IMPLANTED WIRELESS INTRAMEDULLARY FLUID MODULATOR FOR BONE DENSITY AUGMENTATION

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ABSTRACT

Intramedullary fluid flow and pressure modulation has been reported to stimulate bone. However, the lack of engineered and implantable devices has been a stumbling block for exploiting the methodology for treatment of osteoporosis. In this paper, we report a wirelessly operated, battery-less, and implantable intramedullary fluid modulator for *in-vivo* study of intramedullary flow and pressure modulation. Static pressure and dynamic pressure measurements were carried out to investigate the magnetic excitations and pressure responses. *In-vivo* study of intramedullary pressure modulation was conducted to confirm the fluid modulator induce on-demand intramedullary pressure up to ~38 mmHg amplitude in wireless operations.

KEYWORDS

Intramedullary cavity, fluid modulator, osteoporosis, implantable.

INTRODUCTION

Osteoporosis is a bone disorder characterized by reduced bone density and bone strength, giving rise to increased risks of bone fracture. This has become a major public health issue in recent years especially in people of old age. It is estimated that 10 million Americans over 50 years of age suffer from this disease, leading to 1.5 million bone fractures per year in the United States [1]. It is known that increased physical activity (e.g. bone mechanical loading) augments bone mass, while reduced physical activity (e.g. sedentary lifestyle) diminishes bone mass. To date, the exact mechanism of bone remodeling initiated by mechanical loading remains unknown [2]. However, previous studies have demonstrated that modulations in bone intramedullary fluid flow and pressure in the absence of mechanical loading elicits the release of bone stimulating factors and augmentation of bone growth [2-4].

Despite the huge clinical value of applying this methodology for treatment of osteoporosis and bone fracture repair, study of *in-vivo* bone intramedullary fluid modulation and its efficacy for bone growth is rare, and the tools used for such studies have been limited to external hydrostatic columns or syringe pump connected into rat femora with wired catheter [4, 5]. These methods, nonetheless, require catheters surgically inserted through the skin to external equipment (e.g. syringe pumps), imposing great restrictions on the normal activities of test subjects.

The lack of practically engineered and implantable devices is one of the major obstacles for full exploitation of this methodology. In this work, for the first time, we report a wirelessly operated, battery-less, implantable bone intramedullary fluid modulator (WiBi-FM) for *in-vivo* study of bone intramedullary fluid modulation and its efficacy for bone density augmentation.

FABRICATION PROCESS

The WiBi-FM was fabricated using bio-compatible silicone polydimethylsiloxane (PDMS) incorporated with NdFeB magnets for wireless actuation. Fig. 1(a) presents schematic diagram of the fabrication process of the WiBi-FM in cross-sectional views. A set of stainless-steel molds were fabricated in a machine shop, and cleaned with acetone, isopropyl alcohol (IPA) and de-ionized (DI) water before use. PDMS pre-polymer was prepared by mixing two-part silicone (Sylgard 184, Dow Corning, Midland, MI, USA) in a weight ratio of 10:1. The pre-polymer was thoroughly mixed and degassed in a vacuum chamber to remove the bubbles. The liquid pre-polymer was then poured into a glass container and cured in a convection oven at 90 °C for 30 minutes to cast approximately 400 µm thick PDMS sheets. This thin film of PDMS would serve as the diaphragm of the intramedullary fluid modulator.

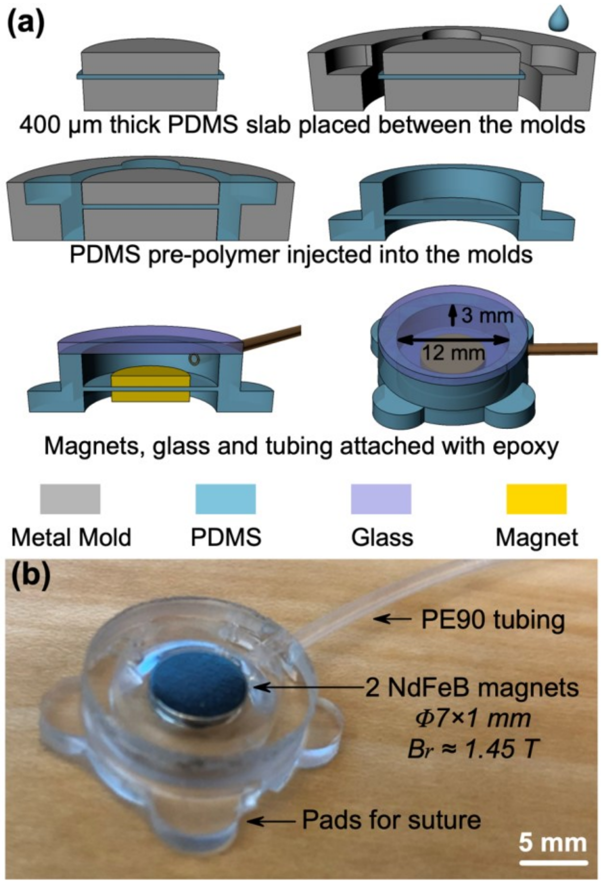

Figure 1. (a) Schematic of the fabrication process and (b) optical image of the fabricated intramedullary fluid modulator with two NdFeB magnets (N50 grade) of size Φ7 × 1 mm.

The 400 μm thick PDMS film was placed between two cylindrical metal molds with the same diameter (12 mm) and varied thickness (3 mm and 2 mm, respectively). The prepared PDMS liquid pre-polymer was then injected into the molds using a syringe, followed by baking in a convection oven at 90 °C for 30 minutes. The cured structure was carefully removed from the molds. Two grade N50 NdFeB permanent magnets (B_r ~1.45 T) of 7 mm diameter and 1 mm thickness, pre-cut circular borosilicate glass of 1 mm thickness, and PE90 tube (ID: 0.86 mm, OD: 1.27 mm, BD 427421, Beckton Dickson, Franklin Lakes, NJ, USA) were bonded using medical grade epoxy (M-31CL, Henkel Loctite, Düsseldorf, Germany). The size of the WiBi-FM chamber is 12 mm in diameter and 3 mm in depth (Fig. 1b).

WORKING PRINCIPLES AND EXPERIMENTAL SETUP

Figure 2 shows the schematic diagram and a photomicrograph of the working principles of wireless intramedullary fluid modulator. The fluid modulator would be filled with 0.9% heparinized saline which prevents blood clotting and implanted into the back of a Fischer-344 rat. The modulator is connected to the intramedullary cavity of the femur through PE90 tube. Due to the small size of intramedullary cavity (~1.7 mm in diameter and ~13 mm in length), the PE90 tube would be connected to ~1 cm long PE50 tube (ID: 0.58 mm, OD: 0.97mm, BD 427411, Beckton Dickson, Franklin Lakes, NJ, USA), and the PE50 tube would be inserted into the intramedullary cavity.

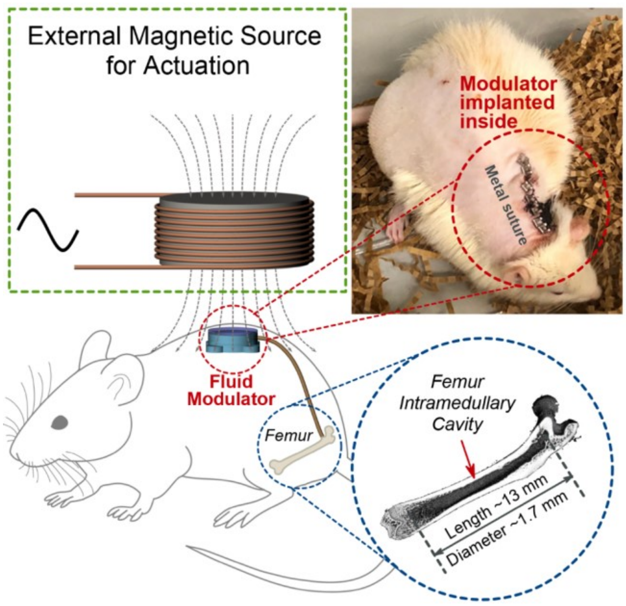

Figure 2. Schematic diagram of animal setup using old aged Fischer-344 rat with the intramedullary fluid modulator implanted in the back of the rat.

In this work, the modulated external magnetic field for actuation was provided by moving an external permanent magnet (N50 grade) reciprocally using a linear reciprocating actuator. The reciprocating linear actuator can be operated at maximum speed of 160 rpm with stroke distance of approximately 70 mm. The reciprocal movement of the external magnet leads to a sinusoidal modulation of magnetic field and magnetic field gradient, which changes the force exerted on the WiBi-FM diaphragm attached with internal magnets. The force is then transmitted into the bone cavity to induce on-demand modulation of intramedullary fluid pressure by incompressible fluid (0.9% heparinized saline), which was measured by a commercial pressure sensor.

STATIC PRESSURE MEASUREMENTS

The static pressure measurement was carried out to study the relationship of pressure change with respect to magnetic force. The pressure of the fluid modulator generated by external magnetic force is given by [6]

$$P \approx \frac{F_z}{A} \quad (1)$$

where, P is the pressure excited by magnetic force, F_z is the axial magnetic force exerted on the internal magnets by external magnetic field gradient, and A is the area of the diaphragm which was calculated as $A = \pi r^2$ ($1.13 \times 10^{-4}\ \mathrm{m}^2$). The axial magnetic force exerted on the internal magnets by external magnetic field gradient can be estimated by [7]

$$F_z \approx \frac{1}{\mu_0} B_r V_m \frac{dB_z}{dz} \quad (2)$$

where F_z is the axial magnetic force caused by external magnetic field gradient, μ_0 is the permeability of vacuum (12.57×10^{-7} H/m), B_r is remanent magnetic flux density of the internal magnets (~1.45 T), V_m is the total volume of the two internal magnets which can be calculated as $V_m = 2\pi r^2 h$, with r and h denoting the radius and height of the internal magnets, $\frac{dB_z}{dz}$ is the external magnetic flux density gradient along the axial direction of the external magnets.

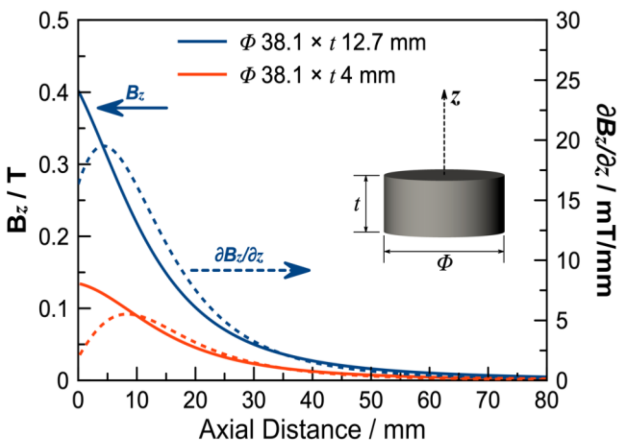

Figure 3. Simulation results of magnetic flux density (solid lines) and magnetic flux density gradient (dotted lines) along the axial direction, with blue lines denoting the larger magnet of 38.1 mm in diameter and 12.7 mm in thickness, and red lines denoting the smaller magnet of 38.1 mm in diameter and 4 mm in thickness.

The magnetic flux density and its spatial gradient was found using finite element method (FEM) by COMSOL Multiphysics. Two different sizes of external magnets of cylindrical shape with 38.1 mm in diameter and varied thickness of 12.7 mm and 4 mm are simulated. Figure 3 shows the simulation results of magnetic flux density and magnetic flux density gradient of the two external magnets with different sizes. As expected, the magnetic flux density and flux density gradient of the thicker magnet is larger than that of the thinner one.

A set of fluid modulators with various internal magnet sizes were fabricated to validate the theoretical model. The distance between the surfaces of the external and internal magnets were set to be constant (~15 mm). The elevated static fluid pressure was measured by a commercial pressure sensor. Fig. 4 shows the theoretical and experimental results of static pressure induced by external magnetic force. The static pressure increases as the size of the magnets increases. This is expected as the magnetic force is proportional to the volume of the internal magnet. It is also worth noting that the experimental results are higher than theoretical values, which is due to fringing field effect of external magnets. Even with potential slight axial misalignment (e.g. off from the collinear axis) and angular misalignment, experimental results turned out to be larger than theoretical values.

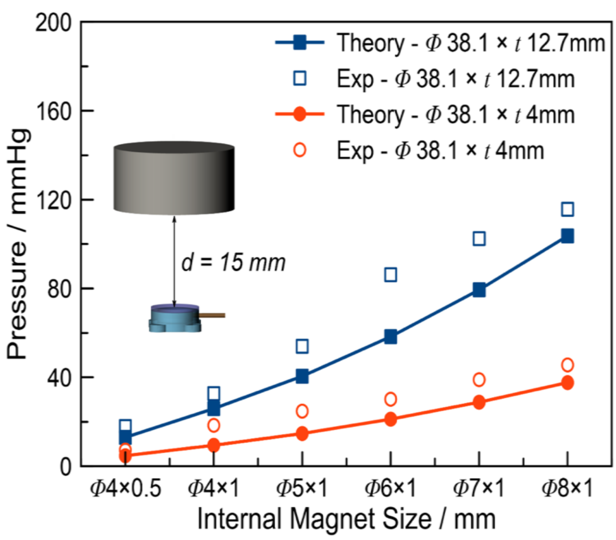

Figure 4. Theoretical and experimental results of static pressure of various internal magnet sizes under external magnetic field caused by two different external magnets. The distance between the surfaces of magnets is controlled to be 15 mm.

DYNAMIC PRESSURE MEASUREMENTS

Ex-vivo dynamic pressure measurements of the fluid modulator were carried out to test the output performance of the fluid modulator. The pressure measurement was conducted with fluid modulator filled with 0.9% heparinized saline, and approximately 40 cm long PE90 tube was used to connect to a commercially available pressure sensor (SP844, MEMSCAP, Durham, NC) to monitor real-time pressure modulation.

As shown in Figure 5, the results show the pressure modulation amplitude reaches approximately 70 mmHg under external magnetic field with a separation distance ranging from 18 mm to 85 mm (~120 mT amplitude) between the external magnet and the internal magnet inside the implanted fluid modulator. Due to low excitation frequency (~0.5 Hz) and low volumetric flow rate, the pressure drops in various tube lengths are relatively small.

IN-VIVO INTRAMEDULLARY PRESSURE MODULATION

The *in-vivo* study of the fluid modulator was also conducted to test the induced on-demand modulation of bone intramedullary fluid flow and pressure. The *in-vivo* experimental measurements were carried out on a Fischer-344 rat of old age, operated with external magnet of 38.1 mm in diameter and 12.7 mm in thickness. The separation distance between the external magnet and the internal magnet ranges from 18 mm to 85 mm to modulate the magnetic force. The same working fluid 0.9% heparinized saline was used to prevent blood clotting.

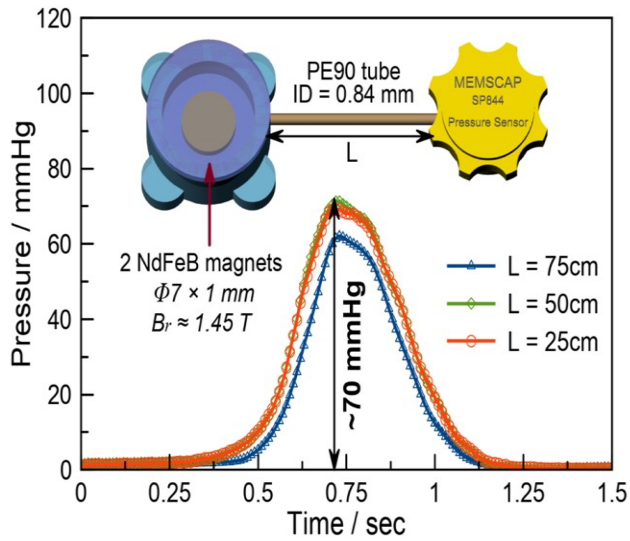

Figure 5. Ex-vivo dynamic pressure response of the fluid modulator connected to PE90 tubes with length 75 cm, 50 cm and 25 cm using 0.9% heparinized saline. The external magnet used is NdFeB magnet with 38.1 mm in diameter and 12.7 mm in thickness operated at distance ranging from 18 mm to 85 mm.

Fig. 6 shows the *in-vivo* experimental results of the fluid pressure modulation in bone intramedullary cavity. The intramedullary pressure modulation amplitude under ~0.5 Hz of external magnetic excitation for the fluid modulator with 25 cm, 50 cm and 75 cm long PE90 tubes are found to be 38 mmHg, 21 mmHg, and 14 mmHg, respectively. In comparison, the pressure fluctuation caused by respiration of the rat is negligible (< 1 mmHg). Compared to the *ex-vivo* dynamic pressure tests, which shows a relatively consistent pressure modulation amplitude of approximately 70 mmHg, the *in-vivo* test results exhibit larger pressure drops and dependence of the tube length. This pressure drop could be partially attributed to the porous structure inside of the bone intramedullary cavity, structured by densely distributed blood vessels and blood cells.

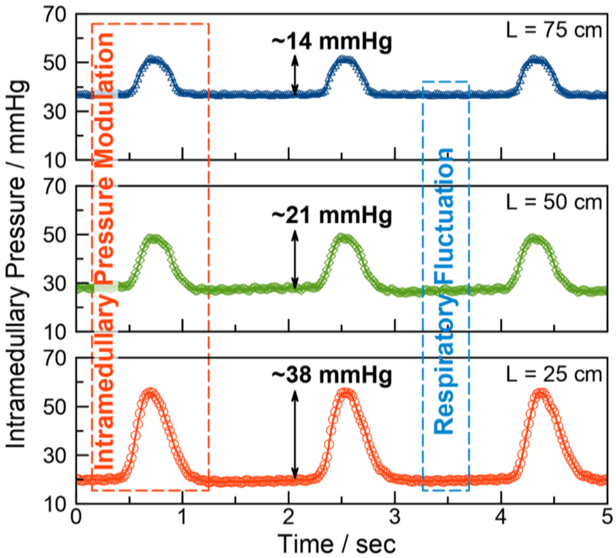

Figure 6. *Test results of in-vivo intramedullary fluid modulation on old age Fischer-344 rat using PE90 tubes with length 75 cm (top), 50 cm (middle), and 25 cm (bottom) under using 0.9% heparinized saline. The external magnet used is NdFeB magnet with 38.1 mm in diameter and 12.7 mm in thickness operated at distance ranging from 18 mm to 85 mm.*

CONCLUSION

In this work, a wirelessly operated, battery-less, and implantable intramedullary fluid modulator for potential bone density augmentation is presented. *Ex-vivo* measurements of static and dynamic pressure modulation are shown to confirm the effectiveness of the fabricated fluid modulator to induce on-demand pressure modulation. The results show that the fluid modulator could induce ~70 mmHg pressure amplitude under external magnetic excitations. The fluid modulator was also tested *in-vivo* with an old age Fischer-344 rat to confirm the implantability and the performance in inducing on-demand intramedullary fluid pressure modulation. The intramedullary pressure modulation amplitude under ~0.5 Hz of ~120 mT external magnetic excitation for the WiBi-FM with 25 cm, 50 cm and 75 cm long PE90 tubes were found to be 38 mmHg, 21 mmHg, and 14 mmHg, respectively. These results confirm that the fluid modulator is fully functional in wireless operation. This implantable intramedullary fluid modulator could be employed to enhance *in-vivo* study of bone intramedullary fluid modulation and its efficacy in bone density augmentation and fracture repair.

ACKNOWLEDGEMENTS

This work was supported by the United States National Science Foundation grant NSF ECCS-1710824. The authors would also like to acknowledge UT Dallas Clean Room staff for their support on this work.

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