**Appendix**

1. **Bench-top Dye Tracking and Data Analysis**

Dye distribution tracking in the spinal SAS uses a solution of trypan blue dye injected through the IT injection port. A HD video camera recorded the full duration of the injection to track the speed of dye front motion and extent of dye spread. Video recording of dye dispersion was acquired up to one hour for data processing.

To calculate dye spread rates, video files are loaded into MATLAB to extract discrete time points. Intensity data is measured from four sagittal vectors covering the spine model and averaged to reduce noise. Dye intensity profiles are plotted against distance for separate instances of time. Dispersion velocity is extracted as two components, the dye mixing front and bulk motion. Dye front location is taken as 10% of the maximum dye intensity value and a linear regression model is fitted to data across the injection phase to calculate dye front velocity. The dye moment, ɸ, finds the position weighted average where the velocity is calculated by:

 ɸ $= \frac{\sum\_{}^{}xA}{\sum\_{}^{}A}$ (A.1)

where A is an intensity integral for a position segment and x is the position of that area. Position for both dispersion parameters is acquired for multiple time points, t = {0, 0.25, 0.50, 0.75, 1, 5, 10, 15, 30, 60 minutes} and a rate of change is calculated to find the mixing front velocity and bulk motion rate.

1. **Subject-specific CNS Model Generation**

Subject specific computational meshes were reconstructed from MRI using tetrahedral elements covering the CSF filled spaces and elements for the tissue domain. Many dimensions for both subjects are listed in Table 2. Supplemental Table 1 compares height and spinal CSF volumes for subject-1 of this study to subjects in a previous clinical study by Carpenter et al. The spinal cord with 31 nerve root pairs and skull are defined as rigid boundaries with impermeable walls. The cranial pial surface and lateral ventricles are periodically displaced to emulate the cerebrovascular expansion driving CSF flow. CSF production is implemented at the choroid plexus in the lateral ventricle at a rate of 0.4mL/min and CSF absorption at the superior sagittal sinus at 0.4mL/min with a zero species transport at the boundary interface.

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| Supplemental Table: Comparison of height and CSF volumes for Subject-1 to prior clinical subjects  |
| Study | Height (cm) | L5 termination from CM (mL) | Cauda equina volume (mL) |
| Current study | 168  | 62 | 51 |
| Carpenter et al. 1998 | 173 ± 12 | 64 ± 5 | 42.7-81.1 |

1. **CSF flow field and species transport**

Drug dispersion as expressed by its concentration, C(x,t), in the CSF and is governed by the convection-diffusion equation, eq. 1, and the flow fields are calculated by the Navier-Stokes equations. The species transport equation is interesting as it contains all the key factors in a simple balance.

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| $$\frac{∂C}{∂t}+\rightharpoonaccent{u}∙\rightharpoonaccent{∇}C\left(x,t\right)=\rightharpoonaccent{∇}∙\left[D\_{CSF}\rightharpoonaccent{∇}C\left(x,t\right)\right]+\frac{1}{V}S\left(x,t\right)-E\left(x,t\right)-T(x,t)$$ | (A.2) |
|  Accumulation Convection Diffusion Infusion Rate Deactivation Tissue Uptake |  |

CSF pulsatility is accounted for by the convection term, u(x,t) its pulse frequency is varied, ω = {40, 72, 120BPM}. The impact of different infusion strategies is explored with a lumbar catheter incorporated into the subject-specific spine model. We tested multiple infusion parameters for volume, INJV = {1, 5, 10mL} and infusion duration, INJD = {1, 5, 10, 60min}, to study continuous IT infusion and bolus injections.

Infused drugs are pharmacokinetically active. The first relevant bioreaction is enzymatic decay in the bulk CSF, which is modeled as a chemical destruction term E(x,t). Drugs can also pass between the CSF and be taken up by tissue, which is modeled by the mass transfer rate T(x,t); drug uptake is accounted for across the spinal pia membrane. DCSF is its diffusivity.

The mass transfer rate of tissue uptake, T(x,t), varies for different opiates, ku = {Morphine, Afentanil, Sufentanil} and is dependant upon their lipophilicity. The tissue uptake rate accounts for the transfer of drug from the CSF space into the extracellular spaces. Species kinetics are adjusted to fit the relative reaction, degradation, and tissue solubility profile of pain medications as taken from PK studies by Ummenhofer et al and as summarized in Table 1. Morphine has a slow tissue uptake and low blood clearance. Alfentanil, an opioid with moderate lipophilicity is modeled with high tissue uptake and high blood clearance. Sufentanil is an opioid with very low tissue uptake and low clearance.

1. **Reaction kinetics in CNS tissue**

In addition, after drugs travel from the CSF across the leptomeningeal layers, they can diffuse through the porous tissue extracellular space (ECS) or be taken up by cells, U(x,t) as described by Sykova and Nicholson, 2008[26]. An additional important biochemical reaction is the elimination of drugs into the bloodstream across the blood brain barrier, R(x,t). Blood clearance is considered an irreversible reaction in this model, and included as a destruction term.

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| $$\frac{∂C}{∂t}=\rightharpoonaccent{∇}∙\left[D\_{t}\rightharpoonaccent{∇}C\left(x,t\right)\right]-R\left(x,t\right)-U\left(x,t\right)+T(x,t)$$ | (A.4) |
|  Accumulation Diffusion Clearance Cell Uptake CSF-Tissue Transfer  |  |