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Modelling the Transport of Fluid and Solutes Through Heterogeneous, Real-World, Tumour Substrates Derived from Optically-Cleared Samples

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Understanding how drugs are delivered to diseased tissue, and their subsequent spatial and temporal distribution, is a key factor in the development of effective, targeted cancer therapies. Preclinical tools to better understand drug delivery are urgently required, which incorporate the inherent variability and heterogeneity between tumour types and deposits, and even within individual tumours[1]. However, few (if any) experimental techniques exist that can quantify drug delivery across whole tumour samples purely through experimental imaging.

To meet this need, the REANIMATE (REAlistic Numerical Image-based Modelling of biologicAl Tissue substratEs) framework[3] has been developed to integrate optical imaging of intact biological tissue with computational modelling. Specifically, REANIMATE enables the microstructure of these large samples to be virtually reconstructed in 3D on the scale of microns. These resultant data act as substrates for our mathematical model which is parametrised and validated against *in vivo* ASL-MRI perfusion data, thereby enabling physiological simulations of fluid delivery through the vasculature and into the surrounding tissue[3].

Here, REANIMATE is applied to imaging data from two murine models of colorectal cancer (LS147T and SW1222) to: 1) simulate steady-state fluid dynamics (such as intravascular and interstitial fluid pressure (IFP)), 2) uptake of the MRI contrast agent Gd-DTPA, and 3) uptake and response to vascular-targeting treatment (Oxi4503). REANIMATE predictions are found to be consistent with the magnitude and spatial heterogeneity of *in vivo* measurements, both in steady-state (blood flow, IFP) and transient (drug delivery) models[3]. Further, simulations predict that, whilst the traditionally elevated IFP in the tumour core[4] can occur, vascular spatial heterogeneity can also induce spatially heterogeneous IFP[3]. Furthermore, loss of vessels as a result of administration of Oxi4503 results in a subtle spatial pattern of perfusion loss in significant tissue volumes that is tumour-type dependent. We hypothesise that the higher connectivity and redundancy typical of SW1222 tumours means they can compensate for loss of vessels by rerouting flow through alternative connected pathways; this is less evident in LS147T tumours, which have a significantly lower connectivity[3]. This demonstrates a mechanism through which tumours can exhibit a form of physical resistance to drug therapies, which manifests via complex interactions across large regions within a tumour.

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