INTEGRATIVE MODELLING

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Complex and dynamic interactions between cancer cells and elements of the tumour microenvironment shape tumour progression and contribute to therapy resistance. To unravel the biological complexity, and to uncover novel vulnerabilities to target, our lab focuses on developing diverse computational approaches, ranging from mechanistic modelling and computer simulations to spatial data analysis and machine learning. Our vision is that these approaches, in integration with clinical and pre-clinical experimental research, will increase our insights into the fundamental mechanisms underpinning tumour progression and therapy resistance and, ultimately, improve our strategies for cancer treatment.

The Integrative Modelling lab was established in August 2023. Since then, we have been developing collaborative interactions and recruiting team members to join the lab in 2024. In our lab, we are interested in developing computational approaches to investigate the evolutionary dynamics and organisational principles of the tumour and its microenvironment. Our goal is to reveal a tumour's vulnerabilities through the lens of computational modelling and identify novel strategies to tackle therapy resistance. We collaborate broadly with cancer biologists, experimentalists, and clinicians, in an iterative manner, to ensure the biological relevance and translational value of our computational research.

Modelling evolutionary dynamics

Our first strand of research evolves from our previous research in modelling tumour evolution, we focus on developing mathematical and computational models to study co-evolutionary dynamics of the tumour and its microenvironment. Inference of dynamic co-evolutionary trajectories from tumour snapshots in patient samples and pre-clinical experimental models will increase our insights into shared or divergent behaviours between subsets of tumours and can potentially reveal windows of opportunity for therapeutic intervention.

In the context of pancreatic cancer, Jayathilake, a postdoc who will join the group at the beginning of 2024, will develop computational models to investigate the co-evolution of tumour, stroma, and the immune compartment, to improve our understanding of therapy resistance mechanisms. Initial stages of the model development will be integrated with previously conducted pre-clinical mice experiments that evaluated the efficacy of drugs or drug combinations, in collaboration with Jen Morton's lab. The established model will then be used to explore treatment strategies for overcoming therapy resistance, with an aim to inform future experiments for validation.

Another postdoc expected to start in our lab in 2024 will develop computational models to investigate growth patterns and microenvironments of colorectal cancer liver metastasis. The computational modelling will establish mechanistic insights into the dynamic integration of biological processes governing the distinct histopathological growth patterns, encapsulated or replacement growth, associated with better or worse patient outcomes, respectively. In integration with pre-clinical mouse modelling work in Owen Sansom's lab, these computational models will have the potential to inform preventive and interventive strategies to disrupt the growth of metastatic colorectal cancer within the liver.

Mapping organisational principles

In the second strand of our research, we focus on mapping organisational principles of the tumour microenvironment. Unravelling key cell behaviours and cell-cell interactions that sculpt the tumour microenvironment will potentially uncover novel therapeutic targets to combat tumour progression. We are interested in two levels of "mapping".

The first level of mapping involves spatial data analysis and machine learning methods. The rapid advances in spatial biology techniques, such as multiplex imaging and spatial transcriptomics, have deepened our insights into the spatial complexity of the tumour microenvironment. We are interested in developing innovative data analysis tools to discover spatial biomarkers within the cellular ecosystems, in collaboration with John LeQuesne's lab and Nigel Jamieson's lab in the School of Cancer Sciences, University of Glasgow. We are currently exploring opportunities to recruit a PhD student to focus on this research area.

The second level of mapping will be achieved through the integration of computational modelling and spatial data analysis. Computer simulations of the mathematical and computational models will result in diverse dynamic co-evolutionary trajectories of the tumour and its microenvironment *in silico*.

Linkage of these simulated tumour snapshots with the static spatial data of patient tumour samples will enable us to infer key cellular mechanisms and organisational principles. To facilitate this level of mapping through an integrative approach, the postdocs starting in 2024 will develop data analysis and statistical inference tools, alongside their computational modelling work.

Concluding remarks

Cancer is a complex, and dynamically evolving, system. In the era of big cancer data, computational approaches are well positioned to tackle the complexity and distil key biological signals to inform clinical and pre-clinical experimental research. In the coming year, we look forward to welcoming our first group members to the ***Integrative Modelling*** lab and taking our research ideas forward together.

Publications listed on page 112

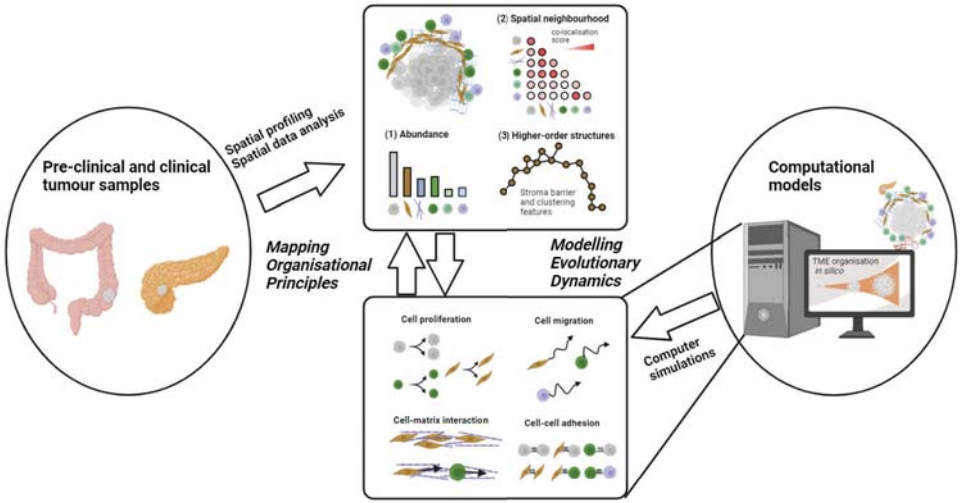

Figure 1. A framework for integrating computational approaches with pre-clinical and clinical work to investigate the evolutionary dynamics and organisational principles of the tumour microenvironment.