

Chapter 2

Implantable Monitoring System for Rodents

2.1 Bio-monitoring Systems

Monitoring of body parameters is essential to treat a patient accurately. In addition, the illness can be discovered, and some precautions can be taken for possible disease. Therefore, some samples such as blood, urine, etc. are collected from the patients body and analyzed. This process becomes invasive for the patient for long-term time. In addition, the patient takes commonly used drugs for the treatment. These drugs have toxicity and also different side-effects on the patient. Accordingly, the personal therapy is required to develop an individual treatment for the patient.

The implantable bio-sensors allow to create a monitoring systems for the personal therapy [1]. They monitor different endogenous and exogenous substances in the body. The amount of the substances gives information about the condition of the patient and the progression of the therapy. In addition, the amount of chemical and biological compounds can change locally in the body. Consequently, the implantable bio-sensor system can measure the value accurately in the interested part of the body. The last but not the least, the system can be implanted for long-term duration that decreases the number of the invasive operations on the patient body. Some treatments need to be monitored continuously and long-term. Therefore, a small and lightweight implantable device is crucial for the comfort of the patient. In conclusion, an implantable bio-sensor system must be hygienic (biocompatible), reliable, durable, small, light weight and comfortable for the patient.

2.2 System Overview and Specifications

The aforementioned requirements are also valid for the animal monitoring systems. Especially, the size and weight of the rodents make the implantable system more challenging compared to the implantable system for human. Figure 2.1 shows the

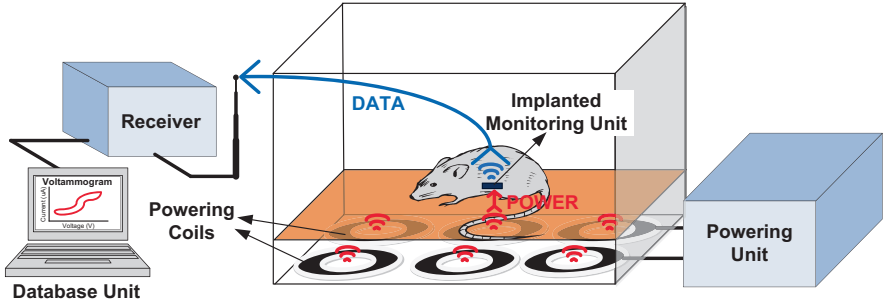


Fig. 2.1 Scenario for remotely powered implanted bio-monitoring system for freely moving animal

miniature concept of a typical implantable bio-sensor monitoring system for freely moving rodents. The developed bio-sensor system will be implanted to a laboratory animal, which can be used for biomedical and genetic researches and also for investigating new treatments. The power is supplied to the batteryless implanted system by a suitable power transfer method continuously. Moreover, this method should not disturb the animal. The data is transmitted by a low-power, reliable transmitter to the external base-station.

2.2.1 Rodents and Housing

Rodents are a crowded family and have many different species. Mice and rats are the commonly used animals in the researches due to the size and housing [2, 3]. An adult rat measures from 40 to 50 cm. The weight of an adult rat changes between 200 and 1000 g. However, an adult mouse can weigh from 20 to 40 g. The length of an adult mouse changes between 12 and 15 cm [4]. Therefore, the size and volume of an implanted device is defined by the mice. The weight of the implanted device is limited and should be less than 10 % of the total body weight of the animal [5]. Therefore, assuming the weight of the mouse is 20 g, the implanted device should be maximum 2 g. In addition, the volume of 2.4 ml is acceptable for a device which is implanted inside a mouse [6]. Moreover, the implanted device should be soft, and the sharp corners must be removed and rounded for the comfort of the animal.

The monitoring system is implanted to the abdominal region where the implanted device is closest to the base of the living space. The distance is crucial to achieve sufficient power transfer. Therefore, the coupling between the coils increases and an efficient power transfer is obtained. Although the implanted device is implanted to as close as possible to the base of the living space, the vertical distance between the coils reaches up to 3 cm due to the required housing conditions. The bottom of the cage should be covered with some materials such as shredded paper, aspen, etc. for bedding of the animal.



Fig. 2.2 Mouse cage ($W \times L \times H = 16 \times 23 \times 14$)

The housing is important for the rodents. Their behavior changes according to the housing conditions. Therefore, the animals must be placed in a proper cage. The animals require a minimum space to satisfy their needs. A rat cage must have minimum 900 cm^2 basement with 18 cm of height. On the other hand, mouse cage must be minimum $12 \times 28 \times 11\text{ cm}$ ($W \times L \times H$) to meet its spatial requirement [4, 7]. Figure 2.2 shows a standard mouse cage which is used during this study.

In addition, the physiological condition of the animal is important to achieve reliable measurement. In general, animals are anesthetized during the measurement. Anesthesia has a negative impact on vital signals [8]. Accordingly, conscious measurements without anesthesia, particularly measurements in a freely moving animal can bring reliable results. Moreover, the housing condition affects on the animal physiology [9]. The limited housing conditions cause the behavioral restrictions and also physical restriction due to the stress [10]. Therefore, the animal welfare is important to obtain reliable measurement [11]. The animals must live in a natural, stressless environment and move freely.

2.2.2 Multi-sensor Systems

The implantable bio-sensor systems are able to detect different kinds of endogenous or exogenous compounds and drugs in the metabolism. This advance of bio-sensors also allows to monitor the amount of drug and body response to the drug for long-term duration for personal therapy. Additionally, the integration of the bio-sensors on the same silicon based platform help to create System-on-Chip (SoC) which

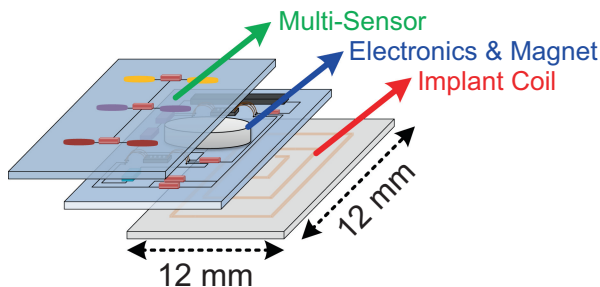


Fig. 2.3 Conceptual design of batteryless implantable multi-sensor system

reduces the overall size and weight of the system [12, 13]. This miniaturization step makes the system implantable even for small animals like mice.

The targeted remotely powered bio-sensor system is consisted of several electrochemical sensors based on cytochrome P450 isoforms, and on-chip pH and temperature sensors. The sensors are fabricated by using multi-walled carbon nanotubes which allow multiple drugs sensing with low sensitivity level [14]. Therefore, the bio-electronic-sensor system can detect the different drugs with improved sensitivity according to different pH and temperature levels of the metabolism [15].

The multiple sensor systems allow to sense different chemical compounds as well as vital signals on the same platform. Additionally, the use of multiple sensors on the same implantable system gives less invasion and optimizes the processing operations. Figure 2.3 illustrates the conceptual design of the batteryless implantable multi-sensor system. The sensors are placed the top of the 3-stage platform to create a good contact with the body. The electrochemical sensors detect the different types of compounds and chemical parameters. The targeted materials are mainly different drugs, ATP and glucose. The temperature and pH of the implanted medium play a significant role on detection capability of the sensors. Therefore, the pH and temperature sensors are also placed the top of the platform to obtain reliable measurement results by taking account the effect of temperature and pH of the medium on sensors during the post-processing of the sensor data. The middle stage houses the electronic components, with integrated circuits used for power management, communication and sensor interface. Moreover, in the middle stage there are a storage capacitor, used to guarantee the longevity of the measurement and a permanent magnet, helps to track the animal in the living space. Finally, the implant coil is placed in the bottom of the platform in order to induce current from available magnetic field.

The electronics of the implantable sensor system include the pre-processing and data conversion needed by specific sensors and have in common the power management and data communication blocks. Figure 2.4 shows the block diagram of the standard sections of the implantable remotely-powered multi-sensor system. A power amplifier which drives a powering coil is followed by an optimized remote

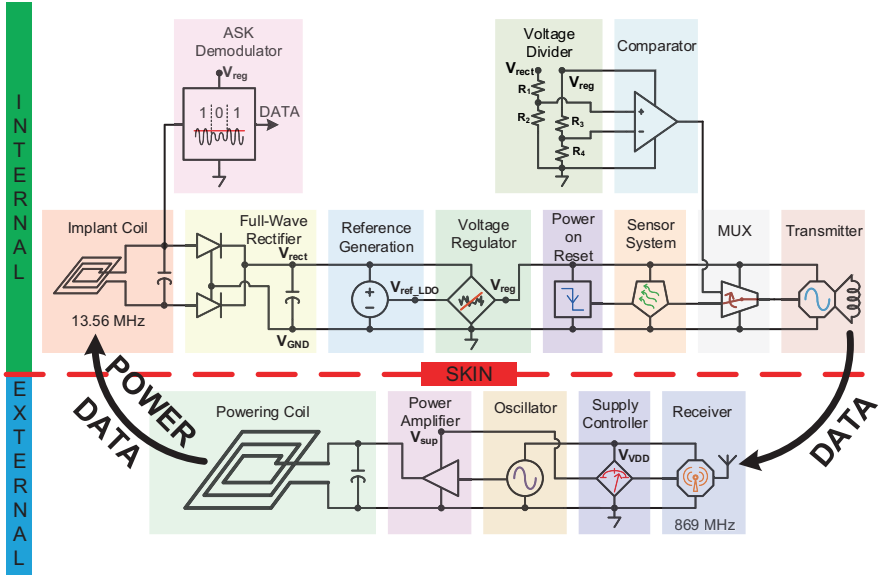


Fig. 2.4 Block diagram of implantable remotely-powered multi-sensor system

powering link. The received AC signal is converted to DC voltage supply for the sensor system by efficient integrated circuits. Some low data rate commands and configurations are transmitted by using the same remote powering link. The measured parameters in the animal body are transmitted by a low-power transmitter to the external unit. The power management unit also monitors the available supply voltage and enables or disables the other blocks. Moreover, a feedback mechanism controls the implanted power level and adjusts the transmitted power level in order to continue the operations by the implantable system.

2.3 State of the Art

There are many recent studies on developing medical systems for rodents. They are mostly for neural activities, electrograph (ECG, ECoG, EEG, EMG) recording and blood pressure or heart rate monitoring. Table 2.1 presents the recent studies on medical systems for rodents. The studies are classified in terms of application, animal condition (mobile or immobile), implant or patch, weight and volume, power consumption, powering method and communication type.

As a summary of the state-of-the-art, the most important challenges are on one hand, to achieve an efficient power transfer to implanted system which is placed in a freely moving animal and, on the other hand, to satisfy the minimum volume

Table 2.1 Recent studies on medical systems for rodents

Reference	Year	Application	Cond.	Imp.	Weight (g)	Vol. (cm ³)	Power (mW)	Dur. (h/d/w)	Powering Type		Communication			
									Type	Freq.	Dist.	Freq.	DR/BW	Dist.
Park [16]	2011	Neural recording	Imm.	N	3.4	N/A	12	–	Cable	–	–	N/A	512 kb/s	N/A
Yang [17]	2011	Microdrive	Mob.	N	1.82	N/A	N/A	–	Cable	–	–	N/A	N/A	N/A
Azin [18]	2011	Microstimulation	Mob.	N	1.7	2.8	0.42	24 h	Battery	–	–	433 MHz	500 kb/s	2 m
Chang [6]	2011	EEG recording	Mob.	Y	N/A	2.4	36	8 w	Battery	–	–	915 MHz	512 S/s	N/A
Fan [3]	2011	Neural recording	Mob.	N	4.5	2.2	N/A	6 h	Battery	–	–	3.05 GHz	7 kHz	4 m
Greenwald [19]	2011	Neural monitoring	Mob.	N	24	24	15.84	40 h	Battery	–	–	N/A	1 Mb/s	1 m
Nolte [20]	2011	Heart rate mon.	Mob.	Y	1.4	1.1	N/A	6 w	Battery	–	–	455 kHz	N/A	41 cm
Senarathna [21]	2012	LSCI microscope	Mob.	N	7	5	N/A	N/A	Battery	–	–	N/A	N/A	N/A
Zhang [22]	2012	Neural recording	Mob.	N	10	2.7	N/A	1 h	Battery	–	–	100 MHz	1 kb/s	200 m
Zuo [23]	2012	Neurostimulation	Mob.	N	27	11.4	18	39 h	Battery	–	–	2.4 GHz	N/A	N/A
Lee [24]	2011	Microstimulation	Imm.	Y	N/A	N/A	0.048	–	Bat. & WPT	4 MHz	N/A	4 MHz/LSK	800 Hz	N/A
Hsieh [25]	2013	EMG, EEG, ECG mon.	Mob.	Y	8.3	8.4	12	–	Bat. & WPT	125 KHz	35 mm	2.4 GHz	N/A	10 m
Cong [26, 27]	2010	Blood pres. mon.	Mob.	Y	0.33	0.168	0.3	–	Wireless	4 MHz	1 cm	433 MHz	48 kb/s	15 cm
Charvet [28]	2011	ECoG recording	N/A	Y	N/A	N/A	100	–	Wireless	13.56 MHz	N/A	402 MHz	480 kb/s	2 m
Russell [29]	2011	ECG monitoring	Mob.	Y	2.4	N/A	16	–	Wireless	606 kHz	N/A	2.4 GHz	2 kHz	N/A
Wentz [30]	2011	Opt. neural control	Mob.	N	3	1	2000	–	Wireless	125 kHz	N/A	2.4 GHz	1 Mb/s	N/A
Chang [31]	2013	ECoG recording	Mob.	N	13.17	N/A	36	–	Wireless	6.78 MHz	N/A	2.4 GHz	120 kb/s	N/A

Cond. Condition, *Imp.* Implantable, *Vol.* Volume, *Dur.* Duration, *Freq.* Frequency, *Dist.* Distance, *DR* Data rate, *BW* Bandwidth, *Imm.* Immobile, *Mob.* Mobile, *Bat.* Battery, *WPT* Wireless power transfer, *LSK* Load shift keying

Cond. Condition, Imp. Implantable, Vol. Volume, Dur. Duration, Freq. Frequency, Dist. Distance, DR Data rate, BW Bandwidth, Imm. Immobile, Mob. Mobile, Bat. Battery, WPT Wireless power transfer, LSK Load shift keying

and weight for implantation inside a mouse. Therefore, in our study, we focused to design a batteryless, implantable, small and light weight system with an efficient and suitable power transfer for continuous and long-term monitoring.

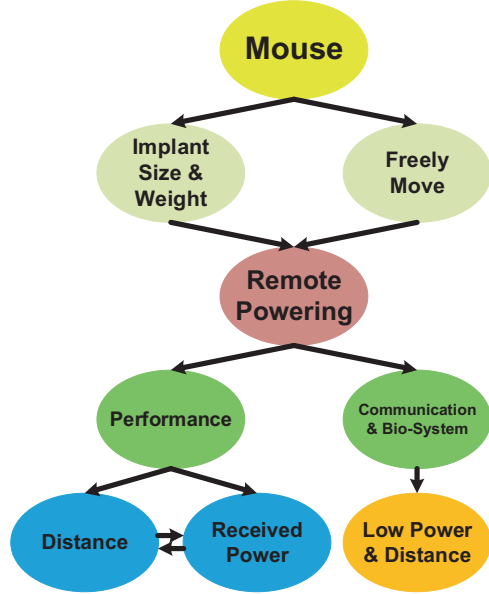
2.4 Challenges and Objectives

The recent studies show that the available implantable systems for animals have several problems and challenges. Firstly, the powering of the system is one of the most demanding part of the project. Especially, the real-time monitoring systems where the high number of samples per minute is required, need high power. One solution is to use transcutaneous cable to supply energy to the implant [16, 17]. However, the holes on the skin for the cables causes also the infections and also the cables limits the mobility of the animal. Other solution is to use battery in the implant [6, 20]. However, the battery has a limited lifetime, and it needs to be replaced at the end of its lifetime that increases the number of the surgery. The surgeries are invasive for the animal, and the animal needs a certain time to recover. Moreover, if the application demands high current, the lifetime of the battery is limited within hours [3]. In addition, the battery increases the overall weight and size of the implanted system [18]. Even the overall weight of the system is dominated by the battery weight [32]. The most suitable solution is to transfer power to the implanted system without battery for long-term duration. Accordingly, the batteryless implanted system can be light and small enough to place inside a mouse and also the system performs until the bio-sensors are degraded.

In many studies, the power transfer efficiency is very low and hence the efficiency is not available. The size of implanted system is limited, therefore, the implant coil is also defined by the implanted system size. Moreover, the size of the implant coil changes the coupling between the coils. The power transfer efficiency is dominated by the coupling of the coils and the quality factor of the coils. Although the coils are designed to make the quality factor very high, the coupling coefficient limits the power transfer efficiency. In addition, there is a certain distance (~ 3 cm) between the coils due to the proper bedding for the animal. This distance also decreases the efficiency of power transfer. The wireless power transfer becomes even more challenging. Efficiency is crucial to reduce the transmitted power level which also affects the comfort of the animal. Accordingly, the coils and the coupling (mutual inductance) need to be optimized simultaneously to achieve the highest efficiency from the wireless power transfer.

In some studies, the subjects are anesthetized (immobile) during operation to deliver the power to the implant [33–35]. However, the results are affected by the anesthesia. Accordingly, the animal should be awake and freely moving. Besides, the cages are homemade and do not satisfy the requirements of minimum space for the comfort of the animal. Their size is limited by the wireless power transmitter size and the powering coil [26, 30, 31]. In conclusion, an efficient and continuous power transfer is required by the implantable system while the animal moves freely in the cage.

Fig. 2.5 Challenges and objectives of a batteryless implantable system for mouse



Finally, the communication is important challenge in the study. Especially the transmitter block is one of the most power hungry blocks in the systems due to the power amplifier (PA) [36]. Therefore, a low-power and reliable solution is required. Thanks to the short distance between the animal and the external receiver, a short-range communication is sufficient which reduce the overall power consumption of the system by eliminating the PA.

Figure 2.5 summarizes the challenges and objectives of this study. The ultimate goal of this study is to design a batteryless remotely powered multi-sensor monitoring system which can be implantable inside a freely moving mouse. There are two main consequences of using a mouse; limited size & weight of the implantable system and freely moving animal in a standard cage. These consequences introduce a challenging remote powering system to be designed. In order to achieve an efficient wireless power transfer, many parameters need to be optimized. In addition, these parameters have cross correlations that make the optimization complex and difficult. For instance, the induced voltage on the implant is proportional to the remote powering frequency. On the other hand, the self resonant frequency (SRF) of a coil must be smaller than the remote powering frequency. Therefore, the coil geometry (outer diameter, number of turns, etc.) has a relation with the remote powering frequency. The coil geometry is important to cover the all the bottom of the cage and deliver the power sufficiently. Additionally, the remote powering link is dependent on the load. The power consumption of the implantable system changes the remote powering link design. The magnetic field strength decreases with the cube of the distance that affects directly the performance of the remote powering or the received power level.

Table 2.2 Objectives of this study

Application	Condition	Implant	Weight (g)	Vol. (cm ³)	Power (mW)	Powering type		Communication	
						Type	Dist.	DR	Dist.
Bio-monitoring	Mobile	Yes	≤2	≤1	2	Wireless	3 cm	100 kb/s	40 cm

On the implanted side, low-power circuits are required to reduce the overall power consumption. The rectifier and voltage regulator should be efficient to reduce the power loss and use the received power efficiently. Also, a low-power transmitter without PA, which dominates the power consumption in the transmitter, is needed. However, the transmission distance decreases if PA is discarded.

Table 2.2 summarizes objective of this study. The system needs to be implantable inside a freely moving mouse. The total weight and volume of the implantable system should be less than 2 g and 1 cm³, respectively. The expected overall power consumption of the system is around 2 mW including the bio-sensors, the sensor interfaces and the communication. The wireless power transfer should be achieved over 3 cm distance due to the housing requirements. The uplink communication needs 100 kb/s of data rate over 40 cm distance. A suitable and optimized remote powering link is designed by considering aforementioned issues. Moreover, an intelligent remote powering system is verified to track the mouse in a cage and deliver the power efficiently. Implanted low-power electronics (rectifier, voltage regulator) are designed to keep the power efficiency as high as possible. Power management block and dynamic power adaptation technique are proposed to keep the implanted system power at a certain level. Finally, a low-power, short-range transmitter is designed for uplink communication.

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