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A MATHEMATICAL HOMOGENISATION APPROACH TO MASS TRANSPORT MODELS FOR ORGANOID CULTURE

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Summary: Organoids are three-dimensional multicellular tissue constructs used in applications such as drug testing and personalised medicine. We are working with the biotechnology company Cellesce, who develop bioprocessing systems for the expansion of organoids at scale. Part of their technology includes a bioreactor, in which organoids are embedded within a layer of hydrogel and a flow of culture media across the hydrogel is utilised to enhance nutrient delivery to, and facilitate waste removal from, the organoids. A complete understanding of the system requires spatial and temporal information regarding the relationship between flow and the resulting metabolite concentrations throughout the bioreactor. However, it is impractical to obtain these data empirically, as the highly-controlled environment of the bioreactor poses difficulties for online real-time monitoring of the system. Mathematical modelling can be used to improve the yield of organoids grown within the bioreactor, by predicting the metabolite concentrations during culture for different operating conditions. However, since millions of discrete organoids are grown simultaneously, modelling the mass transport and organoid growth is computationally infeasible in this multiply connected three-dimensional problem involving many moving boundaries of organoid-hydrogel interface. We present a general mathematical model for the transport of nutrient and waste metabolite to and from organoids growing within the hydrogel. We use an asymptotic (multiscale) approach to systematically determine the correct system of effective equations that govern the macroscale mass transport. We explore the homogenised model for different culture conditions for the bioreactor and show how these influence the hydrogel mass transport properties, highlighting the importance of the role of flow in the bioreactor in enhancing metabolite transport, and consequently improving organoid growth.