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On the preliminary design of hyperthermia treatments based on infusion and heating of magnetic nanofluids

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ABSTRACT

We study a magnetic-nanoparticle-mediated hyperthermia treatment by considering both the nanofluid infusion and the subsequent thermal activation of the infused nanoparticles. Our study aims at providing a quantitative framework, which is currently missing, for the design of hyperthermia treatments. In more detail, we consider a heterogeneous spherical tumor, and we obtain a simplified analytical expression for the nanoparticles concentration profile during the infusion. We then exploit such an expression in order to compute the steady-state temperature profile achieved through the heating step. Despite the simplifications introduced to enable the analytical derivations, we account for many physically relevant aspects including tissue heterogeneity, poroelasticity, blood perfusion, and nanoparticles absorption onto tissue. Moreover, our approach permits to elucidate the effects on the final temperature profile of the following control parameters: infusion duration and flow rate, nanoparticles concentration in the nanofluid, magnetic field intensity and frequency. We present illustrative numerical results, based on parameters values taken from experimental studies, which are consistent with previous numerical investigations and current hyperthermia approaches. In particular, we obtain optimal working curves which could be effectively used for planning real procedures. While not laying any claims of generality, this work takes a preliminary yet quantitative step toward the design of hyperthermia treatments.

1. Introduction

Nanofluids consist of a base-fluid containing suspended nanoparticles (NPs) [1]. Common base-fluids include water, ethylene glycol, toluene and oil, whereas the NPs are typically made of metals, oxides, carbides, or carbon nanotubes. The presence of NPs affects the structure of the base-fluid and enhances its thermo-physical properties, such as thermal conductivity and diffusivity, viscosity and convective heat transfer coefficient [2]. For instance, already with low NP concentrations (1–5% in volume), the thermal conductivity of the suspension can increase up to 20% [3]. Indeed, heat transfer is enhanced by increasing the NPs volume fraction and surface-to-volume ratio, and nanotechnology currently offers powerful tools for modulating the nanofluids thermal properties [4]. As a matter of fact, nanofluids are commercially available as diluted suspensions of NPs, with a volume fraction typically below 5% [5], and they are already used for industrial applications as cooling fluids. Their exploitation in the medical field is being also investigated, specifically for innovative approaches based on NPs transport such as drug delivery, cancer treatment and imaging [4]. Magnetic nanofluids, in particular, are suspensions of magnetoresponsive NPs that are being increasingly considered also for tumor therapy, namely for NPs-mediated hyperthermia treatments [4,6,7].

Hyperthermia is a heating process that can be applied either locally or on a wider tissue region; it consists in exposing cancerous cells to temperatures up to nearly 45°C. This thermal treatment can be particularly advantageous in case of chemotherapy-resistant tumors, and it enhances the clinical outcome when combined with chemotherapy or radiotherapy [4,8,9]. Local hyperthermia approaches based on nanofluids can be performed by infusing the magnetic NPs in the targeted tumor region, so as to focus heating while minimizing side effects on the healthy tissue. In more detail, the NPs surface is often functionalized so as to enhance binding to specific target sites or to minimize NPs clustering [10], and the temperature increase is produced by the relaxation losses induced by an external alternating magnetic field [11]. Equivalent approaches based on laser-induced NPs heating were also proposed [12], and for both approaches responsive NPs with enhanced chemo-physical properties are being developed [13,14]. However, even when exploiting well characterized NPs, the therapeutic outcome strongly depends on the specific procedure, and no fixed protocols have been defined so far in order to optimize NPs-mediated hyperthermia treatments, even if some tools

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were proposed for planning purposes [15]. For instance, in [15] the heating treatment on human patients with glioblastoma is held for 1 h after infusion at multiple sites. Other *in vivo* studies addressing glioma in the mouse brain adopt a 40 min thermal activation after a 20 min infusion step, and heating is incrementally administered by gradually increasing the intensity of the external magnetic field [16]. Moreover, for other experimental approaches the heating duration is in the range 30–60 min [17]. Furthermore, thermal activation is usually performed soon after the infusion, yet the value of such a time lapse is rather variable, up to 24–48 h [15,16].

A unified modeling frame for the NPs-mediated hyperthermia treatment seems to be missing, despite the many results being produced by the mathematical oncology community. Indeed, many contributions focused on tumor growth [18], also accounting for chemotherapy [19] or radiotherapy [20] effects limiting proliferation. Moreover, valuable studies addressed the optimal control of cancer drug therapy [21], up to proposing multi-scale approaches [22]. Nonetheless, some contributions that tackle specific aspects of the NPs-mediated hyperthermia treatment are also available in literature. In particular, as regards infusion in porous media, a basic analytical approach was introduced in [23] for modeling the infusion-induced swelling in the brain. That work aimed at describing the flow field, while merely formulating the associated solute transport problem. Elegant analytical models are still being developed for describing unsteady infusion processes in the brain [24], mainly addressing pathologies associated with altered poroelastic properties, such as hydrocephalus. Moreover, the transport of a nanofluid within a porous medium was originally addressed in [5], and the study of their thermal behavior is a lively issue [25]. Furthermore, several studies addressed the convection-enhanced transport of therapeutic or imaging agents in the brain, by also accounting for poroelastic effects [26]. However, due to the complexity of the involved physical phenomena, a fully numerical approach was mandatory for such investigations. In some cases, patient-specific images were used for calibrating the model, as well as to provide more realistic computational domains [27,28]. Still in [28], some efforts were taken to also model the chemical reactions between the solute and the surrounding anatomical structures. This aspect was also studied by using NPs as transported species, i.e. for the case of our interest. For instance, in [29] the interaction between NPs and cells was studied by considering absorption, desorption and internalization effects (yet without addressing the infusion process). This interaction was further investigated in [30] through numerical simulations, by accounting for the surface properties of the NPs and for the infusion process. In particular, a porous tissue was considered, and the so-called collector efficiency (which affects the absorption process) was estimated by coupling the solution of the advection-diffusion-reaction problem for the NPs concentration with a Langevin equation for the NPs trajectories. This study surely provides a valuable contribution, despite the fact that model validation was hampered by the uncertainty on the involved parameters. Moreover, the same authors addressed the effect of tissue poroelasticity in [7], while discarding absorption mechanisms and accounting for realistic geometries of the infusion set-up. In particular, they described the fluid distribution near the infusion needle tip, including back-flow effects in good agreement with experimental observations. Let us remark that the last two cited works aimed at providing a suitable description of the NPs distribution in view of magnetic hyperthermia treatments, yet they did not address the whole procedure. Conversely, several studies addressed the NPs-mediated tissue heating involved in magnetic or laser-induced hyperthermia without considering the infusion step. In particular, besides contributions focusing on the power dissipated through NPs activation [11], most of these studies exploited the classical bio-heat equation in order to compute the temperature distribution in the tissue [31–34].

Despite the outstanding contributions published so far, to the best of our knowledge a simple model which can support at least a preliminary design of hyperthermia treatments by describing both the nanofluid infusion and the thermal activation process is still missing. We take a first step to fill this gap, by deriving an easily manageable analytical expression for the NPs distribution resulting from nanofluid infusion, which is then input to the magnetically-driven thermal activation phase. As a final result, we obtain the steady-state temperature distribution in a target tumor model, by specifically elucidating the effects associated with the main treatment control parameters through illustrative numerical results. More in detail, our model accounts for physiologically relevant aspects including tissue heterogeneity, poroelasticity, and blood perfusion, as well as for the physical properties of the magnetoresponsive NPs suspended in the nanofluid. Furthermore, we elucidate the effects on the final temperature profile of the following control parameters: infusion duration and flow rate, NPs concentration in the nanofluid, magnetic field intensity and frequency. Moreover, for each of them we consider a suitable range taken from experimental studies, in order to support the applicability of the proposed approach.

The paper is structured as follows: the mathematical models for the infusion and the heating process are introduced in Section 2, whereas supporting details appear in Appendices A–C (prior to bibliography), for the sake of readability. Relevant results are then presented and discussed in Section 3, and concluding remarks are finally reported in Section 4.

2. Material and methods

With reference to the actual, two-step clinical practice, we hereafter introduce two simple models for the nanofluid infusion, and for the subsequent thermal activation of the infused NPs by means of an oscillating magnetic field. In particular, we firstly address the time-dependent nanofluid transport in a poroelastic medium, and we analytically obtain the NPs distribution at the end of the infusion process. We then assume that the NPs concentration does not significantly change after the infusion, so as to directly provide the spatial distribution of the thermal sources that are activated by the magnetic field. In particular, we address a stationary heat-transfer problem (the magnetic field frequency and the application duration are high enough to adopt the stationary approximation) to obtain the steady-state temperature profile in the target domain.

In more detail, we adopt a spherical symmetric approximation, for ease of analytical tractability, with the main aim of obtaining a simple solution able to highlight the role of the involved physical parameters. In this context, we assume that infusion takes place within a small spherical domain having radius r_{inf}, concentric with the target tissue domain (the infusion needle is consequently treated as immaterial). Such a spherical approximation can be acceptable for infusion in the brain tissue, where the maximum flow rates are typically on the order of a few μL/min [26] (conversely, spherical symmetry is broken at higher flow rates, because of the back-flow occurring near the tip of the needle [7]). Despite such a simplification, we account for tissue heterogeneity, so as to describe both the necrotic core and the tumoral tissue adjacent to the healthy one. Indeed, a solid tumor is only partially vascularized and its growth is regulated by nutrients diffusion from the surrounding environment, so that an inner necrotic core develops when this concentration falls below a certain level. Moreover, a layer of tumoral viable cells is present between the core and the outer tissue [35]. We consequently introduce three concentric regions: an inner shell $\mathcal{S}_N$ representing the necrotic core, with outer radius r_N (so that the radial coordinate r spans $r_{\mathrm{inf}} < r < r_N$); an intermediate tumoral shell $\mathcal{S}_T$, with outer radius r_T ($r_N < r < r_T$); an external shell $\mathcal{S}_H$ made of healthy tissue, with outer radius r_H ($r_T < r < r_H$). We hereafter use the subscripts N, T and H, respectively, to denote any parameter which is specifically related to these domains; consistently, a quantity without any labels is understood as having the same value in the whole spherical domain, hereafter denoted by $\mathcal{S}$.