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Computational Modeling of High Throughput Spheroid-on-a-Chip Devices for Design Screening and Optimization

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ABSTRACT

Microfluidic spheroid-on-a-chip platforms are currently being developed for applications involving the formation and culture of spheroids for biomedical research. Spheroid-on-a-chip platforms offer several unique features including control of spheroid size, control of microenvironmental cues, and importantly, the capability to enable drug screening in a high-throughput manner. However, drug delivery to and absorption by spheroids is a multifaceted process that relies on a myriad of biomechanical, chemical, and biophysical factors. Studying the effects of these coupled factors on spheroid culture can be accelerated by employing high-throughput microfluidic devices that allow combining various experimental and operational conditions on independent spheroid samples. To explore these coupled effects efficiently, microfluidic device designs need to be iterated by trial-and-error, which is time-consuming and labour-intensive. Computational modelling has potential to accelerate the design process by enabling rapid *in silico* simulations of different designs without the need for costly physical experiments.

We describe an efficient computational strategy for simulating fluid flow and transport of drugs in a spheroid-on-a-chip platform that has potential to be extended for use across most microfluidic platforms. Our approach enables a "full-factorial" examination of the design parameter space in a combinatorial manner. The developed approach is based on four key aspects: (i) governing physical equations; (ii) parametric sweeping; (iii) parallel computing; and (iv) extensive dataset analysis. CFD modelling was carried out efficiently by combining these elements to significantly reduce computational time. We modelled and simulated more than 15,000 microfluidic device designs and flow conditions in an arrayed spheroid-on-a-chip device to analyze the delivery of anti-cancer drug molecules to the multicellular spheroids. The results of all simulations were summarized in a single dataset consisting of ~10 billion data points requiring ~95 GBs of storage. In addition, to validate our computational model, we performed physical experiments in a representative spheroid-on-a-chip arrayed device that showed excellent agreement between experimental and simulated data. We ventured to create a standalone user-friendly software that can be installed and executed on different devices and operating systems to deliver a helpful design tool for the microfluidics engineer to reduce the device design iteration time and suitable design operating conditions for end-users of the spheroid-on-a-chip platforms. In summary, this study offers a computational pipeline tailored to accelerate the microfluidic device designs optimization process by providing insights into the fluid flow and drug transport in spheroid-on-a-chip and other biomicrofluidic platforms.

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