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A Wireless Batteryless *In Vivo* EKG and Core Body Temperature Sensing Microsystem with 60 Hz Suppression Technique for Untethered Genetically Engineered Mice Real-Time Monitoring

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Abstract—**A wireless, batteryless, and implantable EKG and core body temperature sensing microsystem with adaptive RF powering for untethered genetically engineered mice real-time monitoring is designed, implemented, and *in vivo* characterized. A packaged microsystem, exhibiting a total size of 9 mm x 7 mm x 3 mm with a weight of 400 mg including a pair of stainless-steel EKG electrodes, is implanted in a mouse abdomen for real-time monitoring. A low power 2 mm x 2 mm ASIC, consisting of an EKG amplifier, a proportional-to-absolute-temperature (PTAT)-based temperature sensor, an RF power sensing circuit, an RF-DC power converter, an 8-bit ADC, digital control circuitry, and a 433 MHz FSK transmitter, is powered by an adaptively controlled external RF energy source at 4 MHz to ensure a stable 2V supply with 156μA current driving capability for the overall microsystem. An electrical model for analyzing 60 Hz interference based on 2-electrode and 3-electrode configurations is proposed and compared with *in vivo* evaluation results. Due to the small laboratory animal chest area, a 60 Hz suppression technique by employing input termination resistors is chosen for two-EKG-electrode implant configuration.**

I. INTRODUCTION

Genetic engineering of mice DNA sequences with real-time physiological monitoring has become the most critical research tool for identifying genetic variation susceptibility to diseases. Animal-based research result is expected to make a significant impact in developing treatment methods for similar human diseases. Due to the small size of laboratory animal, such as genetically engineered mice commonly known as knockout mice, a miniature, light-weight, wireless, batteryless, and implantable bio-sensing microsystem is crucial to capture real-time accurate biological signals from an untethered animal in its natural habitat, thus eliminating stress and post-implant trauma-induced information distortion. Remote RF powering based on inductive coupling has been widely used for biomedical implants [1]–[3]. However, the proposed microsystem is implanted in a freely roaming knockout mouse; hence, resulting in a drastically changing magnetic coupling as the mouse tilts and moves its position with respect to the external stationary coil. Therefore, an optimized system design with an adaptive RF power control capability is highly critical. In this paper, we present the design, implementation, and *in vivo* evaluation of an implantable EKG and core body temperature sensing microsystem with an intelligent adaptive RF power control capability for real-time untethered mice monitoring. A 60 Hz interference suppression technique for a practical use of two-EKG-electrode configuration is also presented. An electrical model comparison between 2-electrode and 3-electrode configurations is described with measurement results.

II. WIRELESS BATTERYLESS IMPLANTABLE MICROSYSTEM WITH ADAPTIVE RF POWERING CAPABILITY

Figure 1 depicts the overall wireless, batteryless, and implantable microsystem architecture with an adaptive RF powering capability. An external adaptively controlled power source with a 25 cm x 15 cm RF power transmitting coil underneath the animal cage is used to transmit an RF power to the implant unit for sensing real-time EKG and core body temperature information. The digitized EKG and core body temperature signals together with RF power-level sensing data can be wirelessly transmitted to a nearby receiver. Figure 2 illustrates a conceptual diagram of a packaged wireless implantable system consisting of integrated electronics with external passive components, such as RF power receiving coil, data transmitting coil, filtering capacitors, and bio-potential sensing electrodes. The system occupying a volume of 9 mm x 7 mm x 3 mm with a total weight of 400 mg can be implanted inside an untethered mouse abdomen. The RF power receiving coil is constructed in a planar spiral configuration around the ASIC to reduce the overall system thickness for a compact design. The flat and thin configuration can provide a comfortable fit inside the mouse abdomen. Moreover, the total device size and weight are greatly reduced without the need of a traditional RF power receiving coil containing a magnetic ferrite core due to the low power consumption of the integrated microsystem.

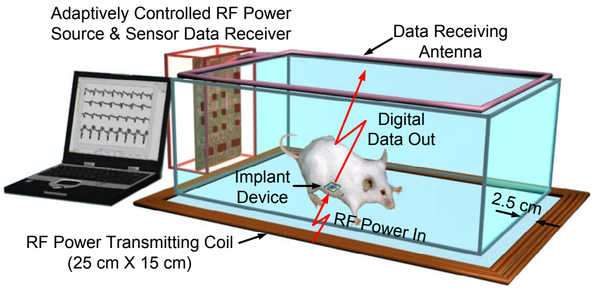

Fig. 1. Proposed wireless batteryless implantable microsystem architecture

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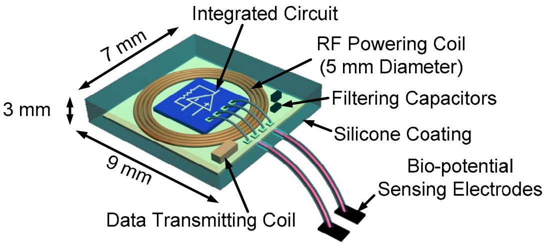

Fig. 2. Wireless implantable microsystem package configuration

III. INTEGRATED CMOS ELECTRONICS DESIGN

Figure 3 presents the overall electrical system design architecture. The integrated implant electronics are designed based on an on-chip 2V DC supply for minimizing system power consumption as well as power dissipated by the external adaptive RF energy source. The EKG signal with a typical amplitude from 20μV - 5mV within 100 Hz bandwidth, corresponding to an 8-bit dynamic range, is obtained by a pair of stainless steel EKG electrodes placed across a laboratory mouse chest. A CMOS PTAT temperature sensor is designed to detect core body temperature by sharing the same 8-bit ADC with 0.1 ºC sensing resolution. A charge-redistribution ADC architecture is chosen for its low power dissipation. The 8-bit EKG and core body temperature data are then appended with a 1-bit RF power-level sensing data. The digital information is processed by a parallel to serial converter and multiplexer to form a serial data bit-stream. In order to achieve system synchronization, the digital data is Manchester-encoded before wireless transmission. A 433 MHz LC-tuned voltage-controlled oscillator is designed to implement an active FSK transmitter employing one discrete high-Q coil inductor for low power dissipation. The inductor is also used as data transmission antenna. The integrated electronic system is designed and fabricated in a 1.5μm CMOS process [4]. The overall microsystem consumes 156μA from 2V.

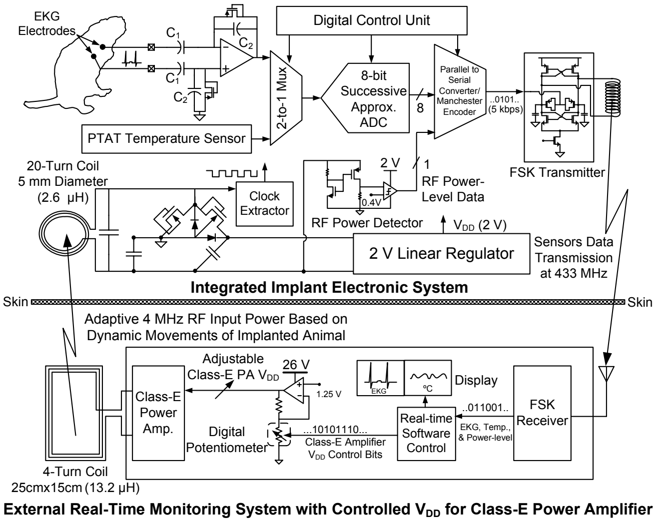

Fig. 3. Electrical system design architecture

The received EKG and core body temperature can be displayed for real-time animal physiological monitoring. An external RF power is coupled into the microsystem via a pair of tuned LC networks followed by a CMOS voltage doubler and regulators to provide an on-chip 2V supply for the implant system as shown in the figure. Our previous study shows that 4 MHz is an optimal frequency to obtain an efficient power coupling for the chosen coil geometry. The received RF power can vary drastically as a function of mouse position and tilting angle with respect to the external 25 cm x 15 cm RF coil implemented as part of the cage floor as shown in Figure 1. An RF power sensor is, therefore, incorporated to detect the incoming RF power level and wirelessly feedback a 1-bit power-level data to adaptively control the external Class-E amplifier V_{DD}, so that the transmitted RF power level is adjusted based on the untethered animal movement to ensure a stable power generations on-chip [5].

IV. MEASUREMENT RESULTS

The prototype implantable microsystem consisting of a 2.2 mm x 2.2 mm 1.5μm CMOS ASIC with an RF powering coil, two external filtering capacitors and one VCO tuning inductor/antenna is presented in Figure 4. To conduct an *in vivo* characterization, the implantable microsystem is packaged by a glob-top based sequential packaging process flow [4]. The final microsystem is coated with biocompatible silicone and exhibits a weight of 400 mg including a pair of 100 mg stainless-steel electrodes.

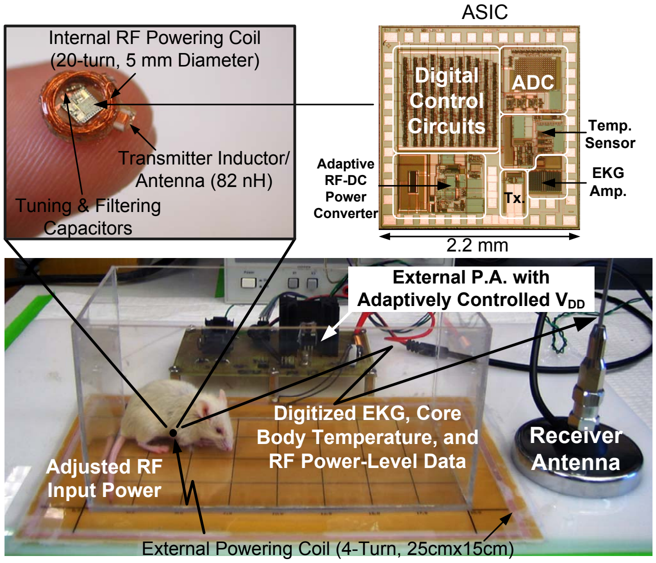

Fig. 4. Overall system testing setup

Figure 4 also presents the overall system testing setup, where an implanted genetically engineered mouse can freely move inside a 20 cm x 10 cm cage. An adaptive RF powering system consisting of an RF powering coil and Class-E power amplifier with an adjustable V_{DD} is used to power the implant system. The digitized bio-sensing data is received by a nearby receiver. Figure 5 presents the wirelessly received real-time EKG and core body temperature data. The EKG signal exhibits a normal QRS complex waveform with a heart rate of 638 beats per minute. Characterization results also reveal that the base-line drift due to low-frequency large motion, such as animal scratching the incision area, can cause a large amplifier output drift and possible saturation. The real-time temperature channel shows an average core body temperature of 35.4 ºC with a peak-to-peak animal body temperature fluctuation of less than 0.35 ºC. The 1-bit RF power-level data together with the real-time adaptively adjusted Class-E power amplifier V_{DD} for tracking the implanted mouse movement is also illustrated in Figure 5. Under a constant coupling condition with an animal's still position, the power-level sensing data bit exhibits a 50 % duty cycle, causing the external Class-E amplifier V_{DD} to remain at a near constant average level. Any increase/decrease in coupling factor due to the animal movement would change the RF power-level sensing data bit, causing a ramp down/up in the external Class-E amplifier V_{DD} to maintain a constant on-chip power supply for the implanted microsystem. The adaptive feedback operation is updated at 10 Hz, which is adequate for tracking animal movement.

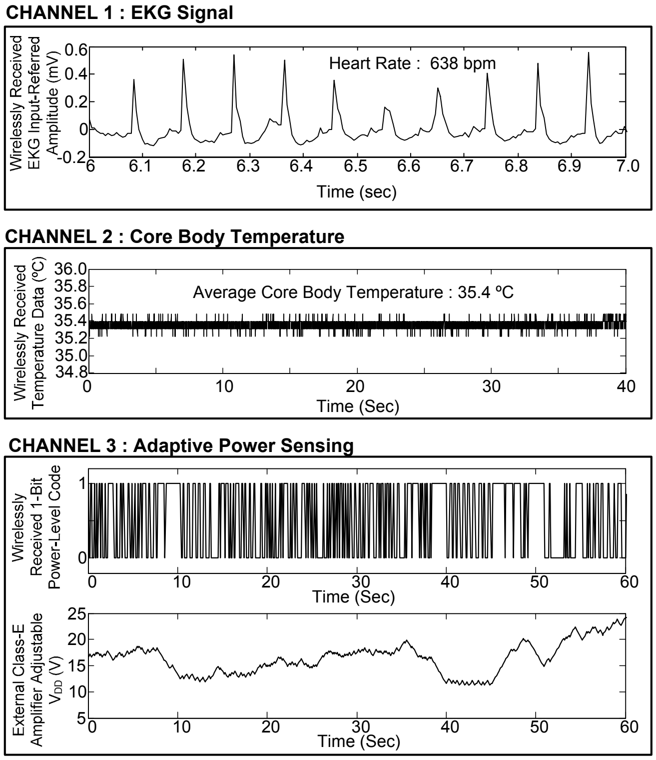

Fig. 5. *In vivo* microsystem characterization results from an untethered laboratory mouse in its cage

V. 60 HZ INTERFERENCE SUPPRESSION TECHNIQUES

A practical problem encountered in EKG recording is the 60 Hz interference. This in-band interference can corrupt the detected EKG signals. To understand and characterize the sources of interference, two EKG monitoring systems based on 3-electrode and 2-electrode configurations are investigated. The 3-electrode configuration consists of two EKG sensing electrodes connected to the input of an amplifier with a third electrode attaching the body to the circuit ground as a common reference. This third electrode is not employed in the 2-electrode configuration. Figure 6 and Figure 7 present the electrical models for the 3-electrode and 2-electrode configurations, respectively. In both figures, i_{wire} and i_{body} represent the 60 Hz interference current induced by the electrode leads and by the animal body. Z_{e1}, Z_{e2} and Z_{e3} are the impedances associated with the three electrodes. Z_{in1} and Z_{in2} represent the single-ended input impedances of the EKG amplifier with the internal body impedance labeled as Z_{body}.

In both systems, the 60 Hz interference signal at the EKG amplifier input, V_{60Hz}, can be expressed as

$$V_{60Hz} = V_{wire} + V_{body}\,, \tag{1}$$

where V_{wire} and V_{body} are the resulting interference voltages caused by i_{wire} and i_{body}, respectively.

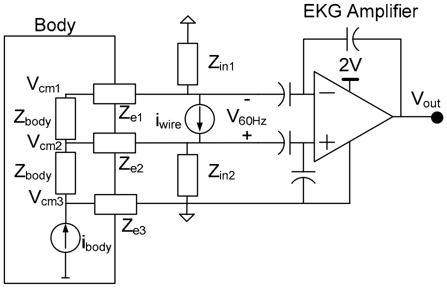

Fig. 6. Electrical model for 3-electrode EKG monitoring

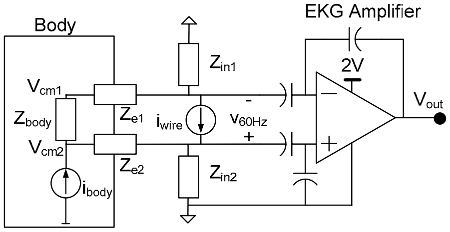

Fig. 7. Electrical model for 2-electrode EKG monitoring

To investigate the interference due to wire coupling, an experiment was first conducted by measuring the 60 Hz signal at the output of an EKG amplifier with the two recording electrodes disconnected from a mouse body. Figure 8 shows the measured output waveform from a commercial amplifier with a closed-loop gain of 8, indicating a large 60 Hz interference signal with an amplitude of $80mV_{p-p}$, or an equivalent $10mV_{p-p}$ input-referred interference. This large interference is mainly caused by i_{wire} and large amplifier input impedances with V_{wire} expressed as

$$V_{wire} \approx i_{wire} \cdot (Z_{in1} + Z_{in2})\,. \tag{2}$$

In an implant with recording electrodes attached to an animal chest, V_{wire} can be expressed as

$$V_{wire} \approx i_{wire} \cdot (Z_{e1} + Z_{e2} + Z_{body})\,. \tag{3}$$

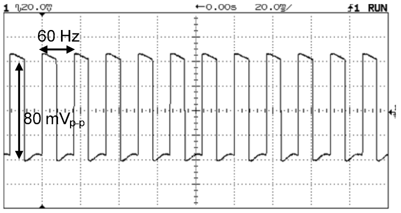

Fig. 8. Measured 60 Hz interference at the output of the commercial EKG amplifier with electrodes disconnected from the mouse body

With a typical impedance of electrodes and body on the order of 1 kΩ, an insignificant 60 Hz interference due to wire coupling is expected at the amplifier input, which was subsequently verified by using a 3 kΩ resistor connected between the two EKG electrodes.

As a result, the 60 Hz interference coupled through the body becomes the major interference source. The coupled displacement current, i_{body}, generates interference voltage signals of V_{cm1}, V_{cm2} and V_{cm3} as shown in Figure 6 and Figure 7. For simplicity of analysis, it is assumed that $V_{cm1} \approx V_{cm2} \approx V_{cm3} \approx V_{cm}$. In the 3-electrode and 2-electrode configurations, V_{cm} can be transformed into 60 Hz interference expressed as

$$V_{body} \approx V_{cm} \left(\frac{(Z_{e1} - Z_{e2})}{Z_{in}} + \frac{1}{CMRR} \right), \tag{4}$$

where CMRR is common-mode rejection ratio of the EKG amplifier, and Z_{in} is the average amplifier input impedance [6]. It can be seen that the mismatch between the electrodes impedance can cause a differential 60 Hz interference signal at the amplifier input.

Considering the 3-electrode configuration shown in Figure 6 with the third electrode connecting the body to the circuit ground, V_{body} can be expressed as

$$V_{body} \approx i_{body} Z_{e3} \left(\frac{(Z_{e1} - Z_{e2})}{Z_{in}} + \frac{1}{CMRR} \right). \tag{5}$$

Due to the low electrode impedance and large Z_{in} and CMRR, V_{body} in the 3-electrode configuration is expected to be negligible. Figure 9 shows the corresponding measured EKG output signal, where the 60 Hz interference is significantly suppressed as predicted by (3) and (5). Instead of directly connecting the third electrode to the circuit ground, an active feedback can be used to deliver an adequate amount of current into the body through the third electrode to cancel i_{body}, thus effectively suppressing V_{cm}. This technique is also known as a driven-right-leg configuration.

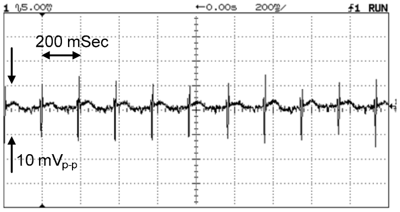

Fig. 9. Measured EKG signal of a laboratory mouse with 3-electrode configuration

For the 2-electrode configuration shown in Figure 7, V_{cm} can be approximated as $V_{cm} \approx i_{body} Z_{in}/2$ assuming $Z_{in} >> Z_{e1}$ and Z_{e2}. Substituting $V_{cm} \approx i_{body} Z_{in}/2$ into (4) results in

$$V_{body} \approx i_{body} \left(\frac{(Z_{e1} - Z_{e2})}{2} + \frac{Z_{in}}{2 \cdot CMRR} \right). \tag{6}$$

It can be seen that the term of $Z_{in}/(2 \cdot CMRR)$ becomes the dominating interference factor. Increasing CMRR can suppress the interference. However, an amplifier CMRR is typically limited to about 120 dB. Therefore, choosing a proper Z_{in} is critical to suppress the 60 Hz interference without attenuating the EKG signal. Figure 10 presents the measured EKG output signal by using a 2-electrode configuration without any additional termination impedance presented at the amplifier inputs. The large 60 Hz interference of approximately 1V_{p-p} corrupts the mouse EKG signal as predicted by (6). However, with two single-ended input termination resistors of 100 kΩ, a greatly suppressed 60 Hz interference can be achieved.

With the low electrode impedance, the 3-electrode configuration has been widely used in biomedical implants to suppress 60 Hz interference. However, for untethered small laboratory animals monitoring, it is desirable to use two electrodes for animal's comfort and ease of electrodes attachment over its small chest area. With the prototype EKG amplifier CMRR of 43 dB, two amplifier input termination resistors of 10 kΩ can significantly suppress the 60 Hz interference with less than 10 % EKG signal attenuation as presented in Figure 5. Furthermore, the termination resistors of 10 kΩ can be readily integrated on chip. Lowering the amplifier input impedance can also be realized capacitively, the required high capacitance value of 270 nF is however undesirable for an on-chip implementation.

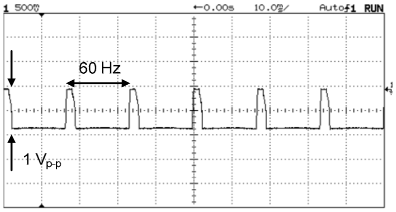

Fig. 10. Measured EKG signal of a laboratory mouse by 2-electrode configuration without input termination resistors

VI. CONCLUSION

A wireless and batteryless *in vivo* EKG and core body temperature sensing microsystem with adaptive RF powering for untethered genetically engineered mice real-time monitoring is developed. A low power 2 mm x 2 mm bio-sensing ASIC consisting of an EKG amplifier, a PTAT temperature sensor, an RF power sensing circuit, an RF-DC power converter, an 8-bit ADC, digital control circuitry, and a wireless transmitter is designed and fabricated in a 1.5 µm CMOS process. The miniature packaged prototype microsystem including EKG sensing electrodes, RF power receiving and data transmitting coils, and the ASIC demonstrates the capability of wirelessly monitoring real-time biological signals from an untethered laboratory mouse. A 2-EKG-electrode configuration with a proposed 60 Hz interference suppression technique by employing input termination resistors is chosen due to small animal chest's area.

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