# A Mathematical Framework for Mechanically Controlled Brain Drug Delivery

Tian Yuan

Supervisor: Prof. Daniele Dini

Department of Mechanical Engineering, Imperial College London, London, SW7 2AZ, UK

Neurological disorders have been a global health challenge, necessitating the imperative for the development of effective treatments. While pharmacotherapy is a common treatment for various brain diseases, delivering drugs into the brain is challenging; because the Blood Brain Barrier (BBB), which prevents harmful substances in the blood from entering the brain, also blocks most of the conventional drug molecules [1]. Despite the development of novel techniques, such as Convection-Enhanced Delivery (CED), to bypass the BBB by delivering drugs directly into the target area via catheters, achieving the desired drug distribution in the brain remains challenging [2]. This is because the anisotropic and heterogeneous drug delivery pathways in the brain are formed by the extremely soft neurons, making the fluid and mass transport within the brain extremely complex, unsteady, and hard to predict [3]. Therefore, highly efficient drug delivery in the brain relies on a fundamental understanding of how drugs interact with the micro-channels and how the microscale drug-neuron interactions affect the macroscale drug transport process in the brain.

To fill these gaps, this thesis has established a new multiscale and multiphysics mathematical framework underpinned by experiments carried out at different scales to provide accurate predictions for the drug delivery process in the brain. By achieving this goal, this PhD project has successfully: (i) gained a deeper understanding of the drug-brain interactions across the scales, and developed consistent mathematical formulations to describe them [4-6]; (ii) built techniques to correlate the drug-neuron interactions to drug transport properties in the brain [4-8]; (iii) established a multiscale framework to predict the drug delivery process in the brain; (iv) corroborated the models by experiments at different scales and validated the whole framework by in vivo drug delivery experiments with sheep; (v) investigated the effects of some important parameters of CED on the drug distribution in the brain.

The combination of this mathematical framework and medical imaging techniques will form a system that can provide fast and one-stop suggestions on pre-operational planning, such as the catheter size, position, and direction, infusion rate and duration. This will allow neurosurgeons to make faster and more precise decisions on brain drug delivery operations. Further extension of this framework can make it able to optimise drug delivery protocols to many other tissues and explore its potential in developing novel drugs and synthetic bio-mimicking materials such as functionalised and composite hydrogels.

**References**

[1] Pardridge, W.M., 2005. NeuroRx, 2, pp.3-14.
[2] Mehta, A.M., et al, 2017. Neurotherapeutics, 14(2), pp.358-371.
[3] Jamal, A., et al, 2020. IEEE Transactions on Biomedical Engineering, 68(4), pp.1229-1237.
[4] Yuan, T., et al, 2022. Pharmaceutical Research, 39(4), pp.767-781.
[5] Yuan, T., et al, 2022. Biomechanics and Modeling in Mechanobiology, 21(4), pp.1299-1316.
[6] Yuan, T., et al, 2023. Acta Biomaterialia, 160, pp.152-163.
[7] Yuan, T., et al, 2023. International Journal of Molecular Sciences, 24(3), p.2534.
[8] Yuan, T., et al, 2024. Acta Biomaterialia, 173, pp.123-134.