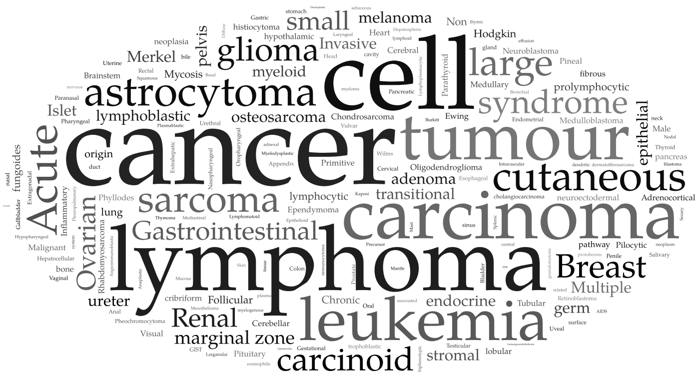
Abstract

This dissertation presents research on the design and implementation of structures for a miniaturised implantable medical system (IMS) to continuously monitor the interstitial fluid pressure and temperature in the body of animals or humans. The information from these variables is vital for physicians and researchers. For instance, cancer research has found a relationship between these bio-parameters and the evolution of a microenvironment that intensifies a tumour's growth behaviour. In the area of pressure measurement, two alternatives for a miniaturised IMS are evaluated: piezoresistive and capacitive pressure transducers. For both types of transducers, a noise analysis is used to define the requirements and design parameters for their interfaces. Furthermore, to verify the performance of the proposed designs, prototypes of such interfaces were implemented and fabricated as part of test chips. Regarding the tumour temperature monitoring, the design and implementation results of an on-chip temperature transducer unit are presented. Moreover, to run these devices, a low-power timing and clock generation unit was developed and implemented. An IMS prototype for the continuous monitoring of pressure and temperature was designed and fabricated. The encapsulation process and mechanical details of such a system are described. The IMS prototype was tested using human cancer xenografts grown in SCID mice without any therapeutic applied. A calibration sequence for the prototype system sensing units is described. The devices were able to run autonomously for 48 hours after every charge cycle. The recorded data showed increasing pressure and decreasing temperature in the tumour following the implantation, which is consistent with the findings from other research groups that have studied growing tumours.

Chapter 1

Introduction



The generations born after the Second World War (mainly in developed countries) have benefited from the cradle to the grave welfare thanks to innovations in medicine as well as a relatively stable economic and social environment. Moreover, and due to these life improvements, nowadays, a significant proportion of the human population has high chances to live into or even beyond their sixties, a positive figure; however, an ageing population also means more people requiring quality healthcare. Therefore, today is the time to innovate and improve medicine through technology, so that the future continuous looking bright.

With the increase in population, and especially an ageing one, certain diseases have become prevalent, and cancer is one of them. In 2018, different types of cancer affected around 18.1 million persons. Furthermore, 9.6 million lives were lost to cancer, representing a third of all premature deaths from non-communicable diseases in adults [1]. However, in the past decades, medical research has not only worked on finding new treatments but to also unveiling the mechanisms that help a tumour to grow and develop. Henceforth, it is prevailing to use each new finding on cancer to produce better technology to help in the cause to cure cancer.

Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) are two of the most used standard techniques for screening, diagnosing and evaluating tumours [2]. These techniques are complementary, and the use of one or the other depends on the type of cancer. However, their use is not always possible due to health risks. CT has a radiation risk involved, and therefore a patient can only undergo a limited number of exams. MRI, and also CT, might require the use of a contrast dye which could trigger allergic reactions. Additionally, the availability of MRI and CT devices in the health systems is by far not large enough for getting the necessary number of exams for continuous monitoring (e.g., in 2013, the average number of MRI and CT units per hundred thousand people in the European Union countries was 1.21 and 1.86, respectively [3, 4]).

As described, the predominant imaging methods (e.g., CT and MRI) for diagnosing and evaluating cancer provide a limited number of samples over time. Furthermore, these limitations result in a significant loss of physiological information that has the potential to bring physicians and researchers a better understanding of the disease evolution. Conversely, miniaturised, semi-autonomous implantable monitoring systems for the continuous measurement of biophysical, biochemical and metabolic variables provides a solution to the limitations described. Therefore, the design of an implantable system for the continuous monitoring of tumours would help to improve current therapies and might help researchers to get a new tool to study cancer.

The conjunction between electronics and medicine has transformed medical research and health care in the last century. Even more, in the last decades, the accelerated development in technologies such as microelectronics and microfabrication has opened tremendous opportunities to develop smaller yet more sophisticated medical electronic systems. This wave of innovation opens the door to new opportunities to develop new or improve therapy and diagnosis tools. Therefore, and given the need for tools to fight cancer, the development of miniaturised implantable systems is an exciting field in the electronics research area.

1.1 Purpose of the work

The use of an implantable system for cancer monitoring provides several advantages, from which the most important is the possibility of continuous monitoring of the tumour physiological variables. In the present work, the

main goal is to set the foundations for the development of a miniaturised implantable monitoring system for the continuous evaluation of the pressure and temperature in tumours. In this way, this document aims to provide the theoretical background regarding the development of the sensing units and the sampling control used in such implantable system. Furthermore, a set of in-vivo experiments were designed to verify the implantable system concept using a prototype unit.

During the development of this work, to achieve the goal previously described the focus was set on the following tasks:

- Define, analyse and implement options for the monitoring of pressure and temperature in a tumour.
- Design and implement a low-power timing unit for low-data rate implantable systems.
- Investigate and test alternatives for the encapsulation (to protect both the implantable system and the host) of an implantable system.
- Produce a prototype implantable system for the measurement of pressure and temperature in tumour xenografts.
- Perform in-vivo experiments with the prototype to prove the implantable system concept.

The final result of this work is the proof-of-concept experiments. These experiments were performed in cooperation with the Universitaẗsklinikum Hamburg-Eppendorf. With these experiments, it was intended to verify the measuring interfaces developed in a real scenario. Figure 1.1 presents the

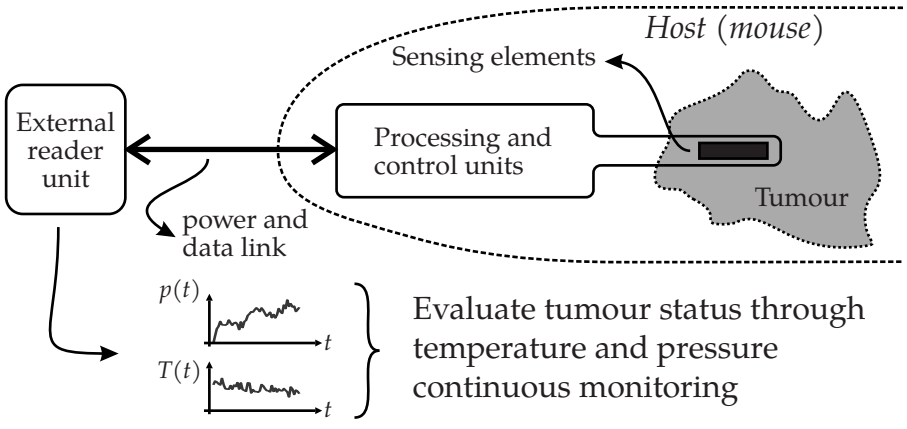


FIGURE 1.1: Basic concept of the developed system.

concept for the proof-of-concept experiments. The prototype system holds the temperature and pressure sensors, interfaces, control circuitry and power storage units. During the experiments, the sensing units in the implantable system prototype are placed inside a tumour xenograft (grown inside a mouse). An external unit is used to provide charge to the implantable system and to read the data gathered by it. The charge received by the implant allows it to perform several measurements autonomously for several days. Here it is relevant to highlight that this work was delimited to study the autonomous bio-parameters acquisition using an implantable system (i.e. the pressure and temperature sensing). Therefore, other blocks (e.g., the data and power link) where implemented straightforwardly and robustly, so that do not interfere with the characterisation of the units under study.

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1.2 Thesis Outline

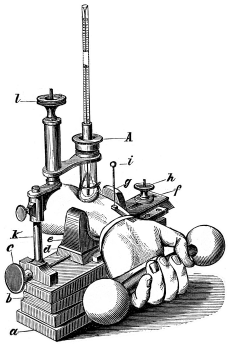
This document is structured as follows: Chapter 2 introduces the concept of implantable medical systems and its design challenges. The biological background of the interstitial space, the area of interest to measure pressure and temperature, is presented in the second part of this chapter.

Chapters 3 and 4 present the theory behind pressure and temperature monitoring, respectively. These two chapters describe the design of sensors to translate these physiological variables into an equivalent digital form. Furthermore, integrated circuit implementations and experimental results are presented for each sensor. Similarly, the design, implementation and verification of a timing unit for the implantable system are described in Chapter 5. Chapter 6 explains the considerations for encapsulation and mechanics for the implantable system prototype.

The first part of Chapter 7 explains the importance of monitoring pressure and temperature in a tumour. The second part presents the design and implementation of an implantable system prototype for the measurement of pressure and temperature in tumours. Additionally, this chapter describes the results obtained from in-vivo tests performed using the developed prototype. Finally, the summary and the future outlook of this work are presented in Chapter 8.

Chapter 2

Fundamentals



[5]

The monitoring of body parameters under traditional medicine practice is limited. Unless the patient remains in a hospital bed continuously connected to equipment, physicians only have access to a limited number of samples of these variables on each visit. This last point represents a problem to get a complete characterisation of a patient's condition. However, implantable medical systems provide a solution for better monitoring of health conditions.

In this chapter, a brief introduction to electronic medical implantable systems is provided. The challenges of encapsulation and integrated circuits design for IMS are also presented. Furthermore, the development of medical systems requires an understanding of the role played by the biological parameters under monitoring. In the case of this work, the implantable systems aim to measure the interstitial fluid pressure. Therefore in the second part of this chapter, a description and a model of the interstitial space is presented.

2.1 Implantable Medical Systems

The area of electronics dealing with the theory and methodology for the research and development of devices and instruments for healthcare is called Medical electronics. The intention behind these devices and instruments is to

improve human life by providing better diagnosis and treatment for diverse diseases. Furthermore, medical research is also benefited from electronics by procuring tools to measure, monitor, and analyse biological signals and markers.

Implantable Medical System (IMS) is a subdivision of medical electronics that delve with apparatuses that are intended to function inside the body of a person or test subject (in case of research it can be human or animal). Based on their functionality, Implantable systems can be classified in one of the following categories (but not restricted to these) :

- An electro-stimulating device. These are devices that provide controlled and periodic electrical pulses to specific muscles, nerves, or regions in the brain. The goal of these pulses is to pace a diseased organ; examples of these devices are pacemakers and implants for Parkinson treatment.
- An automated drug delivery system able to apply the drug not just in a highly localised area but also in the exact time and quantity. With this, treatments become more effective, and their side effects are reduced. A commercial example is implantable insulin pumps.
- A bio-signal recording unit. Examples of these are implantable devices used for getting access to Electrocardiogram (ECG), Electromyogram (EMG), and Electroencephalogram (EEG) signals inside the body. These devices help clinicians and researchers to get better signal quality by avoiding problems related to the use of external electrodes (on the skin).
- A biological marker monitoring system. These devices are equipped with one or more sensors for reading vital parameters such as pressure, temperature, pH, among others. These units can be used to check the status of different conditions on the human body.

In the legal field, the classification of medical systems depends on several factors, as their invasiveness, the risk to the patient and operators associated with a failure of the device, among others. In the United States of America, the Food and Drug Administration (FDA) is the entity responsible for regulating medical devices and instruments. Title 21, Code of Federal Regulations (CFR), presents the basic rules about medical devices [6]. The CFR device volume, Parts 862-892, describes the classification of about 1700 device types into three classes [7]: