Abstract

Cancer is a complex system consisting of a heterogeneous cell population interacting with its environment. Cancer cellular behaviour is guided by intrinsic rules and regulatory dynamics in the interplay with abiotic factors and other cell populations. This influences the evolutionary history of the organism's tumour mass and its reaction to applied therapies. Moreover, the therapies themselves and the selective pressure exerted by the environment, in turn, influence the composition of the tumour mass and its evolution in time. The complexity and the overlap of all these processes make it challenging to find a biologically coherent explanation or observe the underlying dynamics of numerous emerging phenomena. The idea behind the use of mathematical modelling in the biological field, specifically oncology here, is to provide a tool that, built on the scientific knowledge we possess, can fill the gap with the observed phenomena.

In this thesis, we aim to investigate the phenomena of resistance and relapse in cancer treatment. We focus on characteristics of the tumour mass that are relevant for their impact on the outcome of therapies and for the benefit of using the mathematical tools geometry and heterogeneity.

In detail, with geometry, we refer to the mass's growth, movement, shape, and spatial location. Addressing heterogeneity, we consider the different genetic and epigenetic signatures that characterise cell subpopulations, altering their phenotype, together with environmental conditions.

In order to catch these features, in the various models of the thesis, spatial PDEs are adopted and structured, or multiple cell populations are employed, with a predominance of non-local continuous modelling strategies with multi-scale derivation. In all our models, the description of the tumour population is characterised by proliferative, mortality, and motile dynamics, and the (epi)genetic signature determines the performance potential of each. Furthermore, when considered in the models, external factors are directly entered into the framework. In particular, we consider the interaction with abiotic factors and other populations.

In this thesis, the state of oxygenation of the tissues is critical among environmental factors. Many of the models we present include hypoxia, considering its influence on proliferativity as its regulator, mortality as a selective pressure, and cell movement as a trigger of chemotactic drift. Particular attention is given to anti-tumour processes, which include the immune system's defence reaction and therapies such as radiotherapy and oncolytic virotherapy. Even when studying treatments, the influence of oxygenation is taken into account.

Both the works already carried out and the future perspectives move toward therapeutic optimisation from a personalised medicine perspective. In this sense, mathematical modelling represents an adjuvant tool alongside clinical analysis in the diagnosis and treatment. The final aim is to propose an alternative to the systematic use of standard protocols and against the paradigm of aiming at eradication as the only therapeutic strategy in the attempt to avoid the emergence of relapses and extend a patient's life, keeping its quality as uncompromised as possible.

The thesis opens with the **Introduction** chapter, that establishes the framework and introduces the reader to the work structure, organised in three parts. **Part I** presents the biological and mathematical framework for the works. It provides all the basic knowledge needed to understand the mathematical models introduced in the various chapters and the biological processes described. A general state of the art is included. **Part II** collects all the research results obtained so far, including the contents of already published or submitted papers. **Part III** presents ongoing works and future perspectives and summarises the current point of arrival and future steps.

Part I consists of two chapters.

In **Chapter 1**, we introduce the needed biological background to understand the tumour dynamics involved in our mathematical models. We introduce basic knowledge on the biology of healthy and cancer cells, heterogeneity in cancer cell populations, interaction with the microenvironment and therapies (radiotherapy and oncolytic virotherapy). Finally, we explain the meaning of analysing cancer as an evolutionary process, enlightening its

multi-scale nature, describing it in its temporal phases, and considering the trade-offs its cells face.

In **Chapter 2**, we present an overview of the adoptable mathematical strategies (continuous/discrete/hybrid, deterministic/stochastic), and explain the pros and cons of different approacheto describe the biological dynamics introduced in the previous chapter.

In **Part II**, each chapter presents a different model (referring to an already published or submitted paper) built for investigating a specific dynamic. **Chapter 3** and **Chapter 4** are linked by common dynamics of proliferation and survival with respect to the oxygenation of the environment. In particular, **Chapter 3** concentrates on cancer evolution, particularly in the critical tumour-environment interaction. We focus on the central role of oxygen concentration in determining the phenotypic heterogeneity of cancer cell populations, whose qualitative and geometric characteristics are predominant factors in determining the outcome of the cancer mass history. In **Chapter 4**, we stick to the context of the previous chapter but insert radiotherapy as a treatment, considering the pivotal role of eco-evolutionary dynamics in the study of therapeutic strategies for cancer treatment.

Chapter 5 and **Chapter 6** are related due to the presence of migratory dynamics.

Chapter 5 has a specific interest in environmental-driven invasive and metastatic dynamics. The focus is on epithelial-mesenchymal transition in cancer cells, and we introduce novel hybrid modelling in which a discrete structuring variable distinguishes cells according to their genotype while a specific mathematical representation (i.e., individual/pointwise vs. collective/density-based) is assigned to each individual based on its phenotypic hallmarks.

In **Chapter 6**, we put specific interest on hypoxia, and we concentrate on the role of Snail transcription factors, which play a central role in how cells respond to hypoxic conditions, influencing epithelial-mesenchymal transition, migration, proliferation, and invasiveness of the cells.

Finally, in **Part III** we present works still under investigation. **Chapter 7** keeps a link with Chapter 5 and Chapter 6 concerning migration dynamics, focusing on go or/and grow dynamics. Here, we present two modelling strategies for cancer cell dynamics (Fisher-like and anti-crowding), proposing three different epigenetic structure characterisations (different combinations of proliferative and motility epigenetic traits). The idea behind the work is the investigation of the epigenetic and phenotypic stratification of tumour spheroids (quiescent core, proliferative rim and infiltrative fingers). The results obtained so far are part of a joint project with the Mathematical Oncology Laboratory (MOLAB) in Ciudad Real.

Chapter 8 introduces a novel mathematical approach to oncolytic virotherapy, accounting for the effect of hypoxia. The main idea of the work, based on the investigative approach of Chapters 3 and 4, is to determine the impact of the epigenetic evolution of the mass, both in terms of composition and geometry, on the effectiveness of the treatment, evaluated in terms of eradication or growth control of the tumour mass.

Chapter 9 introduces the immune system with a future perspective on immunotherapy. We present the early results of an initiated project in collaboration with Professor José A. Carrillo (Oxford University). We start from an already presented model built to describe the behaviour of two cell populations, characterised by adhesive properties, which cohabit in a shared space, and we propose an adaptation of the same to catch interaction dynamics between the cancer population and the immune system. We are interested in quantifying the impact of tumour characteristics on the possibility of eradication and the outcome in terms of hot/cold tumours. Cancer mass is defined by its geometry and composition and via subpopulation characterisation concerning their proliferative rate and immunoevasion capabilities.

In the **Conclusions**, we summarise the results obtained and the future perspectives specifically related to each work and already presented in every chapter. We deduce a *fil rouge*, which we show as a proposed path for the next steps in this research direction.