University of Leicester

EPSRC DLA Studentship

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Section 2 – *Project Information*

Project Title	A multi-modal computational platform to engineer user desired multicellular systems

Project Summary

When an aerospace engineer designs a new spacecraft, their next step entails using a computer simulation toolkit to assess the functional viability and structural robustness of the design – **not** real-life testing. This results in secure, reliable, and sustainable practices/products with high success rates. The biomedical and pharmaceutical sector **lacks** this capability entirely. As such, in **comparison**, designing new therapies (drugs or regenerative medicine) is prohibitively expensive (>$2B spent/drug), lengthy (~10 years/drug), and with high failure rate (96%). With ageing populations living longer and experiencing more complex health needs, there is an immediate need to develop software capability that much like aerospace simulation toolkits enable the biomedical and pharmaceutical companies rigorously test new design and assess efficacy **before** conducting more expensive clinical testing.

The **critical challenge** to overcoming this gap is that single paradigm approaches are not broadly applicable in the biomedical context. For example, **continuum models** do not consider system heterogeneity (a signature of biology), **cellular automata** models do not scale easily, **Boolean regulatory network models** lack inherent space and time, and **stochastic models** (AI and LLMs) are devoid of underpinning biology and physics. As we have shown, this can be overcome by considering a multi-paradigm approach. For example, we previously showed that coupling computational fluid dynamics (CFD) with cell interactions can help **design** effective bioreactors that output user desired multicellular systems (Kaul et al, PLoS One, 2013), accurately recapitulating cell interactions can help predict the impact of novel drugs on patients (Saunders et al, Science Translational Medicine, 2019), and embedding regulatory networks into virtual cells can help predict human developmental milestones with **unprecedented robustness** (Kaul et al, Stem Cell Reports, 2023).

This project is focused on developing novel software capability that will link regulatory networks with agent-based models and computational fluid dynamics solver to capture how a growing multicellular system shapes its microenvironmental gradients and in turn gets shaped by the very same gradients. We will also add design of experiments (DoE) module to the software so users can explore the 'phase space' of inputs to predict the most optimal combination required for a specific product output.

Aim 1: Link multiple modalities. The candidate will use the Flexible Large-scale Agent-based Modelling Environment (FLAME) to couple regulatory network models, virtual cells, and CFD solver. This system will enable 1:1 correlation between multicellular systems in silico and in vitro (novelty).

Aim 2: Add DoE module. The candidate will next embed a DoE module into the FLAME-based multi-paradigm framework above. They will either “plug-in” a third-party software or create a pipeline of existing libraries within FLAME depending on feasibility.
Aim 3: Develop and validate the webapp. The FLAME-based multi-paradigm framework will be packaged into a webapp, which will be designed in collaboration with BiologIC Technologies. Once developed the app will be implemented within the company to simulate cell growth rates and differentiation potential within one of their patented bioreactors.
Success will be measured by our ability to guide fate of multicellular systems within the bioreactors and by high-quality research outputs.

References

1. A multi-paradigm modeling framework to simulate dynamic reciprocity in a bioreactor. PLoS One 8(3), e59671.
2. Virtual cells in a virtual microenvironment recapitulate early development-like patterns in human pluripotent stem cell colonies. Stem Cell Reports 18(1), 377-393.
3. Predicting and controlling collective fate in multicellular systems. Biorxiv, doi: 10.64898/2025.12.11.693804