Project title: Digital twin agent-based simulation to in vitro "tissue-on a chip" device to understand radial dysplasia vascular malformations

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Aim of the project

This project will aim to investigate establishment of the first digital twin agent-based-model simulation matched to a specific in vitro experimental biology cell-based device where vascular networks spontaneously form under different controllable conditions in order to better understand how fibroblast cells alter vascular growth during muscle formation. This will allow us to:
1) research best practice in designing efficient, scalable digital twin simulations for biomedical cell-based discovery research, and
2) allow us to test specific biological hypotheses as to how and why the mutated fibroblasts found in radial dysplasia patients drive malformations in patient vasculature, as there is a critical clinical need to improve treatment strategies in radial dysplasia patients.

Project description

Simulations are becoming more widely used in biomedicine to understand collective cell behaviour during tissue growth and to predict interventions and therapeutic strategies. For example, our lab has developed highly predictive agent-based models, where cells are modelled as autonomous agents during the process of blood vessel growth. The models were validated as predictive by followup biological experiments e.g. [1,2].

However, the models are usually: 1) very simple in their design, capturing in some abstracted way just a few cells in a simplified arrangement lacking the actual geometry or larger tissue context real cells would be in; 2) they are calibrated to data obtained from a variety of different experimental cell systems or organisms, published in the literature or available through collaborators, which 3) may not reflect values or tissue geometry/features needed to capture in the experimental setup later used to validate the model, which is usually again different t those used to calibrate it. It is widely known that cells adapt their behaviour, gene expression and signaling to different environment contexts and will have secies and cell type slecfici properties, it is imperative for models to be optimally predictive to ideally have one single experimental setup which can be used to both calibrate and validate the model, otherwise the mismatch between the real contexts and the simulated one may well limit the potential predictive power.

Digital Twins, which closely couple the simulation directly to one specific real case context are becoming widely used in industry across domains and now more in healthcare for example to personalise medicine [3]. As yet the approach is under used in biological cell-to -tissue based modelling despite having huge potential. This project will aim to investigate establishment of a digital twin agent-based-model simulation matched to a specific in vitro tissue on a chip device, where vascular networks spontaneously form under different controllable conditions in order to

both investigate best practice in designing large scale cell biology digital twins and test hypotheses as to why the mutated fibroblasts found in radial dysplasia patients [5] drive malformations in patient vasculature aswell as muscle alignment problems, as there is a critical clinical need to improve treatment strategies in these patients.
Candidate expectations: the ideal candidate will be highly proficient in C++ and principled software engineering practices to ensure the digital twin simulation is as scalable, extendable and reusable as possible given the commercialisation potential of the approach to map to other cell-based devices and biomedical questions in the future. Experience with agent-based or multiscale modelling advantageous, as is experience of calibrating/validating models against real world data. An interest or experience in biological problem solving or modelling desirable but not essential as training can be given in all biology required for the project. Excellent communication skills to handle discussion across disciplines essential.

References:

1. Bentley,K et al. "Do endothelial cells dream of eclectic shape?." *Developmental cell* 29.2 (2014): 146-158.
2. Bentley, K. "The temporal basis of angiogenesis." *Royal Society PTB* (2017): 20150522.
3. Björnsson, B, et al. "Digital twins to personalize medicine." *Genome medicine* 12.1 (2020): 1-
4. Akinbote et al “Classical and Non-classical Fibrosis Phenotypes Are Revealed by Lung and Cardiac Like Microvascular Tissues On-Chip”. Frontiers in Physiology 2021
5. Logan, MPO, et al. "Individual limb muscle bundles are formed through progressive steps orchestrated by adjacent irregular connective tissue fibroblasts during primary myogenesis." *Cell Reports* (2020).