6th European Conference on Computational Mechanics (ECCM 6)
7th European Conference on Computational Fluid Dynamics (ECFD 7)
11 – 15 June 2018, Glasgow, UK

A novel in-silico modelling framework for cytotoxic drug delivery simulations in animal cancer models

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Key Words: *mathematical modelling, multiscale, tumour/host microenvironment, drug transport, chemotherapy, tumour normalisation.*

Tumour/host microenvironment heterogeneity is a well-documented factor in the development of cancer and the treatment of the disease. As such, significant efforts have been dedicated in biological experiments – using in-vitro or in-vivo models – to test relevant drugs and interrogate their efficacy against cancer. Nonetheless, due to the complex nature of the tumour/host microenvironment, in-silico models could help improving our understanding in the underlying mechanisms in the progression of solid tumours and the major factors affecting the transport of tumour-targeting molecules.

In this contribution, we present an in-silico biophysical model of tumour growth, angiogenesis and drug delivery, which is an extension on our recently published in-silico framework [1]. The novel aspects of the model are that it describes in a multiscale fashion: *(a)* small-molecule drug transport in the tumour vascular network and the extravascular space, *(b)* tumour regression as a function of the cytotoxic drug concentration, *(c)* the biomechanics of the (tumour and host) tissue and *(d)* the micro-vasculature dynamics in response to drugs.

We carried out a parametric analysis of tumour growth, neo-vascularisation and cytotoxic drug delivery simulations with respect to the properties of the chemotherapeutic agent and the tumour capillaries permeability and perfusivity. The simulations describe a single-dose bolus injection of a small-sized molecule, with the drug modelled to regress the solid tumour growth. Our results suggest that tumour response to chemical treatment is strongly dependent on the binding affinity of the drug to cancer cells rather than the permeability of the tumour blood vessels. More importantly, by increasing the binding rate of the drug, the tumour vasculature becomes better structured and the fraction of perfused vessels elevates, thus, improving vessel functionality. Furthermore, we find that tumour regression is improved if neoadjuvant vascular normalisation is not performed prior to treatment with cytotoxic drugs; and that the combination of large-sized vascular pores and binding affinity enhances cytotoxic drug delivery efficiency.

REFERENCES

[1] Vavourakis V, Wijeratne PA, Shipley R, Loizidou M, Stylianopoulos T, Hawkes DJ (2017) A Validated Multiscale In-Silico Model for Mechano-sensitive Tumour Angiogenesis and Growth. PLoS Computational Biology 13(1): e1005259. https://doi.org/10.1371/journal.pcbi.1005259.