

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 stratification and treatment of patients.

The Integrative Modelling lab was established in August 2023. We are delighted to have welcome multiple team members to the lab in 2024. In our lab, we are interested in developing computational approaches to investigate the co-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 co-evolutionary dynamics

The first strand of research evolves from our previous research in modelling evolutionary dynamics of tumours. 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 molecular and spatial profiles of tumours 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 therapeutic targets and windows of opportunity for intervention.

Jayathilake Pahala Gedara, a postdoc who joined the lab in January 2024, has been investigating the crosstalk between tumour and its microenvironment in pancreatic cancer, with the goal to improve our understanding of resistance mechanisms and

identify more effective treatment strategies. The computational model will be integrated with pre-clinical mouse experiments that tested the efficacy of drugs or drug combinations, in collaboration with Jen Morton's lab. The longer-term view is to establish an *in-silico* therapy testing platform for computationally screening treatment strategies for better outcomes and identifying promising candidates for experimental validation.

Philip Liu, a postdoc who joined the lab in September 2024, has been investigating early dynamics and determinants of colorectal cancer liver metastasis. The computational modelling will establish mechanistic insights into the dynamic integration of biological processes driving the distinct histopathological growth patterns, encapsulated or replacement growth, associated with better or worse patient outcomes, respectively. In integration with pre-clinical mouse experiments in Owen Sansom's lab, these computational models will have the potential to inform early preventive and interventional 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. **Anh Nguyen Phuong**, a PhD student who joined the lab in October 2024, has been investigating spatial biomarkers within the cellular ecosystems of colorectal cancer, in collaboration with Joanne Edwards's and Nigel Jamieson's labs in the School of Cancer Sciences, University of Glasgow. We are exploring further funding opportunities to grow this research area, in collaboration with John Le Quesne's lab.

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

simulated tumour snapshots with molecular and 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, modellers in the lab will also be developing quantitative data analysis and statistical inference frameworks, 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, alongside clinical and pre-clinical research, in an integrative and iterative manner.

We are very excited about contributing our integrative modelling perspectives and approaches to the multidisciplinary research at the CRUK Scotland Institute and wider cancer research community.

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.

