Convection Enhanced Drug Infusion into the Soft Brain Tissue

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EXTENDED ABSTRACT

Summary

Many diseases of the Central Nervous System (CNS) require treatment by novel drugs and special techniques (e.g. viral vector). However, the efficiency of the treatment may be hampered by the lack of methods to administer the drug in regions of the brain in therapeutically effective concentration range. The difficulty to deliver drugs in the brain is due to Brain Blood Barrier (BBB) that prohibits large molecules to pass through the capillary bed into the brain. Invasive drug delivery techniques aim at overcoming the BBB by directly injecting large molecules into the brain parenchyma by a catheter [1]. Recently there is interest for treating diseases of CNS with such invasive techniques.

Delivery of drugs by diffusion-only does not provide effective penetration depths. On the other hand convection enhanced drug delivery has been proven effective to substantially increase the penetration depth creating a core of high concentration sufficient for many drug therapies [2]. However, there is still a need of engineering such therapies due to the lack of understanding the drug transport processes into the brain with diffusion and convection. Currently there is a lack in systematic understanding of the transport properties at cellular level and the force interactions between the fluid field and the brain tissue.

Methodology

In an effort to systematically design catheters and invasive drug therapies we propose to quantify the interaction of the drug with the soft brain tissue and its transport in the parenchyma using a first principles model.

Mathematical model. The transport of a drug released from a catheter tip accounts for diffusion, bulk flow in a porous medium and chemical reactions. The continuity equation describes the mass balance for the bulk medium (i.e. water). The drug is very dilute so it does not affect the bulk flow velocities in the continuity equation. The momentum balances for the infusate are the incompressible Navier-Stokes equations (constant density) with an additional pressure drop term accounting for the interaction of the fluid flow within the extracellular space.

The transport and reaction system for drug infusion consists of a set of coupled, non-linear partial differential equations (PDEs). The PDE system is discretized using a finite volume (FV)

approach enforcing the conservation balances on a staggered grid expressed in generalized curvilinear coordinates [3].

In this study we describe the convective transport of the drug in the porous tissues using Biot consolidation theory that accounts for the interaction of the cell matrix as a solid skeleton and the dissolved drug in a bulk medium [4].

Complex brain geometry. We model the complex geometry of the human brain by integrating imaging techniques with computational fluid mechanics methods [5]. As a result, we are able to resolve very accurately the brain geometry and render physiologically consistent the distribution of the complex brain inner organization. We distinguish between gray and white matter and assign transport properties of relevance according to the data obtained by MR images or histological data (Figure 1). This approach is capable to resolve the anisotropic brain tissue properties such as permeability and the directionality along the strands of the oriented axons in the white matter.

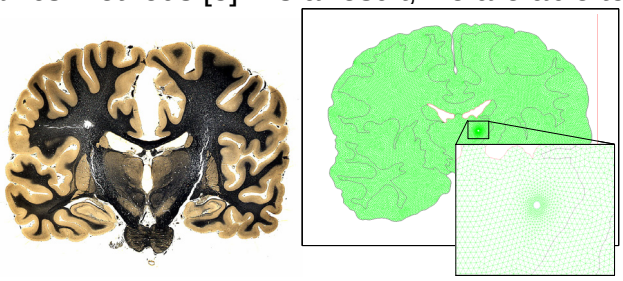

Figure 1. The detailed two-dimensional brain geometry (right) extracted from histological data (left).

It will be shown that the treatment of the brain with physiologically consistent transport coefficients (diffusivity and porosity) is necessary to quantify the achievable penetration depths and treatment volumes into the porous tissue. However, the improvement of the drug therapeutic volume by convective field is limited by the allowable stresses and strains sustainable by the brain tissue at the vicinity of the injection area. Therefore, very large convective fields may injure the tissue and must be avoided.

Significance

Numerical methods for studying the optimal parameter combinations for invasive drug delivery will allow physicians and scientists to develop and optimize therapeutic approaches, complementing animal trials.

Current approaches are limited by the omission of soft tissue deformation caused by the fluid traction associated with high bulk flow velocities [6], [7]. It is well known that high infusion can also cause edema and other damages to the tissue. These effects are of particular importance in high flow infusion policies, which also lead to the desired hat-shaped concentration plateaus as depicted in Figure 2 [5]. For finding an optimal trade-off between acceptable tissue shear stresses and high penetration depths, the interaction between fluid and solid cell matrix need to be quantified. The proposed model will be capable of predicting the deformation of the cell matrix under the fluid traction consistent with clinical observations. We would like to quantify the adverse effect of the drug seeping upwards the catheter tip (leak-back) [8]. With the proposed approach we will be able to predict deformations of the cell matrix and the drug concentration in the presence of these fluid-structure interactions in the human brain.

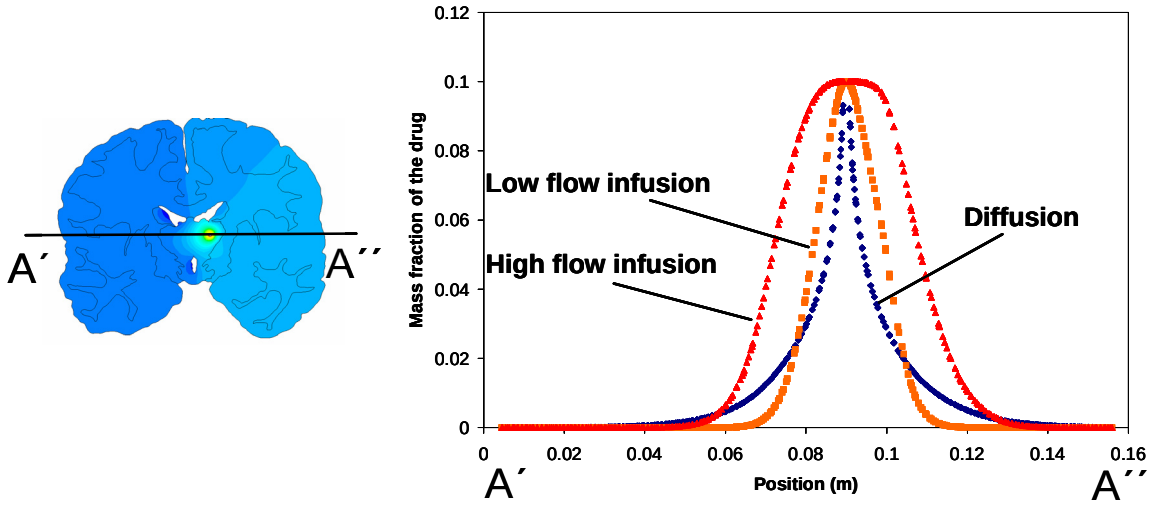

Figure 2. Mass fraction of the drug versus the position for diffusion, low and high flow micro-infusion.

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