MRI Controlled Magnetoelastic Nano Biosensor for in-vivo pH monitoring: A Preliminary Approach

Arnaud Chanu, *Student Member, IEEE* and Sylvain Martel, *Senior Member, IEEE*

***Abstract*—Biosensors are a predominant research field and aim at providing small and novel methods for bio-recognition, bio-actuation and embedded data analysis to the medical and bioengineering domains. Typical biosensor technologies exploit optical, electrochemical or mechanical detection methods. Although many biosensors are designed to use biological samples for recognition and treatment, some are designed to be implantable on animals or human for direct detection. The presented work suggests the use of a magnetoelastic based biosensor for the wireless transmission of physiological data through the human body at capillary level. When excited by an external magnetic wave at a given frequency, the magnetoelastic core enters in a vibrating state and emits an alternative magnetic field in response. Using an external RF coils such as the one found in a magnetic resonance imaging (MRI) system, the magnetic flux generated by the magnetoelastic sensor core is received and analyzed during its transient response. Using a pH sensible functional polymer coated on the sensor core, physiological data fluctuations are translated into resonant frequency shifts which, in turn, are picked up by the coil. A preliminary approach for the sensor design and system architecture is presented.**

***Index Terms*—Magnetoelastic, polymers, magnetic resonance imaging, nanomedicine, biosensor, pH.**

I. Introduction

BIOSENSORS are usually defined as devices having the ability to detect, sense or recognize a given biological element or process and emit a given response signal whether optical, mechanical, magnetic or electrochemical to inform the presence of the studied element [1]. As mentioned above, several transducer methods exist in order for a biosensor to respond to a given environment. The most widespread and published method concern the optical based transducers [2] where biological elements are marked either by fluorescence [3], radioactivity or surface plasmon resonance (SPR) [4, 5] to name a few. In all cases, photons are directly or indirectly emitted from the studied element and received by a camera, optical fiber or microscope for detection and analysis. Another well studied transducing option consists in a mechanical response such as thermometric [6], piezoelectric [7, 8], surface acoustic wave (SAW) [9, 10] or other mechanical vibration monitoring techniques where the studied element induces a detectable change in the mechanical state of the sensor. The emergence of MEMS in the past years has greatly improved the use and research of micromechanical biosensors for *in-vivo* monitoring applications [11]. Electrochemical based biosensors are usually specifically designed for the detection of ionic species in solution and are thus continuously active and sometimes referred to as metabolic biosensors. It is usually categorized as either potentiometric [12, 13], amperometric [14, 15] or impedimetric [14, 16]. Finally, magnetic based transducers biosensors are able to detect nanoparticles magnetic field fluctuation when the particles are bound to specific biological elements. Potential applications involve DNA fragments tagging as described in [17].

Most of the above described biosensors are designed to be used in *in-vitro* only environments and are thus mainly oriented towards lab-on-chips or external diagnosis tasks. Such biosensors face fewer miniaturization and biocompatibility issues compared to implantable *in-vivo* biosensors. Besides, *in-vitro* biosensors usually require complex external equipments for detection and analysis as it is the case for optical biosensors, making this transducing method inappropriate for potential *in-vivo* validation. In this paper we study the possibility of adapting common standard clinical magnetic resonance imaging (MRI) system to detect and guide micro and nano blood pH magnetic biosensors in the human vasculature system. Although implantable biosensors already exist for blood pressure[18-21], blood flow [22] or blood glucose [3, 23] measurements, none allow the autonomous guidance of the sensor for multi site measurements. Previous MRI assisted magnetic carrier navigation [24-26] suggested that MRI systems can be used to guide a ferromagnetic device in the human blood arterial system. Although current devices are in the millimeters macro scale range, miniaturization of such device into particles [27] could lead to new potential automated medical tools development.

The presented biosensor is studied to reach the capillary level of the human vasculature system and to allow the wireless pH

A. Chanu and S. Martel. are with NanoRobotics Laboratory, Computer Engineering Department, Ecole Polytechnique Montreal (EPM), Montreal, QC, H3C 3A7, Canada (corresponding author: Sylvain Martel, phone: 514-340-4711 #5029; fax: 514-340-5280; e-mail: sylvain.martel@polymtl.ca, arnaud.chanu@polymtl.ca).

level probing using a combination of magnetic and mechanical transducers through the use of magnetoelastic materials. We first introduce in the following sections a primary design for the sensor before providing an overview of the functionality of the sensing procedure. Some preliminary theoretical results are given.

II. Sensor Design

A. Magnetoelastic core

In order to provide a potential implantable *in-vivo* device such as a biosensor, many challenges must be overcome. One of the major challenges is the ability for the device to communicate with the external environment throughout the body for data sending. Since embedded electronics on the device must be either limited or ideally absent in order to allow the sensor to reach a specific micro scale size, technologies such as RFID or Wi-Fi are inappropriate for capillary size dimensions ranging from 3 to 10 µm.

When placed inside a solenoid or an MRI RF antenna, certain ferromagnetic materials made of iron-rich alloys exhibit magnetoelastic behavior. An alternative current circulating inside the solenoid will induce a time varying magnetic field which, in return will induce a change in the magnetization of the material as well as a vibrating state [28]. If the initial current is stopped, the material's vibration will alter the magnetic flux and generate a time varying current in the solenoid known as the transient response in the form:

$$i(t) = Ae^{-\gamma\omega_n t}\cos(\omega_r t - \varphi) \tag{1}$$

where A is the signal amplitude, γ the damping ratio, ω_n the natural frequency of the undamped oscillation, ω_r the transient oscillation frequency and φ the phase shift. Although any given initial alternating current frequency will induce a mechanical vibration in the magnetoelastic material, a specific frequency excitation will result in a minimal damping ratio during the transient response and is considered the resonant frequency of the material. From [29] we show that the resonant frequency of a ribbon shaped magnetoelastic sample is defined as:

$$f_0 = \frac{1}{2L}\sqrt{\frac{E}{\rho}} \tag{2}$$

where f_0 is the resonant frequency in Hz, L is the sensor's length in m, E is the Young modulus of the sensor and ρ the magnetoelastic's density. This equation stays accurate for a length L much greater compared to the thickness and the width.

A change in mechanical properties such as mass or size will produce a change in the resonant frequency of the sensor. Through a common frequency characterization technique such as the one described in [29], it is possible to track the frequency shift due to such mechanical alteration with a standard RF coil or solenoid.

The ability to detect a slight shift in the resonant frequency is related to the sensor sensitivity also known as the spectrum quality factor or simply, the Q factor which is defined as:

$$Q = \frac{f_0}{\Delta f} \tag{3}$$

where f_0 is the sensor's resonant frequency and Δf is the peak width where the signal amplitude decreases to half of its maximum value. For devices of small dimensions, the resonant frequency is important, significantly reducing the ability to detect a slight shift. This quality factor must be taken into account when designing the sensor.

B. pH sensible polymer coating

In order for the magnetoelastic sensor core to exhibit a resonant frequency shift related to an external physiological modification, a pH sensible functional polymer is coated on the sensor core. Element specific sensible polymers have been the subject of many investigations in the biomedical engineering domain [30].When subjected to a targeted agent modification in the surroundings, the polymer chain will either swell or shrink with an amplitude related to the change as expressed in [31-33]. This structural reorganization will induce mechanical stress and mass load alteration on the magnetoelastic core, resulting in a resonant frequency shift. Within a given range, this shift is linearly related to the pH fluctuation [32] and can thus be used to track the later during the transient response period of the magnetoelastic core. After it has been excited by an alternative magnetic flux circulating inside the solenoid or RF coil, the acquired signal's Fourier transform will show a measurable shift used to determine the change of local pH level. As describe in more details in the next section, this signal analysis operation is executed via the MRI real-time pulse sequence in a dedicated process.

As explained above, bonding such polymers to a magnetoelastic material, produces a significant resonant frequency shift that is detectable by a common RF coil as stated in [29]. We show from [29] that a uniformly applied coating of density ρ_c and Young modulus E_c will induce a new resonant frequency f defined as:

$$f = f_0 \cdot \sqrt{\frac{m_0}{m_t} + \frac{E_c/\rho_c}{E_s/\rho_s}\left(1 - \frac{m_0}{m_t}\right)} \tag{4}$$

where m_0 is the magnetoelastic mass, m_t the total sensor mass after the coating is applied, and E_c , ρ_c , E_s , ρ_s are respectively the coating Young modulus and density and the magnetoelastic Young modulus and density.

C. RF Coils

In this paper we suggest the use of an MRI RF coil to excite and obtain the incoming response of the magnetoelastic biosensor. Magnetic resonance imaging RF coils are used in nuclear magnetic resonance for the proton excitation process as well as for the signal acquisition during the relaxation. Standard MRI RF coils are able to operate in a range from 10 MHz to 100 MHz, allowing a theoretical minimum sensor length of:

$$L_{\min} = 5\times10^{-9}\sqrt{\frac{E}{\rho}} \tag{5}$$

where E and ρ are respectively the overall biosensor Young modulus and density.Since RF coils are intimately related with MRI functionality, most standard clinical MRI could be adapted to provide such new implantable biosensor technology

III. System Architecture Overview

In order for such biosensor to be seamlessly integrated and operated via an MRI system, a dedicated pulse sequence and software architecture must be considered. Existing real-time pulse sequences as well software architecture for the real-time navigation of a ferromagnetic device inside the carotid artery of a living swine under anesthesia were previously presented and could easily be adapted for the presented biosensor [25]. The software architecture and real-time pulse sequence [24] were designed to constantly monitor the device's position and correct its trajectory for adequate control.

In the presented biosensor case, the derived pulse sequence is responsible for the sensor excitation process as well as the data acquisition and analysis during and after the transient response. The data analysis process takes care of the FFT and frequency shift determination based on the amplitude of the pH fluctuation around the sensor. The excitation and signal treatment steps are incorporated in a pulse sequence for continuous sensor operation. Since the required signal processing is achieved in parallel in another computer process outside the running sequence environment, additional standard imaging or ferromagnetic tracking sequences [34] could also be integrated for concurrent sensing and visualization capabilities. Figure 1 shows an overview of the pulse sequence and necessary steps during the sensor operation.

IV. Results

Potential medical application for such nano biosensor could involve physiological brain capillaries or even cell surrounding pH measurements through the transportation of such device through the blood brain barrier implying a sensor size that could range from 5 to 10 nm according to [35].

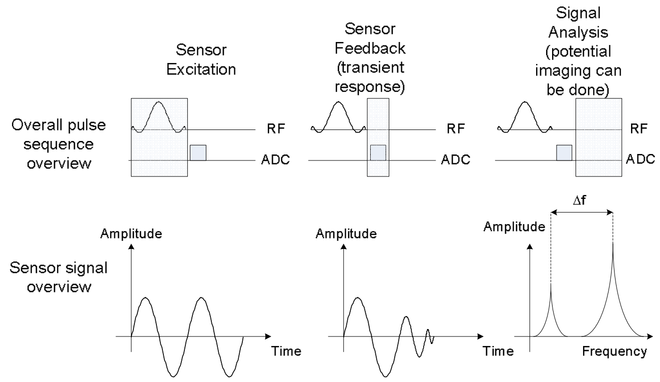

Figure 1: Overview of the functionality and MRI sequence for the sensor operation and data analysis.

Such miniaturization would in turn necessitate specialized RF coils being able to operate at higher frequencies than the above discussed standard MRI coils. Figure 2 below illustrates the theoretical resonant frequencies of an uncoated and pH sensible polymer coated magnetoeslatic sensor core for different length L ranging from 10 nm to 100 nm. The magnetoelastic material considered for the model is Metglas 2826 MB (FeNi based) with a Young modulus E_s =100 GPa and a density ρ_s =7900 kg/m^3. The magnetoelastic sensor core width and thickness are respectively w =10 nm and h =10 nm. The pH sensible polymer considered is a standard poly(acrylic acid-coisoocylacrylate) as described in [29] with a measured density of ρ_c =1040 kg/m^3 and a Young modulus of approximately E_c =1 GPa. Finally, three sets of coating thickness are considered namely 5 nm, 10nm and 20 nm.

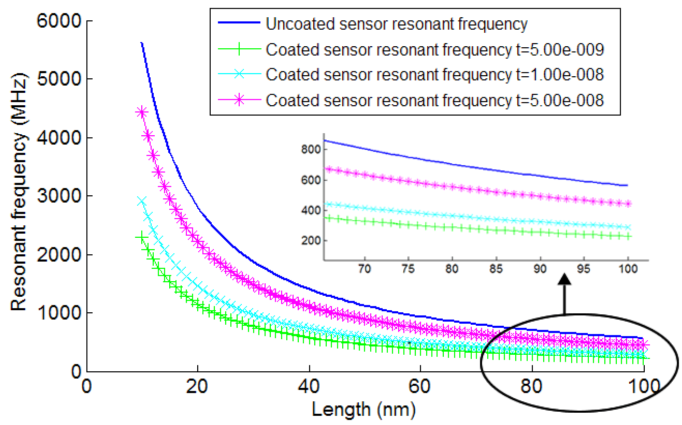

Figure 2: Resonant frequency of a uncoated and pH polymer coated magnetoelastic material in function of the selected length of the sample

From Figure 2 we see the theoretical impact of the coating and its thickness on the resonant frequency. Also, we observe that below 100 nm size, the necessary RF coils operating frequency is out of range for standard MRI RF coils which implies the consideration of custom made ultra high frequency

(UHF) RF coils dedicated for physiological data transmission and reception.

V. Conclusion

Many challenges arise when considering biosensors operating at micro or even nanoscale. One of the major obstacles is the sensor sensitivity that might limit the miniaturization of the device. Also, supposing such a sensor can be held in place in the capillary vasculature, high frequency waves emerging from the RF coil are quickly absorbed by the human body in part due to the skin effect which might considerably reduce the available signal for pH fluctuation determination. Finally, the tracking and navigation of such small sensor remains a great challenge, but recent major accomplishments in the MRI assisted magnetic device navigation field at millimeter scale have been obtained [25] and constitute and interesting starting point for further exploration.

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