periodic section along $y$ axis          | $V_a$                              | applied voltage                                          |
| $d$          | :holes diameter                                     | $t$                                | time                                                     |
| $a$          | :separation between holes in the triangular lattice | $\mathbf{S}$                       | surface                                                  |
| rGO          | :reduced graphene oxide                             | HPLC                               | high-performance liquid chromatography                   |
| ELISA        | :enzyme-linked immunosorbent assay                  | NH                                 | nanohole                                                 |

near infra-red

NIR :

:scanning electron microscopy

SEM

# Perspectives

There are two possible outcomes: if the result confirms the hypothesis, then you've made a measurement. If the result is contrary to the hypothesis, then you've made a discovery.

---

Enrico Fermi

## Outlook

The first *Chakana* is summarising the outcomes. In the three Chapters of this work we have tried to put forward a series of results that can be summarised as follows.

By surveying in the first Chapter the wearable technologies in the digitally connected age, we have found an emerging trend of designing more and more sophisticated applications for smart phones in the healthcare field. In this additional effort of seizing the state-of-the-art, not detailed in Chapter 1, we have noticed that smart phone applications are understood today as a unique technological opportunity to explore novel approaches for detecting inflammation. Inflammation and diabetes are connected since once type 2 diabetes is developing, the body becomes not so much sensitive to insulin. In turn, the provoked insulin resistance triggers inflammation. Accordingly, a feedback loop is enabled with more insulin resistance causing more inflammation and conversely.

In the second Chapter we have inquired into the energy harvesting technologies for wearable systems, especially ambient radio-frequency (RF) energy harvesting. Looking back, the challenge was monumental. First, our goal was to validate a prototype of such energy harvesting system on Kapton using metasurface antennas built with small resonators. Then, our aim was to translate all parts of the wearable energy harvesting system on textile, by hybrid embroidery and sewable tech-

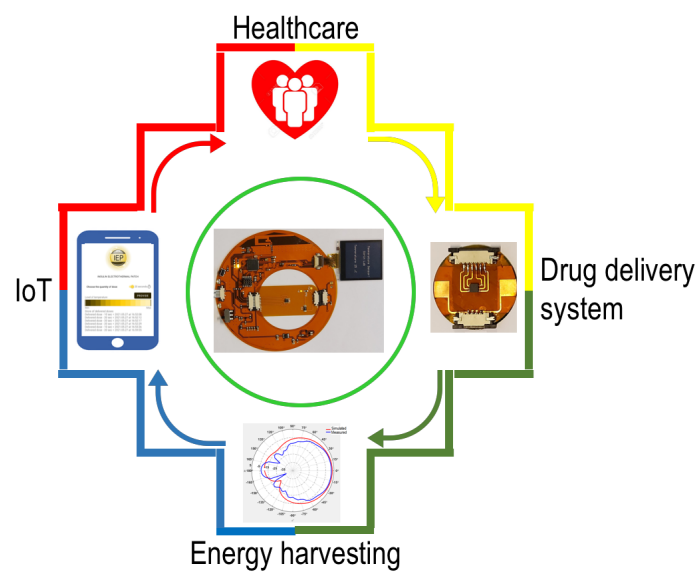
nology. We have achieved only partial validation of the Kapton-based prototype, mainly because for the moment we only can envisage it as an auxiliary power supply source for intelligent wearables, rechargeable batteries being the primary source. Mechanically flexible antennas were designed and fabricated for responding to two basic objectives: (i) to correctly miniaturise the antennas in order to obtain operation in useful bands and (ii) to improve their performance in terms of impedance and gain adaptation. The possibility of RF energy harvesting, integrated to wearables, was confirmed experimentally with fabricated metasurface antennas on mechanically flexible substrates. Moreover, the other blocks of the energy harvesting system were implemented, based on a commercial ultra-low voltage step-up converter and power manager, specifically the LTC<sup>®</sup>3108 from Analog Devices, and a generally purpose 16-bit MSP430<sup>™</sup> microcontroller from Texas Instruments.

In the third Chapter we have looked into patient centricity from the wearable drug delivery systems perspective. A new solution for transdermal delivery of insulin has been studied, based on electrothermally-activated dose administration. It is widely accepted that once a medication, like insulin, has been formulated and approved for subcutaneous administration, a patient could self-deliver their prescribed medication via a wearable injector in their living environment, while previously they would have benefit from the appropriate dose likely administered via intravenous administration only with help from a caregiver. We have challenged this scenario with a transdermal patch where the patient suffering from diabetes could benefit from a non-invasive insulin treatment. *In vivo* studies were carried out by our partners at Lille University, France: the integration of nano-patterned heaters into patches loaded with insulin enabled efficient release, capable to reduce the blood glucose level in mice in a comparable manner to insulin injections. The nanoporous metallic layer defining the heater is highly mechanically compatible with both stretchable electronic interfaces designed on porous elastomeric substrates, offering air and moisture permeability, and micro-patterned hydrogels for drug encapsulation. With the need of power densities below 250 mW/cm<sup>2</sup> to reach steady state temperatures of 52°C in few seconds, the transdermal drug delivery device is adapted for wearables using commercially available handheld battery systems and smart phones.

The perspectives of this work are certainly not limited to those mentioned above. In fact, I firmly consider that there are many exciting research opportunities ahead.

The first, most obvious extension is to fabricate patches of larger size and with more sensors on board, for instance for the pH quantification. Indeed, first steps were already taken into this direction and results are





*Chakana* summarizing the outcomes: A new solution for transdermal delivery of insulin has been studied, based on electrothermally-activated dose administration. The possibility of RF energy harvesting, integrated to wearables, was confirmed experimentally with fabricated metasurface antennas on mechanically flexible substrates. A prototype for integration of the electro-thermal patch into the IoT network has been achieved.

| Medical Application   | Description                                                                                                                                              | Ref.       |
|-----------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|------------|
| Substrate engineering | <ul style="list-style-type: none"> <li>• Define hydrogel-based supports.</li> <li>• Restore different circuit parts by liquid metal printing.</li> </ul> | [205, 206] |
| Drug delivery systems | <ul style="list-style-type: none"> <li>• Define sensors and actuators.</li> <li>• Define drug reservoirs and pharmaceuticals.</li> </ul>                 | [130, 208] |
| Organ printing        | <ul style="list-style-type: none"> <li>• Define skin flap or graft devices.</li> <li>• Print skin or wound dressings.</li> </ul>                         | [209, 210] |

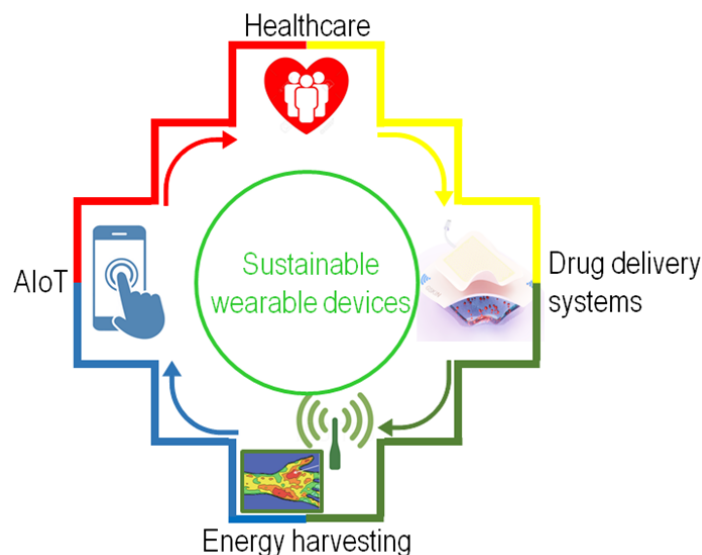
Table T1: Printing applications in the medical field (adapted from ref. [204])

promising towards patches of 38 mm diameter, built on Kapton and accommodating more circuitry for sensors and actuators. This direction relies also on the rapid development of printing technology (Table T1). It has potential in the healthcare sector beyond wearables for diverse biomedical applications such as tissue engineering and biorobotics. [130, 203–210]

The second extension of the present work is in the field of energy harvesting. There are many hurdles to be addressed for achieving computing textiles or autonomous textiles for the patients with diabetes. As biomechanical energy harvesting is useful for wearable technology, textiles incorporating, besides antennas, piezoelectric or flexoelectric devices producing electrical energy will be useful in designing "skin micro-grids" for prompt treatment with advanced drug delivery systems. Combined heat and mechanical energy harvesting it is also a possible solution to scavenge energy for the wearables of the future, but will require as well novel circuit design methodologies for minimising the uncomfortableness of the computing textiles dedicated to healthcare.

The artificial intelligence prospects are the most visionary as they play a major role in connecting the behavioural and lifestyle aspects of diabetes management to wearable technology. For example, Medtronic is developing behaviour tracking software able to detect meals and revealing the eating behaviour of users relying on insulin pumps. Since food consumption is interlinked to the insulin dependence for people suffering with type 1 diabetes, the capability to automate meal identification and synchronise it with insulin delivery could hugely simplify the day-by-day management of this disease. Such machine learning technologies that can analyse behavioural patterns from electronic healthcare records or sensor datasets will provide significant respite to patients, in remote

places or not, and will help with monitoring their dietary habits and lifestyle.



*Chakana* summarizing the perspectives: Sustainable wearable devices - exemplified by advanced drug delivery systems incorporating new sensors and actuators, boosted by smart energy harvesting - exemplified by flexible antennas in conjunction with piezoelectric/flexoelectric or thermal energy harvesting, and Internet-of-Things (IoT) - exemplified by emerging artificial intelligence technologies, for applications in healthcare.

Based on these considerations, we can incorporate the future actions of our initiative in the second *Chakana*, the symbol of the ancient Andean cultures.

Health is appraised as a fundamental human right by United Nations. It is considered pivotal in the context of the third Sustainable Development Goal "Ensure healthy lives and promote well-being for all at all ages". Thus, health is judged as a key pillar for the development strategy for southern countries. This thesis has been developed in the framework of the ARES (Académie de Recherche et d'Enseignement Supérieur) program for countries in South America. One central goal of this project was to contribute to the discussion of how nanoscience and enabling technologies can support solutions for critical issues in the healthcare field in this region, because Andean countries have similar health needs and problems to solve for the public health systems. During the PhD

program in Dr. Sorin Melinte's research group, different emergent technologies in the healthcare and IoT areas were studied, with a particular focus on the benefits of smart wearable nano-engineered systems for the networked patients suffering from type 1 diabetes. As highlighted in the text, diabetes is the second cause of death in Ecuador. This work is central to patient-centered aid, since telehealth allows patients to be involved in the healthcare process.

We can conclude that the results achieved in this thesis for the diabetes field could serve as a starting point for the usage of modern technologies in the development of the healthcare systems in the Andean states, especially Ecuador. Furthermore, the IoT framework delineated here can be adapted to apply to other fields such as agriculture and forestry, where the focus is on monitoring key parameters of the environment.

It is necessary to continue promoting this kind of academic cooperation between young researchers from the southern hemisphere and Universities in Belgium, at doctoral and post-doctoral level. Indeed, I would like to acknowledge that the PhD program helped me to develop novel research skills as well as invaluable transferable educational skills, which will strongly support my academic life at Central University of Ecuador.

## Publications featured and non-featured in this thesis

- P1 *Electrothermal Patches Driving the Transdermal Delivery of Insulin*, Q. Pagneux, R. Ye, C. Li, A. Barras, N. Hennuyer, B. Staels, D. Caina, J.I. Avila Osses, A. Abderrahmani, V. Plaisance, V. Pawlowski, R. Boukherroub, S. Melinte, and S. Szunerits, *Nanoscale Horizons* **5** (2020), 663. [**Cover page**].
- P2 *Kinked Silicon Nanowires: Superstructures by Metal Assisted Chemical Etching*, Georgiana Sandu, J.I. Avila Osses, Marine Luciano, D. Caina, A. Stopin, Ph. Leclère, D. Bonifazi, J-F. Gohy, A. Silhanek, O. Ersen, S. Gabriele, A. Vlad, and S. Melinte, *Nano Lett.* **19** (2019), 7681-7690.
- P3 *Super-resolution Imaging with Patchy Microspheres*, Q. Shang, F. Tang, L. Yu, H. Oubaha, D. Caina, S. Yang, S. Melinte, C. Zuo, Z. Wang, and R. Ye, *Photonics* **8** (2021), 513.

## Appendix A

# Communication systems for wearables

For this work, we developed a first version of an electronic control system communicating with a smart phone by Bluetooth 5.2.<sup>1</sup> This version is a milestone in the sense that the rigid framework is designed as an one-side printed circuit board with multiple functionalities (like remote software update capabilities), facilitating thus further transposition to both flexible substrates and compact rigid substrates for handheld control systems of drug delivery.

While smart phones make their way into pre-clinical studies, one should not forget that such endeavour must provide detailed information on dosing and toxicity levels. Furthermore, smart phones need to be harmonized with current regulations and comply with a minimum set of requirements for firmware version and calibration, written protocols and standard operating procedures available via cloud services, as well as robust storage and retrieval of data. The research toolkit needs to include preclinical systematic reviews and meta-analyses. To consolidate a ‘modus operandi’ that could be widely accepted by the community, all interested stakeholders, including developers and users, should be aware that the quality of preclinical data for translational research needs to be robust, reproducible and less focused on novel and sensational results. It is important that apps could be designed for proof-of-concept pre-clinical studies or clinically-oriented ones that are aimed at obtaining the toxicology data package required for drug approval. The following points are important for designing apps for healthcare: ultra-low-power consumption, interoperability for multi-brand devices, license free, avail-

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<sup>1</sup>Due to time constraints, the rigid version is included here, while the equivalent flexible version is nearly completed.

ability anywhere, regular updates, and connectivity with nearby devices. Bluetooth Low Energy (BLE) is a low power wireless communication technology, commonly used over a short distance to enable nearby devices (smart phones, smart watches, and so on) to communicate each other. Devices with BLE can be powered by a small coin cell battery for months or even years. Importantly, while BLE works with a central device (client), it often scans for nearby devices. A peripheral device (server), advertises availability for connection. On the one hand, the client initiates commands and requests, and accepts responses. On the other hand, the server receives commands and requests, it returns responses.

## A.1 Design of the electronic system

We present here the core of the electronic system, which main function is to supply power to the electrothermal patch for driving the drug delivery. It was designed to be implemented using flexible printed circuit board (FPCB) technology. The SimpleLink™ CC1352R wireless microcontroller unit (WMCU) is the main component which can be programmed on-board through the Texas Instruments XDS110 JTAG debug probe. The WMCU has an 32-bits 48 MHz Arm Cortex-M4F central processor unit (CPU). The CC1352R includes a radio-frequency (RF) module that contains an Arm Cortex-M0 processor; it manages the data from and to the CPU core. It is multi-protocol and multi-band, offering sub-1 GHz and 2.4 GHz capabilities. It is commonly used in medical devices due to low-power and connectivity requirements. It supports a wide voltage range from 1.8 to 3.8 V. Here it is powered with 3 V using by two batteries AA of 1.5 V each one.

Since it has a RF module, the system receives (and sends) data from (and to) the smart phone via Bluetooth communication. In fact, WMCU supports BLE. The system receives data from the smart phone to activate an output voltage pulse of 1 or 2 V. This activation can be done in 2 ways to get the output voltage pulse with two different times. The first option is to activate the output voltage for a short period of time of 5 s, and the second option is to activate the output voltage during a longer period of time of 50 s. The first option is assumed to deliver a low-dose of insulin to the patient, whereas the second option is for a high-dose delivery. These values can be arbitrary set in the software.

The design of the PCB was done using DipTrace software. The software has four tools Pattern Editor (design component pads), Components Editor (design component symbol), Schematic Capture (design

schematic circuit) and PCB Layout (board design and routing). Using these four tools, we designed a PCB with 15 sub-modules as shown in Figure A.1. At the same time, the code for the WMCU was programmed by a real-time operating system for Texas Instruments devices using the Code Composer Studio (CCS) Integrated Development Environment (IDE).

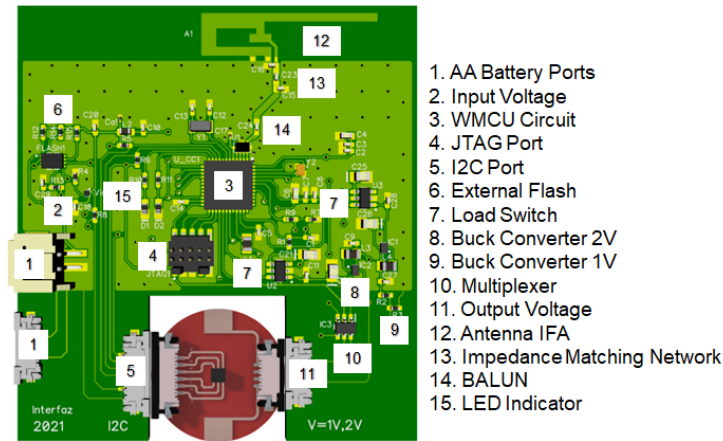


Figure A.1: Electronic system for smart phone communication and its sub-modules.

A second function of the electronic system is to enable readout from the 16-bit temperature sensor TMP116, which is placed on the electrothermal patch. It operates in the temperature range, according to the data sheet, from  $-55$  to  $125^{\circ}\text{C}$ . The communication between the WMCU and TMP116 is through Inter-Integrated Circuit (I2C) protocol. The TMP116 reads continuously the temperature from the patch and the WMCU receives the data from the temperature sensor. The received data are shown in real-time in the smart phone, which acts as a display. At the same time, the WMCU monitors that the patch temperature is always below  $52^{\circ}\text{C}$ . If the temperature is greater than  $52^{\circ}\text{C}$ , the WMCU deactivates the output voltage. Therefore, damage to patient's skin due to high temperature can be prevented. Finally, the novel design of this platform combined with the smart phone is modular, allowing one to add more functionalities for monitoring and treatment remotely.

#### A.1.1 Fabrication, soldering, and tests of the electronic system

The fabrication of the PCB was done by Eurocircuits. The PCB has two layers with all components to be placed on the top layer. The PCB

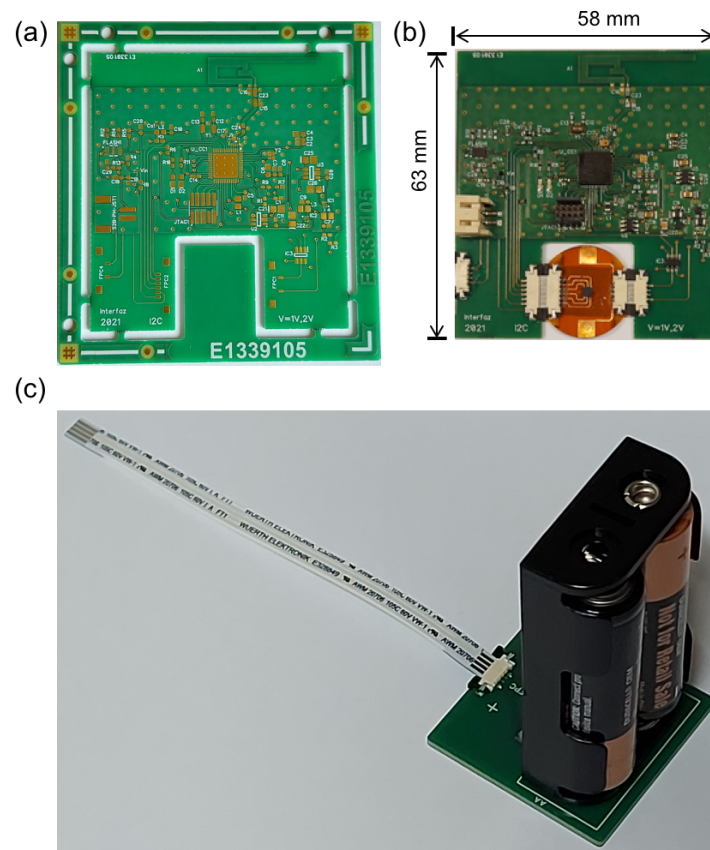


Figure A.2: The electronic system prototype. (a) Fabricated PCB by Eurocircuits. (b) The welded prototype. (c) The PCB adaptor to the two AA batteries holder.



width is 58 mm and the PCB length is 63 mm. The board thickness is 1 mm. The value of the thickness allowed to get the  $50\ \Omega$  impedance for the transmission line between the antenna and the WMCU. The PCB was fabricated on FR4IMP base material with an outer layer copper foil of  $18\ \mu\text{m}$  thickness. Figure A.2.a shows the fabricated PCB. Figure A.2.b shows the welded PCB with all the components. In order to deposit properly the solder paste on the component pads of the PCB, a stencil was fabricated. The stencil width is 152 mm and the stencil length is 172 mm, with a thickness of  $130\ \mu\text{m}$ . The SMD291AX10 solder paste was used. The surface mount devices were placed carefully on the pads using a microscope due to the small dimensions of around 60 electronic components. The mounted PCB was placed inside an infrared T962A reflow-oven to weld the components. The temperature in the oven for the welding process was around  $200^\circ\text{C}$  for 7 minutes.

After finishing the welding process, each component on the PCB was tested to verify its correct operation. The code for WMCU was flashing and the 2 AA batteries were attached. The output voltages of 1 and 2 V were tested and verified with a multimeter. The performance of the temperature sensor was tested to ensure the correct operation of the electrothermal patch. Finally, the complete electronic system was tested with the mobile application through the smart phone.

### A.1.2 Design of customized mobile application

A mobile application (App) was designed to communicate with the patch and manage the board via a smart phone. The App offers thus a user-friendly bidirectional interface for the electrothermal patch. The custom App programming was coded by the programming language Kotlin using the Android Studio IDE. The custom App is called Insulin Electrothermal Patch (IEP) App as depicted Figure A.3. The App sends data to the electronic system for activating the selected output voltage with a high value (2 V) or a low value (1 V) during a selected period of time short (for example, 5 s) or long (for example, 50 s). The App records the profile of the dose delivery temperature pulse and the time when the output voltage was activated, and consequently the drug delivery. Once the patient selects the type of dose, the button named PROVIDE will send the command to the electronic system (upon confirmation), which activates the output voltage to supply power to the electrothermal patch.

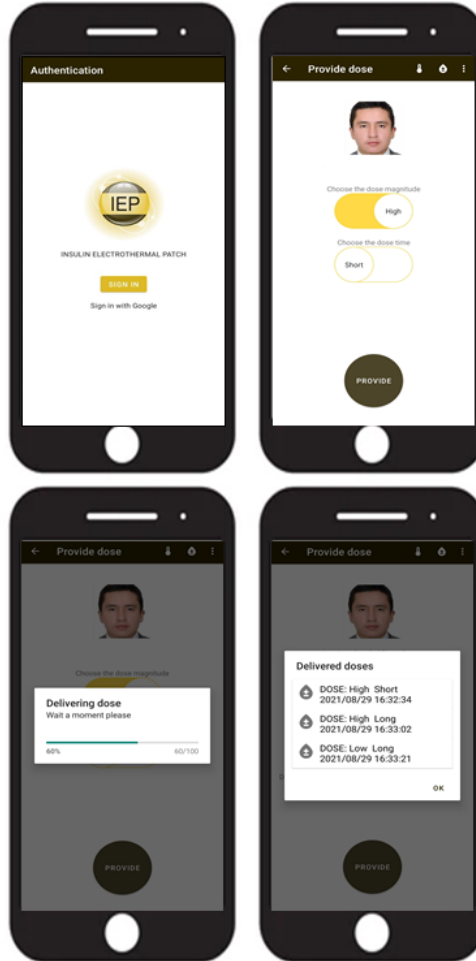


Figure A.3: IEP App to manage the electrothermal patch through the electronic system. The left top photograph shows the home screen, where the patient must login. The right top photograph shows the main screen, where the parameters for the dose should be chosen. The left bottom photograph shows the delivery screen, where drug delivery is ongoing. The right bottom screen shows the history screen, with the recordings of the delivered doses.

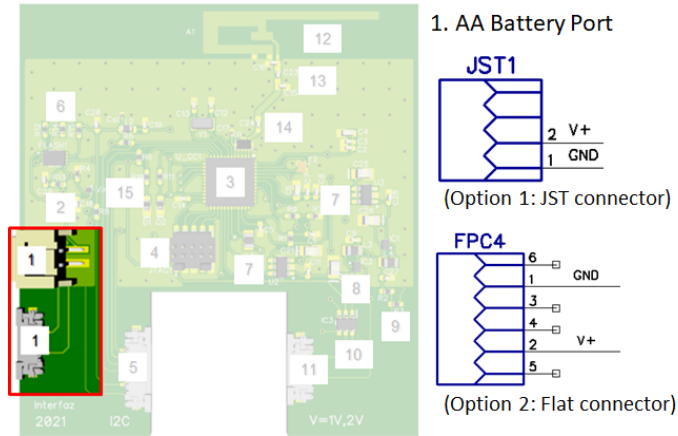


Figure A.4: Circuit diagram showing the AA battery port (Circuit Component #1) of the electronic system. Two AA batteries are connected to provide 3 V to the electronic system.

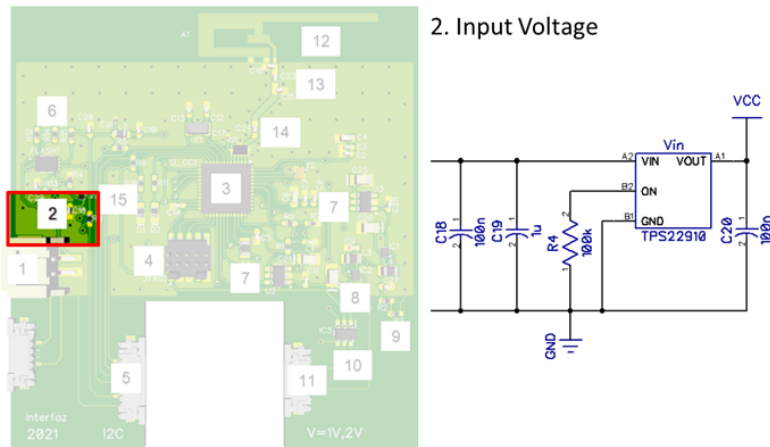


Figure A.5: Circuit diagram showing the input voltage circuit (Circuit Component #2) of the electronic system. It has a TPS22910A switch with controlled turn on. It operates over an input voltage range from 1.4 to 5.5 V, and provides reverse current protection.

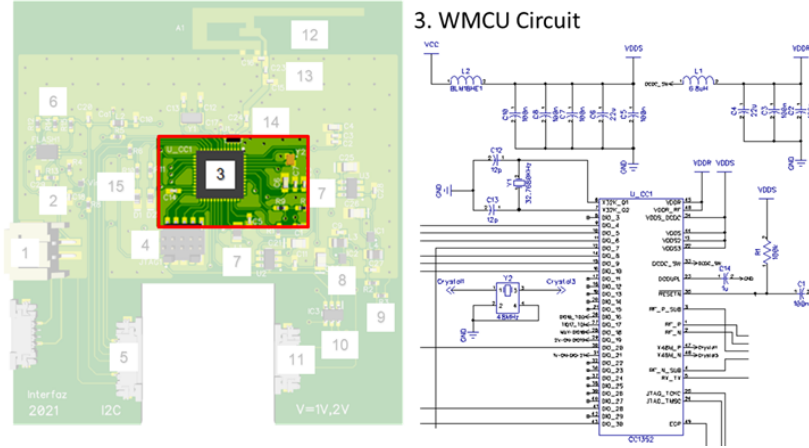


Figure A.6: Circuit diagram showing the WMCU circuit with the minimum elements (Circuit Component #3) for the electronic system. The schematics has a CC1352R wireless microcontroller unit, 32.768 kHz and 48 MHz crystals, a reset circuit and decoupling capacitors. The WMCU controls the activation of the output voltage for the electrothermal patch. It sends a value ON signal to the TPS22860 component to activate the output voltage. The WMCU has a RF module which is used to send the data through Bluetooth protocol to the smart phone.

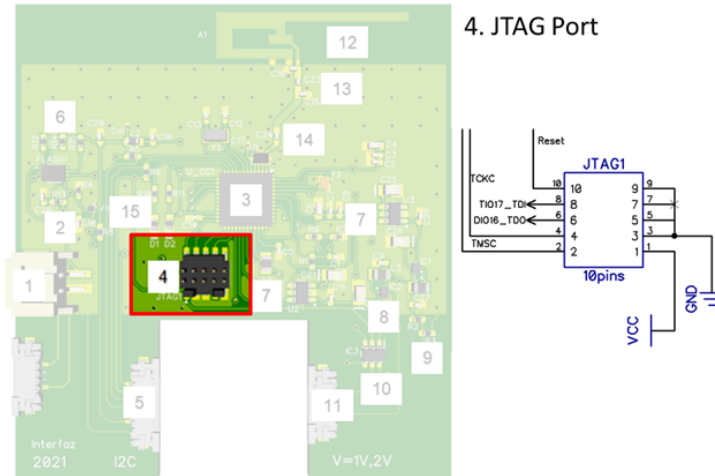


Figure A.7: Circuit diagram showing the JTAG port (Circuit Component #4) of the electronic system. It is the port to debug and program the WMCU. It allows to communicate with the CCS software for debugging and flashing the code.

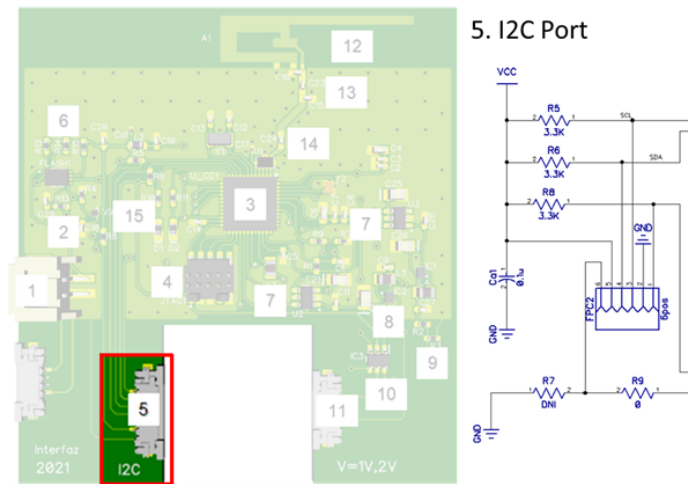


Figure A.8: Circuit diagram showing the I2C port (Circuit Component #5) of the electronic system. This port allows communication between the temperature sensor TMP116 and the WMCU using the protocol I2C. The WMCU controls the temperature of the electrothermal patch. If the temperature value is greater than  $52^{\circ}\text{C}$ , while the electrothermal patch is being powered, the WMCU stops the output voltage.

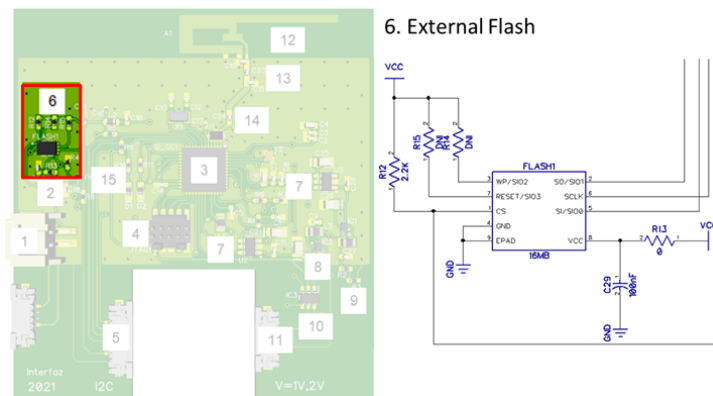


Figure A.9: Circuit diagram showing the external flash (Circuit Component #6) of the electronic system. It has a serial NOR flash memory MX25R8035FZUILO of 8 MB with 33 MHz serial peripheral interface. This sub-system allows external flash over-the-air download.

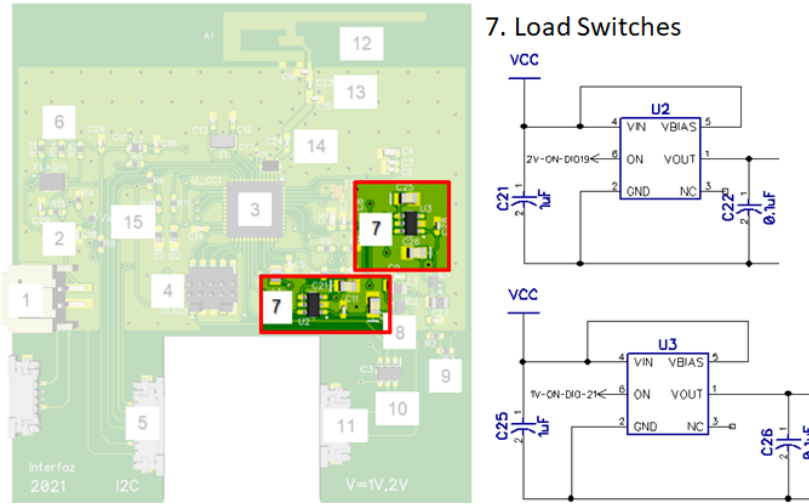


Figure A.10: Circuit diagram showing the two load switches (Circuit Component #7) of the electronic system. The load switches contain TPS22860 ultra-low leakage load switches, which are controlled by an ON/OFF input. They receive from the WMCU the ON signal allowing to bridge the output voltage circuit with the input voltage. The output voltage circuit by default is isolated. It can just be enabled from the WMCU.

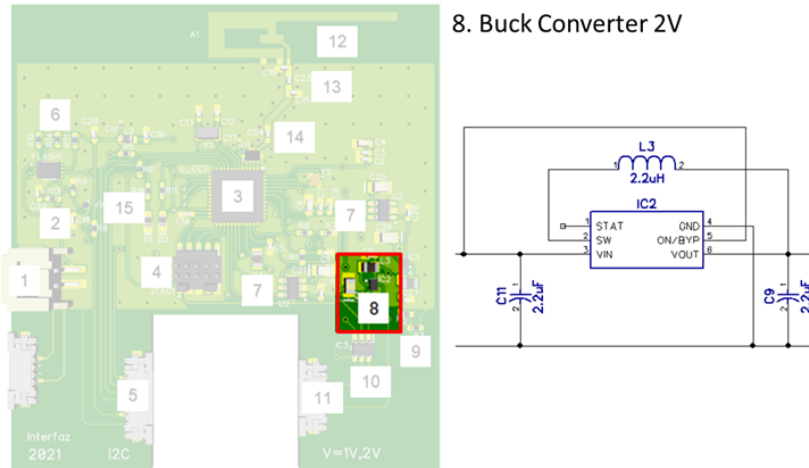


Figure A.11: Circuit diagram showing the 2 V buck converter (Circuit Component #8) of the electronic system. The buck converter is a TPS62730 step down converter. The input voltage range is from 1.9 to 3.9 V, but it keeps a constant output voltage of 2 V, which is one of the output voltage values to supply power to the electrothermal patch.

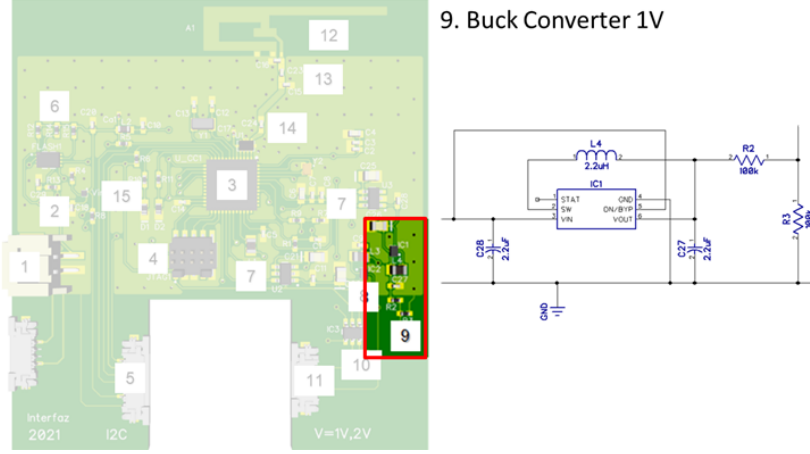


Figure A.12: Circuit diagram showing the 1 V buck converter (Circuit Component #9) of the electronic system. The buck converter is a TPS62730 step down converter together with a voltage divider. The input voltage range is from 1.9 to 3.9 V, but it keeps a constant output voltage of 1 V, which is one of the output voltage values to supply power to the electrothermal patch.

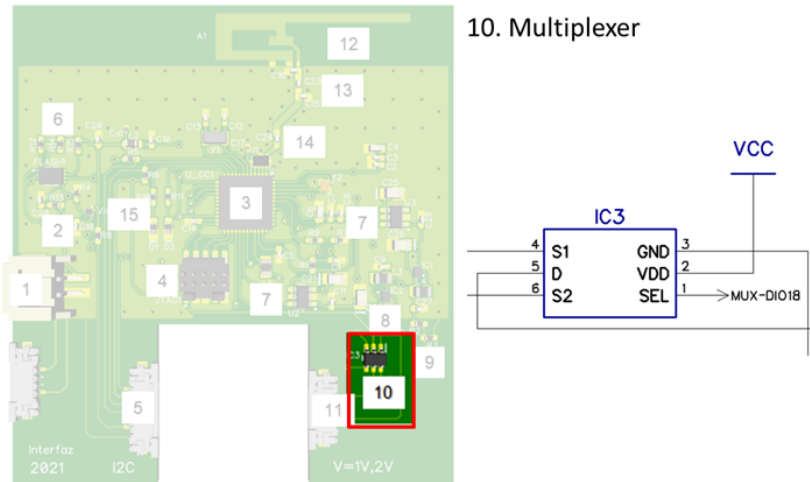


Figure A.13: Circuit diagram showing the multiplexer (Circuit Component #10) of the electronic system. It is a TMUX11119 single-pole double-throw (2:1) switch. It allows to select 1 V or 2 V at the output voltage connector. The input is controlled through the WMCU.

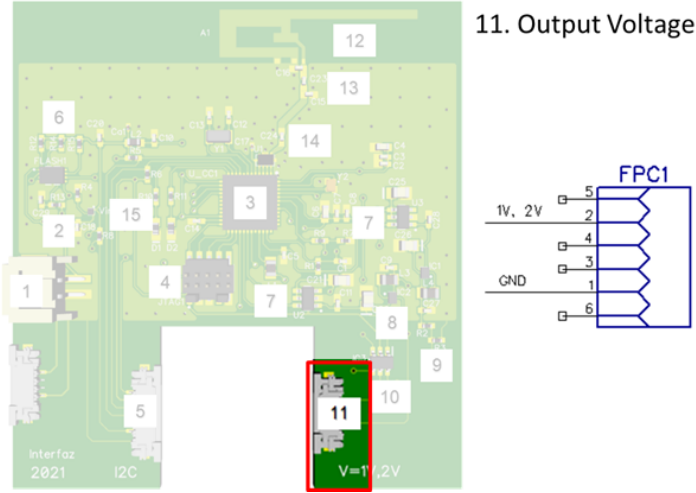


Figure A.14: Circuit diagram showing the output voltage connector (Circuit Component #11) of the electronic system. It is a flat flexible connector of 4 pins. The two outer pins are used for the output voltage.

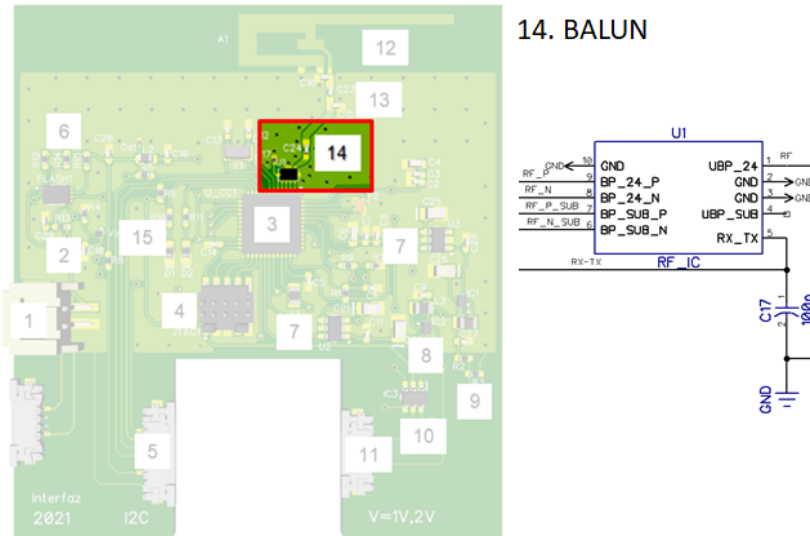


Figure A.15: Circuit diagram showing the antenna (Circuit Component #12) of the electronic system. The inverted-F antenna is fabricated on PCB. It has  $50\ \Omega$  and works at 2.45 GHz. It is used for the Bluetooth communication between the WMCU and the smart phone.



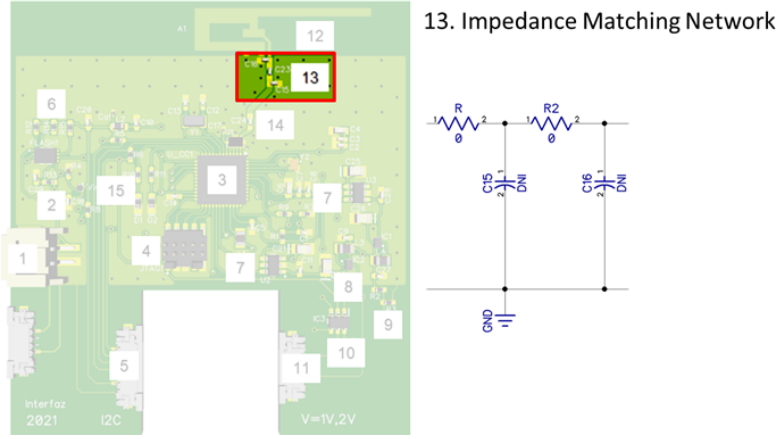


Figure A.16: Circuit diagram showing the impedance matching network components (Circuit Component #13) of the electronic system. Due to the geometry of the PCB and the size of the ground plane, some elements could be added to tune the antenna at the working frequency of 2.45 GHz. In this design, no elements are needed, because the impedance of the antenna, transmission line and balun match well each other.

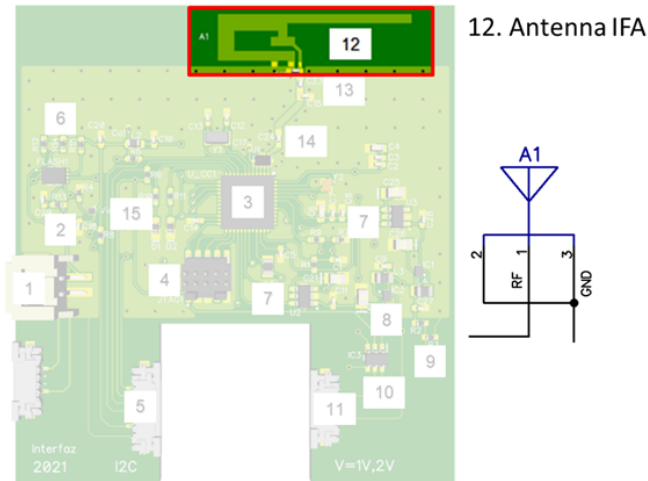


Figure A.17: Circuit diagram showing the BALUN (Circuit Component #14) of the electronic system. It is a 862-928 MHz, 2.4-2.5 GHz integrated impedance-matched balun filter which is suitable for the CC1352R. It allowed to integrate the inverted-F antenna with the WMCU to get optimal RF performance.

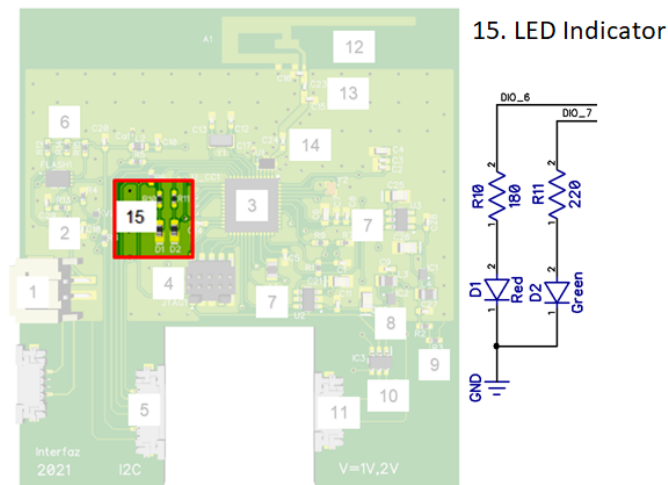


Figure A.18: Circuit diagram showing the LED indicator elements (Circuit Component #15) of the electronic system. The D1 LED turns on when the temperature value is greater than  $52^{\circ}\text{C}$  on the electrothermal patch. The D2 LED turns on when the output voltage is activated.

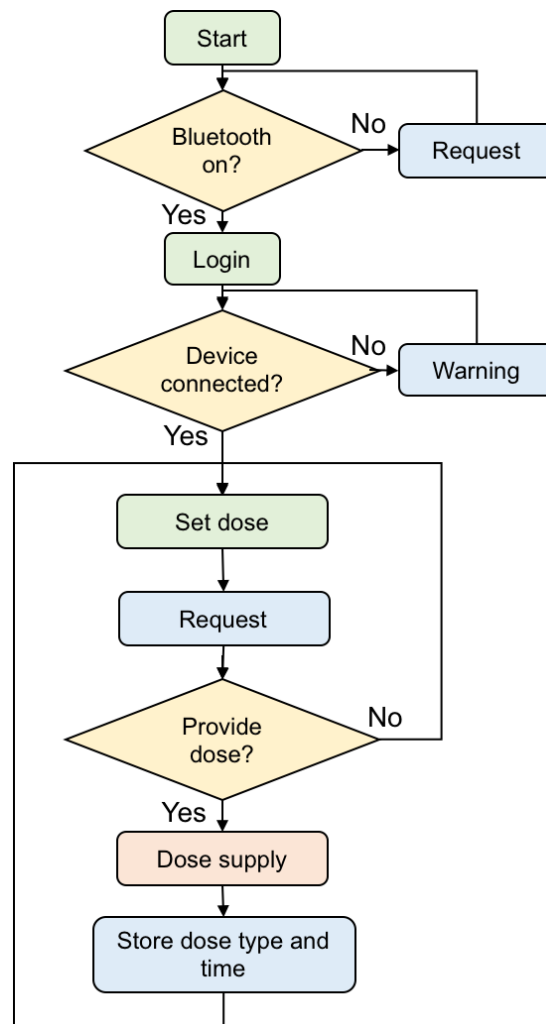


Figure A.19: The flowchart of user interface design of the IEP App. To manage wirelessly the electrothermal patch, a mobile application was designed. At the beginning, the user needs to log into the App with an user name and a password. If the login is correct, the App is linked directly with the electronic system. Afterwards, the user can select the dose parameters, before pressing the activation button. Once the user presses the activation button the output voltage will be enabled in the electronic system according to requested parameters. This will allow the drug delivery. When the activation button is pressed the App will also start to record the type of the dose temperature pulse and the time for each dose. The App provide a user-friendly interface to interact with the electrothermal patch from the smart phone through Bluetooth protocol. The design of the App is envisioned to be integrated next to the cloud and completed with machine learning functionalities.

## A.2 Materials

| Component            | Value or Part Number |
|----------------------|----------------------|
| Circuit component #1 |                      |
| FPC4                 | FPC 4 ports          |
| Circuit component #2 |                      |
| C18, C20             | 100 nF               |
| C19                  | 1 $\mu$ F            |
| R4                   | 100 k $\Omega$       |
| Vin                  | TPS22910             |
| Circuit component #3 |                      |
| C1,C2,C3,C5          | 100 nF               |
| C7,C8, C10           | 100 nF               |
| C4,C6                | 22 $\mu$ F           |
| C12,C13              | 12 pF                |
| C14                  | 1 $\mu$ F            |
| L1                   | 6.8 $\mu$ H          |
| L2                   | BLM18HE1             |
| R1                   | 100 k $\Omega$       |
| U_CC1                | CC1352               |
| Y1                   | 32.7680 KHz Crystal  |
| Y2                   | 48 MHz Crystal       |
| Circuit component #4 |                      |
| JTAG1                | FTSH10501FDVKTR      |
| Circuit component #5 |                      |
| Ca1                  | 0.1 $\mu$ F          |
| FPC2                 | FPC 6 ports          |
| R5,R6,R8             | 3.3 k $\Omega$       |
| R9                   | 0 $\Omega$           |
| Circuit component #6 |                      |
| C29                  | 100 nF               |
| FLASH1               | MX25R1635FZUIL0      |
| C4                   | 10 $\mu$ F           |
| R12                  | 2.2 k $\Omega$       |
| R13                  | 0 $\Omega$           |

Table A.1: Bill of materials for the communication system. 1/2

| Component             | Value or Part Number |
|-----------------------|----------------------|
| Circuit component #7  |                      |
| C21,C25               | 1 $\mu$ F            |
| C22,C26               | 0.1 $\mu$ F          |
| U2,U3                 | TPS22860             |
| Circuit component #8  |                      |
| C9,C11                | 2.2 $\mu$ F          |
| L3                    | 2.2 $\mu$ H          |
| IC2                   | TPS62730             |
| Circuit component #9  |                      |
| C27,C28               | 2.2 $\mu$ F          |
| L4                    | 2.2 $\mu$ H          |
| R2,R3                 | 100 k $\Omega$       |
| IC1                   | TPS62730             |
| Circuit component #10 |                      |
| IC3                   | TMUX1119             |
| Circuit component #11 |                      |
| FPC1                  | FPC 4 ports          |
| Circuit component #12 |                      |
| A1                    | IFA antenna 2.4 GHz  |
| Circuit component #13 |                      |
| R                     | 0 $\Omega$           |
| Circuit component #14 |                      |
| C17                   | 100 nF               |
| U1                    | 0900PC15A0036E       |
| Circuit component #15 |                      |
| R10                   | 180 $\Omega$         |
| R11                   | 220 $\Omega$         |
| D1                    | Red diode            |
| D2                    | Green diode          |

Table A.2: Bill of materials for the communication system. 2/2

### A.3 Power Analysis

Power consumption analysis is key for the design of low-power wearable devices. One crucial aspect to consider is the wireless connection link, typically influenced by the type of chipset, BLE version and parameters. The Generic Access Profile (GAP) is a layer of the BLE stack which handles the connection functionality. The GAP layer offers four options to operate a BLE-based device as central, peripheral, broadcaster, and observer. The electronic system in our application is

the peripheral device and the smart phone is the central device (Figure A.20). In principle, the peripheral device advertises its existence through advertising events to a central device.

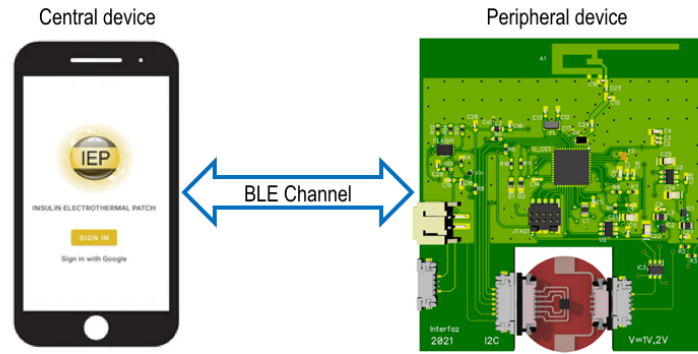


Figure A.20: Central device (left) and peripheral device (right).

Figure A.21 shows the measurement setup for the analysis of the power consumption of the device under test (DUT). First, the Code Composer Studio software by Texas Instruments includes the EnergyTrace tool. EnergyTrace is an analysis tool to obtain the current and power profiles of an electronic device. Second, the XDS 110 probe by Texas Instruments is connected to the PC and to the DUT. The XDS 110 probe and DUT are connected by 4 pins (UARTRX, UARTTX, TGTSUPPLYOUT, GND). Once the measurement setup is ready, the power analysis is performed.

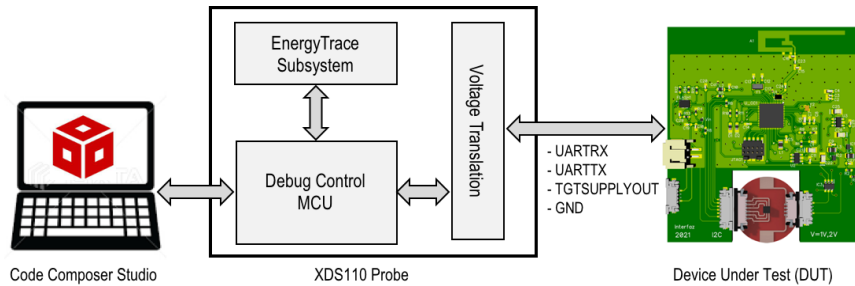


Figure A.21: Block diagram of the measurement setup for the analysis of the power consumption.

A peripheral device starts sending advertising events before accepting a connection. The advertising events consume a certain amount of power which can be measured by using the measurement setup. The current consumption for the advertising events (A1-A10) was obtained as

depicted in Figure A.22.a. A zoom out of the A4 event is shown in Figure A.22.b. Table A.3 (reproduced from Texas Instruments <sup>2</sup>) explains each component indexed in the graph. Finally, Figure A.22.c shows the device name (IEPatch) and its physical address (80:6F:B0:2B:37:E8). They can be obtained by using a smart phone App like BLE Scanner which can detect BLE-based devices in surroundings.

BLE sends data packets for a few milliseconds and sleeps for long periods as shown in Figure A.22.a. For example, the periodic advertising events, lasting cca 4 ms, are sent almost each 100 ms. The detail of an advertising event is shown in Figure A.22.b.

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<sup>2</sup><https://www.ti.com/lit/an/swra478d/swra478d.pdf>

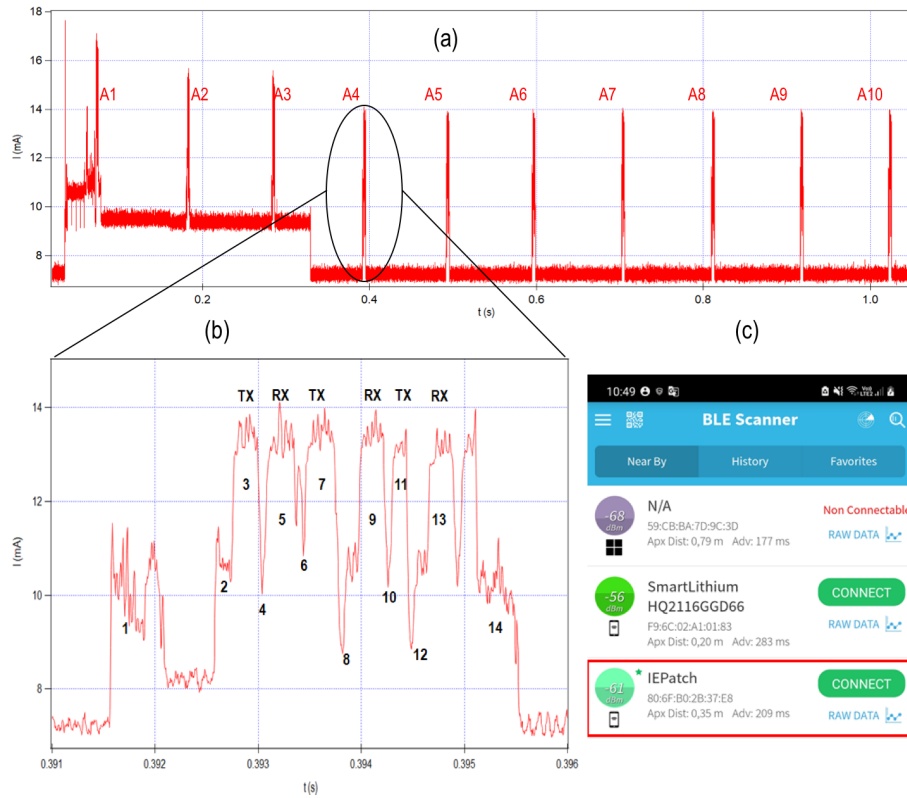


Figure A.22: Advertising events for BLE connection. (a) Advertising events in cca. 1 s. (b) Detail of an advertising event. (c) Smart phone App showing the name and physical address of the peripheral device. Note that the WMCU performs the power-on reset and the system initialization for about 330 ms. The current spike at the beginning, of around 17.65 mA, is caused by the decoupling capacitors. Afterwards the real time operating system (RTOS), clocks, and BLE stack are initialized. At the end of the initialization sequence the WMCU goes to a low-power mode. Then, the WMCU wakes up from the low-power mode when an event is available to be processed like the advertising event or data sending via Bluetooth.



| No. | State                                | Comments                                                                                                                                  |
|-----|--------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | Pre-processing                       | RTOS wake-up, radio setup, XTAL guard time. XTAL is the output of the crystal oscillator amplifier                                        |
| 2   | Radio preparation                    | Radio is turned on and in transition to TX                                                                                                |
| 3   | TX                                   | The radio transmits an advertisement packet with 3 bytes data on Channel 37. Time is dependent on amount of transmitted data              |
| 4   | TX to RX transition                  | TX to RX transition                                                                                                                       |
| 5   | RX                                   | Time depends on advertising interval and Sleep Crystal Accuracy (SCA)                                                                     |
| 6   | RX to TX transition                  | RX to TX transition                                                                                                                       |
| 7   | TX                                   | The radio transmits an advertisement packet with 3 bytes data on Channel 38. Time is dependent on amount of transmitted data              |
| 8   | TX to RX transition                  | TX to RX transition                                                                                                                       |
| 9   | RX                                   | Time depends on advertising interval and SCA                                                                                              |
| 10  | RX to TX transition                  | RX to TX transition                                                                                                                       |
| 11  | TX                                   | The radio transmits an advertisement packet with 3 bytes data on Channel 39. Time is dependent on amount of transmitted data              |
| 12  | TX to RX transition                  | TX to RX transition                                                                                                                       |
| 13  | RX                                   | Time depends on advertising interval and SCA                                                                                              |
| 14  | Post-processing and going to Standby | BLE protocol stack processes the received packets and sets up the sleep timer in preparation for the next event, and then goes to Standby |

Table A.3: Advertising event and state analysis for BLE. Channels 37 (first, at 2402 MHz), 38, and 39 (last, at 2480 MHz) are used only for sending advertisement packets. During BLE advertisement, a BLE peripheral device transmits the same packet on the 3 advertising channels, one after the other. BLE has 40 physical channels in the 2.4 GHz ISM band, each separated by 2 MHz. Bluetooth defines a single packet format for both advertising and data transmissions. This packet consist of four components: preamble (1 octet), access address (4 octets), Protocol Data Unit – PDU (2-257 octets), and Cyclic Redundancy Check – CRC (3 octets).

By using the EnergyTrace software tool, the current, the power and the lifetime of the battery can be calculated. Considering the start mode when the electronic device turns on, the lifetime of the battery has been estimated to 11 days and 10 hours considering 2 AA batteries. The results are shown in Table A.4.

To analyze the BLE packets while they are transmitted over the

| Values | Current  | Voltage | Power    |
|--------|----------|---------|----------|
| Min    | 6.75 mA  | 3.3 V   | 22.27 mW |
| Max    | 14.00 mA | 3.3 V   | 46.20 mW |

Table A.4: Current consumption profile in start mode.

air, two specific tools are needed: the CC2540EMK-USB module as a packet sniffer (hardware) and the SmartRF Packet Sniffer BLE (software), both by Texas Instruments. Figure A.23 shows the obtained advertising packets by using packet sniffer tools for the advertising events from Figure A.22.a. The type of packet and the physical address of the device are highlighted. The most common advertising packets sent by a peripheral device are advertising indications (ADV\_IND). They help any central device to find the peripheral device and start the connection process.

|     |        |                    |         |                |              |                |       |       |            |                |                   |                   |          |     |     |            |     |
|-----|--------|--------------------|---------|----------------|--------------|----------------|-------|-------|------------|----------------|-------------------|-------------------|----------|-----|-----|------------|-----|
| A1  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 40     | +4248<br>=2257878  | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A2  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 44     | +73108<br>=2366876 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A3  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 51     | +55363<br>=2468874 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A4  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 58     | +11444<br>=2577872 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A5  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 62     | +72849<br>=2677870 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A6  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 69     | +55571<br>=2780868 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A7  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 74     | +9725<br>=2887867  | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A8  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 78     | +80841<br>=2995864 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A9  | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 85     | +67122<br>=3101862 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |
| A10 | P.nbr. | Time (us)          | Channel | Access Address | Adv PDU Type | Adv PDU Header |       |       |            | AdvA           | AdvData           |                   |          |     | CRC | RSSI (dBm) | FCS |
|     | 92     | +18140<br>=3207861 | 0x25    | 0x8E89BED6     | ADV_IND      | Type           | TxAdd | RxAdd | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61 | 74 63 68 02 01 06 | 0xA20906 | -33 | OK  |            |     |

Figure A.23: Capture of advertising packets over the air by using packet sniffer tools.

When the central device establishes a connection with a peripheral device, in addition to the advertising event, it is also possible to see a connection event. This indicates that both devices are already paired and they are ready to exchange data (Figure A.24). Table A.5 shows the current and power values for this connected mode; during the connection event the current rises up to values close to the advertising event.

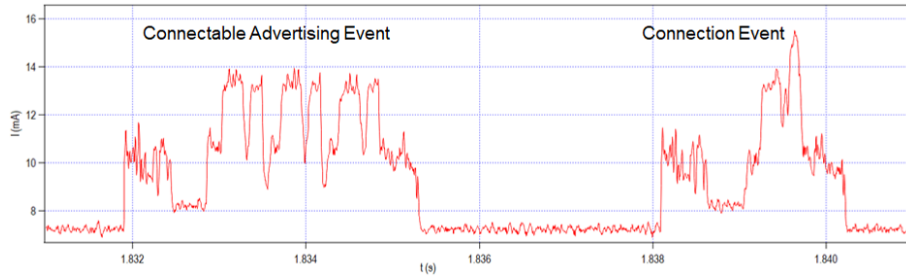


Figure A.24: Shape of advertising and connection events in connected mode.

| Values | Current  | Voltage | Power    |
|--------|----------|---------|----------|
| Min    | 6.73 mA  | 3.3 V   | 22.21 mW |
| Max    | 14.37 mA | 3.3 V   | 47.41 mW |

Table A.5: Current consumption profile in connected mode.

It is also possible to sniff the BLE packets during the connection between central and peripheral device by using the same above mentioned tools as depicted in Figure A.25. The packet #1709 appears as the starting point for the connection process; right after, the connection is established with additional BLE packets.

|                                                                 |                      |         |                |                 |                |           |             |            |                |                                        |                   |              |                                    |         |            |                |           |            |          |            |     |
|-----------------------------------------------------------------|----------------------|---------|----------------|-----------------|----------------|-----------|-------------|------------|----------------|----------------------------------------|-------------------|--------------|------------------------------------|---------|------------|----------------|-----------|------------|----------|------------|-----|
| P.nbr.                                                          | Time (us)            | Channel | Access Address | Adv PDU Type    | Adv PDU Header |           |             |            | AdvA           | AdvData                                |                   |              |                                    | CRC     | RSSI (dBm) | FCS            |           |            |          |            |     |
| 1708                                                            | +67309<br>=40572100  | 0x25    | 0x8E89BED6     | ADV_IND         | Type           | TxAdd     | RxAdd       | PDU-Length | 0x806FB02B37E8 | 08 09 49 45 50 61<br>74 63 68 02 01 06 | 0xA20906          |              |                                    |         | -29        | OK             |           |            |          |            |     |
| P.nbr.                                                          | Time (us)            | Channel | Access Address | Adv PDU Type    | Adv PDU Header |           |             |            | InitA          | AdvA                                   |                   |              |                                    |         |            |                |           |            |          |            |     |
| 1709                                                            | +375<br>=40572475    | 0x25    | 0x8E89BED6     | ADV_CONNECT_REQ | Type           | TxAdd     | RxAdd       | PDU-Length | 0x4504DBB45DC9 | 0x806FB02B37E8                         |                   |              |                                    |         |            |                |           |            |          |            |     |
| LLData (Part 1)                                                 |                      |         |                |                 |                |           |             |            |                |                                        |                   |              |                                    |         |            |                |           |            |          |            |     |
| AccessAddr                                                      |                      |         |                | CRCInit         |                | WinSize   |             | WinOffset  |                | Interval                               |                   | Latency      |                                    | Timeout |            | ChM            | Hop       | SCA        | CRC      | RSSI (dBm) | FCS |
| 0x65CD7C8F                                                      |                      |         |                | 63 65 E8        |                | 02        |             | 0x001D     |                | 0x0024                                 |                   | 0x0000       |                                    | 0x01F4  |            | 1F FF FF FE 00 | 0x09      | 0x00       | 0x7CEB43 | -36        | OK  |
| P.nbr.                                                          | Time (us)            | Channel | Access Address | Direction       | ACK Status     | Data Type | Data Header |            |                |                                        |                   |              |                                    |         |            |                |           |            |          |            |     |
| 1710                                                            | +38983<br>=40611458  | 0x09    | 0x65CD7C8F     | M->S            | OK             | Control   | LLID        | NESN       | SN             | MD                                     | PDU-Length        |              |                                    |         |            |                |           |            |          |            |     |
|                                                                 |                      |         |                |                 |                |           | 3           | 0          | 0              | 0                                      | 9                 |              |                                    |         |            |                |           |            |          |            |     |
|                                                                 |                      |         |                |                 |                |           |             |            |                |                                        | LL_Opcode         |              | LL_Feature_Req                     |         |            |                | CRC       | RSSI (dBm) | FCS      |            |     |
|                                                                 |                      |         |                |                 |                |           |             |            |                |                                        | Feature_Req(0x08) |              | FeatureSet<br>00 00 00 00 00 7D FF |         |            |                | 0xE8CAFD  | -35        | OK       |            |     |
| P.nbr.                                                          | Time (us)            | Channel | Access Address | Direction       | ACK Status     | Data Type | Data Header |            |                |                                        | CRC               |              | RSSI (dBm)                         | FCS     |            |                |           |            |          |            |     |
| 1711                                                            | +301<br>=40611759    | 0x09    | 0x65CD7C8F     | S->M            | OK             | Empty PDU | LLID        | NESN       | SN             | MD                                     | PDU-Length        | 0x333A63     | -30                                | OK      |            |                |           |            |          |            |     |
|                                                                 |                      |         |                |                 |                |           | 1           | 1          | 0              | 0                                      | 0                 |              |                                    |         |            |                |           |            |          |            |     |
| P.nbr.                                                          | Time (us)            | Channel | Access Address | Direction       | ACK Status     | Data Type | Data Header |            |                |                                        | CRC               |              | RSSI (dBm)                         | FCS     |            |                |           |            |          |            |     |
| 1712                                                            | +314697<br>=40926456 | 0x23    | 0x65CD7C8F     | ?               | OK             | Empty PDU | LLID        | NESN       | SN             | MD                                     | PDU-Length        | 0x3337C5     | -34                                | OK      |            |                |           |            |          |            |     |
|                                                                 |                      |         |                |                 |                |           | 1           | 1          | 1              | 0                                      | 0                 |              |                                    |         |            |                |           |            |          |            |     |
| P.nbr.                                                          | Time (us)            | Channel | Access Address | Direction       | ACK Status     | Data Type | Data Header |            |                |                                        | L2CAP Header      |              |                                    |         |            |                |           |            |          |            |     |
| 1713                                                            | +229<br>=40926685    | 0x23    | 0x65CD7C8F     | ?               | OK             | L2CAP-S   | LLID        | NESN       | SN             | MD                                     | PDU-Length        | L2CAP-Length | ChanId                             |         |            |                |           |            |          |            |     |
|                                                                 |                      |         |                |                 |                |           | 2           | 0          | 1              | 1                                      | 24                | 0x0014       | 0x0004                             |         |            |                |           |            |          |            |     |
| ATT_Read_By_Group_Type_Rsp                                      |                      |         |                |                 |                |           |             |            |                |                                        |                   |              |                                    |         |            |                | CRC       | RSSI (dBm) | FCS      |            |     |
| Opcode Length AttData                                           |                      |         |                |                 |                |           |             |            |                |                                        |                   |              |                                    |         |            |                | 0x7CDD9EF | -32        | OK       |            |     |
| 0x11 0x06 01 00 0B 00 00 18 0C 00 0C 00 01 18 0D 00 1F 00 0A 18 |                      |         |                |                 |                |           |             |            |                |                                        |                   |              |                                    |         |            |                |           |            |          |            |     |

Figure A.25: Capture of connection packets over the air by using packet sniffer tools.

Finally, Figure A.26 shows the current consumption profile for sending data from the central device to the peripheral device. The current consumption increases up to 22.09 mA when data is sent through the BLE channel. Table A.6 shows the current and power consumption in the transmission mode. In the transmission mode, battery lifetime has been estimated for 10 days and 8 hours considering 2 AA batteries.

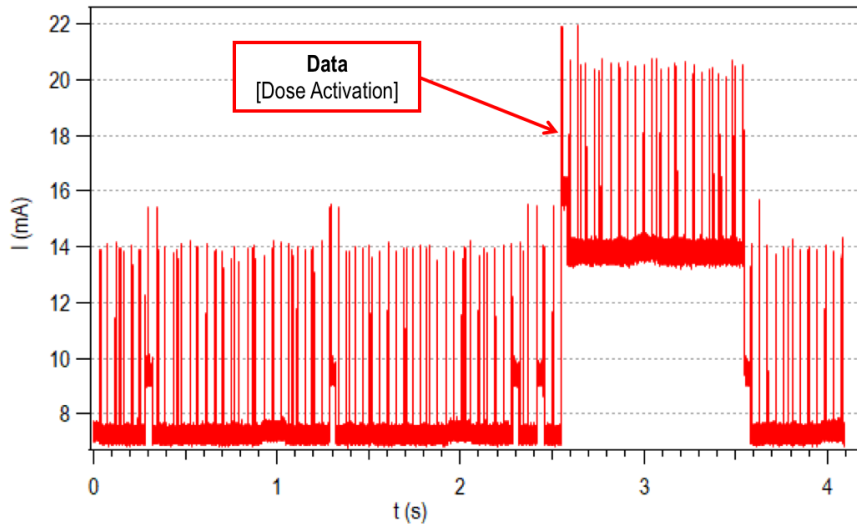


Figure A.26: Current consumption profile in transmitting mode.

| Values | Current  | Voltage | Power    |
|--------|----------|---------|----------|
| Min    | 6.75 mA  | 3.3 V   | 22.28 mW |
| Max    | 22.09 mA | 3.3 V   | 72.89 mW |

Table A.6: Current consumption profile in transmitting mode.

Additionally, the peripheral device was tested attaching a Murata battery UMAL361421B024TA01 to it. This battery has a nominal capacity of 24 mAh and a nominal voltage of 2.3 V. The battery was employed with an initial operation voltage of 2.4 V. After delivering continuously a certain number of doses, the battery voltage drops to 2.2 V, for which the electronic system stops working.<sup>3</sup> This type of

<sup>3</sup>The LL\_TERMINATE\_IND packets contain the info about the disconnection event as well as the error code indicating the reason for the terminated connection. We guess that in this case the error is 0x14 - peripheral device terminated connection due to low resources. This hypothesis needs further inquiry to be confirmed.

battery is rechargeable, therefore in order to reuse it again it needs to be unplugged and recharged.<sup>4</sup> The electronic system was linked with the App IEP via Bluetooth. A first test was performed with the following selected values: dose magnitude of 2 V and dose time of 50 s. The peripheral device was able to deliver 15 doses during the battery operation. A second test was performed with the following selected values: dose magnitude of 2 V and dose time of 5 s. The peripheral device was able to deliver 50 doses during the battery operation.

---

<sup>4</sup>A better way is to implement an energy harvesting circuit in order to recharge the battery continuously avoiding interruption of the operation of an electronic device, especially for healthcare applications.

## A.4 List of abbreviations

|     |                                   |         |                                    |
|-----|-----------------------------------|---------|------------------------------------|
| App | :Mobile application               | BALUN : | Balancing unit                     |
| BLE | :Bluetooth low energy             | CCS :   | Code composer studio               |
| CPU | :Central processing unit          | FPCB :  | Flexible printed circuit board     |
| I2C | :Inter-integrated circuit         | IDE :   | Integrated development environment |
| IEP | :Insulin electrothermal patch app | IFA :   | Inverted-F antenna                 |
| LCD | :Liquid crystal display           | LED :   | Light emitting diode               |
| RF  | :Radio frequency                  | WMCU :  | Wireless microcontroller unit      |



## Appendix B

# Integrated flexible circuit boards for driving drug delivery systems

This Annex presents the first two prototypes on which subsequent work has been developed to build the electronic communication systems for the electrothermal patches. Given the fact that in the long term many other sensors and actuators can contribute to the overall architecture of the patch, whose shape can vary as well, several topologies have been tested for the flexible electronic boards and we have chosen to present two of them.

### B.1 Prototype 1

The prototype 1 (P1) is a flexible printed circuit board (FPCB), which is able to supply power to the electrothermal skin patch. The FPCB offers output regulated voltages of 0.8, 1.0, and 1.2 V. This prototype is described in [Figure B.1](#), [Figure B.2](#), and [Table B.1](#).

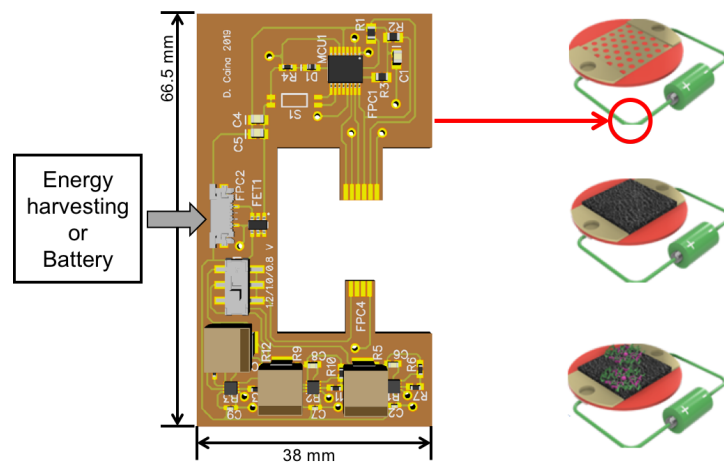
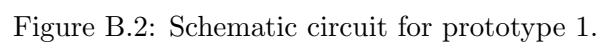


Figure B.1: (Left) Flexible printed circuit board (prototype 1) to power the electrothermal skin patch. (Right) From top to bottom, different stages of the functional patch.



| Component  | Value or Part Number |
|------------|----------------------|
| B1, B2, B3 | TPS62080DSGR         |
| C1         | 0.1 $\mu$ F          |
| C2         | 10 $\mu$ F           |
| C4         | 10 $\mu$ F           |
| C5         | 100 nF               |
| C6         | 22 $\mu$ F           |
| C7         | 10 $\mu$ F           |
| C8         | 22 $\mu$ F           |
| C9         | 10 $\mu$ F           |
| C10        | 22 $\mu$ F           |
| D1         | DIODE_0603           |
| FET1       | TPS27081A            |
| FPC1       | FPC 6Pins            |
| FPC2       | FPC 4Pins            |
| FPC4       | FPC 4 Pins           |
| L1         | 1 $\mu$ H            |
| L2         | 1 $\mu$ H            |
| L3         | 1 $\mu$ H            |
| MCU1       | MSP430FR23xx         |
| R1         | 5 K $\Omega$         |
| R2         | 5 K $\Omega$         |
| R3         | 5 K $\Omega$         |
| R4         | 499 $\Omega$         |
| R5         | 178 K $\Omega$       |
| R6         | 64.9 K $\Omega$      |
| R7         | 39.2 K $\Omega$      |
| R8         | 178 K $\Omega$       |
| R9         | 178 K $\Omega$       |
| R10        | 47.5 K $\Omega$      |
| R11        | 39.2 K $\Omega$      |
| R12        | 30.5 K $\Omega$      |
| R13        | 39.2 K $\Omega$      |
| R14        | 4.7 K $\Omega$       |
| R15        | 4.7 K $\Omega$       |
| S1         | dip Switch-2p        |
| U1         | Switch DPDT          |

Table B.1: Bill of materials for the prototype 1.

## **B.2 Prototype 2**

For the second prototype a flexible printed circuit board was designed to sense the temperature of the electrothermal skin patch as well. At the same time, it can supply power to the patch with a voltage pulse of 2 V up to 20 s. A Bluetooth capability to connect with an Android App has been tested, in order to activate the voltage pulse remotely. Instead of a smart phone readout, a display has been connected to the board. This prototype is described in Figure B.3, Figure B.4, Figure B.5, Figure B.6, and Table B.2.

The electronic system was designed using DipTrace software. The code 1 was coded using Code Composer Studio (CCS) for the 2.4 GHz CC1352 wireless microcontroller unit (WMCU) by Texas Instruments. The App was developed using Android Studio by Google.

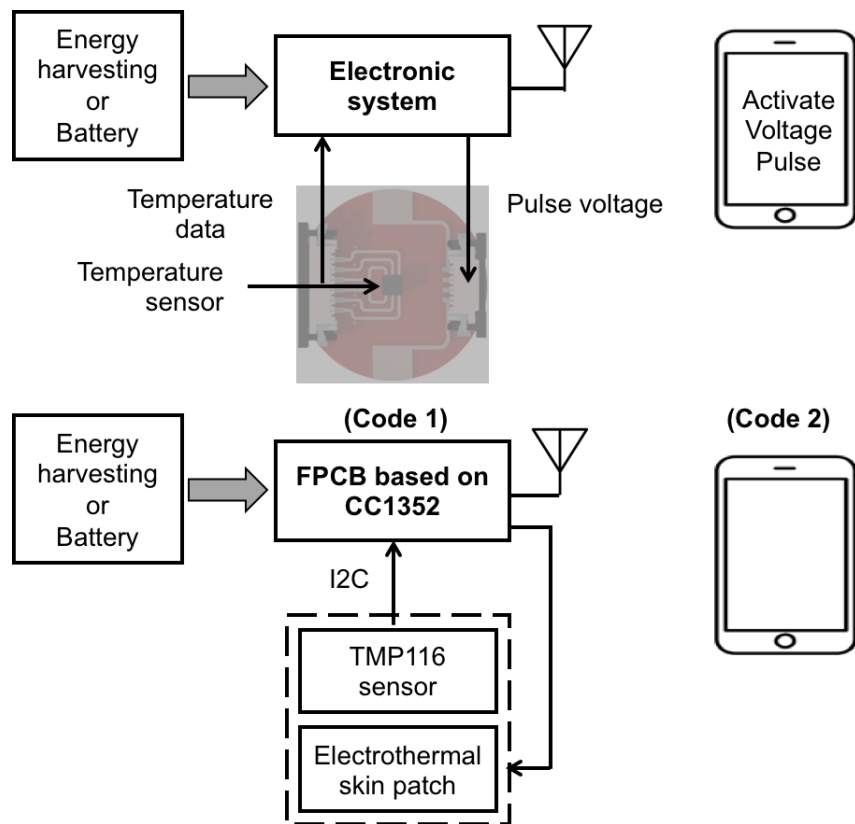


Figure B.3: Block diagram of an electronic system for sensing the temperature and providing a voltage pulse of 2 V until a threshold temperature of 52°C is attained. A TMP116 sensor has been used for temperature sensing.



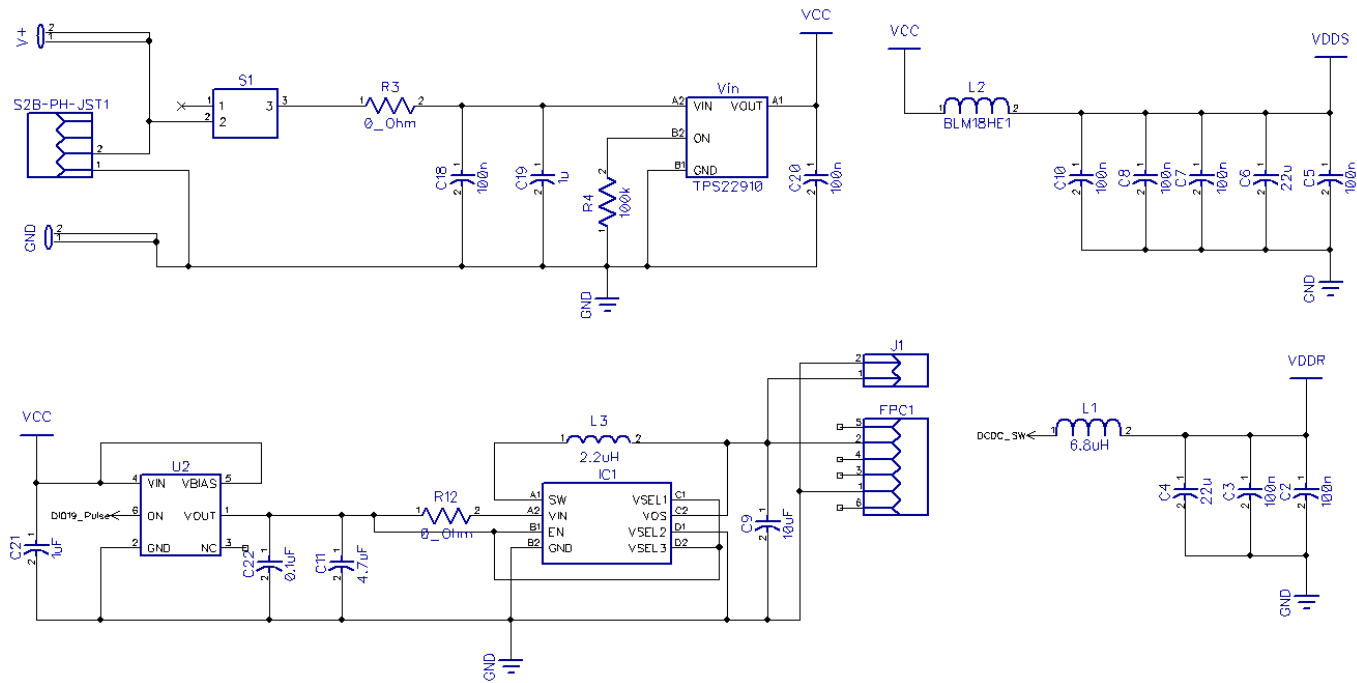
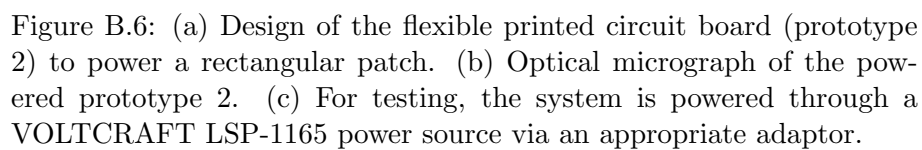


Figure B.5: Schematic circuit for prototype 2 (2/2).



| Component              | Value or Part Number |
|------------------------|----------------------|
| C1, C2, C3, C5, C7, C8 | 100 nF               |
| C10, C17, C18, C20     | 100 nF               |
| C9                     | 10 $\mu$ F           |
| C11                    | 4.7 $\mu$ F          |
| C4, C6                 | 22 $\mu$ F           |
| C12, C13               | 12 pF                |
| C24                    | 12 pF                |
| C14, C19               | 1 $\mu$ F            |
| C15, C16               | DNI                  |
| C21                    | 1 $\mu$ F            |
| C22                    | 0.1 $\mu$ F          |
| C23                    | 1.2 pF               |
| C24                    | 12 pF                |
| Ca1                    | 0.1 $\mu$ F          |
| D1                     | Red                  |
| D2                     | Green                |
| FPC2                   | 6 pins               |
| FPC1, FPC3             | 4 pins               |
| ES1                    | Switch               |
| IC1                    | TPS627431            |
| J_LCD1                 | LCD 128 x 128        |
| JTAG1                  | 10 pins              |
| L1                     | 6.8 $\mu$ H          |
| L2                     | BLM18HE1             |
| L3                     | 2.2 $\mu$ H          |
| R1, R4                 | 100 K $\Omega$       |
| R2, R3, R12            | 0 $\Omega$           |
| R5, R6, R8             | 3.3 K $\Omega$       |
| R7, R9                 | DNI                  |
| R10                    | 180 $\Omega$         |
| R11                    | 220 $\Omega$         |
| R13                    | 100 $\Omega$         |
| S1                     | JS102011S            |
| U1                     | 0900PC15A0036E       |
| U2                     | TPS22860             |
| U_CC1                  | CC1352               |
| Vin                    | TPS22910             |
| Y1                     | 32.7680 KHz          |
| Y2                     | 48 MHz               |

Table B.2: Bill of materials for the prototype 2.



### B.3 Battery bank

In order to provide a long-term power autonomy for the electronic devices, a battery pack was developed. The Figure B.7.a shows a fabricated battery pack on 50  $\mu\text{m}$  thick Kapton substrate and patterned 35  $\mu\text{m}$  thick copper. The tracks have a width of 0.5 mm, like the pitch of the flat connector used in this application. We soldered the Li-ion batteries to the Kapton using the Kester EP256 solder paste no-clean 63/37 (tin/lead) with syringe dispenser. The parallel-arranged eight battery bank provides 2.3 V and 96 mA (1C rate) at the end of the flat connector side. This prototype is described in Figure B.7 and Table B.3.

The Figure B.7.b shows a fabricated battery pack on transfer paper with polyurethane coating as interfacial layer (see red rectangle). The soldering process of components is different on the silver ink tracks - same geometry like the Cu tracks used for integration on Kapton, because we have to use two-part, low temperature conductive epoxy CW2400 (CircuitWorks) to attach each item to the screen-printed transfer paper. The parallel-arranged eight battery bank provides 2.3 V and 96 mA at the end of the flat connector side.

To obtain wearability and comfort, we developed a similar battery pack on a textile with *École nationale supérieure des arts et industries textiles*, Roubaix, France (<http://www.ensait.fr/>). Here the conducting layer is offered by sewing a conductive thread that is completed by an 1.5 micron thick Al coating, obtained by vapour deposition. Another solution for battery integration to textiles is to laminate the power bank onto a textile via a transfer paper, and this work is under development as well with *CENTEXBEL*, Belgium (<https://www.centexbel.be/>). The serial/parallel-arranged eight battery bank shown in Figure B.7.c provides 6.0 V and 50 mA (non-continuous discharge) at the end of the flat connector side. These are  $\text{MnO}_2/\text{Li}$  primary batteries with tin over nickel-coated tabs from Renata (CP042350) and the flat connector has 10 pins with 1 mm pitch, which is required by the sewing protocol on the fabric. The specification of the 1 mm pitch flat flex cable shown in Figure B.7.c is AWM 20624 80C 60V VW-1.

| Component             | Value or Part Number |
|-----------------------|----------------------|
| Battery (8 pieces)    | UMAL201421A012TA01   |
| Flat connector 4 pins | 686104183422         |
| Surface mount fuse    | SF-1206S050-2        |

Table B.3: Bill of materials for battery banks built with Murata batteries.

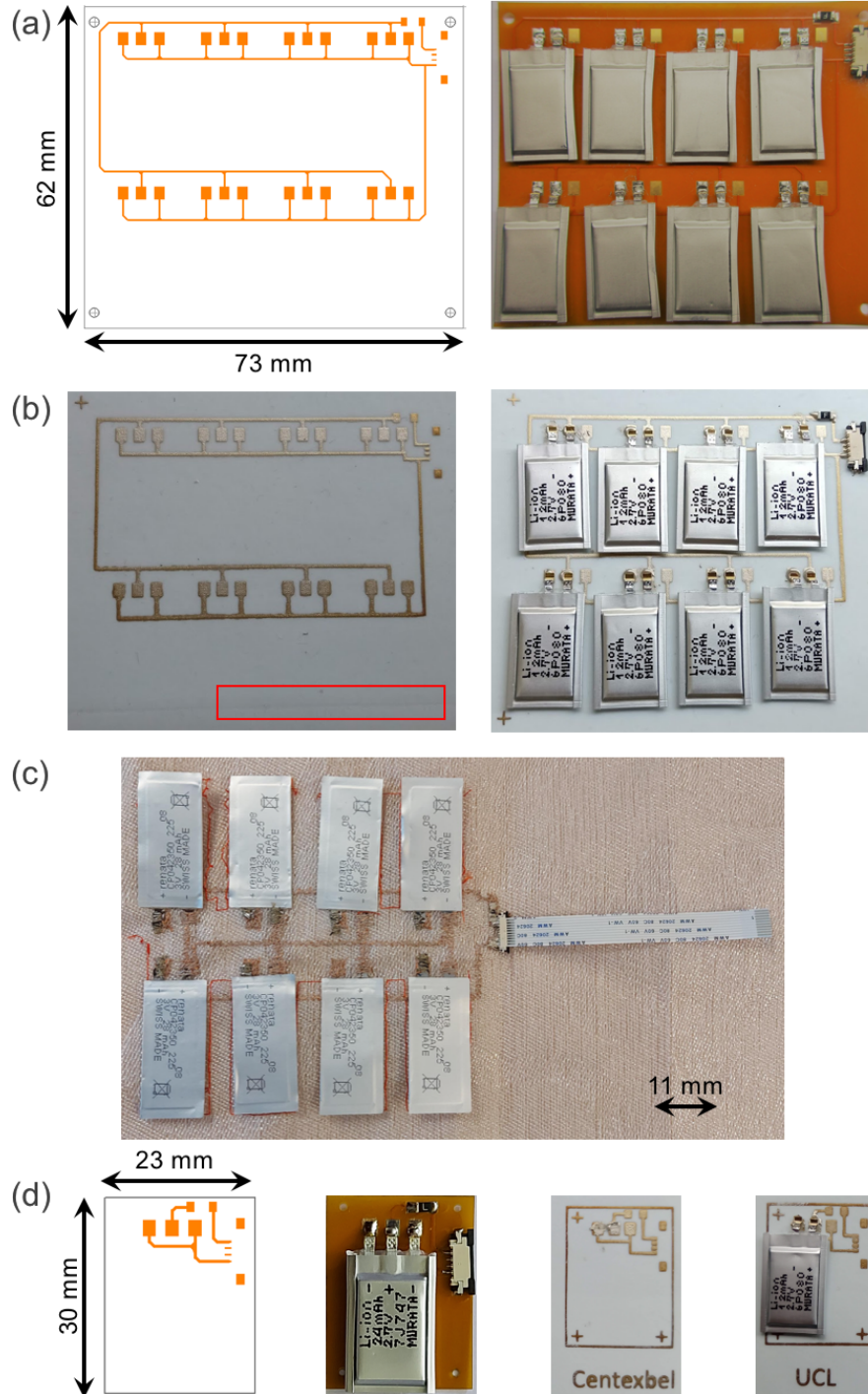


Figure B.7: (a) Battery pack on Kapton. (b) Battery pack on transfer paper. (c) Battery bank on polyethylene woven fabric with a coarse yarn and a finer cross yarn (Renata primary batteries). (d) Option of single battery on Kapton and transfer paper (Murata rechargeable battery prototypes).

## Appendix C

# Fabrication of the thermal patch

The fabrication process of the thermal patch is described in this appendix. Figure C.1 shows the front side and the back side of the final thermal patch. The electronic circuit was patterned on the Cu side of a Kapton laminated on Cu substrate using standard micromachining methods. The colloidal lithography was used to fabricate the heater elements based on gold nanoholes [AuNHs] on the Kapton side of the Kapton laminated on Cu substrate.

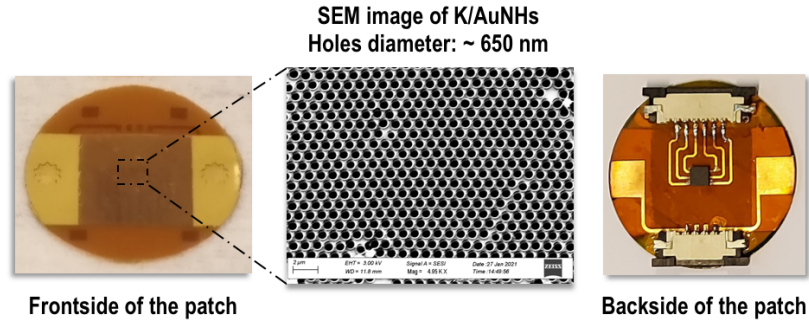


Figure C.1: Thermal patch: back side (right) and front side (left).

### C.1 Backside copper circuit fabrication

#### C.1.1 Mask design

The Layout Editor software was used to design the circuit for patterning the Cu side of the Kapton laminated on Cu substrate.

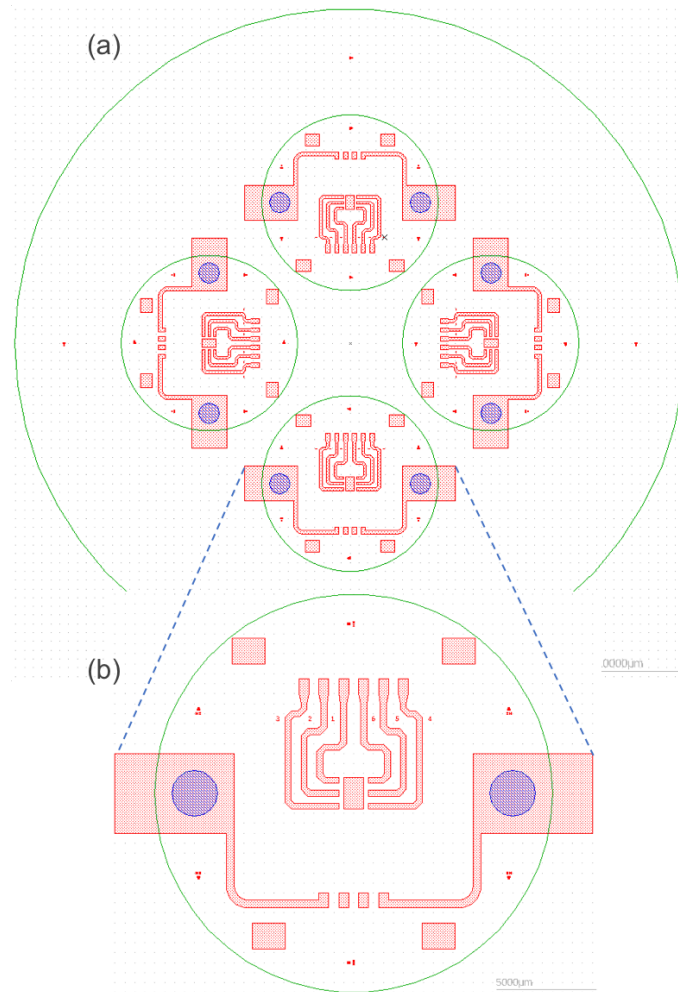


Figure C.2: (a) Mask design for Cu patterning of four patches on a 3-inch wafer size. (b) Dimensions of the circuit in the single patch.

### C.1.2 Materials

Kapton laminated on Cu substrate:

- Supplier: Goodfellow Cambridge Limited
- Product: DuPont™ Kapton® HN
- Dimension: 100 mm × 100 mm
- Thickness: 0.16 mm
- Kapton thickness: 0.075 mm
- Copper thickness: 0.070 mm

### C.1.3 Fabrication of the backside copper circuit

Photolithography is used to transfer the circuit design from the mask (Figure C.2) into the Cu side of the Kapton laminated on Cu substrate. The different steps are described in the Figure C.3.

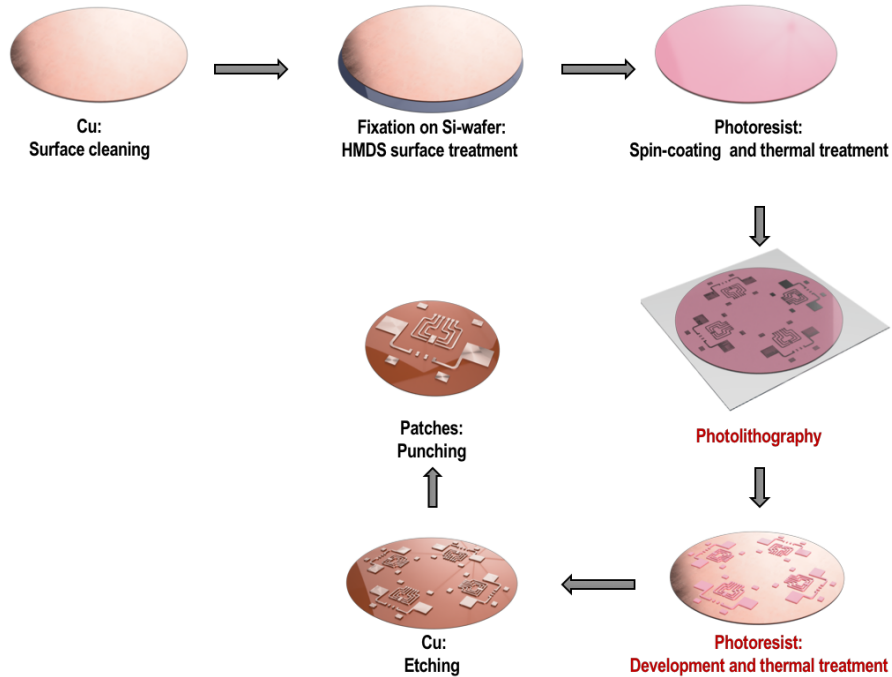


Figure C.3: Photolithography process for Cu patterning of the Kapton laminated on Cu substrate.

Table C.1: Summary of the Photolithography process for Cu patterning of the Kapton laminate copper.

| No.                    | Step name                           | Description                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                      | Substrate preparation               | <ul style="list-style-type: none"> <li>• Cut the substrate into a 3-inch round shape.</li> <li>• Clean the substrate with acetone, isopropanol alcohol (IPA) in an ultrasonication bath for 5 min and blow dry it with N<sub>2</sub>.</li> <li>• Fix the substrate to a silicon wafer using double sided scotch tape (copper side facing up) to facilitate the manipulation of the substrate.</li> </ul> |
| 2                      | Hexamethyldisilazane (HMDS) coating | <ul style="list-style-type: none"> <li>• Coat the copper side of the substrate with HMDS in the LP-III oven.</li> <li>• Parameters: 120 °C, overnight.</li> </ul>                                                                                                                                                                                                                                        |
| 3                      | Photoresist coating                 | <ul style="list-style-type: none"> <li>• Spin coat manually the S1818 photoresist (~5 ml) on the copper side of the substrate.</li> <li>• Parameters: 3000 rpm at 1000 rpm/s for 60 s at room temperature.</li> </ul>                                                                                                                                                                                    |
| 4                      | Soft bake                           | <ul style="list-style-type: none"> <li>• Soft bake the coated substrate.</li> <li>• Parameters: 110°C, 60 s.</li> </ul>                                                                                                                                                                                                                                                                                  |
| 5                      | Exposure                            | <ul style="list-style-type: none"> <li>• Machine: MA6/BA6.</li> <li>• Mask name: Kapton laminate 1.</li> <li>• Parameters: 365 nm, dose 200 mJ/cm<sup>2</sup>, flood exposure, exposure time 7.3 s.</li> </ul>                                                                                                                                                                                           |
| Continued on next page |                                     |                                                                                                                                                                                                                                                                                                                                                                                                          |



Table C.1 – continued from previous page

| No. | Step name   | Step description                                                                                                                                                                                                                                                                                                                                    |
|-----|-------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 6   | Development | <ul style="list-style-type: none"> <li>• Photoresist development in the hood, by AZ 726 MIF developer.</li> <li>• Parameters: Soak for 60 s without shaking in the developer at room temperature, then move the substrate in fresh developer for another 20 s rinse with de-ionised water (DI water) and dry it with N<sub>2</sub> flow.</li> </ul> |
| 7   | Hard bake   | <ul style="list-style-type: none"> <li>• Hard bake the developed substrate.</li> <li>• Parameters: 130 °C for 3 min in the oven or 120 °C for 3 min on a hot plate.</li> </ul>                                                                                                                                                                      |
| 8   | Cu etching  | <ul style="list-style-type: none"> <li>• Cu pattern etching.</li> <li>• Parameters: Soak the substrate into the FeCl<sub>3</sub> solution (CIF-AR 43) for ~ 1 h with shaking at room temperature.</li> </ul>                                                                                                                                        |
| 9   | Cleaning    | <ul style="list-style-type: none"> <li>• Cleaning of the photo-patterned substrate.</li> <li>• Parameters: Soak the sample into DI water for 30 min, then soak the sample into acetone for 15 min, then rinse the sample with IPA, then blow dry the sample with N<sub>2</sub> flow.</li> </ul>                                                     |

## C.2 Laser etching of Kapton laminated on copper substrate

### C.2.1 Materials

- Goodfellow: Kapton laminated on Cu substrate
- Oxford Lasers J-Series with Jig vacuum holder
- 4-inch wafer or an other flat plate to protect the Jig vacuum holder if the laser passes through the Copper film
- Adhesive tape
- Glacial acetic acid
- Ultrasonic bath
- Acetone
- Isopropanol

### C.2.2 Laser etching: Holes patterning on the Kapton side of the Kapton laminated on Cu substrate

We use the program Cimita, in which two recipes were encoded to drill the holes on the Kapton side of the Kapton laminated on Cu substrate. For the two vertical patches **D:/Winfab Cimita Program/JAvila/Ran stars vertical.pgm**.

For the two horizontal patches **D:/Winfab Cimita Program/JAvila/Ran stars.pgm**.

The parameters set in the program are as follows:

- Typical focus distance ( $Z$  axis): 51.083 mm
- DIV: 4
- UV Galvo: 355 nm
- Autofocus: No
- Number of passes: 5
- Attenuation: 70%
- Etch speed: 50 mm/s

- Focus: Mirror
- Offset: 0.7 mm

**Practically:** Since the Kapton is not visible on the camera, we need to add some references on the Kapton side of the Kapton laminated on Cu substrate.

- Make small holes using a needle on the corners of each big pad outside the 2 cm diameter circles (yellow small circles in Figure C.4).
- Fix the 3-inch Kapton laminated on Cu substrate on a flat plate (4-inch wafer, for example) using scotch tape. Keep Kapton side upwards.
- Align one border of the flat plate to the stage border.
- Find one reference, positioned at one corner of a pad, on the 3-inch sample with the vision camera.
- The (0,0) coordinates set in the program are at the center of the patch circle (2 cm diameter circles).

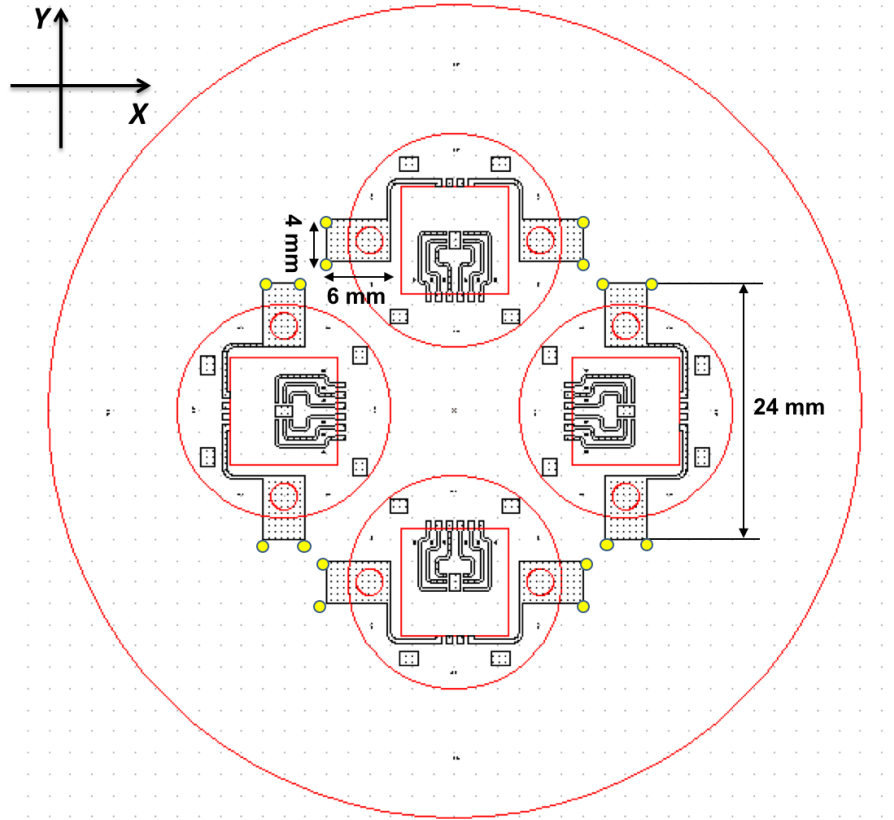


Figure C.4: Reference points for laser drilling and corresponding dimensions on the 3-inch support for patterning the Kapton side of the Kapton laminated on Cu substrate.

- Choose the right recipe (load button): for vertical or horizontal patterns.
- Move 2 mm in  $X$  or  $Y$  and 12 mm in  $Y$  or  $X$  inward; it depends if we are etching the vertical or horizontal patterns.
- Start to etch the pattern when you are at the reference (0,0).

When two holes are patterned the laser stops. So you need to find either in the horizontal or vertical direction the next pattern. To do so:

- Move -12 mm in either direction  $X$  or  $Y$  then -2 mm in  $X$  or  $Y$  to find the first reference.
- Move in  $X$  or  $Y$  to find the new reference for the next pattern.

- Move 2 mm in  $X$  or  $Y$  and 12 mm in  $Y$  or  $X$  inward; it depends if we are etching the vertical or horizontal patterns.
- Start to etch the pattern when you are at the reference  $(0, 0)$ .
- Repeat until finishing area.

### C.2.3 Chemical etching: Copper oxide cleaning

After performing the above laser etching, remains of copper oxide must be removed. **Wear suitable protective equipment for acid treatment and work under a ventilated hood.**

- Prepare 2:1 v:v water:acetic acid solution at room temperature, enough to cover the Kapton laminated on Cu substrate in vertical position.
- Run ultrasonic bath including the 3-inch wafer and the etching solution for 3 min.
- Rinse the 3-inch wafer with DI water.
- Clean beaker, fill it with DI water, put the 3-inch wafer and run ultrasonic bath to remove acetic acid remains.
- Rinse each 3-inch wafer with acetone and isopropanol.
- Blow each 3-inch wafer with dry nitrogen.

### C.2.4 Patch cut

Each 3-inch wafer contains 4 patches of 2 cm diameter.

- Cut each patch using the punch tool carefully.
- Clean the patches with acetone and isopropanol.
- Blow the patches with dry nitrogen.
- Store the patches in appropriate wafer or sample trays.

## C.3 Fabrication of heaters on the Kapton side

After the fabrication of the copper circuit on the back side of the patch, and holes by laser drilling of the Kapton, the colloidal lithography is performed to prepare the gold nanoholes (AuNHs) heater on

the Kapton side. The different steps of the fabrication of the heater are depicted in the Figure C.5. The detailed description is reported in the Table C.2.

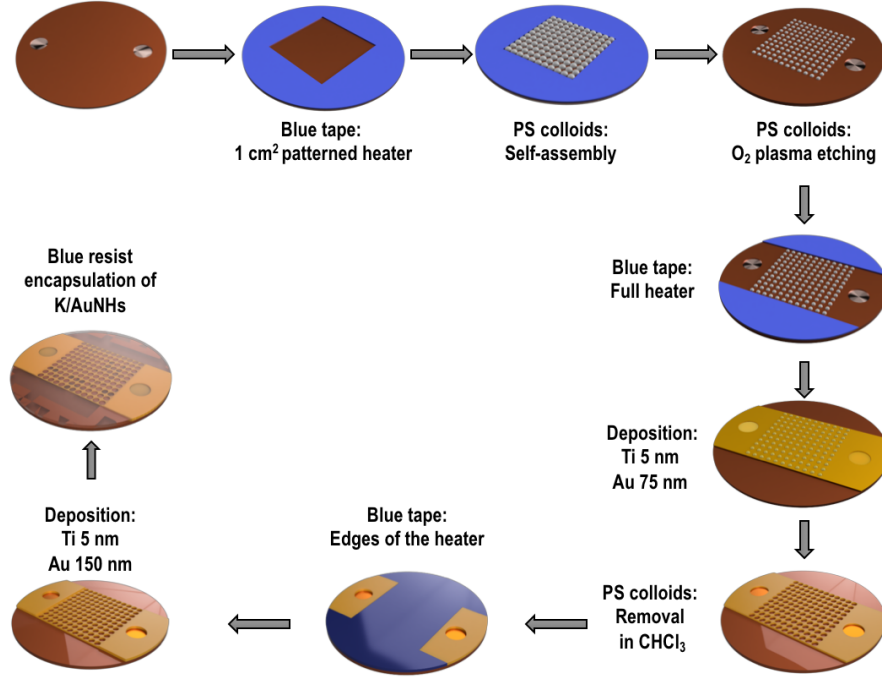


Figure C.5: Fabrication of Kapton/AuNHs arrays on Kapton using colloidal lithography.

Table C.2: Summary of the colloidal lithography process for heater fabrication on the Kapton side.

| No.                    | Step name              | Description                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
|------------------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1                      | Substrate preparation  | <ul style="list-style-type: none"> <li>• Cut Kapton patches of 2 cm diameter.</li> <li>• Use blue tape to cover the two edges of the patches [Kapton side] leaving a square of <math>\approx 1 \text{ cm}^2</math> at the center.</li> <li>• Use blue tape to cover the circuit behind.</li> <li>• Cleaning: No cleaning is performed.</li> <li>• Treat the substrates with oxygen plasma to make their surface hydrophilic in a plasma asher [K1050X, Emitech]. The process parameters used here are radio-frequency (RF) power: 25 W, time: 43 s, pressure: 6 mbar.</li> </ul>                                                                                                                                                                 |
| 2                      | Colloids self-assembly | <ul style="list-style-type: none"> <li>• Ultrasonic dispersion of 30 <math>\mu\text{l}</math> polystyrene (PS) colloidal suspension [960 nm diameter, 10 %, Microparticles GmbH] for 10 s at room temperature.</li> <li>• In a small glass vial mix 30 <math>\mu\text{l}</math> of the PS colloids suspension with 30 <math>\mu\text{l}</math> <math>\text{H}_2\text{SO}_4</math> solution [1 vol% in ethanol] and 90 <math>\mu\text{l}</math> of styrene [1 vol% in ethanol].</li> <li>• Ultrasonicate the mixture at room temperature 10 s.</li> <li>• Use a glass pipette to prepare the PS colloids self-assembly on the water/air interface in a glass Petri dish by using the protocol developed by Jian-Tao Zhang.<sup>1</sup></li> </ul> |
| Continued on next page |                        |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

<sup>1</sup>Jian-Tao Zhang, Luling Wang, Daniel N. Lamont, Sachin S. Velankar, Sanford A. Asher, *Fabrication of large-area two-dimensional colloidal crystals*, Angew. Chem. Int. Ed., **2012**, 51, 6117-6120.

Table C.2 – continued from previous page

| No.                    | Step name             | Parameters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
|------------------------|-----------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        |                       | <ul style="list-style-type: none"> <li>• Use 1 vol% Triton X-100 in DI water <sup>2</sup> (Sigma-Aldrich) as a surfactant to compact the colloids in a monolayer assembly floating on the water surface via drop cast of a volume corresponding to 10 brush drops.</li> <li>• Place a substrate underneath and lift it up to transfer the floating colloidal monolayer onto the 1 cm<sup>2</sup> at ther Kapton side center of the substrate.</li> <li>• Deposit carefully the substrate on a wipe and leave it to dry at room temperature.</li> </ul> |
| 3                      | Substrate preparation | <ul style="list-style-type: none"> <li>• Cover a Si-wafer with aluminum foil.</li> <li>• Remove all the blue tape used during the self-assembly.</li> <li>• The patches were fixed to the aluminum cover [4 patches by wafer] using small pieces of double sided Kapton tape.</li> </ul>                                                                                                                                                                                                                                                               |
| 4                      | Oxygen Plasma Etching | <ul style="list-style-type: none"> <li>• Machine: Oxford Plasmalab 100.</li> <li>• <b>Recipe: RY-CML-PS O<sub>2</sub>-etch.</b></li> <li>• Parameters: SF<sub>6</sub> 1 sccm, O<sub>2</sub>: 30 sccm, table temperature: 19 °C, table height: 20 mm, pressure: 6 mTorr, forward power: 30 W, Inductively Coupled Plasma: 0 W, reflected power: 0 W, DC bias: 136-147 V.</li> </ul>                                                                                                                                                                     |
| Continued on next page |                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |

<sup>2</sup>Prepare 1 vol% Triton X-100: mix 10  $\mu$ l Triton X-100 and 1000  $\mu$ l DI water.



Table C.2 – continued from previous page

| No.                    | Step name              | Parameters                                                                                                                                                                                                                                                                                                                                                                                               |
|------------------------|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 5                      | Substrate preparation  | <ul style="list-style-type: none"> <li>• Before metallization the desired zones of the patches have to be defined using the blue tape as a mechanical mask.</li> <li>• Use blue tape to cover the two ends of the patch [Kapton side] leaving a band of <math>\approx 1</math> cm width and 2 cm length at the center.</li> </ul>                                                                        |
| 6                      | Metallization          | <ul style="list-style-type: none"> <li>• The Kapton substrates were metallized with 5 nm Ti and 75 nm Au using E-gun VACOTEC machine in lift-off mode. The deposition rate is kept constant at 1 Å/s for both materials.</li> </ul>                                                                                                                                                                      |
| 7                      | Lift-off               | <ul style="list-style-type: none"> <li>• Remove the blue tape from the substrates.</li> <li>• Press blue tape on the substrates to remove the colloidal PS spheres.</li> <li>• Ultrasonicate the substrates in chloroform for 1 min to remove the PS residuals.</li> <li>• The samples were washed with isopropyl alcohol and blown dry with N<sub>2</sub> flow.</li> </ul>                              |
| 8                      | Metallization of edges | <ul style="list-style-type: none"> <li>• Substrate Preparation. Use blue tape to cover the two edges of the patch and the K/AuNHs zone [Kapton side] leaving the two bands containing the holes.</li> </ul> <p><b>Remark:</b> To facilitate the application of the bias voltage, 20 nm Ti and 150 nm Au contacts were further deposited on the two bands containing the holes near the K/AuNHs zone.</p> |
| Continued on next page |                        |                                                                                                                                                                                                                                                                                                                                                                                                          |

Table C.2 – continued from previous page

| No.                    | Step name                                     | Parameters                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------------------|-----------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        |                                               | <ul style="list-style-type: none"> <li>• The Kapton substrate was metallized with 20 nm Ti and 150 nm Au using E-gun VACOTEC. The deposition rate is kept constant at 1 Å/s for Ti and 1.5 Å/s for Au.</li> </ul>                                                                                                                                                                                                                          |
| 9                      | Kapton/AuNHs side protection before soldering | <ul style="list-style-type: none"> <li>• Use the blue photoresist to protect the Kapton/AuNHs side before soldering connectors on the Cu side.</li> <li>• Spin coating: 3000 rpm at 1000 rpm/s for 60 s. <b>Recipe: 3000 rpm 1 min.</b> Spincoater: Model WS-650MZ-8NPPB.</li> <li>• Hard bake the samples with the blue resist facing up at 120 °C using a hot plate for 2 min.</li> </ul>                                                |
| 10                     | Flat flexible connectors (FFCs) soldering     | <ul style="list-style-type: none"> <li>• Use the SMD291AX10 solder paste with compressed air.</li> <li>• Soldering temperature is kept at 183 °C.</li> <li>• Solder under the microscope: the soldering is instantaneous.</li> </ul>                                                                                                                                                                                                       |
| 11                     | Resistance measurement                        | <ul style="list-style-type: none"> <li>• Use the digital multimeter [Keithley 2000].</li> <li>• Put the digital multimeter in low resistance range to avoid huge current through the circuit.</li> <li>• Connect the patch via the soldered FFC connector using a 1 mm FFC jumper cable and the rigid printed circuit board for banana connectors.</li> <li>• Measure the resistance [the values have to be in the Ohms range].</li> </ul> |
| Continued on next page |                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                            |

Table C.2 – continued from previous page

| No. | Step name                  | Parameters                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-----|----------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 12  | Second edges metallization | <p><b>Remark:</b> When the resistance is very high, likely the contact between Au-coated surface and copper pads at the edges of the holes in the Kapton is poor. Thus, a second metallization of the edges is needed.</p> <ul style="list-style-type: none"> <li>• The Kapton substrates should be metallized with 20 nm Ti and 280 nm Au using E-gun VACOTEC in a rotate mode using a tooling factor of 10%. The deposition rate is kept constant at 1 Å/s for Ti and 1.4 Å/s for Au.</li> </ul> |



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