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Backflow-free catheters for efficient and safe convection-enhanced delivery of therapeutics

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ABSTRACT

Convection-enhanced delivery (CED) is an invasive drug delivery technique used to target specific regions of the brain for the treatment of cancer and neurodegenerative diseases while bypassing the blood-brain barrier. In order to prevent the possibility of backflow, low volumetric flow rates are applied which limit the achievable drug distribution volumes from CED. This can render CED treatment ineffective since a small convective flow produces narrow drug distribution inside the treatment region. Novel catheter designs and CED protocols are needed to improve the drug distribution inside the treatment region. This is especially important when administering toxic chemotherapeutics which could adversely affect other organs if backflow occurred and these drugs entered the circulating blood stream. In order to help elucidate the causes of backflow and to design backflow-free catheters, we have studied the impact that microfluid flow has on deformable brain phantom gels experimentally as well as numerically. We found that fluid injections into porous media have considerable effects on local transport properties such as porosity and hydraulic conductivity. These phenomena not only alter the bulk flow velocity distribution of the microfluid flow due to the changing porosity, but significantly modify flow direction and even volumetric flow distribution due to induced local hydraulic conductivity anisotropy. These studies led us to the development of novel backflow-free catheters with safe volumetric flow rates up to 10 μL/min. The catheter designs, numerical simulations and experimental results are described throughout this article.

1. Introduction

Neurodegenerative diseases of the central nervous system (CNS) are often treated by systemic delivery of large molecular weight drugs either orally or intravenously. However, the blood brain barrier (BBB) prevents most of these molecules from entering the interstitium, rendering systemic delivery methods highly ineffective [1]. One solution to bypass the BBB is through a direct intracranial injection, a technique known as convection-enhanced delivery (CED). This invasive technique utilizes a positive pressure gradient created by an infusion pump to infuse drugs through a catheter and into the brain tissue. CED directly distributes therapeutic agents to a specific target area at dramatically increased doses and has been shown to achieve much larger drug distribution volumes compared to diffusion driven methods [1,2]. These major advantages of CED offer great potential for more efficient treatment of neurodegenerative diseases such as Alzheimer's and Parkinson's, as well as for the treatment of brain tumors.

Alzheimer's disease (AD) and Parkinson's disease (PD) collectively affect 6 million people within the United States, and around 42 million people worldwide [3–5]. These numbers are expected to grow substantially as the average age of the population increases. For AD alone, it is estimated that by 2050 between 11 and 16 million Americans will have AD and 115.4 million people worldwide [3]. The estimated cost of providing care for AD patients in the US is $200 billion per year, while for PD patients it is $14.4 billion [6]. The cost of providing care for AD patients alone is projected to grow to over $1.1 trillion per year by 2050—an overwhelming economic burden [3]. It is also estimated that more than 688,000 people are currently living with a diagnosis of a primary brain or CNS tumor in the United States, and 79,270 new cases are expected to be diagnosed in 2017 [7,8]. Due to the BBB limiting the delivery of systemically administered drugs to the brain and CNS, an appealing mode of delivery of therapeutics to these populations is through CED.

Clinical trials treating gliomas that utilized CED, such as the TransMID and PRECISE trials, have failed to demonstrate statisti-

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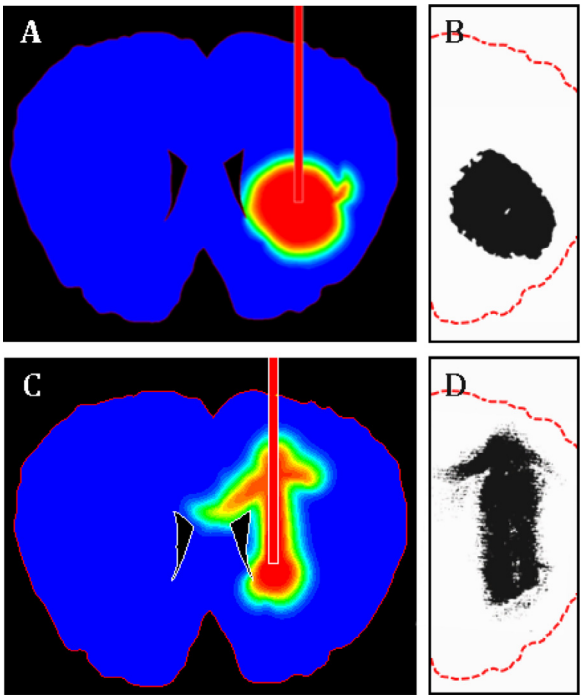

Fig. 1. Unpredictable and non-uniform distribution geometries from in silico (A and C) and in vivo (B and D) CED experiments even though very low volumetric flow rate of 0.5 μL/min were used. (Adapted from our previous work. [12]).

cally significant improvement in survival [9] despite the proven efficacy of therapeutic agents in animal models [10,11]. PRECISE is an acronym for "**P**hase III **R**andomized **E**valuation of **C**ED of **I**L13-PE38QQR Compared to GLIADEL® Wafer with **S**urvival **E**ndpoint in Glioblastoma Multiforme Patients at First Recurrence". Retrospective analysis of the PRECISE trial found that infusate distribution was highly variable among patients; therefore, any potential efficacy of drugs delivered by CED may be hindered by ineffective drug spread [12–14]. Alternative catheter designs may improve delivery, thereby increasing the efficacy of drugs delivered by CED [14]. This is an engineering problem where the therapeutic does not reach the site of disease.

One undesirable effect often associated with CED is known as backflow or reflux, which is characterized by fluid discharge along the catheter shaft instead of entering distally into the soft tissue. Backflow is especially dangerous when toxic drugs used for treating CNS diseases and cancer escape from the target region and negatively affect other regions of the brain and spinal cord through flow through the cerebrospinal fluid (CSF) space. Backflow can also render treatments unsuccessful when therapeutics fail to reach an efficacious concentration within the target region. This may be one explanation as to why the PRECISE trial failed. Unpredictable distribution of a therapeutic agent due to backflow and anisotropic tissue properties is a serious obstacle to the safe clinical application of CED. Fig. 1, adapted from our previous work [12], shows CED's non-uniform distribution geometry in both computer simulations (A and C) and a rat model (B and D) while using a very low volumetric flow rate of 0.5 μL/min and infusing with a common 32 G single-port catheter. Low volumetric flow rates limit the achievable drug distribution volumes from CED. Although Fig. 1A and B show relatively spherical distributions, Fig. 1C and D clearly show backflow even while operating at a low volumetric flow rate and delivery through a thin 32 G single-port catheter. In order for CED to become a clinically viable treatment option, CED protocols and catheter design need to be optimized to prevent backflow and make drug distribution geometries more predictable.

A main goal in the optimization of CED methods is to determine the causes of backflow phenomena. Once the causes of backflow are known, optimal catheter designs for CED can be developed. Therefore, the transport processes which occur during drug delivery into porous media such as a human brain should be elucidated using experiments [15]. Several theories describing the effects of fluid flow in porous media have been developed [16–20]. However, most of these theories are based on the idealized soil model of porous media and are not able to describe backflow.

1.1. Background

Live brain tissue is known to be comprised more than 80% water; therefore, it can be considered as a porous deformable matrix with incompressible elements (cells). Interstitial fluid fills the space (porosity) between these cells. Due to the cell incompressibility, deformation of the solid matrix is linked to the porosity or fluid fraction change. The deformation is associated with a volumetric strain, $e(\vec{x},t)$, that is directly related to the porosity, $\zeta(\vec{x},t)$, as shown in Eq. (1), where ζ_0 is an initial porosity.

$$\zeta(\vec{x},t) = \frac{e(\vec{x},t)+\zeta_0}{1+e(\vec{x},t)} e = \sum_{i=1}^{3} \varepsilon_i = \sum_{i=1}^{3} \frac{du_i}{dx_i} \tag{1}$$

Since the deformation influences the local tissue porosity, $\zeta(\vec{x},t)$, it also impacts the fluid continuity equation shown below in Eq. (2).

$$-\nabla \cdot \left[\zeta(\vec{x},t)\vec{v}_f\right] + q = \frac{d\zeta(\vec{x},t)}{dt} \tag{2}$$

Here q accounts for the fluid injection and $\vec{v}_f$ is the superficial flow velocity vector which induces stress in the porous matrix. Deformation also causes hydraulic conductivity change, K, as shown in Eq. (3) where M is a coefficient of approximately one.

$$K(\vec{x},t) = K_0 exp[Me(\vec{x},t)] \tag{3}$$

Darcy's law, shown below in Eq. (4), is used to describe a relationship between the velocity, $\vec{v}_f$, and pressure gradient, ∇p, inside the porous media.

$$\vec{v}_f = K(\vec{x},t)\nabla p \tag{4}$$

Fluid flow affects the porous media's characteristics by inducing a deformation. The reasons for this deformation are fluid pressure gradient, shear stress induced by fluid friction (related to fluid velocity), and fluid pressure. For example, Terzaghi's consolidation theory states that the local stress is related to a fluid pressure, and this pressure can be utilized to calculate the porous media strain [19–21]. However, the brain's solid matrix consists of incompressible elements (cells). Therefore, we have to look for the porous matrix deformation rather than compression of matrix elements. In this case, the dominating effects are the fluid pressure gradient and the shear stress induced by fluid friction. According to Darcy's law, fluid flow induces friction forces and pressure gradients in the flow direction. This results in volumetric forces inside the deformable porous media/matrix. For this model, the strain as well as an effective stress does not depend on the absolute fluid pressure, but instead depends on the fluid flow velocity which is proportional to the pressure gradient. This statement agrees with our experimental observations which revealed that local fluid-induced stresses in the porous matrix are related to fluid pressure gradients [15]. This experimental data was used to validate a computational model. The deformation of the porous matrix was found to be linked to the porosity and consequently hydraulic conductivity change induced by the microfluid injection [15]. Another important aspect that affects tissue deformation and catheter performance is catheter geometry.