Multiscale Analysis of Flow and Transport for Modeling Targeted Drug Delivery in the Cerebrovascular System

Omar Tanweer[1], and †*Vittoria Flamini[2]

[1]Department of Mechanical and Aerospace Engineering, Tandon School of Engineering, New York University, USA.
[2]Department of Neurosurgery, Langone Medical Center, New York University, USA.

*Presenting author: vittoria.flamini @nyu.edu
†Corresponding author: vittoria.flamini@nyu.edu

Abstract

Traumatic Brain Injury (TBI) is recognized to have a lasting impact on patients. In fact, after emergency, often care is administered following the injury, TBI and the cascade of events that surround brain damage and attempt to repair, can have long-term effects including epileptic episodes, the development of psychiatric and cognitive disabilities, and neurodegenerative pathologies such as Alzheimer disease. A solid body of research has identified the disruption of the Blood Brain Barrier (BBB) as the main culprit behind the long-term changes that affect the cognitive, behavioral and emotional functioning of the brain following TBI.

More specifically, BBB breakdown has been found to activate slow pathophysiological mechanisms, such as neovascularization, inflammation, and remodeling of brain parenchyma and of synaptic wiring, which in turn lead to the chronic manifestations of TBI. Lately, BBB stabilization has come up as the ideal strategy to counteract the secondary neuronal injury after TBI. BBB can be stabilized using hormones, such as ghrelin and progesterone, or by intervening on vascular growth factors, such as VGEF, or pro-inflammatory peptides such as bradykinin. However, all these strategies fall short of the objective because they do not treat the additional, passive mechanisms associated with BBB breakdown, and can have unwanted systemic effects for patients. By contrast, a targeted, multi-agent approach has the potential to relieve patients from the secondary effects of TBI.

In this work, we lay out a framework for the definition of mathematical models to determine the effectiveness, defined as concentration of drug in the target area, of intravenous therapies delivering BBB stabilizers and neuroprotectors to TBI lesions in the brain. Variables that can alter effectiveness are: increased tortuosity of the arterial tree; deployment site of the therapy; location of the lesion; neuroprotectant agent used; kinetics of release; and different diffusion parameters between brain parenchyma and TBI lesion. This framework is based on multiscale computer simulations. In particular, in our approach brain circulation is decomposed in two scales, macrocirculation and microvascular districts. Macrocirculation is reconstructed using medical image processing, while microvasculature is represented via analytical approaches. In fact, model reduction techniques are used to model blood flow and drug transport using equations defined on networks of 1D manifolds.

We foresee that this multiscale, multiphysics, multimodel approach for the study of targeted TBI treatments will reduce the impact of systemic therapies on TBI patients, in turn reducing the occurrence of the disabling long-term effects observed in this patient population.