

IN-VITRO BLOCKAGE OF A SIMULATED VASCULAR SYSTEM USING MAGNETORHEOLOGICAL FLUIDS AS A CANCER THERAPY

G. A. Flores & J. Liu

California State University, Department of Physics and Astronomy, Long Beach, CA 90840 USA

INTRODUCTION: Tumors need a constant blood supply to keep them alive. Therapies to eradicate the tumor include chemotherapy, radiation and surgical removal and often result in toxic doses to the patient and side effects. New developments are underway to aim at more effectively eliminating cancer cells with minimal side effects, such as anti-angiogenesis drugs to prevent the growth of new blood vessels, and brachytherapy to localize radioactive “pellets” to kill the tumor [1].

Here we report a cancer therapy whose effect is similar to anti-angiogenesis drugs with lower cost and easy to produce, and to brachytherapy with localized treatment. We use magnetorheological (MR) fluids injected into the blood vessels leading to a tumor and apply an external magnetic field over the tumor area to localize the magnetizable (iron oxide) particles in MR fluids. These micrometer-sized particles will form a solid seal near the magnetic poles and thus block the blood flow to the tumor, leading to tumor necrosis.

In-vitro experiments, as a continuation of our earlier work [2-4], were done using silicone tubes to simulate human blood vessels. We have reported in the last two conferences the relationship between seal formation time and seal strength as a function of significant controlling parameters, such as magnetizable particle volume fraction, size and types, as well as magnetic field strength and fluid flow rate. We also compared different carrier fluids such as water, human plasma and blood [2-4].

Last year, we performed simulation experiments for four branches of “blood vessels” connected to a 3- and 5-mm diameter cavity cell to simulate a tumor [4]. We used both water and sheep blood as our carrier liquid. Seals were formed immediately after the magnetic field was turned on for water-based MR fluids. However, the seal was unstable for our sheep blood-based MR fluid in a 5-mm cavity cell where the magnetic field was 0.43 – 0.48 T. For this paper, we report experimental simulations for up to six branches of “blood vessels” encased in a cavity cell simulating a tumor. The magnetic field has been increased to between 0.6 – 1.1 T. Water is still used as a carrier fluid, but future tests will include whole human blood. The tube diameter and the fluid flow rate have been decreased to be more realistic in simulating a human circulatory system.

METHODS: A suspension of pure magnetite particles (MAG) from Chemicell GmbH, Germany is used with water as the carrier liquid. The magnetite particles are coated with a hydrophilic starch derivative to make them biocompatible and to reduce electrostatic repulsive interactions with red blood cells (RBC). Two different diameters ($2a$) of MAG particles are used: 0.25- μm particles are designed for intra-venous applications, while 1.0- μm particles are intended for increasing the efficiency of mechanical blockage of the fluid flow and are suited for an intra-arterial application. Based on our earlier study, a particle volume fraction (F) of 1.0% is chosen in order to seal the tubes within a reasonable time frame (~ 30 min.) and with the minimum number of particles [3].

The simulated vascular system consists of a network of silicone tubes with various inner diameters (D) ranging from 1.6 mm in the “arteries” and “veins”, to 0.8-mm and 0.4-mm branches. Finally, they divide down to 0.2 mm, simulating human arterioles. As seen in Fig. 1, a 1.6-mm tube is placed inside the MR source beaker to draw the sample toward a peristaltic pump from Manostat (“SARAH” model, Barnant Company, USA) that will send the fluid through the system. The fluid flow rate ($Q \sim 0.007$ ml/min per tube) is similar to that within a human arteriole, but with a lower fluid flow velocity (~ 3.7 mm/s for $D = 0.2$ mm, compared to ~ 7.5 mm/s for $D = 0.050$ mm arteriole).

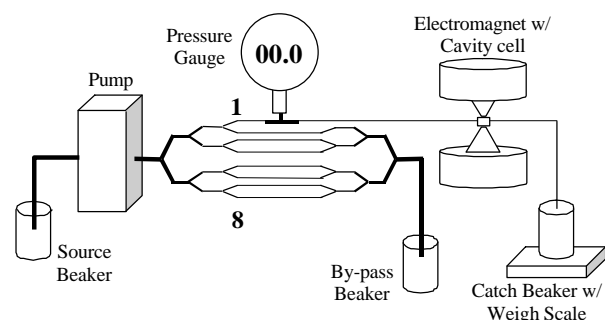


Fig. 1: Experimental setup for 2-branch cavity connection. In 4- and 6- branch cavity connection, tubes N^o. 2 and 3 also connect to the cavity cell and pass through the magnetic poles.

The top tube ($D = 0.2$ mm), labeled N^o. 1, leads to a DSF26 digital pressure gauge, manufactured by Kolbold USA, Inc. to measure the resistive pressure (P) exerted on the tube wall. The gauge is connected

to a PC computer through a Data Acquisition (DAQ) board from National Instruments Inc. The incoming data is sent as a voltage from 0 to 10 V as set by the factory, which corresponds to a pressure range from 0 to 200 mm Hg. Due to the use of multiple tubes, the pressure in any tube is not very sensitive to the seal formation. The remaining tubes N^o. 2-8 ($D = 0.2$ mm each) are sent to the By-pass beaker to “complete” our circulatory system.

From the pressure gauge and tube N^o. 1 are our cavity cells of diameters (S) 3.0 mm or 5.0 mm, which are used to “simulate” a Stage II and III breast cancer or melanoma [4]. Once the tube is inside the cavity cell, it is not connected the same way as before [4]. Instead, in order to simulate the complex capillary patterns within a tumor, the 0.2-mm tube is looped or coiled a few turns, as seen in Figs. 2 and 3. Thus, the fluid travels inside the confines of the tube and do not accumulate inside the cavity as before. For multiple tubes, i.e. using two or three tubes, these tubes are connected the same way. The number of loops within the cavity cells, and the number of tubes connected to the cells vary. The following table shows how long these tubes are within the cavity cells.

Table 1: Tube lengths for each 0.2-mm tube within the cavity cells used for the experiment.

3-mm cavity		End-cap thickness = 6 mm	
N ^o . of tubes	N ^o . of loops/tube	Tube length inside cell (mm)	Total tube length (mm)
1	2	18.8	30.8
2	1	9.4	21.4
5-mm cavity		End-cap thickness = 5 mm	
N ^o . of tubes	N ^o . of loops/tube	Tube length inside cell (mm)	Total tube length (mm)
1	4	62.8	72.8
2	2	31.4	41.4
3	1	15.7	25.7

To create the seals, a pair of electromagnets with 1150 turns each, and two poles made of 1018 steel of maximum diameter 25.4 mm and a pole diameter of 16 mm generates and focuses an external magnetic flux density (B) to the cavity cell. This B -field, which is driven by a current of 5.0 A (DC), gives us 0.6 T for the 5-mm cell, and 1.1 T for the 3-mm cell, measured at the center.

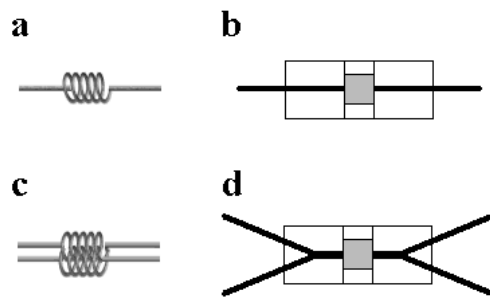


Fig. 2: Looping of 0.2-mm tubes for a 3-mm cavity cell. Figs. 2a, c show the new configuration, while Figs b, d show the old configuration. The old tubes ($D = 0.4$ mm) filled the cavity (shown in gray) to form the seal. Overall length of the cavity cell is 15 mm.

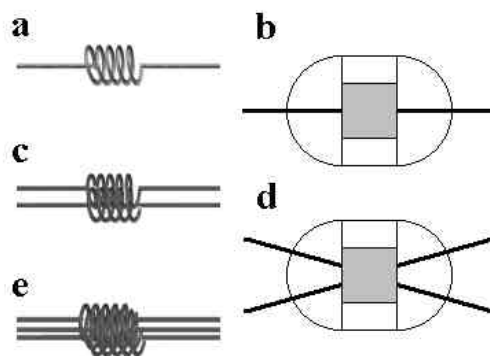


Fig. 3: Looping of 0.2-mm tubes for a 5-mm cavity cell. Figs. 3a, c, e show the new configuration, while Figs b, d show the old configuration. Previously, only 2- and 4-branches were done. Overall length of the cavity cell is 15 mm.

The fluid leakage downstream from the magnetic poles is used to monitor the seal formation. To measure the fluid weight (W), we used a Mettler-Toledo PB-153 balance connected to the computer via a RS-232 port. This data from the balance, as well as the data from the pressure gauge was analyzed using the software LabVIEW.

RESULTS: Figure 4 shows the result of W vs. time for water-based MAG fluids. The magnetic B -field is switched on at $t = 15$ minutes. It is clear that W has saturated once the field is on. Thus a seal has formed within the tubes inside the cavity cell for all cases for our water-based MAG sample. Visually, we observed the seal formation since the particles are brown-gray and the tube is transparent. This extended seal (covering the 16-mm pole diameter plus 3-5 mm in some cases after the pole) is concentrated near the poles with a clear water area of about 15–20 mm in length on both ends of the seal that separate the seal from the rest of the MAG fluid. This is due to the B -field near the poles that attracts nearby particles to the poles.

a (3-mm cell, 0.25 mm particles)

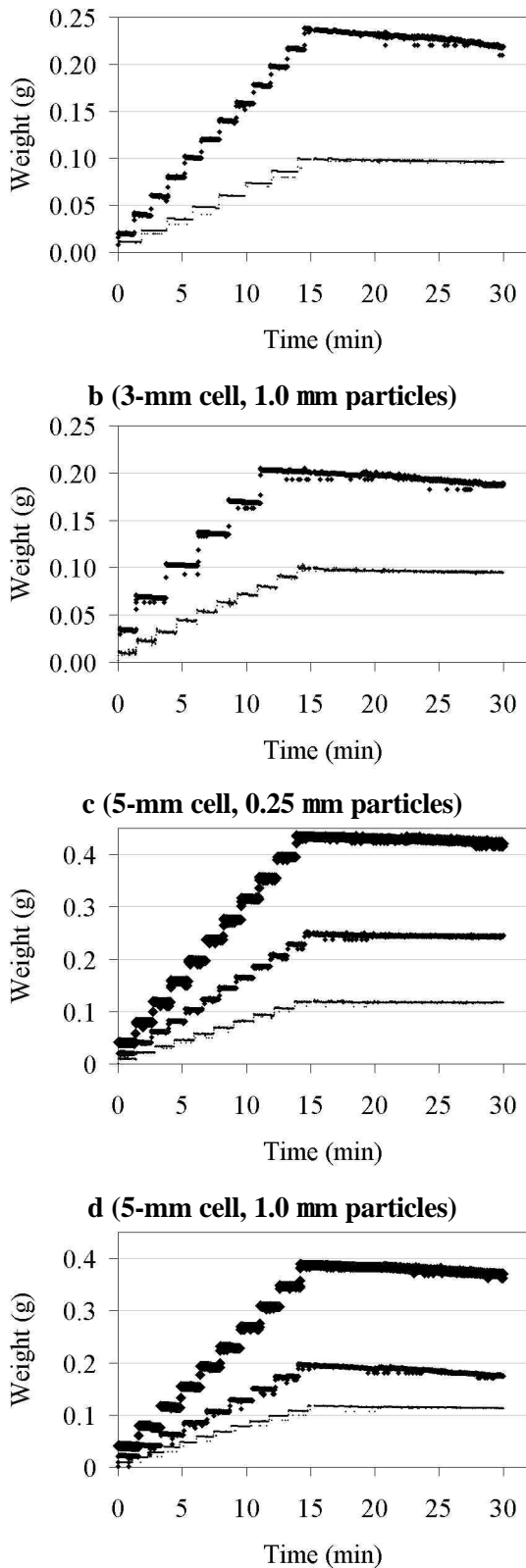


Fig. 4: Graph showing fluid weight vs. time within the cavity cell. Magnetic B -field for the 3-mm cell is 1.1 T at the center of the cell, while the B -field for the 5-mm cell is 0.6 T. Lighter points show 2-branch construction, medium points show 4-branch construction, while heavier points show 6-branch construction.

The seal formation increases P so that no more particles are pushed toward the poles.

In most cases, P , which was initially 3-5 mmHg in the beginning, rose to nearly 8-12 mmHg once the field was active. Thus the clear region shows the range of the magnetic force.

DISCUSSION & CONCLUSIONS: In a multiple-branch vascular simulation, a fluid flow blockage was simulated. We used 0.2-mm tubes looped inside 3-mm and 5-mm cavity cells to simulate a Stage II and III tumor. To facilitate this blockage, two different-sized magnetite particles were tested: 1.0 μm for intra-arterial treatments, and 0.25 μm for intravenous treatments. Using water as our carrier liquid and an external magnetic field of between 0.6 and 1.1 T, the MR fluid forms a stable seal for both cell sizes and for both particle sizes almost immediately after the field is turned on. This seal formation prevents the carrier liquid from passing through our cavity cell. Previously, we used 2- and 4-branch connections to the cavity cells which led to the fluid being deposited directly into the cells. This did not result in a tight seal for the larger 5-mm cells. When sheep blood was used, the seal would often collapse [4]. It is much easier to block a river than a lake. Because of this, we decided to use a new approach of looping the tubes inside the cell. One concern is to balance the magnetic field availability against the tumor size. Further work is needed to understand the details of the seal strength when using blood as a carrier liquid as compared to using water.

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