Research Grants for PhD from the China Scholarship Council

Details of the PhD proposal

- **Title**:

  Modeling and control of brain tumor treatment using therapeutic magnetic microrobots

- **Keywords**: microrobotics, mathematical modeling, magnetic theory, control of nonlinear systems, tumor growth, cancer treatment.
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1 PhD proposal description

1.1 Context

Glioblastoma multiform (GBM) is the most frequent and aggressive cancer of the nervous system. GMBs are characterized by extensive infiltration into the brain and are highly resistant to treatment, being associated with poor prognosis and high rates of morbidity. Classical anti-cancer therapies commonly show poor efficacy due to their low specificity and toxic effect on healthy tissues. Despite the progressive research and the efforts made to improve tumor treatment, the overall median of survival time for GBM patients remains only approximately about 12 to 15 months [1]. Therefore, many efforts have been focused on getting a comprehensive and thorough understanding of the tumor cell diffusion in the brain. Especially, this can be achieved by computational simulation of both tumor growth and the anti-tumor treatment.

In parallel, the use of magnetic microrobot has emerged as a promising tool for biomedical applications [2–4]. They are minimally invasive and allow reducing trauma, scarring, infection risks, postoperative pain, recovery time… They can be wirelessly driven and controlled by manipulating an external magnetic field, which enable a number of medical applications, including drug delivery, *in vivo* sensing and stimulation [2, 3]. To accomplish such biomedical tasks, the premise is to develop suitable navigation strategies for microrobots in complex biological media. To enable such high-impact biomedical applications, the behavior of the microrobot and its interaction with its environment should be carefully studied. Therefore, magnetic microrobot is a promising solution to achieve a better tumor control with minimal complications on healthy tissues. The basic idea is to control the direction of the therapeutic microrobot which is composed of magnetic particles and anti-cancer agents, inside the vessel networks to the tumor area. To this aim, external magnetic fields are applied to propel and steer the magnetic robots to the targeted area. Figure 1 illustrate this concept.

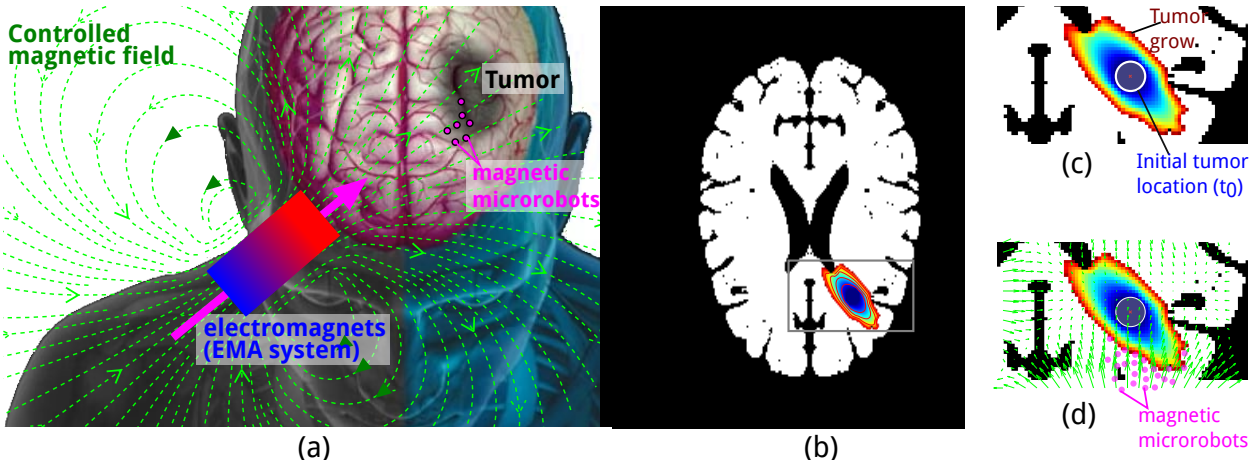

Figure 1: (a) Controlled magnetic microrobot to deliver drugs in brain tumors: (b) tumor is located with medical imaging (e.g. from MRI); (c) without treatment, the tumor is growing that can be predicted thanks to mathematical models; and (d) the control of magnetic field allows targeting the brain tumor.

1.2 State of the art

1.2.1 Mathematical modeling of tumor growth

There are many review articles which provide comprehensive details on the sequential development of mathematical models that deal with different stages of cancer growth [5–9]. For instance, Araujo and Mc Ewain [5] presented a comprehensive discussion of the history of studies on the development of solid tumors, which illustrates the role of mathematical modeling techniques since the early twentieth century. In this PhD, we would mainly consider macroscopic strategy that use complex mathematical models guided by medical images (e.g. from MRI as in Fig. 1(b)) to study the tumor growth. In this context, the majority of the published works use the reaction diffusion (RD) formalism to describe the growth [10], as in Fig. 1(c). The RD model is widely used due to its simplicity and consistency with the biological tumor growth process.
On the other hand, one of the most important motivations of studying tumor growth is the therapy planning and control. Tumor growth models can incorporate the treatment effects into the model either to evaluate its efficacy or to tailor the therapy, e.g. calculate the effective doses and fractions of specific therapy. Commonly, treatment of GBM considers either surgery, radiotherapy, or chemotherapy. In practice, combinations of these methods are usually concurrently or adjuvantly used [1]. The treatment effect can be included as a loss term in the RD model to represent the number of the dead cells due to the treatment. Linear quadratic (LQ) model is the most widely used methodology to determine the effect of radiotherapy doses by estimating the probability of cells surviving due to dose of radiation [11]. The loss term due to chemotherapy can be embedded into the RD model as a proportion of the tumor growth rate [1]. But to date, only limited models include the magnetic microrobots as therapeutic agent [12].

1.2.2 Magnetic microrobot control

Magnetically actuated microrobots have been proposed for numerous applications, as their small scales enable the access to complex environments [2, 13–15] Basically, an external electromagnetic actuation (EMA) system wirelessly transfer power to set microrobots in motion. Motion con-

trol technology enables the development of magnetic microrobots with various controllable motion modalities, high motion accuracy (e.g. closed-loop control), and high task efficiency (e.g. motion planning) [15, 16]. These advances promote real microrobotics applications in environments that may be complex and dynamic. In addition, the ability to exert independent control over a group of microrobots working together on a task has potential to increase task speed and capability [15]. Controlling swarms on the order of hundreds to thousands micro/nano-robots is one of the great challenges in magnetic microrobotics [4]. Contrarily to individual or multi-agent control, the interactive force should not be ignored. This aspect increases the difficulty of the theoretical modeling of swarm behaviors of several magnetic microrobots. Simulation becomes then a powerful tool for their control. To date, global input are the only feasible method to control a swarm of microrobots [17, 18].

1.3 Objective

This research work aims to extend conventional therapy for GBM treatment by using therapeutic magnetic microrobots, also termed therapeutic magnetic microcarrier (TMMC). Our goal here is to develop mathematical model of the growth of GBM that includes the use of magnetic microrobot. Computational modeling offers interesting methodology that can give insights into a better understanding and control of these biomedical problems. The developed model should take into account constraints from the TMMC delivery rates and the evolution of the tumor, e.g. by solving an optimization problem at regular time intervals. Moreover, the control of these microrobots on the targeted area by manipulating the external magnetic field has also to be investigated (see also Fig. 1). Specifically, this magnetic field is induced from an electromagnetic actuation (EMA) system by controlling the electric current flowing in a set of electromagnetic coils to drive the magnetic microrobots. It is then necessary to determine the proper magnetic field, and the corresponding current, allowing the optimal targeting and treatment of the GBM with the TMMC. The integration of these aspects from the modeling step would significantly improve the effectiveness of the overall cancer therapy.
The different steps of this research work are the following :

- State of art study on modeling of tumor growth [8, 9] and of magnetic microrobots [15];
- Modeling and simulation of GBM treatment by using TMMC;
- Optimization of the targeted therapy using magnetic microrobots;
- Control of the magnetic field to drive the magnetic microrobots on the GBM site;
- Experimental validation of the methodology with the EMA platform (OctoRob) of our Laboratory.

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