Design and development of a magnetic device for mesenchymal stem cell retaining in deep targets

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Abstract. This paper focuses on the retaining of mesenchymal stem cells in blood flow conditions using the appropriate magnetic field. Mesenchymal stem cells can be tagged with magnetic nanoparticles and thus, they can be manipulated from distance, through the application of an external magnetic field. In this paper the case of kidney as target of the therapy is being studied.

1. Introduction
Super paramagnetic iron nanoparticles (SPIONs) and magnetic techniques are being used for various applications and play a significant role in the field of drug delivery [1-6]. They can be used as a means of carrying a drug or a molecule to a specific site due to their magnetic susceptibility, via the force applied by an external magnetic field, while monitoring their position by magnetic field sensors [7-11].

Mesenchymal stem cells' positive effects have been proved and their potential uses can be countless due to their regenerative character. However, it is crucial to guide them precisely at the target otherwise, other vital organs and tissues are susceptible to teratogenesis, cancers and other unwanted effects [12-18].

2. Theoretical background
The force applied by a magnetic field with magnetic field intensity H at a magnetic nanoparticle of radius $\alpha$(m) and magnetic susceptibility $\chi$ is:

$$F_M = \frac{4\pi\alpha^3}{3} \frac{\mu_0 \chi}{1 + \chi f_2} \nabla \left( \frac{H^2}{3} (1 + \chi f_2) \right)$$

(eq. 1)

The magnetic susceptibility of the SPIONs is $\chi \approx 20$ and that of the human body is $\chi \approx 10^{-6} - 10^{-4}$ hence, the efficiency of the magnetic field on the SPIONs is not being remarkably affected by the human tissues [19-20]. The small radius of the magnetite assures a super paramagnetic behavior under the influence of the magnetic field. Therefore, in the absence of magnetic field, the nanoparticles are not magnetized and vice versa. The magnetic force depends strongly on the size of the nanoparticles. Furthermore, the magnetic force is being increased accordingly to the increase of the magnetic field gradient; the steeper is the gradient, the bigger the force applied on a nanoparticle [21-23]. It is worth notifying that in stem cells, the SPIONs are aggregated into lyssosomes and create clusters of a few $\mu$m and thus, the force applied on them is bigger than that applied on one nanoparticle [24-30].

3. Experimental components
The experimental setup consisted of two main components. First, the electromagnet, which had the characteristics shown in figure 1. A KEPCO BOP 72-6M was used to apply 32V at the coils. Secondly, regarding, the circulatory system, a mix of ethanol and oleic acid was used for the
dispersion of the SPIONs. The pump used, provided 833ml/min which is approximately 200ml/min more than the blood flow in each renal artery. The tubes were 2400mm long, with inner diameter 5 mm, approaching the diameter of the blood vessels.

| Parameter                        | Value                  |
|----------------------------------|------------------------|
| Gap                              | 100*100*80mm³         |
| Magnetic circuit length           | 870mm                  |
| Core surface                     | 10,000mm²              |
| H(A) from BH curve for B=1T      | 200A/m                 |
| Current Intensity J              | 2.5(A/mm²)             |
| Copper wire diameter             | 2mm                    |
| Number of turns/coil N           | 1250                   |
| Resistance/coil R               | 4.12Ω                  |
| I*N at 6³                        | 15000                  |
| Max magnetic field at the gap B  | 0.23T                  |

Figure 1: Characteristics and shape of the electromagnet

4. Experimental setup
The purpose of the experiment was to locate the areas and define the conditions under which the SPIONs could be retained in the gap of the electromagnet. The tubes were placed at specific positions in the gap between the poles of the electromagnet and after a few circles of the circulatory system, the flow was being shut off so that measures could be obtained. The tube was shaped as a loop and four sets of measurements were conducted. At each location four flows were tested: Upwards (U), downwards (D), clockwise (C) and counterclockwise (CC). During the first experiment the loop was in touch with the corner of the right core of the electromagnet and the concentration of the SPIONs was rich, as expected. The second experiment was conducted 3mm away from the same core. The concentration was still rich, while upward and clockwise flows provided the best results. The third experiment was conducted 6mm away from the core and the concentration was lower in all the cases although, a higher concentration could be observed at the same flow cases (upwards and clockwise). Similar results were provided at 9mm distance while, at 12mm, the SPIONs retained were significantly decreased. The direction of the flow played a major role on the effectiveness of each trial. More specifically, at the upward flow, the fluid pressure drop was gradually increasing at the direction of the flow, due to the vertical elevation ($\Delta p = \rho \times g \times \Delta H$) (eq. 2) and thus, the force from the flow was decreasing as well, providing a more efficient retaining of the SPIONs, comparing with the downwards flow.

At the clockwise direction the SPIONs, after passing through the curve, which created a pressure drop of the flow, they were approaching a higher magnetic field. Due to their decreased velocity and thus, decreased force from the fluid flow, the magnetic force provided more effective results, in contrary with the counter clockwise flow.
The next step was to add magnetic tips at the poles of the electromagnet in order to provide a steep gradient and higher magnetic field intensity in specific locations of the gap.

The magnetic field provided by the new geometry enabled SPIONs to be retained at 30mm away from the cores in contrast to 9mm which was achieved previously using the homogeneous magnetic field.

5. Conclusions
The effectiveness of the magnetic field regarding the retaining of the SPIONs, was quantified optically. In order to retain SPIONs, the magnetic force on a SPION (eq. 1) should overcome the force of the fluid flow derived from Stoke's Law [31-34]:

\[ F = 6\pi\eta R v \]  
(eq. 3).

The gradient of the magnetic field plays a significant role in the case, as seen from eq. 1. However, gradient can be provided either by the magnetic field heterogeneity or by the fluid flow stream which add up.

By defining the centerline radius of bend and by knowing the internal diameter of the tube, it is possible to calculate the pressure drop at each point.

Applying this conclusion to a human kidney model, the curvy and multidirectional character of the blood vessels would provide major retaining efficiency. Hence, the locations that the mesenchymal stem cells would be retained and aggregated can be predicted and therefore the therapy could be customized, depending on the needs of each patient, by focusing the magnetic field at the area of the kidney where localized therapy is demanded [35-38].
6. References

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