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## Compact MRI bioreactor for real-time monitoring 3D printed tissue-engineered constructs.

### Synopsis

Tissue engineering for regenerative medicine is a growing field which faces structural and functional challenges at different scales. Real-time quantitative 3D characterization of tissues both *in vitro* and *in vivo* would help biologists assessing their methods. Magnetic Resonance Imaging (MRI) offers the possibility to perform such characterization non-invasively. We propose here a 7T MRI coil integrated within a perfusion tissue engineering bioreactor to perform tissue assessments throughout its growth. This MRI bioreactor is built using 3D printing and plasronics. This work resulted in a successful observation of a bioprinted tissue with a 75  $\mu\text{m}$  in plane resolution.

### Introduction

Tissue engineering and regenerative medicine have been developing for a few decades now and the number of applications is growing <sup>1</sup>. From cartilage to skin, a wide range of tissues are currently being studied and constructed. However, along with the increasing number of applications, comes an increasing number of different parameters of interest for tissue characterization depending on its application. With multiscale and multiparametric acquisitions, MRI is best suited for characterizing various types of key properties in tissue development. Recent advances <sup>2</sup> highlighted the interest of real-time monitoring of tissues during their growth. As a non-invasive and non-ionizing modality, MRI also qualifies as a potential candidate for this task. In this context, the development of dedicated MRI apparatus specifically designed for this field becomes mandatory. Here we study the feasibility of integrating an MRI sensor directly into the bioreactor to monitor in real time cell fate and tissue growth in 3D printed tissue-engineered constructs.

### Method

Different MRI setups have been designed for small tissue samples over the years <sup>3, 4</sup>. The present case is different as the tissue is living and growing while being probed, to our knowledge, only one group <sup>5</sup> tackled this issue. This implies the combined integration of a coil and a non-magnetic bioreactor within the bore of the scanner. Merging these two functions can be done by addition with a conventional FR4-based circular coil placed on top of an operating bioreactor. This method is simple to setup, on the downside, the loss in coil sensitivity due to the bioreactor being placed

between the sample and the coil can be detrimental. In addition, this loss would be bioreactor-dependent, leading to poor setup transferability between applications. On the other side, another solution exists with the integration of the coil within the bioreactor itself. This integration has been made possible by the previous advances in plasmonics techniques<sup>6</sup>. Once the design of the bioreactor was conceived in SOLIDWORKS, simulations were conducted using CST MICROWAVE STUDIO. The purpose was to evaluate the influence of the dielectric environment of the coil on its sensitivity and field homogeneity compared to a conventional FR4 coil that would be considered as a reference (figure 2).

A 12mm reception circular coil was designed and integrated within a perfusion bioreactor based on a previous design<sup>7</sup>. This type of bioreactor is commonly used in tissue engineering<sup>8</sup> and fits the scope of this work as it contains no active parts. The cell culture medium is flowing through to the sample via 2 inlets connected to external fluidic circulation pumps. The bioreactor was 3D printed using high temperature resin. The copper coil was then deposited on the surface of the bioreactor following the method described in<sup>6</sup>. X-ray fluorescence measurements showed a copper thickness of 45µm and a 4-points method placed the resistivity around  $1.75 \times 10^{-8} \Omega \cdot m$ . As illustrated in figure 1, the coil and its passive decoupling circuit were conceived in 3D using via through the wall of the bioreactor. The 300 MHz tuning/matching of the coil was done remotely with a tuning box with two trimmer capacitors, one in parallel (tuning) and one in series (matching). Finally, a mechanical support was built to allow the bioreactor to fit inside a 36mm radius birdcage transmission coil.

Bench characterization of the coil included unloaded/loaded quality factor measurements. For comparison purposes, bench characterization has also been conducted on a coil made with copper tapped on an FR4 plate. Additional characterization of the bioreactor coil has been conducted in imaging conditions with a 7T Bruker MRI scanner. SNR measurements were performed on an echographic gel using 3D Flash sequence with following parameters: matrix 128×128×64, a FOV 19.2×19.2×9.6 mm<sup>3</sup> i.e. 150µm<sup>3</sup> isotropic resolution, TR 33.81ms, TE 15ms, 16 averages for a total acquisition time of 74min. As proof of concept for our bioreactor, a 2D turboSPGR MRI acquisition was performed on a tissue engineering construct with following parameters: matrix 256×256×64, a FOV 19.2×19.2mm<sup>2</sup> i.e. 75µm<sup>2</sup> in-plane resolution, 12 slices of 500 µm thickness, TR 3000ms, TE 15ms, Rare factor 8, 4averages for a total acquisition time of 4min 48s

## Results

For long TE sequences, an important image artifact appeared. Numerical simulations showed that this is due to the 3D structure of the bioreactor coil leading to a parasitic loop causing field extinction near its location (figure 4). This parasitic loop could explain that the SNR was 1.36 times lower than the SNR obtained with a larger commercial single loop coil available at the imaging facility (16 mm diameter). An in-plane 75 µm<sup>2</sup> resolution on the bioprinted sample was achieved with the bioreactor.

## Conclusion

The 3D integration of the MRI coil to the bioreactor needs to be improved to open the way for the first real-time monitoring of a constructing tissue. A validation step for this integration would require a B1 mapping using recent methods<sup>9</sup>. The integration of a piezoelectric vibrating membrane is also studied for elastography purposes. In conclusion, this work demonstrates the feasibility of an integrated coil inside a bioreactor and paves the way for a democratization of the MRI tool for biologists using tissue-tailored fully integrated MRI- bioreactors.

## Acknowledgements

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## Figures

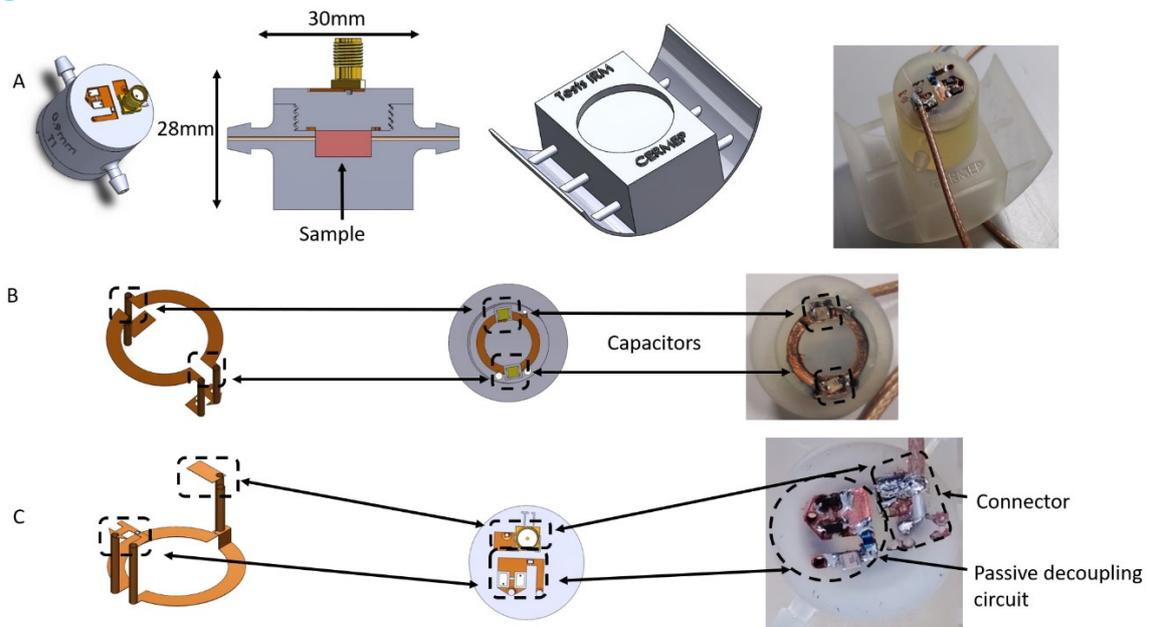


Figure 1: Design and conception of the bioreactor (A) 3D model of the bioreactor and its support (B) Detailed view of the bottom of the 3D coil circuit and its integration. (C) Detailed view of the top of 3D coil circuit and its integration.

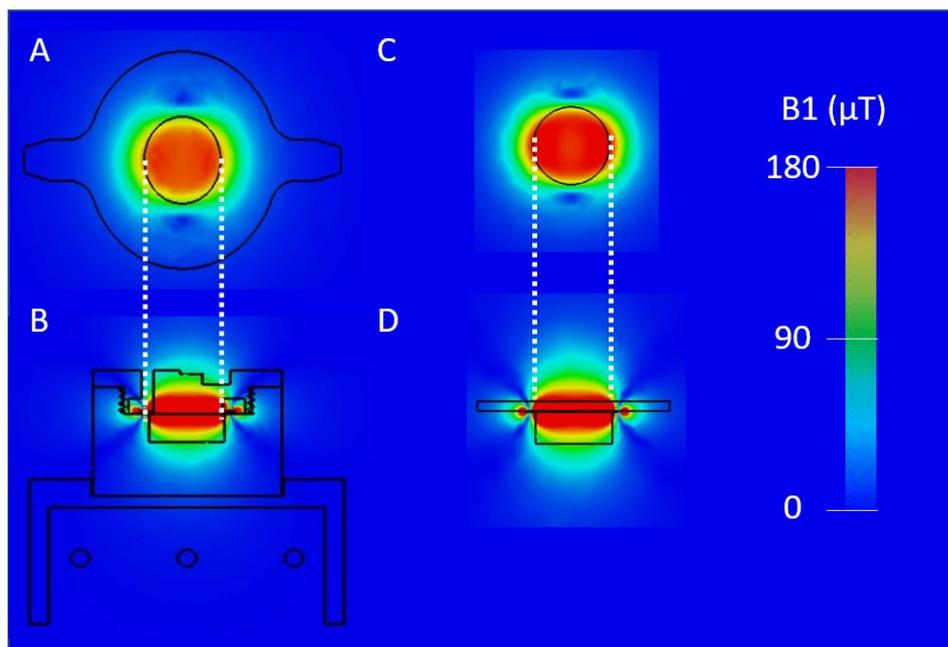


Figure 2 : Results of CST Microwave simulations of 1W-normalized B1-field. (A) In plane XZ view of the bioreactor. (B) In plane YZ view of the bioreactor. (C) In plane XZ view of the FR4 coil. (D) In plane YZ view of the FR4 coil.

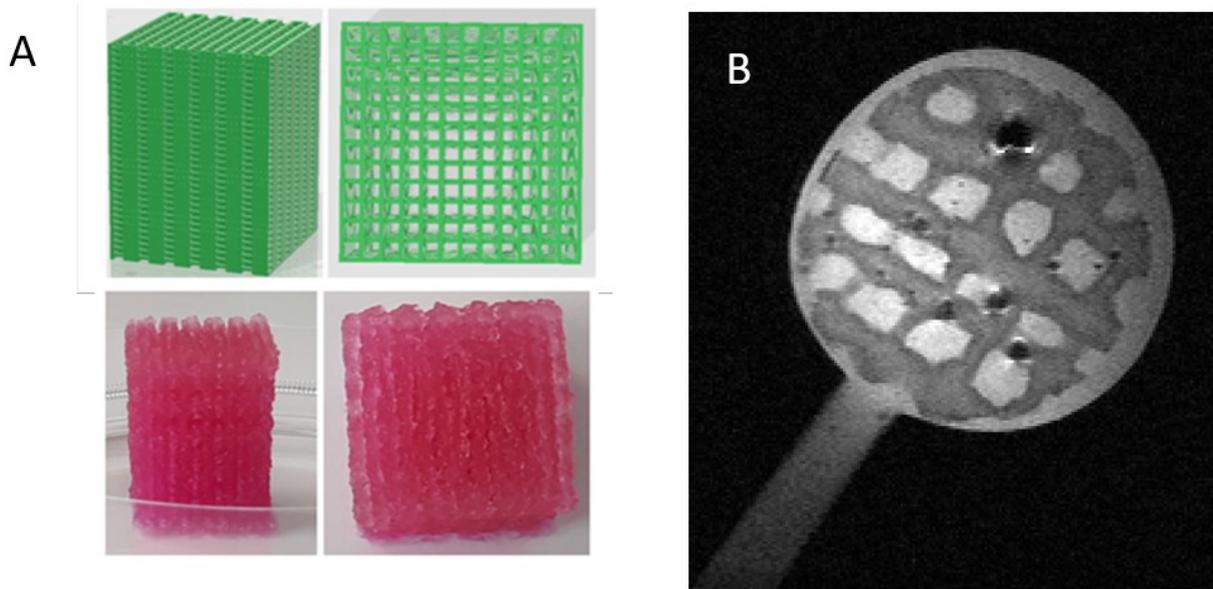


Figure 3 : (A) Picture of the bioprinted tissue after construction. (B) 2D Turborare image of the tissue using the bioreactor acquired on a 7T MRI scanner with a 75  $\mu\text{m}$  in plane resolution.

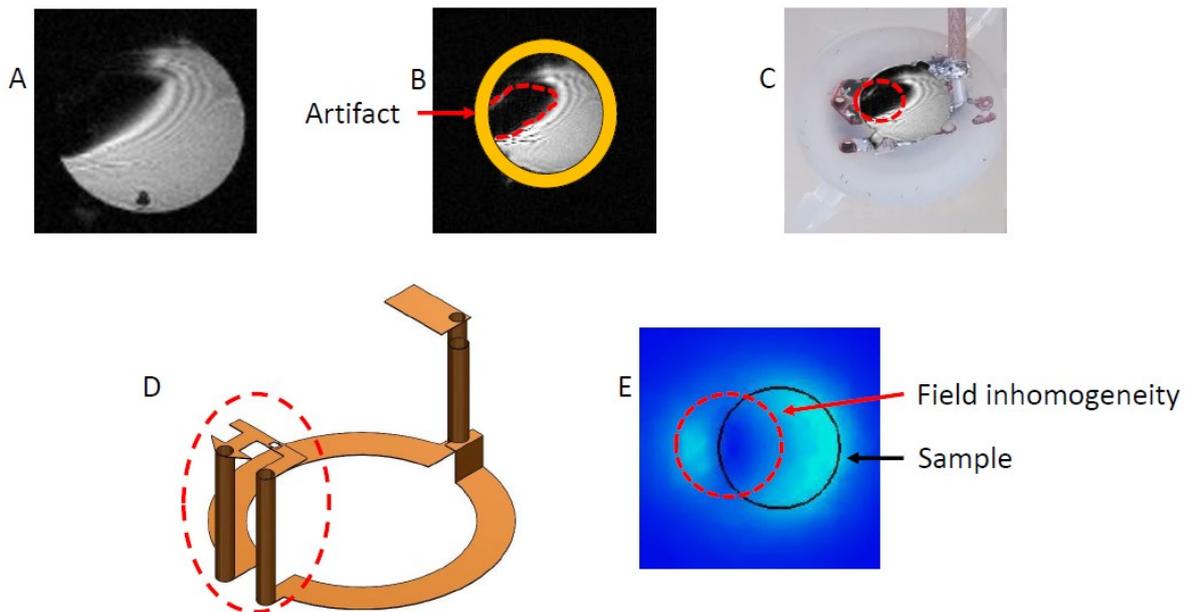


Figure 4 : (A) Image acquired on the 7T MRI scanner with a 3D flash sequence. (B) Image artifact underlining. (C) Superposition of the location of the image artifact on top of the bioreactor. (D) Location of the parasitic coil responsible for the heterogeneous field (E) B1-field simulated on the XZ plane at the center of the sample.

	FR4-based coil	Bioreactor
Measured Q unloaded	130	110
Measured Q loaded	110	108

Table 1 : Quality factors of the bioreactor and a conventionnal FR4 coil.

1. Shafiee, A. & Atala, A. Tissue Engineering: Toward a New Era of Medicine. *Annu. Rev. Med.* **68**, 29–40 (2017).
2. Welter, J. F. & Baskaran, H. Monitoring and real-time control of tissue engineering systems. in *Principles of Tissue Engineering* 1459–1467 (Elsevier, 2020). doi:10.1016/B978-0-12-818422-6.00079-4.
3. Meadowcroft, M. D. *et al.* Direct magnetic resonance imaging of histological tissue samples at 3.0T. *Magn. Reson. Med.* **57**, 835–841 (2007).
4. Sengupta, S. *et al.* High resolution anatomical and quantitative MRI of the entire human occipital lobe ex vivo at 9.4 T. *NeuroImage* **168**, 162–171 (2018).
5. Othman, S. F., Wartella, K., Khalilzad Sharghi, V. & Xu, H. The e -Incubator: A Magnetic Resonance Imaging-Compatible Mini Incubator. *Tissue Engineering Part C: Methods* **21**, 347–355 (2015).
6. Gerges, T. *et al.* 3D Plastronics for Smartly Integrated Magnetic Resonance Imaging Coils. *Front. Phys.* **8**, 240 (2020).
7. Pourchet, L. LARGE 3D BIOPRINTED TISSUE\_ HETEROGENEOUS PERFUSION AND VASCULARIZATION. 13.
8. Gaspar, D. A., Gomide, V. & Monteiro, F. J. The role of perfusion bioreactors in bone tissue engineering. *Biomatter* **2**, 167–175 (2012).
9. Sacolick, L. I., Wiesinger, F., Hancu, I. & Vogel, M. W. B1 mapping by Bloch-Siegert shift. *Magn. Reson. Med.* **63**, 1315–1322 (2010).