Project title: Digital twin model of the cytokinetic contractile ring during cell division

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Aim of the Project

This project will develop a novel computational model to query hypothesised mechanisms on the currently missing or poorly understood aspects of the core cytokinetic machinery driving the fundamental process of cell division. The detailed study of this process has so far eluded current wetlab capabilities due to the complex feedback and emergent dynamics of the molecular components involved; which integrated simulations will allow to be systematically investigated.

The simulation model will be twinned directly to previous and ongoing wetlab experimental data aswell as building upon known aspects of eukaryotic cell division, including signalling pathways, cytoskeletal proteins, and membrane dynamics.

The primary aim of this project is to elucidate the currently unclear role of cytoskeleton- membrane interactions during contractile ring closure as cells divide. A secondary aim is to then use the established digital twin model to study the differences between healthy and diseased cells, e.g. dysregulated asymmetric divisions during cancer.

Project Description

In animal cells, the physical cleavage of a cytokinetic cell into two daughter cells is driven by a Contractile Ring (CR) that forms at the cell's equator and progresses inwards in the axis of division. This membrane-bound supramolecular structure is composed of actin and myosin (collectively, actomyosin), forms in the cellular cortex, and is known to provide the mechanical force necessary to partition the cell. Importantly, the precise spatiotemporal regulation of the CR is critical to successful cytokinesis and is mediated by the RhoA GTPase signalling network.

Rho-dependent actomyosin networks control a breadth of biological processes other than cytokinesis such as cell polarity, cell motility and wound healing. Yet, many questions remain about the molecular interactions driving these networks. In cytokinesis, the Rho-dependent actomyosin cytoskeleton does not operate in isolation. Active RhoA also assembles a filamentous network of anillin and septins at the furrow membrane. Since it can bind both actomyosin and RhoA/septins, anillin is proposed to regulate the coupling of actomyosin and septin-based cytoskeletal networks (Henson et al., 2024). Furthermore, the contributions of CR-membrane attachments to CR tension regulation are unknown but likely important (Carim 2020).

This project will study the RhoA-dependent interactions between the actomyosin cytoskeleton, the anillin-septin cytoskeleton, and the underlying plasma membrane by coupling simulation with wetlab approaches. The dynamic nature of the system, its subcellular spatial scale, and its short temporal scale, makes the CR notoriously challenging to isolate and observe in vivo. Thus, the project will make up for the technical limitations faced in the wetlab by building a complimentary computational model which recapitulates and explains observed phenotypes under varying experimental conditions. Such a model, once correctly calibrated to available evidence of eukaryotic cytokinesis, will open a new avenue for studying in full the contractile mechanisms of eukaryotic cells.

The Bentley lab and Hickson lab have together developed a prototype agent-based model (ABM), derived from the accepted "SCPR" model by Pollard, where each molecular component is an autonomous agent following rules determining its interaction behaviour, position and dynamics. ABMs have the particular property that simple, local rules of interactions can lead on mass to unexpected emergent dynamics of the system as a whole, thus it is a very useful method for tackling the open questions in this project. The student can use this prototype as a basis for extension or learning tool for their own novel model design.

Requirements:

This project requires a strong computational background (e.g. C++/Python strong competency) and a general understanding/enthusiasm to learn the biology of the system as well as strong communication skills required for cross-disciplinary research.