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Striving to overcome the (blood-brain) barrier: models for intrathecal drug delivery and infusion into brain tissue

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Intrathecal drug delivery is a procedure to release therapeutic agents within the cerebrospinal fluid (CSF). It holds promise for treating high-impact pathologies of the central nervous system (CNS) for which systemic administration routes are ineffective, mainly because of the shielding effect of the blood-brain barrier (BBB) to macromolecules. Despite being used in clinical practice, intrathecal delivery protocols are not yet optimized.

Using a 3D patient-specific geometry, we investigated the effects of injection parameters on solute distribution within the spinal subarachnoid space [1]. We used the FEniCS computing platform, adopting linear finite elements for integrating the incompressible Navier-Stokes equations, and Lagrangian particle tracking for solute transport. We found that both catheter position and angle can alter the drug spread rate (more than 80%), and catheter flow rate can alter drug peak concentration (up to nearly 80%). Still using FEniCS, we then considered a Discontinuous Galerkin formulation in order to simultaneously account for solute transport in the CSF and in the spinal cord [2], and we found that lateral injection perpendicular to the cord was more effective than the other configurations we considered. Even if our current results cannot be directly translated to the clinics (we only considered twenty cardiac cycles, and correspondingly scaled transport properties, to limit the computational cost), our modelling approach takes a step towards therapy control.

We also studied direct infusion of therapeutic agents into brain tissue (convection-enhanced delivery) [3], by deriving simplified analytical expressions for the time-dependent nanoparticles concentration during nanofluid infusion into poroelastic tissue (as functional to tumour thermotherapy [4]). Simplified approaches can elucidate the role of the involved physical aspects (tissue poroelasticity, infusion parameters, physico-chemical properties underlying nanoparticle binding to tissue), thus complementing more ambitious/expensive numerical models.

Finally, we also exploited simplified analytical approaches for developing a 3D real-scale physical model of the BBB, serving as scaffold for the co-culturing of endothelial-like and tumour (glioblastoma) cells [5]. The complementarity of our current approaches also reflects the intrinsic multiscale/multiphysics nature of solute transport into CSF and CNS tissue, which could be further unveiled by novel computational frameworks.

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