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Deep Tissue Tumors and Magnet-Directed Chemotherapy: Modeling Blood Flow through Tumors

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Abstract:

The method of magnet directed drug delivery of chemotherapy drugs on magnetic nanoparticles is a new form of cancer treatment designed to increase the efficacy of chemotherapy and decrease side effects. Prior research has shown that by using one magnet, an inoperable tumor just below the skin can be treated. The next step is to combine multiple electromagnets to dynamically focus the ferrofluid to a target location. In future experiments, three different types of phantoms will be developed to test the proposed drug delivery system so that it can ultimately be used to treat human subjects. In this report, various methods of monitoring blood flow and collecting images are explored in order to assist in future design and anticipate any possible problems between the transfer from treatment of the phantoms to the human subjects.

Introduction:

Chemotherapy is a widely used treatment for cancerous tumors because it targets cells responsible for growth in the body. Because some healthy cells also undergo growth, there are unwanted side effects from chemotherapy. These side effects limit the amount of chemotherapy that can be administered and therefore are not set by the concentrations needed to eliminate the cancerous cells. The body-wide suppression method of chemotherapy is ineffective for locally advanced and pretreated tumors

because the dosage needed to remove the tumor would severely endanger the life of the subject. Thus, a new viable treatment must be created to combat this problem.

A hypothesized method of effective treatment of tumors is using a magnetic drug delivery system to direct chemotherapy drugs to the specific site of the tumor. In directed chemotherapy, the location of the tumor must be found in the body by ultrasound, gamma imaging, or computer tomography prior to treatment. This method of treatment would be most viable for inoperable tumors, when radiation therapy has or will be ineffective, as well as locally advanced tumors because dosage is concentrated on the areas of cancerous cells found by the initial body scan. Magnetic nanoparticles (ferrofluid) coated with chemotherapy drugs are injected into the subject's vein, allowed to circulate through the blood stream, and then directed to the tumor using magnets of medium strength (0.5-0.8 Tesla). This method will increase the efficacy of the chemotherapy drugs as well as limit the side effects of normal body-wide chemotherapy.

Using a single safe magnet, this treatment is highly effective on tumors less than 5 *cm* under the surface of the skin. Prior research has shown this technique successful in patients with inoperable tumors such as in Figure 1. The injected ferrofluids were directed to the tumor and effectively treated the tumor. Prior to studies conducted on human subjects, it was demonstrated that nanoparticles could be directed to tumors in small animals. In figure 2, the black spots on the rats indicate the concentration of ferrofluid at the target site. Because the magnetic field is stationary, the particles would only be able to concentrate at the skin's surface, as shown in these two examples.
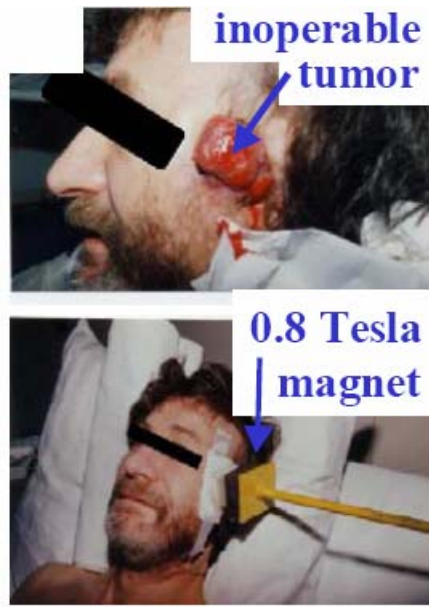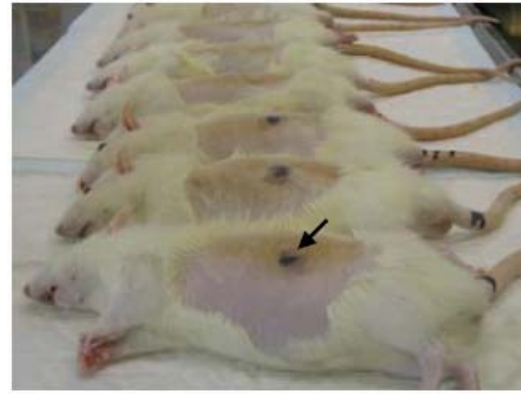
Figure 1

Figure 2

The next goal is to direct the drug-coated ferrofluid to deep tissue tumors using multiple magnets. The electromagnets will dynamically control the magnetic ferrofluid by changing the strength of the magnets at different times throughout the treatment to effectively focus normal or lower dosage of chemotherapy to the site of the deep tissue tumor. In these trials, nanoparticles made by Chemicell of 250 *nm* in diameter will be used because their size allows the nanoparticles to flow freely through both small capillaries as well as blood vessels in and around tumors. Despite the fact that micro-scaled particles are easier to control, nanoparticles are still capable of being manipulated by the dynamic magnetic fields. Because it has been previously shown that magnetic direction of chemotherapy coated ferrofluid is effective in surface tumors, it is now imperative to show that this method can also be effective in the treatment of deep tissue tumors of a depth of 30 *cm* or greater.

Deep Focusing Inside Phantoms:

The first goal of the proposed research is to prove that dynamically controlled electromagnets can concentrate ferrofluids to a specific tumor location of 30 *cm* or greater. Custom designed magnets of approximately 1.5 Tesla will be used to focus ferrofluid inside of a 50 *cm* by side cube filled with glycerol to mimic blood. Surrounding the cube will be two or three cameras oriented orthogonally and outfitted with frame grabbers to observe the real time flow of ferrofluid to the specific targeted location. This proposed phantom is shown in Figure 3. Imaging algorithms camera will be performed to determine the position of the ferrofluid in the cube. This technique is imperative to show that ferrofluid in blood-mimicking fluid is able to be manipulated at distances greater than 30 *cm* by the dynamic magnetic fields.
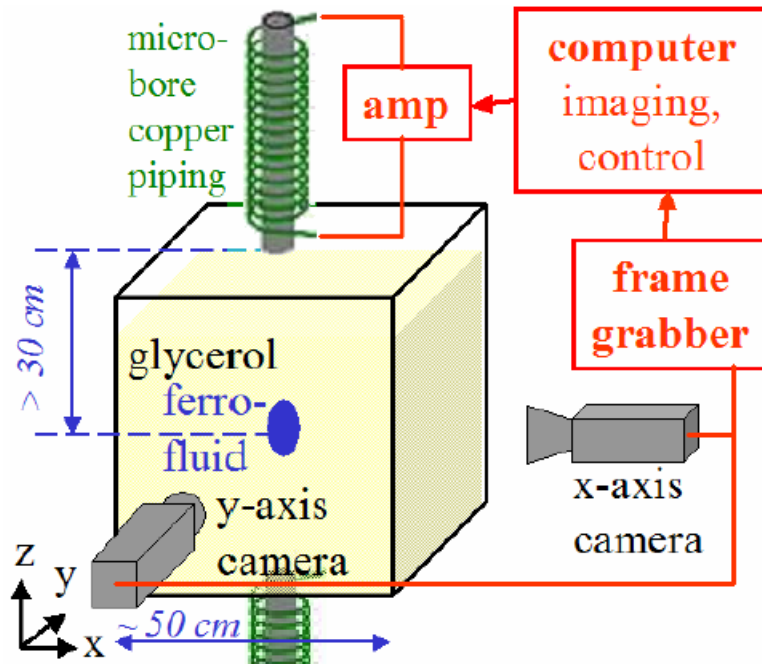

Figure 3

After verifying that the electromagnets can dynamically control the location of ferrofluid in blood-mimicking fluid, a phantom would be developed to approximate blood

flow in the body. Because the goal is to inject magnetic nanoparticles into a vein, it must be shown that the ferrofluid can be controlled while in an approximated vascular system with blood-mimicking fluid. This is a very important process to demonstrate because the 250 *nm* diameter nanoparticles being used can be stopped by slow blood flow of less than 0.12 *mm/s*. Blood velocity in vessels is approximately parabolic with the maximum velocity at the center of the blood vessels and less at the walls, due to shear forces. This procedure proposes that the best place to control the nanoparticles is in a thin layer at the surface of small blood vessels slowly through dynamic maneuvering of electromagnets to the target tumor site.
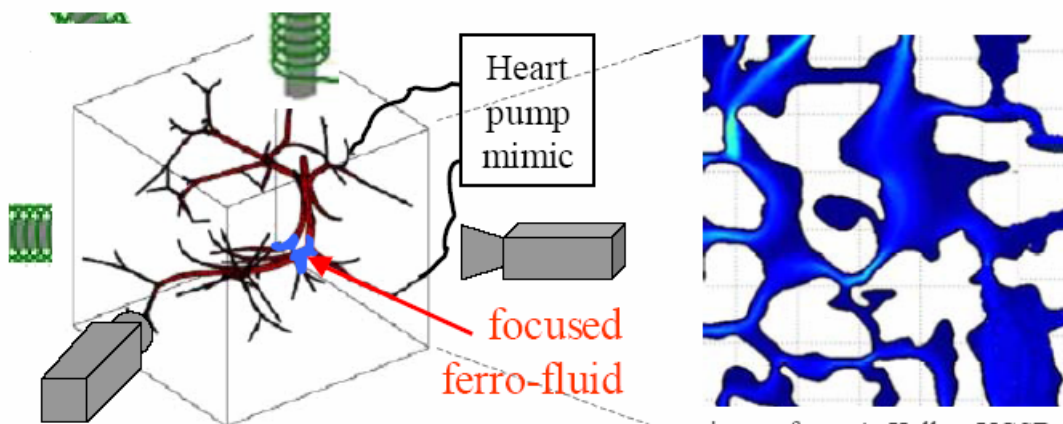

Figure 4

     A phantom must be designed to mimic the flow of blood in order to demonstrate the ability to actively control the flow of ferrofluid to the target tumor site, as shown in figure 4. The phantom will be designed using stereolithographic techniques from CAD drawings to approximate vasculature using the stereolithographic machines at the University of Maryland. Multiple electromagnets will surround the phantom as well as two to three orthogonally oriented cameras with fast frame grabbers to monitor the position of the ferrofluid in the phantom vasculature system. Blood-mimic fluid comprised of 85% water, 10% glycerol, and 5% additives will be circulating through the

phantom vasculature system aided by a heart pump mimic to best approximate actual blood flow. The cameras will use real-time filtering, smoothing, and registration algorithms to monitor the location and motion of the ferrofluid through the phantom. The phantom will be an approximation of human vasculature with accuracy of ~1 *mm*.

The third and final type of phantoms will be produced from real-body plastination. This is where a cadaver is used to make a model of an actual vasculature system, including micro-capillaries, in which there is air where blood vessels were and clear plastic everywhere else. The first attempts will focus mainly on the head and neck area and then will expand from there to include whatever cadavers are available for plastination. This will be the most accurate test of the magnetic directing technique developed because it will be actual vasculature geometry. After testing all of the phantoms, the goal is to use the magnetic directed chemotherapy to treat deep tissue tumors in human subjects.

Blood Flow Approximation Methods:

The phantoms to be designed rely heavily on blood flow in the human vasculature, so it is imperative to understand blood flow and the mathematical laws that control the vasculature. Notably, it is also important to understand the flow of blood in capillaries and in tumor blood vessels for real-body assessment. The focus of this summer's research has been to find different ways of mathematically modeling blood flow in human vasculature through 2-D and 3-D modeling to assist in phantom design as well as methods to monitor blood flow through a human vasculature system for the

realistic application of the electromagnet directing of chemotherapy drugs to deep tissue tumors.

Because the phantom will utilize a heart-mimicking pump, it is important to understand blood flow in the heart. The first method is the use of 2-D modeling using ultrasound and the estimation of the Doppler Shift to visualize a 3-D model of blood flow. This method of modeling blood flow in the heart is useful to detect cardiac disease and congenital cardiac disease in children. The visualization of blood flow patterns is examined using the color flow imaging ultrasound mode. Two dimensional images of cross sections of the heart are pieced together by the experimenter to create a visualized three dimensional model of the blood flow in the heart. The raw data is made up of cardiac tissue and blood flow, which must be separated prior to analysis. The separated data is sequenced and labeled with gray value, which allows the observer to easily distinguish the gray values different from the grounding, or base measurements. These values represent velocity differences inside the heart in two directions varying from the initial data acquisition and rotation of the probe. The images collected will be colored according to a scale set by the experimenter and then 3-D reconstruction can occur. The data is organized by a set of Cartesian coordinates with linear interpolation employed where there is a missing data point. After the data has been reconstructed, the experimenter can manipulate the 3-D reconstruction and select specific parts of the heart and visualize the blood flow at that specific point, which will then show arrows representing the speed of the blood flow by size and pointing the direction of blood flow. This method is important because it not only describes the movement of blood flow in the heart but it also lays the ground work for other methods using ultrasound imaging of

blood flow in the vasculature. This method, however, is subjective and is not accurate enough to ensure complete awareness of blood flow when applied to other parts of the vasculature when velocity is not as high.[2]

Another method that utilizes ultrasound imaging is the real-time technique of 2-D blood flow imaging (BFI). Instead of only using the color flow imaging as described in the previous procedure, BFI also utilizes the power Doppler ultrasound mode and combines these techniques to create a more cohesive estimation of blood flow in axial and lateral directions. After the ultrasonic beam has been scanned over the area of interest, base conditions are set for blood flow and velocity detection. The images of the speckle patterns are collected at a high frame rate at pulse repetition frequency, but the movement of the ultrasonic beam must always be greater than blood flow velocity using this technique. The BFI technique has been demonstrated as successful in vascular imaging.[3]

Ultrasonic high frequency BFI can also be used in small mammals to measure blood flow in systems with tumors. One system developed was able to successfully perform *in vivo* imaging of injected tumor cells in mice. A much higher frequency than is normally used in humans was necessary because smaller systems require higher frequencies to get optimal spacial resolution and swept-scan was utilized in the data collection. A gelatin-based phantom with graphite powder with a 500 *nm* channel to mimic a blood vessel containing blood-mimicking fluid controlled by a low speed pump was employed as the speckle-generating tissue, similar to the phantoms described in previous sections. Flow estimation algorithms were used to model the data and it was shown that the butterfly search technique was the best technique to model the blood flow.

For the phantom, repeated firings of a transducer were echoed and resampled along set trajectories of constant velocities based on theoretical values. The feedback and repetition of the firings gave the best approximation of blood flow among many different bandwiths, which is why the method was preferred. For the *in vivo* experiments involving the mice, tumor cells called WF-3 that modeled ovarian cancer were injected into the mice subcutaneously and allowed to grow for four to six weeks. The high frequency ultrasonic method was able to successfully model the growth of the tumor and show vasculature when the tumor was more than 2 *mm* in diameter. As the tumor grew larger, an increased blood flow velocity was seen around the outside of the tumor and slower in the interior of the tumor, which could be attributed to necrosis. This method was successful in showing the blood flow behavior within tumors as well as blood flow as the tumor increased in size. This method is relevant to the real world application of the magnetic directing of the ferrofluid to deep tissue tumors because the tumors best treated by the concentration of chemotherapy drugs may have sections of necrosis similar to the mice tumors where lack of blood flow to the center of the tumor could impede treatment.[4]

A different method of estimating blood flow *in vivo* utilizes dynamic functional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) for relatively noninvasive and high resolution imaging of regional blood flow. An intravenous bolus injection of a tracer is tracked as it travels through the human vasculature system through sequential image collecting. The changes in concentration over time are monitored within the tissues of interest by sequencing the images collected through dynamic functional imaging. When a bolus enters an area of interest, such as

tissue containing multiple capillaries, each pathway in the capillaries would require a different amount of time to exit the tissue and thus a mean transit time (MTT) must be found through a probability density function to average the different exit rates. When the vascular volume is divided by the MTT, the constant blood flow can be determined. By monitoring the concentration of the tracer bolus over time, the constant blood flow can be determined in the specific region of interest. After Monte Carlo simulation experiments had been executed, it was determined that lower rates of blood flow were detected more accurately than higher rates of blood flow and as the signal to noise ratio increased, the standard deviation of the measurements decreased. This method is of interest because the bolus is similar to the use the magnetic directing of ferrofluids. Both the bolus and the ferrofluids must be constantly monitored inside the vasculature using dynamic imaging systems for real-time results. The Monte Carlo simulations and deconvolution processes may be helpful for understanding the motion of ferrofluids through the vasculature.[5]

The final method examined was a model of fluid flow in solid tumors examining the multiple fluid pathways in and surrounding a tumor. Solid tumors are made of a porous interstitium and neoplastic vasculature with very permeable capillary walls. In normal chemotherapy, the effect of the drugs is lessened both because of the inefficient amount of dosage due to safety concerns as well as the low transport of drugs into the main body of tumors. The structure of a mammary tumor consists of arterial vessels in the tumor of average length 67 *um*, average diameter of 10 *um*, and average spacing of 49 *um* and the diameters of the venous vasculature was a range of 650 to 20 *um*, so it was hypothesize that to Darcy's law could model the interstitium as a porous material. Axial flow rate through the surrounding capillaries was modeled by Poiseulle's law, assuming

smooth changing radii of the capillaries. The flow of the fluid leaving the tumor can be modeled by Starling's law with a changing rate of vascular wall permeability as well as differences in pressure. The flow of fluid through the system is shown as the difference between the flow rate of inlet fluid and outlet fluid is the rate of fluid leaking from the permeable vascular walls. The fraction of fluid that will leak out of the tumor is approximately 10%. The models formulated are flexible because the model allows for arbitrary vasculature configuration and variations in the size of capillaries and the permeability of the vasculature. The single tube theoretical model produced relatively the same results as in an actual tumor. The method also showed the collapse of vascular structure in the tumor is secondary to actual fluid flow in the tumor. This method is useful in the study of fluid flow in tumors and to help determine how effectively chemotherapy drugs transport into the main body of the tumor even if they are concentrated. It seems beneficial to concentrate on this particular method for further research in order to prepare for the human trial.[6]

Conclusion:

There are many different aspects of developing a successful new treatment for any type of cancer. In this case, it is imperative to have safe dynamic electromagnets that can effectively focus the magnetic drug-coated ferrofluid to a specific point, be able to maneuver slowly and purposefully along the walls of the vasculature to focus at the location of interest, as well as be able to replicate this process in human vasculature and successfully deliver the chemotherapy to the tumor cells. Blood flow throughout the human body, however, must be thoroughly examined to monitor the flow of the ferrofluid

through the vasculature and dynamically maneuver the magnetic fields to concentrate movement to the target area. The methods of studying the real-time monitoring of blood flow through ultrasonic imaging have their limits, so the method of using dynamic imaging such as CT, MRI and gamma imaging is beneficial to this project for monitoring the flow of the ferrofluids. It is important to note the differences between blood flow through vasculature and fluid flow in solid tumors as well, because many of the tumors this method hopes to treat involve highly progressed and therefore most likely solid tumors. Combining this knowledge allows the researcher to gain a perspective on possible ways to approach problems within the proposed technology as it arises in the future as well as plan for the transition from phantoms and cadaver plastination to human subjects. In the future, if the magnetic drug delivery system is effective, this treatment could be used on localized bacterial infections as well as a multitude of other applications.

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