Modeling direct injection of drugs into the brain

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The World Health Organization (WHO) estimates that one billion people worldwide suffer from central nervous system (CNS) disorders [1]. One major issue in treating these disorders is inadequate drug penetration which can be attributed to an effective blood-brain-barrier that limits passage across blood vessels. Low diffusivity of large classes of drug compounds restricts transport across blood vessel walls and subsequent passage through surrounding brain tissues. Tissue transport is emerging as an increasingly important area of research in drug delivery since the vast majority of therapeutic agents must traverse this space before reaching their targets. The need for this research has only increased with improved engineering of therapeutic agents such as biologics and nanoparticles. To cover large tissue volumes, investigative drug studies can use local delivery methods that introduce compounds directly into targeted regions. Controlled injections directly into brain tissue can enhance transport of macromolecular drugs through tortuous tissue spaces, though it has proven challenging to achieve targeted and consistent delivery. For these studies, computational models that capture effects of complex brain structure on drug transport are useful in determining the potential of new drug compounds and designing effective treatment regimes.

In computational brain models that simulate regional drug delivery, tissues are usually treated as porous media. Fluid transport properties, such as hydraulic conductivity and diffusivity, vary regionally with tissue composition and have been found to have significant influence on drug distributions. For example, regions with bundles of myelinated axonal fibers show preferential transport along the direction of fiber tracks. We have developed cross-property relationships that allow us to predict the influence of such fibers on infusion drug delivery [2] using data collected from diffusion weighted imaging (DWI). DWI is a magnetic resonance imaging (MRI) technology that measures the effective diffusivity of water in tissue and has been used for brain fiber track mapping. Other studies utilizing directional data encoded in DWI have been developed to predict sucrose diffusivity, electric fields, and mechanical properties in the brain. Our 3D computational models account for underlying tissue structures, as well as, normal and injection flow conditions. We used these models to predict tracer spread and residence times for injections into the spinal cord and brain [3]. These spreads provide an important metric of initial drug coverage that ultimately establishes drug efficacy. These predictions were then compared with experimental studies. In clinical application, uncertainty in targeting continues to be a major factor hindering direct infusions. MR-based, computational models developed in this study have the potential to capture major modes of fluid deviation, improve predictions of drug coverage, and provide more accurate surgical planning.
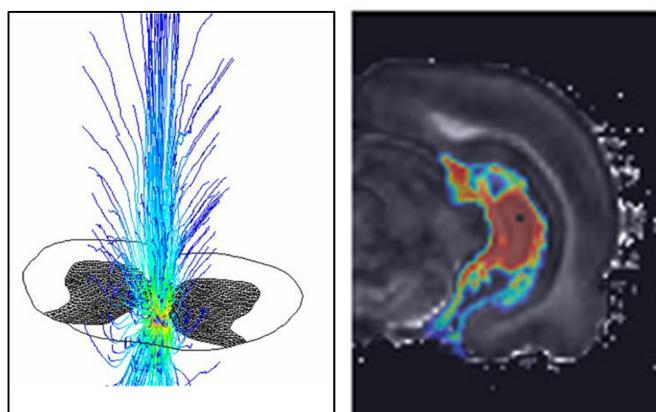

Figure 1: Computational models of infusion in the spinal cord and brain. (Left) Predicted flow pathlines for injection into the dorsal horn of the rat spinal cord. (Right) Tracer distribution following injection in the rat hippocampus showing fluid diversion into neighboring fluid spaces.

References

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