Special Delivery

Researchers use simulation and medical imaging to explore new options for managing pain.

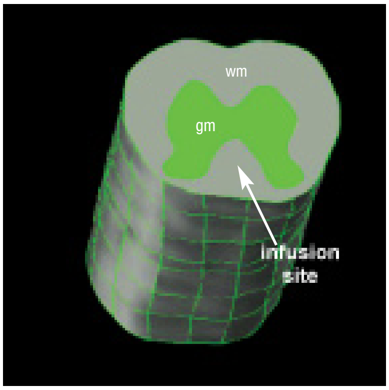
By Malisa Sarntinoranont, Xiaoming Chen, Jianbing Zhao and Thomas Mareci, University of Florida, U.S.A.

The latest therapeutic agents for chronic pain, spinal injury and other neurodegenerative diseases are characterized as macromolecular (large) proteins. Delivering these drugs at the site of action is gaining popularity. However, the transport environment in the spinal cord and other nervous tissue must be taken into account when designing direct infusion therapies.

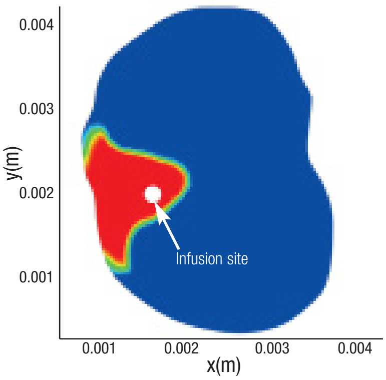
Since macromolecular drugs diffuse relatively slowly, transport factors affect the effectiveness of delivery greatly. The delivery of drugs through the spinal cord is dependent on a variety of factors, including variations in material properties and flow regions within the cord itself. Specialized analysis methods that correctly predict the related transport behaviors are required before one can develop general, and possibly patient-specific, delivery protocols.

By coupling medical imaging with computational fluid dynamics (CFD) analysis, a research group at the University of Florida in the United States recently developed methods for predicting the distribution of a drug tracer injected directly into the rat spinal cord [1, 2]. Traditional magnetic resonance imaging (MRI) was used to determine the geometry and structure of the spinal cord. Diffusion-tensor MRI (DT-MRI), which provides information on how water molecules spread through tissue, was used to determine the preferred and most likely transport directions in the cord.

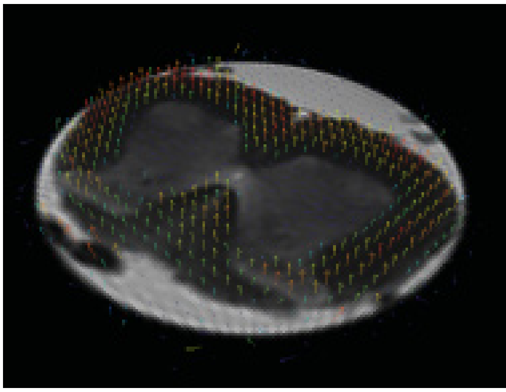
Analyses of interstitial pressure, velocity and tracer distribution within the porous media in the spinal cord were performed using FLUENT software. An anisotropic hydraulic conductivity (K) was applied in the white matter, a transport region located at the periphery of the spinal cord, to model the flow through it. The magnitude of K was assigned based on experimental data [3]. DT-MRI technology was used to identify the direction of maximum water diffusivity, which, since it was assumed to be parallel to the local fiber orientation, was used to determine fiber tract directions. This alignment data was used to assign behavior properties to the model.



MRI-derived three-dimensional geometry of the rat spinal cord. White matter (wm) is in grey and grey matter (gm) is in green. Drug is delivered into the white matter, near the boundary with the grey matter.



Predicted albumin tracer distribution in the spinal cord 20 minutes after a 2.0 μl infusion. Red areas represent sites of higher concentrations.



Maximum eigenvectors (identified by arrows in the image) identify the locations of maximum water diffusivity and preferred tissue transport for a fixed rat spinal cord. The red arrows represent aligned eigenvectors.

Using FLUENT technology, the distribution of a small volume infusion of the tracer then was predicted. Convection-dominated transport along white matter tracts was found, and the preferred distribution was identified along the cord axis with little penetration into adjacent gray matter zones. These results correspond well with small volume distribution trends found experimentally [3].

A model of this type could be used further to analyze the effectiveness of different injection protocols, such as continuous versus discontinuous injections or the effect of injection site on drug distribution. Eventually, this type of image-based modeling effort may allow customized medical care that inherently factors in patient-specific physiological differences. ■

References

[1] Sarntinoranont, M.; Banerjee, R.K.; Lonser, R.R.; Morrison, P.F., A Computational Model of Direct Interstitial Infusion of Macromolecules into the Spinal Cord, *Annals of Biomedical Engineering*, 2003, 31, pp. 448–461.

[2] Sarntinoranont, M.; Chen, X.; Zhao, J.; Mareci, T.M., Computational Model of Interstitial Transport in the Spinal Cord Using Diffusion Tensor Imaging, *Annals of Biomedical Engineering*, 2006, 34, pp.1304–1321.

[3] Wood, J.D.; Lonser, R.R.; Gogate, N.; Morrison, P.F.; Oldfield, E.H., Convective Delivery of Macromolecules into the Naive and Traumatized Spinal Cords of Rats, *Journal of Neurosurgery (Spine 1)*, 1999, 90, pp. 115–120.