Computational modelling of cancer biology and treatments

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1 Overview of the Field

According to the Special Report on Cancer Prevalence published by the Canadian Cancer Society, Statistics Canada, and the Public Health Agency of Canada in November 2022, cancers affect 2 in 5 Canadians, with an estimated 1.5 million Canadians living with and beyond cancer as of 2018 [1]. The prevalence of cancer both globally and in Canada motivates ongoing research to understand how cancers begin, develop, and are treated. Cancer biology and treatment involves complex, dynamic interactions between cancer cells, the tumour microenvironment, and therapeutic molecules. Common standard-of-care therapies generally involve cytotoxic chemotherapies that are hard to tolerate. Thus, much research effort in oncology is focused on the development of improved anti-cancer treatments that will more effectively and more rapidly remove a patient's tumour, while inducing fewer toxic side-effects. At the biological level, many open questions remain about the cells of origin of a variety of tumours, how tumours interact with and adapt to the immune system, and how metastases are seeded.

Mathematical oncology is a young but mature field focused on the development of mathematical models of cancer to respond to gaps in our knowledge of cancer biology and therapy [2]. Since its outset in the 1990s, mathematical oncology has encompassed a wholly interdisciplinary approach through the integration of experimental and clinical data, and in collaboration with researchers in the pharmaceutical industry. Previous research has improved our understanding of a variety of liquid and solid tumours, how they interact within themselves and with the immune system, and the mechanisms and effects of treatment.

The questions related to how cancer begins, develops, and is treated are integral to the drug development process. The drug development pipeline is costly in terms of annualized costs (average 2.7 Billion USD per drug [3]), time, and burden to patients. In oncology, attrition along this pipeline is particularly pronounced. Thus, new solutions to drug development are required. The pharmaceutical industry has increasingly relied on model-informed drug development and quantitative systems pharmacology that integrate mathematical and computational models to facilitate drug discovery and development. Mathematical oncology has evolved in step with this paradigm [4]. Indeed, quantitative approaches combining mechanistic disease modelling and computational strategies are increasingly leveraged to rationalize pre-clinical and clinical studies, and to establish effective treatment strategies. In this way, mathematical approaches lay the foundation for computational virtual laboratories that offer fully controlled, and non-invasive conditions in which we can investigate emergent clinical behaviours and interrogate new therapeutic strategies [5].

Among new approaches in this vein are virtual clinical trials that integrate mechanistic mathematical and

computational models of cancer development and treatment to predict the effects of therapy on a heterogeneous population of "virtual patients" [6, 7, 8, 9, 10, 11, 12, 13, 14]. Virtual (or *in silico*) clinical trials are useful computational platforms that draw on a range of mathematical techniques and help distinguish mechanisms of therapeutic successes and failures, stratify patient risk classes based on an individuals physiology, and optimize drug-specific parameters. In these platforms, *in silico* patients are generated by drawing from distributions of patient-specific characteristics and used to form virtual clinical trials, in which new treatment strategies can be evaluated prior to human trials. Data fitting, probability theory and optimal control theory are cornerstones of this computational platform and are used to generate realistic virtual patients and evaluate individualized therapies. Such *in silico* clinical trials have been used to understand how to best implement combination therapy, decipher the mechanisms of treatment response, and motivate early phase clinical trials.

Other new approaches in mathematical oncology include agent-based models (ABMs), a computational formalism that describes the way individual agents (e.g., cancer cells) interact through probability distributions based on defined characteristics [17]. ABMs have contributed significant insights into cancer biology at the intra-patient tissue level. In oncology, this technique has been applied to model spatial tumour formation, tumour cell heterogeneity, and the dynamics of treatment in the tumour microenvironment. Modelling individual cells as agents allows for direct translation of biological observation into simulation rules and, like virtual clinical trials, the investigation of new hypotheses and treatment strategies.

This workshop was focused on bringing together researchers working on developing and applying the novel techniques of ABM modelling, virtual clinical trials, and other areas of computational modelling to improve the way we model cancer biology and treatment. Participants were invited with an eye on several factors, including diversity, career stage, career type (e.g., academia and industry), and research focus (e.g., fundamental, methodological, preclinical, and/or clinical). In total, 26 participants attended in-person at BIRS and another 20 joined online. Of these 46 attendees, 20 were women and 26 were men, and 22 were early-career researchers (of which nine were students or postdoctoral researchers).

2 Workshop Overview

2.1 Workshop Objectives

This workshop aimed to provide an overview of cutting-edge research in mathematical oncology. One of the goals was to further a variety of techniques of critical importance to the mathematical oncology community for their continued development. For example, with the increased integration of data-driven and computational approaches in oncology, the technique of virtual clinical trials is to be more readily applied for evaluating model robustness and understanding how heterogeneity impacts on disease trajectories and treatment outcomes. In this vein, ABMs represent an important component of computational modelling in oncology however there is still a lack of consensus on the translation and implementation of basic modelling assumptions in ABMs of tumour growth. In addition to highlighting models using ordinary differential equations and stochastic approaches, we aimed to discuss and explore the advantage of different modelling assumptions with regards to specific goals in oncology, helping to establish commonalities between modelling approaches and advance the field. Lastly, the rate of generation of high-dimensional data requires the development of new mathematical and statistical techniques for their analysis. Thus, a focus of this meeting was to understand cutting-edge bioinformatics techniques and their integration within mathematical modelling in oncology. Importantly, the rapid pace with which new biological insights and treatment modalities are discovered and implemented implies that meetings such as this are necessary for our community.

Overall, the objectives of this workshop were to:

- provide insight into the range of mathematical modelling techniques used to analyze preclinical and clinical data in oncology, including basic tumour biology;
- introduce different techniques for developing *in silico* clinical trials and their ability to account for within- and between-patient heterogeneity;

- review ABM platforms for modelling in cancer biology and treatment;
- discuss the intersection of current modelling approaches to develop improvements to each approach;
- understand state-of-the-art treatment approaches and the ways they can be modelled.

2.2 Workshop Structure

We adopted several modalities to address the workshop goals stated above. These include lightning talks of 3-4 minutes delivered by each participant (in-person and virtually) to provide an overview of their work, six plenary (60 minute) talks delivered by experts in the field, and breakout group discussions. Each of these aspects is discussed in the sections below.

3 Lightning Talks

A total of 35 lightning talks were delivered over the first day of the workshop. Each of these presentations highlighted either a specific aspect of the participant's research (e.g., modelling to improve the treatment of acute myeloid leukemia, insights from mathematical models of gene regulatory networks, treating stem cells with oncolytic viruses etc.) or provided an overview of their research program (e.g., cell fate decision making in stem cells and cancer, real-life tumour simulations as test beds for potential cures etc.). The goal of these talks was to quickly familiarize the group to the research being carried out by attendees, helping to shape the discussion groups that would carry on throughout the week (see below).

4 Keynote Talks

Six plenary presentations were delivered. Keynote speakers were chosen to highlight research excellence and the diversity of our community. Efforts were made to ensure gender parity in speakers and to ensure that presenters represented a range of research (from fundamental biology to clinical work). A brief description of each talk is provided below.

1. **Mohit Kumar Jolly: "What does not kill cancer cells makes is stronger: Dynamical modeling of drug-induced cell-state switching"** Dr. Jolly presented mathematical models of gene regulatory networks and phenotypic interactions to study heterogenity in cell killing and combination strategies in melanoma and non-small cell lung cancer [15].

2. **Ivana Bozic: "Evolutionary dynamics of tumor progression"** Dr. Bozic's talk centered on chronic lymphoblastic leukemia and colon cancer. In her presentation she described recent work describing the Bayesian classificiation of tumour growth as either 1) logistic, 2) exponential, and 3) indeterminate, and further discussed the dynamics of pre-leukemic expansions [16].

3. **Paul Macklin: "A cell behavior grammar for real-time modeling and knowledge curation"** Dr. Macklin described updates to the PhysiCell (www.physicell.org) agent-based modelling framework that he and his team have developed. These include a GUI and a standard dictionary of cell types and functions to build models interactively, helping to break down barriers between the modelling community and experimentalists/clinicians who may not be familiar with mathematical models [17].

4. **Natalia Komarova: "Evolutionary modeling of cancer treatment"** Dr. Komarova described her work on the stochastic analysis of combinatorial mutation networks during combination therapy with applications to leukemia and colon cancer. She provided an overview of how straightforward models can be used to distinguish mechanisms of drug resistance and treatment success, and discussed minimal data requirements to respond to model parameter non-identifiability [18].

5. **Adam MacLean: "Inference of cancer cell state dynamics in complex tumor microenvironments"** Dr. MacLean spoke about how cancer was a multiscale problem. He described his work on using transcriptomics to understand calcium signalling and cell responses. He also presented recent work on myeloid-derived suppressor cells in the metastatic niche [19]

6. **Renee Brady-Nicholls: "Improving Prostate Cancer Hormone Therapy Through Dynamic Modeling"** Dr. Brady-Nicholls presented her work aimed at reducing racial disparities in metastatic prostate cancer through extensions to adaptive therapy protocols tailored to improve outcomes for underrepresented minorities. She discussed range-bounded adaptive therapy in this context, which is based on the idea that treatment cycling improves the duration of treatment efficacy because it provides sensitive cells the ability to outcompete resistant cells [20].

5 Breakout Group Discussions

Based on the lightning talks, we met as a group in the afternoon of the first day of the workshop to discuss the elements common to the participants. Several topics were explored, including standardization, what tools do we need to develop?, combination therapies, phenotypic/genetic transitions, parameter identification, cancer immunology and immuno-oncology, multiscale modelling, agent-based models, modelling frameworks, gene regulatory networks, parameter estimation, and virtual clinical trials. We decided to divide into three groups focused on 1) Frameworks (e.g., agent-based models, modelling standards, high performance computing in mathematical oncology, etc.), 2) Treatments (e.g., combination approaches, immunotherapies, etc.), and 3) Biology (e.g., tumour development, cancer stem cells, etc.). Outside of keynote talks, we met in these groups for the rest of the week.

Discussions in the Frameworks group centred on how a standard of modelling in oncology could greatly assist the mathematical oncology. Our group discussed, how with the exponential increase in mathematical modelling works in oncology, we may be losing our ability to validate and reproduce results, which then reduces the reliability of mathematics in cancer research. We discussed how a framework for how a model should be developed and what minimum information was necessary in papers is crucial moving forward in the field. In our discussions, we sketched out what this framework should look like, and hope to share it with the community imminently.

The Treatment group decided to focus on combination therapies, given their importance for anti-cancer therapy. We held extended discussions about a toy model framework that could be developed as a guide for deciding modelling elements to describe combination treatments. The idea behind this basic model was to represent in the most general framework the fundamental building blocks of polytherapy, including sensitive and resistant cells, and the immune response. Conversations also centred on what data we would need to properly parameterize the toy and other more complicated models (e.g., cell counts, cell kinetics etc.) and what data we could expect to be able to access (e.g., pharmacokinetics and pharmacodynamics, etc.) with the goal of providing practical utility and application. In this vein, we performed a literature review of existing models of combination therapies including chemotherapies, immunotherapies, surgeries, radiotherapies, among others. At least one paper is under development as a result of these discussions.

The biology group discussed the problems we encounter when translating cancer biology into mathematical models. These conversations were focused on multiscale models, how to simplify or find the simplest model to describe a biological phenomenon, and the power of the information provided by such simple models. Relatedly, we also wondered whether a complicated model was necessarily best to define the biology for the specific question to answer, i.e., do we care about the output of a biological system or the multiple pathways leading to the response? As was also discussed in the Frameworks and Treatment groups, a major question we asked ourselves was about the translation between modellers and experimentalists, specifically is it possible to measure the data needed to accurately model the biological question? With respect to model calibration, if we had access to such data, how many data points and how close in time must they be to accurately represent the dynamics of the system in question? This question was answered for simple models describing colorectal cancer and leukemia by Dr. Komarova in her plenary talk later in the week.

6 Feedback from the Meeting

After the meeting, we received a number of messages and comments from participants about the workshop. A sampling of these is provided below.

"*...The conference was truly remarkable, and I am so grateful for the opportunity to participate. It was great to catch up with everyone on the latest advances in mathematical oncology and it was an awesome learning experience for me. Especially the networking opportunities were invaluable. I had the chance to connect and discuss collaborations with many people. I am sure that some of these would pan out to be exciting new research projects. Once again, thank you for the invitation and for putting together such a wonderful event and at such a beautiful venue. Loved every bit of it!*"

"*...Thanks for organizing and great week at BIRS. I had a great time at the conference and am looking forward to the next one! I was inspired by the keynote speakers and the research of the participants. This workshop stood out from others due to the time devoted to discussion on current themes in computational modeling. I found these discussion sessions immensely valuable as they provided a forum to debate different approaches, share and listen to new ideas, and connect with other researchers.* "

"*Thank you so much...for...making it possible for me to participate online.*"

"*The Computational Modelling of Cancer Biology and Treatments workshop was one of the most important networking events during my training as a PhD student. Talks by keynote speakers opened my eyes on the diversity in the computational approaches used to study the field as well as in the researchers themselves. However, the group discussion sessions were the highlight of the event. They were great opportunities to get to know the scientists in this community, those that can potentially be my next mentors, colleagues, or collaborators. I learned from more experienced researchers about the differences in the restrictions and goals of cancer research for scientists in academia and in industries. We also discussed the challenges of working in collaborations with experimentalists and the multiple problems we encounter when translating tumour biology into mathematical and computational models. Finally, inputs from the more senior researchers influenced me to look at my own research with a new perspective and inspired new ideas to apply in my studies.*"

7 Conclusions

Mathematical oncology is a significant subfield of mathematical biology. As discussed above, we believe that this workshop achieved its aims, namely to bring together a diverse group of researchers across a swath of research focuses and career-stages to forward computational modelling in cancer biology and treatments. Feedback received from participants was overwhelmingly positive, and talks are ongoing to organize a follow-up event. We wish to thank the Banff International Research Station staff for helping to organize this successful event and hope to be back soon.

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