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PUSHING THE FRONTIERS OF RADIOBIOLOGY: A SPECIAL FEATURE IN MEMORY OF SIR OLIVER SCOTT AND PROFESSOR JACK FOWLER: REVIEW ARTICLES

The many faces of mathematical modelling in oncology

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ABSTRACT

The application of modelling to solve problems in biology and medicine, and specifically in oncology and radiation therapy, is increasingly established and holds big promise. In this review, we provide an overview of the basic concepts of the field and its current state, along with new tools available and future directions for research. We will outline radiobiology models, examples of other anticancer therapy models, multiscale modelling, and we will discuss the mechanistic and phenomenological approaches to modelling.

INTRODUCTION

In comparison with other disciplines such as physics, engineering or economics, the application of mathematical models in biology and medicine has been, until recently, somewhat limited.¹ However, past decades have seen a vast outspread of mathematical modelling in biology and medicine. In oncology, the use of mathematical modelling has increasingly been recognised as an invaluable tool for the generation of experimental and clinically testable hypotheses, and to guide study design.²

A mathematical model is a distillation of biological complexity into a manageable representation, which is both complex enough to keep the general properties of the real system and simple enough to give us insight that can be used to make predictions.³ Mathematical models can help us understand complex biological systems by providing approximations and abstractions that can generate testable hypotheses on how biological components evolve and interact with each other to produce a particular outcome (Figure 1).

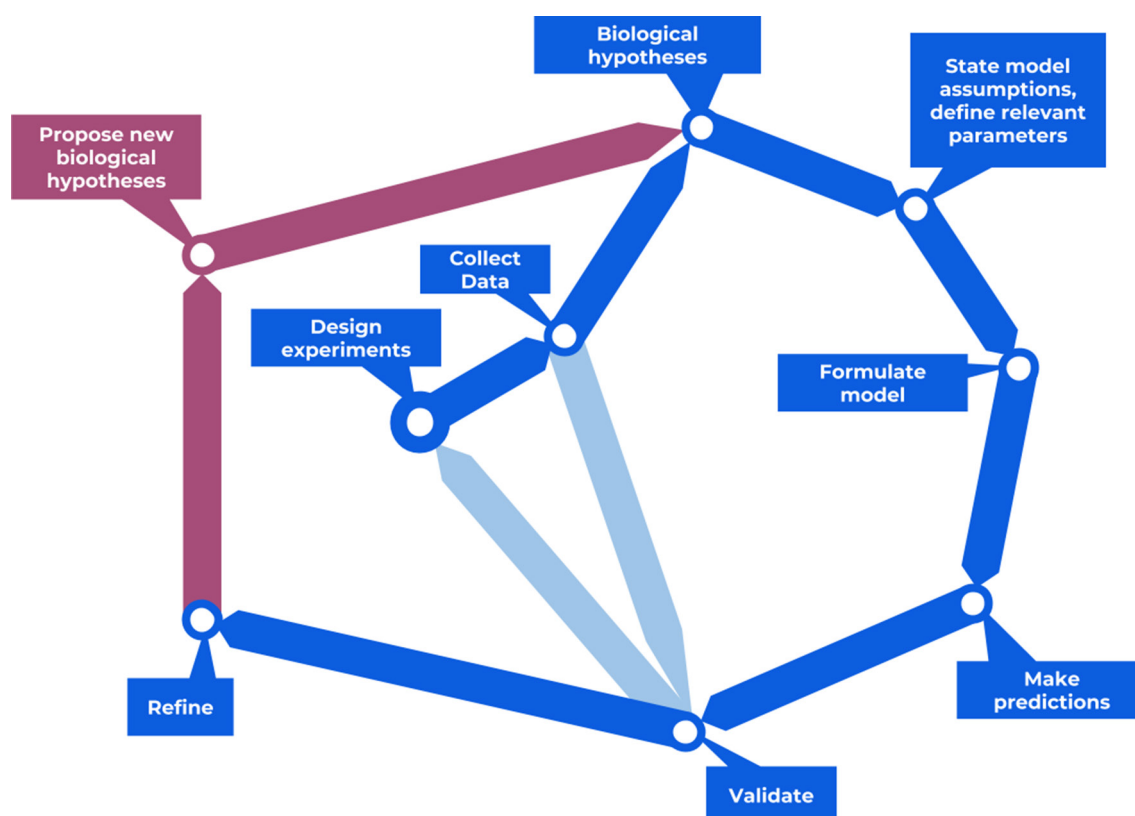
Modelling can provide us with greater insight into the fundamental mechanisms regulating biological systems, and deepen our understanding of disease. As computers become more powerful, the efficiency and range of tasks that can be accomplished increases. At the same time, recent advances in high-throughput technology has enabled the acquisition of an increasing amount of data in several biological systems, including whole genome sequencing

data in disease models and samples from clinical trials. We are now able to build predictive models of therapy outcome using genomic data collected from thousands of clinical samples, or investigate how signalling networks work using functional data from experiments inhibiting the expression of thousands of genes.

It is now accepted that cancer is a heterogeneous disease, and that different cancers present different genetic, transcriptomic and epigenetic footprints with important implications on their evolution and progression, and therefore on clinical recommendations.^{4,5} It is increasingly evident that one size does not fit all and instead, each type of tumour should be treated in a way that reflects its biological characteristics. This is the goal of “precision medicine”,⁶ which aims at stratifying patients into coherent groups based on their likelihood to respond to a given therapy, in order to achieve the most effective treatment and minimal risks.⁷

Stratification has been pursued in the context of several types of cancer, both in the quest for better drugs to use in combination with existing treatments and in the development of biomarkers.^{8,9} However, when it comes to anticancer therapies, the number of drugs, their possible combinations and the different existing strategies of dosage scheduling make predicting the patient's response to therapy a very complex task, requiring very large clinical data sets and extraction of meaningful and clinically relevant data from them. Mathematical modelling and powerful computational techniques enabling the implementation and development

Figure 1. The cycle of designing and refining a model (blue lines), and using it to generate new hypotheses (purple lines).



of increasingly complex models can help greatly in this task, by bringing a new sophisticated set of tools to carry out integrated analysis of different data types (e.g. genetic, transcriptional and epigenetic) and experimental systems (*in vitro*, *in vivo* and clinical). It is becoming increasingly possible, e.g. to perform systematic large-scale and multiscale *in silico* experimentation and, once validated models are established, predict individual patient response to specific treatments. As a result, sufficiently validated models could inform decisions such as the combination of drugs to be administered to specific groups of patients, or the dosage that has maximum efficacy and minimal toxicity.

An important issue that must be considered when discussing the role of mathematical modelling in oncology is tumour plasticity. Individual cancer genomes are heterogeneous, which in turn fosters rapid evolution, cancer cell adaptation and treatment resistance through clonal selection.¹⁰ Genomic profiling on multiple spatially separated cancer samples is showing increasing evidence of clonal evolution, with more than half of all somatic mutations detectable in different subregions of the same tumour.¹¹ Therefore, there is a need to determine both location and time of driver events, and understand how the prevalence of different subclones over time affects therapeutic response. Mutational landscape is not the only characteristic which changes during treatment. It is well known that a radiotherapy treatment can modify the tumour microenvironment both in terms of physiological characteristics, such as the presence of nutrients or oxygen,¹² and the populations of cells present.¹³ All this implies that therapies should be

adjusted or adapted to the emerging context, instead of using a static approach whereby the treatment is mostly determined upfront.^{14,15}

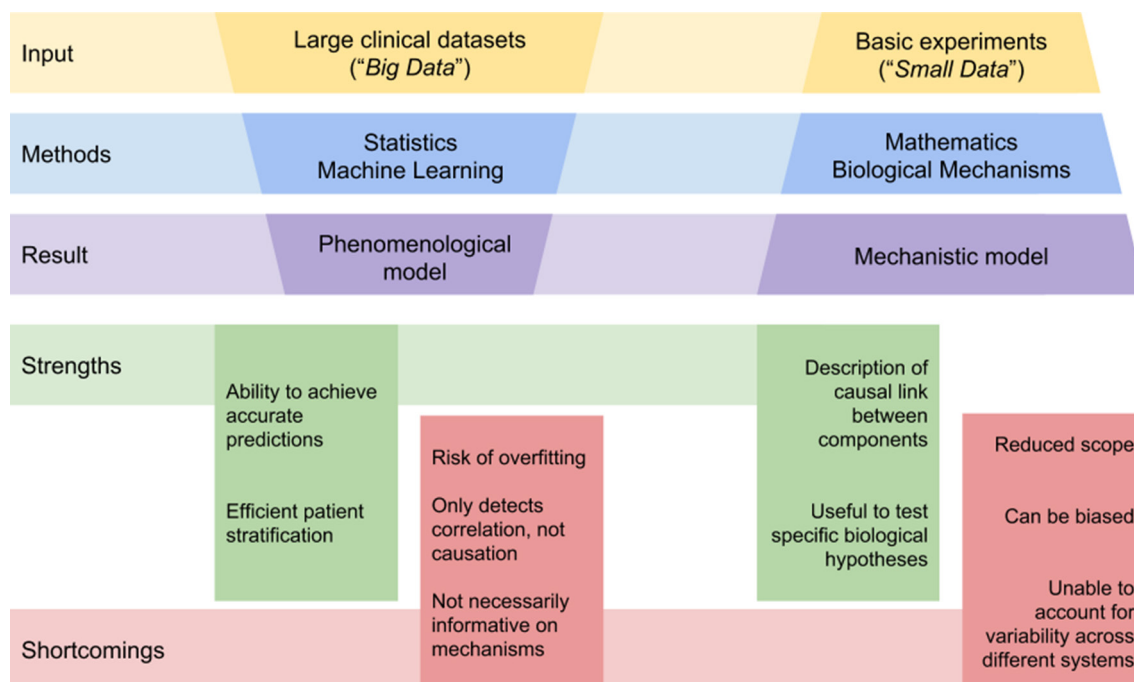
The use of imaging and multiple tumour-biopsy samples is producing extremely important insights into tumour progression, invasion and response to treatment,¹⁶ and could have a great role in helping adapting the therapy. However, these approaches are currently limited by the feasibility and cost of obtaining the necessary data at repeated time points, and thus unlikely to provide the answer for routine clinical practice. Consequently, mathematical modelling and computational tools present a tremendous potential to complement these methods and to reduce the number of data points required to predict the best treatment schedule and the necessary adaptation for each patient.

An exciting new trend in cancer modelling is spatial models. These can mimic the progression from normal tissues all the way to invasive tumours by representing each cell as a three-dimensional (3D) or two-dimensional object. There has recently been a lot of interest for this kind of approach, and it constitutes a promising avenue in cancer modelling (for a recent review see Karolak et al).⁷

PHENOMENOLOGICAL AND MECHANISTIC MODELLING APPROACHES

Most sciences present two main approaches to mathematical modelling, reflecting two different philosophies: The mechanistic

Figure 2. Phenomenological and mechanistic approaches to biological modelling, with their strengths and shortcomings.



("bottom-up") and the phenomenological ("top-down") (Figure 2). There is not a clear hard border between the two, and often the same mathematical or statistical methods can be applied to one or the other. They differ on how they attempt to explain the relationship between the variables to be modelled.

A mechanistic approach attempts to build mathematical models based on specific hypotheses that seek to explain the data obtained based on fundamental principles, and as such, they aim to describe causal relationships between biological components. On the other hand, phenomenological models infer relationship between variables based on their correlation and build statistical associative models to predict the outcome of biologically similar experiments.²

They both have advantages and limitations. Since mechanistic models attempt to simulate networks of real biological components, they are prone to overcomplexity and overfitting due to the large number of these components that are often needed to describe biological systems. Overfitting occurs when a model includes too many variables from a particular set of data and therefore matches very closely with it, but is unable to generalise to other data sets and generate reliable predictions for these. The scope of the mechanistic approach has been typically narrower than that of the phenomenological approach, because the model components tend to be specific for the system they describe. Nevertheless, this makes these models very good tools for the generation of testable hypotheses, which can inform in a very detailed manner the design of new experiments that manipulate in a specific manner those biological components.

A phenomenological approach to build models aims at making predictions based on previous associated observations. They

avoid data overfitting by reducing the number of parameters to those statistically significant to describe the collective behaviour of the system. However, it is important to emphasize that statistical significance does not necessarily imply biological relevance, and thus the variables selected in these models might increase the overall predictive ability but are not always useful to describe how the systems truly work. In other words, association, even when strong and highly significant, does not necessarily imply causality or real interaction. Lastly, since they do not provide mechanistic explanations, it is more difficult to predict how two different systems will interact or behave under new conditions.³

In many scientific disciplines, these two approaches have been used together in a complementary manner. In cases where the number of variables involved is small, the two approaches can lead quickly to similar results whether one starts from the hypotheses or from the data. Still, this is an important discussion in biological modelling because biological systems are incredibly complex entities to model, with hundreds of variables determining their behaviour. Therefore, it is important that while the number of components implicated in, e.g. a biochemical pathway or a gene regulatory network is huge (and so is the amount of data scientists have gathered), a model needs to faithfully represent this complexity while reasonably reducing it to a manageable representation for it to be capable of making predictions that are clinically useful.

A phenomenological approach to modelling has been more widely adopted in medicine as a data-driven approach can often be more effective at conveying the general properties of complex systems.¹⁷ On the other hand, whilst models developed in such a way have been useful to predict the effect of specific therapies in certain patients, they have not provided alternative actionable

solutions for those patients who do not respond to those particular therapies. Thus, a parallel mechanistic method would need to complement those models with a biologically led simplification of the system. This would allow to predict how a system will behave in response to different drugs, and their possible combinations, or after further acquired gene mutations. Recent studies, including our own work,¹⁸ are focusing on trying to bridge both approaches into integrative models.³ We propose that spatial models are particularly suitable candidates for this bridging between approaches as they provide a framework in which to simulate a system at several levels of complexity.

MATHEMATICAL MODELLING IN RADIOTHERAPY

In radiobiology, the use of mathematical modelling has a long-standing tradition and is especially useful, because every treatment is made up of a large number of variables (such as total dose, dose distribution, dose-rate or patient geometry and physiology) which all need to be considered during treatment planning.

Modelling allows researchers, starting from basic assumptions, to estimate the separate contribution of each of these variables and biological parameters to treatment outcome, *e.g.* local control of the tumour, and the likely risks associated with said treatment. The alternative to this (mechanistic) approach would be a complex series of randomised clinical trials where every change in each of these variables was assessed on its own in a data-driven (phenomenological) manner.¹ This would be prohibitively costly both in terms of time and money, and in most cases unfeasible.¹⁹ These are the reasons why a simple model such as the linear-quadratic (LQ) model, first formulated in 1942,²⁰ is still used today, either as originally devised or, more often, as the underlying conceptual basis for more evolved and clinically relevant models.

The LQ model has been the most used radiobiological model in conventional X-ray radiotherapy, and one could argue that its development has taken a middle ground between a mechanistic and phenomenological approach.²¹ It estimates the inability, or reduced ability, of irradiated cells to produce colonies in a clonogenic assay,²² often considered as a measure of cell radiosensitivity. The LQ model started as a phenomenological model which described the association of dose and cell survival curves, but its parameters has been linked to different mechanisms of induction of radiation damage.^{20,23} Furthermore, the LQ model has been used in various forms, and within various more complex models, to guide decisions about dose adjustments, dose rate, dose-fractionation optimisation and clinical trial design, as discussed in this issue by Jones and Dale.²⁴ Its simplicity, yet relative robustness, made it outlast other models, and evolve to the modern interpretation.

The LQ model predictions have been shown to be not always consistent with experimental observations of cell survival after irradiation^{19,22}; however, its simple form and ability to predict survival accurately for the dose fractions normally used in clinical radiotherapy have in part determined its success.²⁵ The initial model was oversimplistic and had several limitations; however since then, the LQ model has been used as the basis

for more evolved models that account for other modifiers of the dose-response curve. These include physical parameters such as those describing the changes in survival with varying dose-rate or number of dose fractions,²⁴ physiological parameters, such as varying levels of oxygen, known to affect cell survival after irradiation (*e.g.* a recent study by Scott *et al*²⁶), and biological conditions such as the differences in DNA repair between different cell types.²⁷

A multitude of models have been generated, many based on the LQ model itself, to estimate the probability of locally controlling the tumour (tumour control probability) and of compromising the surrounding healthy tissues (normal tissue complication probability). A comparative of models can be found in an example study to determine the optimal fraction scheme for patients with small peripheral non-small cell lung cancer included in the references.²⁸

A current limitation of modelling in radiotherapy is that it does not provide an appropriate framework to study the response to irradiation of multiple populations of cells which are normally present in the tumour microenvironment, such as stroma cells or immune cells.²¹ This is particularly relevant for current clinical radiotherapy, where combination with agents targeting the tumour microenvironment, such as immune therapy, is increasingly being experimented in combination trials.

Extensions that include other radiotherapy modalities have also been considered. One such method is the local effect model, which extends the LQ model to high-LET ion beams, used in ion beam therapy. Ion beam therapy results in better tumour control probability with reduced normal tissue complication probability.²¹ The local effect model describes the cell survival curve for the ion beam by combining the LQ pattern with a linear part at high doses, to which the model transitions when a threshold parameter is surpassed.

A number of recent modelling efforts are related to the exciting field of spatial 2D and 3D modelling, which could be promising in terms of modelling the tumour microenvironment.

These models have been also applied to radiotherapy. For example, in a study on glioblastoma multiforme the net rates of proliferation and invasion, as well as radiation sensitivity for a given patient, were estimated using data from two pre-treatment MRI scans. This was then applied in a 3D architecture of the brain to quantify the effects of regional resistance to radiation as a consequence of heterogeneous intratumoral hypoxia.²⁹ In another example, Powathil *et al* created a hybrid multiscale model that incorporated cell-cycle behaviour, diffusion-reaction equations for oxygen and drug kinetics, and agent-based models for cells and vessels. The model was then used to study multimodality treatments of cell-cycle-dependent chemotherapies and radiation therapy, and their optimal sequencing and scheduling.^{30,31} These examples are still limited in both number and scope, but they illustrate how spatially aware mathematical modelling can potentially aid the planning of radiotherapy.

MODELLING OTHER THERAPIES AGAINST CANCER

Modelling has been applied to a broad range of therapeutic modalities. In this section, we provide some examples of current approaches to the modelling of cancer therapies other than radiation

Many models have been developed to date to predict the effect of chemotherapy.^{2,32,33} One major problem in chemotherapy is the delivery of the drug to the cell, ensuring that it arrives in a sufficient quantity and that systemic toxicity is kept in check. A big reason for the failure of many chemotherapeutic agents is the complexity of interstitial drug transport, which is hard to reproduce experimentally. To investigate drug penetration, Rejniak et al developed a model of interstitial transport with the biophysical properties of the tumour tissue that, using the regularised Stokeslets method, allowed the simulation of both advective and diffusive interstitial transport.³⁴ The model showed that if both modes contribute to drug movement equally, the depth of tissue penetration by the drug molecules strongly depends on tissue architecture. This means that a histology sample from a patient could help determine how well a specific drug will perform on a given tumour.

In glioblastoma, an aggressive brain tumour, the vasculature is disorganised and presents a disrupted blood–brain barrier (BBB). It is not clear if the restoration of BBB integrity resulting from antiangiogenic therapy improves or limits the delivery of drugs. Boujelben et al applied mathematical models of blood flow, vascular permeability and diffusion within the tumour microenvironment, and found that these three parameters interact non-linearly to determine the concentration of drug in any given point. Restoration of the BBB could reduce the delivery of the drug, but increased blood flow could increase it.³⁵

Targeted drugs are a promising development since they reduce systemic drug toxicity and are specific to the tumour cells that express the target receptors; however, not all targeting drugs are equally effective. Karolak et al developed an off-lattice agent-based model to examine which biochemical and biophysical properties are essential for effective spatial distribution within the tumour and cellular uptake. They showed that drug agents with moderate affinity, but that are quickly released, are similarly effective to high affinity drugs released slower.³⁶

Targeted therapy has also exploited nanoparticles (NPs) technology. Curtis et al studied an important factor in its effectivity, namely the NP vascular affinity, which represents the likelihood of endothelial adhesion. They used a hybrid model with a discrete vasculature, continuous description of tumour mass and drug kinetics. Their results show that small (100 nm) NPs with high vascular affinity should be more effective than larger (1000 nm) NPs with similar affinity, even though small NPs have lower drug loading and local drug release.³⁷

Macrophages accumulate in hypoxic regions of tumours. This makes them promising candidates for targeting cancer cells in those regions, where conventional drugs might not be able to

reach, and where their efficacy is anyway limited in many cases. Owen et al developed a cellular automaton model that incorporates spatial and temporal dynamical parameters of vascular tumour growth. This model showed that the combination of conventional therapies with macrophage therapies would be synergistic, and that the greatest effect would be obtained where the macrophage-based, hypoxia-targeted therapy is administered shortly before or concurrently with conventional chemotherapy.³⁸

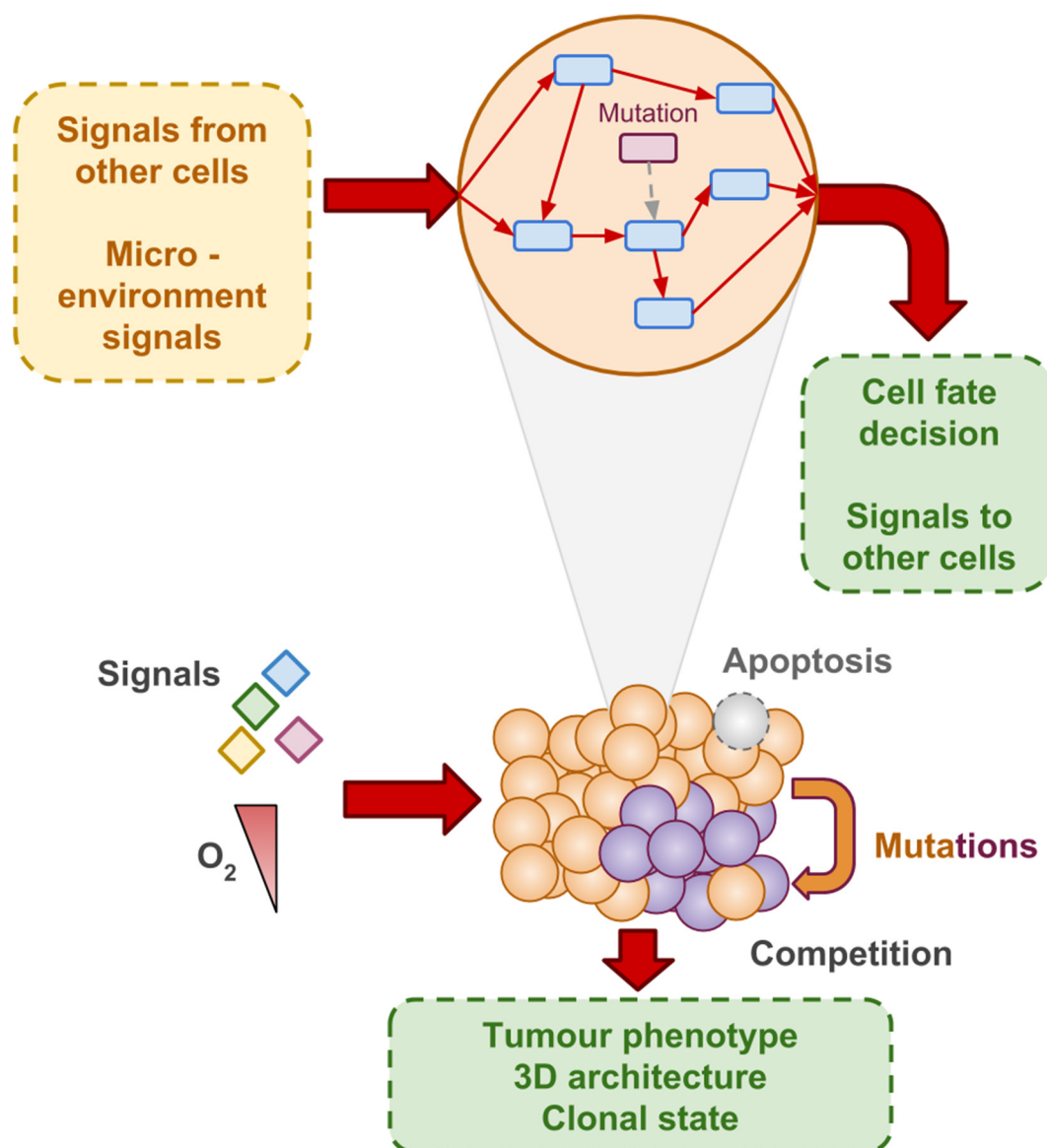
Another modelling effort in this area has been published by Leonard et al, who studied how macrophages can be used to deliver nanodrugs to hypovascularized metastatic lesions. Their model combines the simulation of the evolving tumour, a representation of the vasculature and diffusion equations for the drug distribution. Both the model and the *in vitro* and *in vivo* experiments showed that the addition of macrophages significantly increases the drug efficacy.³⁹

Lastly, a very promising area in cancer treatment which can also be studied through mathematical modelling is combination therapy. There is substantial evidence, *e.g.* that chemotherapy and radiotherapy, when combined, can achieve a greater effect than that of any of these therapies alone.^{40–42} However, the success of this kind of interaction is greatly dependent on the exact parameters of the combination: namely the doses, the radiation fractions and the type of drug administered.⁴³ The large number of possible combinations is the reason why mathematical modelling can be of great help to evaluate different multimodality strategies before testing on patients. Several efforts have been made in this respect,^{30,43} but models that explore in detail the interplay between the effects of combination therapy, as well as the optimal scheduling and sequencing of the combination treatment are still a work in progress.⁴⁴

OPENING THE CELL “BLACK-BOX”

Cells can be thought as entities where inputs arrive and which in response will return outputs. Most biological models to date have treated the cell as a “black box”⁴⁵: they have ignored the interplay between the environment around the cell and the events inside it which determine the specific output. The reality is that cells are vast networks with thousands of components interplaying, complex economies in which scarce resources are carefully invested depending on fluctuating environmental and cell intrinsic conditions.⁴⁶ In addition, gene mutations can have subtle but unique effects on the whole network, leading to diverse phenotypes across cancer patient populations.⁴⁷ At the same time, cells do not exist in a vacuum, but they coevolve with their environment.^{48,49} Modelling gene networks in isolation ignores the impact of the cell context on its phenotype. It has been argued that establishing a direct relationship between single genes and phenotypic traits is an over simplification, since in most cases no sole gene can cause any observable difference.⁴⁹ And of course, genes are not the sole influence on phenotypes, they depend on a cellular environment and on specific physicochemical conditions.

Figure 3. Overview of the main characteristics of our recently proposed spatially aware modelling framework.¹² 3D, three-dimensional.



Cancer genomes are very complex, including 50–100 somatic alterations in each tumour.⁴⁷ Although in the past genetic mutations in cancer have been approached as if they entirely change gene function, it must be noted that each mutation could influence protein function or affect networks in subtle ways, and different mutations in the same gene can lead to different phenotypes.⁵⁰ All the above contribute to increase diversity across cancer patient populations even further.

We have recently proposed a modelling framework which tries to address these needs, and merge pathway to spatial modelling.¹⁸ In it, models combine the 3D architecture and conditions of the tumour microenvironment (Figure 3), the genotype inside each of the cells, and the signalling networks determining the responses to environmental stimuli. In this view, collective behaviour and phenotypes rise from the profiles of individual cells, which rely on the simulation of metabolic and

genetic networks inside each cell. These individual behaviours can mutate and evolve, allowing one to study causal relationships between the system emergent properties and the genotype of each cell.

DATA EXPLOSION AND OPEN ACCESS REPOSITORIES

High-throughput technologies and genomewide analyses have provided us with enormous amounts of biological data that are measured in petabytes, with estimates indicating that by 2025, we will need more than 2 exabytes of storage capacity just for human genomes.⁵¹ Some of these resources are dedicated to cancer, like The Cancer Genome Atlas (TCGA)⁵² and the International Cancer Genomics Consortium (ICGC),⁵³ and it is clear that cancer models can benefit immensely from using them (Table 1). Some projects, like The Cancer Genome Atlas and International Cancer Genomics Consortium have focused

Table 1. Cancer genomics databases

Project	Website	Description
Sanger Institute databases	https://www.sanger.ac.uk/science/data	An array of databases to manage and interpret large-scale data
CTdatabase	http://www.cta.lncc.br/	Cancer-Testis antigens database
miRCancer	http://mirancer.ecu.edu/	miRNA cancer association database
OMIM	http://www.ncbi.nlm.nih.gov/omim	Causative genes for cancer and other diseases
TCGA	http://cancergenome.nih.gov/	Genomic profiling and analysis of multiple cancer types
ICGC	http://dcc.icgc.org/	Study of genomic abnormalities in cancer
CellLineNavigator	http://www.medicalgenomics.org/celllinenavigator/	Compendium of cancer cell line expression profiles
CGAP	http://cgap.nci.nih.gov/	Gene expression profiles of normal, precancer, and cancer cells
COSMIC	https://cancer.sanger.ac.uk/cosmic/	Catalogue of somatic mutations in cancer
IntOGen	http://www.intogen.org/	Integrative cancer genomics
Mitelman Database	http://cgap.nci.nih.gov/Chromosomes/Mitelman	Chromosome aberrations and gene fusions in cancer
NCG 4.0	http://ncg.kcl.ac.uk/	Network properties of cancer genes
TGDBs	http://www.tumor-gene.org/tgdf.html	Database of tumour genes
Tumorscape	http://www.broadinstitute.org/tumorscape	Copy number alterations across multiple cancer types
Gene Ontology	http://www.geneontology.org/	Classification of genes according to their function and biological context
BioMuta	https://hive.biochemistry.gwu.edu/biomuta	SNV and disease association in cancer
CGC	https://cancer.sanger.ac.uk/census/	Genes with mutations that are causally linked to cancer
DriverDB	driverdb.ym.edu.tw/DriverDB	Cancer-driver genes/mutations
IARC TP53	http://p53.iarc.fr/	Human TP53 gene variations related to cancer.
CancerDR	http://crdd.osdd.net/raghava/cancerdr/	Cancer drug resistance database
CancerResource	http://data-analysis.charite.de/care/	Drug-target relationships related to cancer

ICGC, International Cancer Genomics Consortium; LINCS, Library of Integrated Network-based Cellular Signatures; TCGA, The Cancer Genome Atlas.

on the characterization of samples from patients and their outcome, while others like the Library of Integrated Network-based Cellular Signatures⁵⁴ and the Integrated Cancer Biology Program⁵⁵ have characterised the molecular response of several cancer lines to a range of different perturbations. Furthermore, many other resources exist which are not necessarily linked with cancer, such as repositories of biological pathways (KEGG,⁵⁶ WikiPathways,⁵⁷ Pathway Commons,⁵⁸) but could also be used to inform modelling of signalling network in normal and cancer cells.

This abundance of data comes with many perks, of course, but it is not devoid of challenges. A recurring theme in biological data science is that currently the ability to integrate and interpret data across platforms lags behind the ability to generate data.⁵⁹ First, one needs to sieve through the data, determine the level of evidence or the noise associated with the deposited data, and recognise what could be relevant to usefully fit cancer models. Secondly, none of the platforms is comprehensive enough to capture the whole array of changes in the genome of a cancer cell, or to properly differentiate between driver and passenger mutations.⁶⁰ Thus, these collections present different formats and paradigms, and it is quite a challenge to integrate several sources of information and to transform

them to formats that can be fitted to the model, since they are not always directly comparable. To attempt to address these problems, several computational tools and databases have been developed (Tables 1 and 2).^{60,61}

There are some new ways to approach the analysis of such vast amount of data, like crowd sourcing methods, which have already produced promising results.^{62,63} Aside from the specific analysis results, and despite the problems that inevitably arise from large-scale collections of data, making these available to the community makes it easier to detect errors. Sharing of data and crowd modelling also prevents the self-assessment trap, by which models are built and tested by the same group, with the risk of partiality in the results.⁶⁰

FUTURE DIRECTIONS

As it has been mentioned throughout this review, the future of systems oncology modelling lies on the development of models which better represent the complex multiscale nature of cancer. Models have already been produced that simulate many of the biological processes at different scales. These models, from the molecular to the systems scale, have succeeded, to a certain extent, in integrating information, providing insight and being robust enough to inform predictions. Development of

Table 2. Other tools

Project	Website	Description
Cytoscape	http://www.cytoscape.org/	Visualising networks and integrating them
IGV	http://www.broadinstitute.org/igv	Visualisation software for genomics datasets
Protein Atlas	http://www.proteinatlas.org/	Antibody-based human proteomics
The Cancer Proteome Atlas	http://www.tcportal.org/tcpa/	Facilitates the accessing, visualising, and analysing of cancer functional proteomics
STRING	http://string-db.org/	Physical and functional protein interactions
Pathway Commons	http://www.pathwaycommons.org	Biological pathway information collected from public pathway databases
LINCS	http://www.lincsproject.org/	Changes in gene expression in response to perturbations
MoKCa	http://strubiol.icr.ac.uk/extra/mokca/	Prediction of phenotypic consequences of cancer mutations
Virtual cell	http://vcell.org/	Platform to model and simulate cell biology
COPASI	http://copasi.org	Tool to simulate and analyse networks and their dynamics
cBioPortal	http://www.cbioportal.org/	Platform to visualise and analyse large-scale genomic data sets
Bioconductor	http://www.bioconductor.org	Tools for the analysis of high-throughput genomic data
UCSC Xena	https://xena.ucsc.edu	Visualise and analyse functional cancer genomics data
NCBI dbGAP	http://www.ncbi.nlm.nih.gov/gap	Human genotype and phenotype interactions
GEO	http://ncbi.nlm.nih.gov/geo	Functional genomics and gene expression data
GeneCards	http://www.genecards.org/	Human genes with data on known and predicted genes
GenePattern	http://www.broadinstitute.org/genepattern	Analysis of gene expression and networks
ENCODE	https://www.encodeproject.org/	List of functional elements in the human genome
UCSC Genome Browser	https://genome.ucsc.edu/	Allows to visualise and analyse functional genomics data

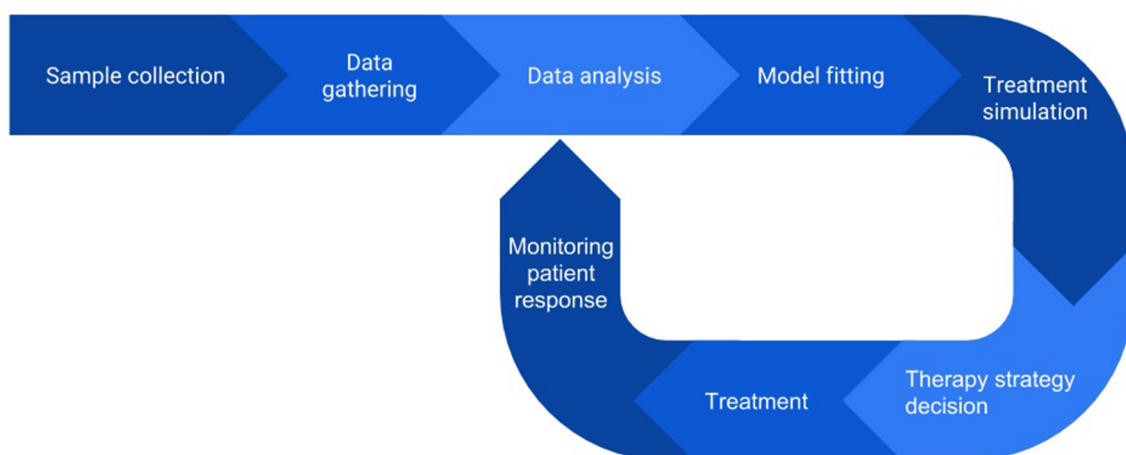
LINCS, Library of Integrated Network-based Cellular Signatures.

multiscale “super models” that link together all these different levels of biological function is the next logical step for cancer modelling.

Connecting the different spatial and temporal scales of cancer and radiotherapy is a challenging task that entails the gathering of several types of data, and the design of experiments

that can validate the predictions made by the models. The development of “super-models” would necessitate of collaboration between many interdisciplinary groups. This includes collaboration to gather genomic data, to develop gene regulatory networks, to define 3D structure, interactomics and microfluidics and to measure characteristics of a changing microenvironment.

Figure 4. A pipeline for using multiscale tumour models to decide the best therapy for a given patient profile, and the cycle that involves monitoring patient response to treatment, the gathering of new data and the refitting of the model accordingly, so to make the therapy adapt to the tumour evolution.



Although challenging, the most exciting outcome of this is the ability to quantitatively explain patient response to treatment, determine what the best combination of therapies and their schedule is likely to be, and predict possible side-effects.

An standardised pipeline for the treatment of cancer can be envisioned as a series of the following steps: (1) detection, gathering data and samples from the patient, (2) analysing said data and samples with modern molecular biology techniques, including next generation sequencing; (3) inputting these data in a model, simulating the outcomes of an array of therapy strategies, (4) coming up with the best candidate schedule, (5) treating the patient accordingly, (6) monitoring patient response to treatment and (7) eventually refining the model, with special attention to the changes in the tumour profile and the patient's body that emerge as a side effect of the treatment (Figure 4). The latter is also an interesting field to be explored by modellers: the effects of therapies on surrounding normal

cells that can cumulatively or in a synergetic manner affect the outcome of multimodality treatments.

To conclude, biological models in oncology, as in all medical sciences, need to be complex enough to explain the biological system accurately and maintain its main properties, but simple enough to be manageable and insightful for clinical application. A key point is that models need to be robustly validated so that one can estimate the error associated with their predictions. If on one hand, robust validation of the models is paramount to produce clinically useful tools, on the other hand, validation of models is also extremely important as it provides a chance to deepen our understanding of cancer. While trying to validate a model, one will typically discover gaps in the biological understanding and point at important parameters that could be missing from the scope of experimental biologists. This opens the door to new discoveries and generates further knowledge of the disease, which in turn will increase the likelihood of producing useful therapeutic solutions.

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