A model for magnetic delivery of cells with an MRI scanner and its validation via confocal endoscopy

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Introduction One of the major challenges for cell transplantation therapies is the spatial localization and tracking of cells over time. Magnetic targeting of cells has been demonstrated previously using permanent magnets[1], while magnetic resonance (MR) imaging is conventionally used for *in-vivo* cell tracking, it is conceivable that it could also be used to interactively guide cells to areas of tissue damage "Magnetic Resonance Targeting" (MRT). High performance MR gradient coils produce homogeneous magnetic field gradients that penetrate the whole body. Work by others has shown that these field gradients are strong enough to move magnetic objects inside the scanner[1-3] and that magnetic delivery and tracking of objects can be combined. In this work we compare theoretical predictions for magnetic delivery with experimental results. We demonstrate the feasibility of targeted cell delivery by steering magnetically labelled cells using MR imaging gradients in a vascular bifurcation flow model[5]. As yet, the contribution and impact of magnetic cell aggregation on targeting is unclear. In this study we demonstrate that the cell aggregation, during targeting, is an important factor and that the predicted cell aggregation from the model could be confirmed by a real-time confocal endoscope during targeting in the MRI scanner.

Methods Experiments were performed using a custom designed vascular bifurcation model (Figure 1), connected to an infusion pump (Harvard Instruments PHP2000). The bifurcation was placed into the centre of a 9.4T MRI scanner (Varian, 60 mm bore size, gradients: rise time 5 T m^{-1} ms^{-1}, max. 1T/m), with the direction of flow parallel to B_0 (Z). Human mononuclear cells were labelled with micrometer sized superparamagnetic iron oxide particles, Bangs Particles (diameter: 1.5 µm). 0.6 ml of labelled cells ($2x10^6$ cells/ml) or ($4x10^6$ cells/ml) were infused at flow rates of 0.3 ml/min to 2.5 ml/min leading to a mean velocity of 1 cm/s to 8 cm/s whilst gradients (amplitude 500mT/m) were applied in the X direction, perpendicular to the direction of flow. Cell suspensions leaving each bifurcation outlet tube (volume 0.25ml each) were collected and cells were counted. Gradient echo images were acquired using the following parameters: TE 1.24 ms, TR 100 ms, FA 30°, FOV 50x30 mm, Matrix 192x128. A simplified mathematical model was constructed which takes magnetic force, drag force, inflow distribution and shape of cell aggregates into account. Finally a confocal endoscope (Cellvizio, Mauna Kea Technologies, France) was placed into the inflow channel of the flow phantom and confocal images with a resolution of 2 µm at a frame rate of 12 images per second were acquired inside the scanner and outside of the magnetic field of the scanner.

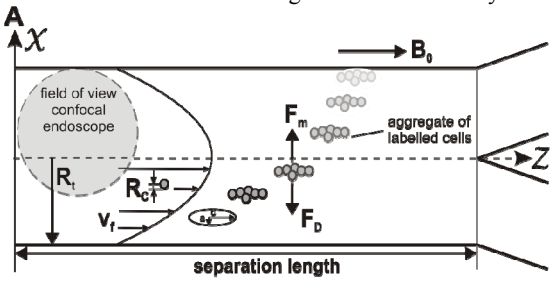
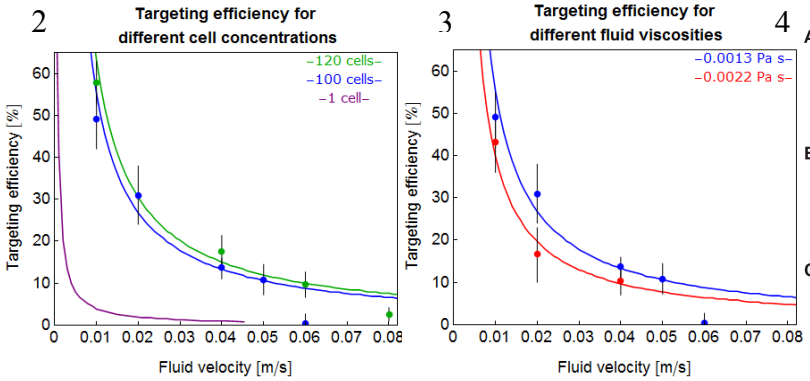


Figure 1: Sketch of the longitudinal cross-section of the vascular flow phantom indicating cell aggregation, forces and the position of the confocal endoscope probe.

Results Following application of the magnetic field gradient from the MRI system, there was an up to 55% increase in the number of cells reaching the outlet to which the gradients were directed. **Figure 2** shows experimental results for 2 million cells/ml (*blue dots*) and 4 million cells/ml (*green dots*). An increase in flow rates lead to decreased targeting efficiency. The theoretical prediction without aggregation is shown by the *purple line* while the *blue* and *green lines* show the targeting efficiency for the aggregation of 100 and 120 cells respectively. It was necessary to incorporate cell aggregation into the model in order to explain the difference between the theoretical (*purple line*) and the experimental data (*green and blue dots*). However, keeping the number of cells per aggregate constant leads to a discrepancy at higher flow rates. For **Figure 3**, 2 million cells/ml were suspended in 3% serum (*red dots*) and 50% serum (*red dots*). Continuous lines show the theoretical predictions for a viscosity of 0.0013 Pa*s (*blue*) and 0.0022 Pa*s (*red*). This data indicates that increasing the viscosity leads to a decrease in targeting efficiency. **Figure 4** shows confocal endoscopy (4D) outside and inside the MRI scanner for 1cm/s (4A), 2cm/s (4B) and 3cm/s (4C). We observed marked cell aggregation during MRT (4B). From Fig 4 it can be appreciated that the predicted aggregation could be validated experimentally. **Figure 5** shows a gradient echo image indicating reduced signal intensity in the exit branch to which the cells where directed (*red arrow*).



Conclusions Our results show that an MRI scanner can be used to steer cells into the desired direction in a vascular bifurcation model. Additionally we show that cell aggregation is an important factor to explain our experimental results which was confirmed via confocal endoscopy. We also show the possibility of using MR imaging to confirm targeting success. These preliminary findings provide evidence to support the potential of MRT of cells for future clinical applications, allowing image guided targeted delivery of cells and other therapeutic agents to sites of the body which cannot be reached with external permanent magnets. Furthermore, an understanding of cell aggregation during MRT may have significant implications for the experimental design of future magnetic targeting studies.

References: **[1]** P. Kyrtatos et al. JACC Cardiov Interv 8 (2009), pp. 794-802, **[2]** N. J. Darton et al., Nanotechnology **19**, 395102 (2008), **[3]** S. Martel et al., Applied Physics Letters **90**, 114105 (2007), **[4]** J. B. Mathieu, S. Martel, Biomedical Microdevices **9**, 801 (2007), **[5]** J. Riegler et al., Biomaterials **31**, 5366-71 (2010)