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Cancer modeling: From mechanistic to data-driven approaches, and from fundamental insights to clinical applications

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ABSTRACT

Cancer is still one of the major causes of death worldwide. Even if its comprehension is improving continuously, the complexity and heterogeneity of this group of diseases invariably make some cancer cases incurable and lethal. By focusing only on one or two cancerous molecular species simultaneously, traditional *in vitro* and *in vivo* approaches do not provide a global view on this disease and are sometimes unable to generate significant insights about cancer. *In silico* techniques are increasingly used in the oncology domain for their remarkable integration capacity. In basic cancer research, a vast number of mathematical and computational models has been implemented in the past decades, allowing for a better understanding of these complex diseases, generating new hypotheses and predictions, and guiding scientists towards the most impactful experiments. Although clinical uptake of such *in silico* approaches is still limited, some treatment strategies are currently under investigation in phase I or II clinical trials. Besides being responsible for new therapeutic ideas, *in silico* models could play a significant role in optimizing clinical trial design and patient stratification. This review provides a non-exhaustive overview of models according to their intrinsic features. *In silico* contributions to basic cancer science are discussed, using the hallmarks of cancer as a guidance. Subsequently, *in silico* cancer models, that are a part of currently ongoing clinical trials, are addressed. In a forward-looking section, issues such as the need for adequate regulatory processes related to *in silico* models, and advances in model technologies are discussed.

1. Introduction

Cancer is a disease caused by a malignant growth (or tumor) resulting from an uncontrolled division of cells. The prevalence of cancer is dramatically rising and continues to reach epidemic proportions. More than 18 million new cases of cancer have been observed worldwide in 2018, with 9.6 million people dying from cancer during that year [79]. Unfortunately, this cancer burden is likely to be maintained in the future because of the increasing population growth and ageing. Even if the comprehension of this group of diseases is continuously improving and certain cancers have become chronic diseases rather than swift killers, others are still untreatable and lethal. The complexity and heterogeneity of those malignant variants often make treatment strategies ineffective [42,176]. By focusing only on one or two key factors simultaneously, traditional *in vitro* and *in vivo* approaches do not allow to obtain a global vision of cancer, which could result in the failure of the recommended therapy. Intertwining *in vitro* and *in vivo* experiments with computational methods leads to more integrative approaches, thereby bringing novel insights into cancer research [53,84,95].

Defined in analogy to "*in vitro*" and "*in vivo*", the term "*in silico*" refers to the studies performed on a computer or with computer simulations. It usually consists of mathematical models supported by computational tools. *In silico* studies represent an essential step for problem solving and product development in classical engineering fields such as in chemical, electrical, automobile and aviation engineering. Using the available information about the system under scrutiny, such *in silico* approaches allow to obtain an integrated picture of the system and then design strategies to optimize the said system by analyzing the parameters and the variables used in the model. Many mathematical and computational approaches have been implemented in basic cancer research over the last few decades (Fig. 1). They allow a better understanding of this complex group of diseases, they generate new hypotheses and predictions, and they guide scientists towards the next series of – more informative – experiments [4].

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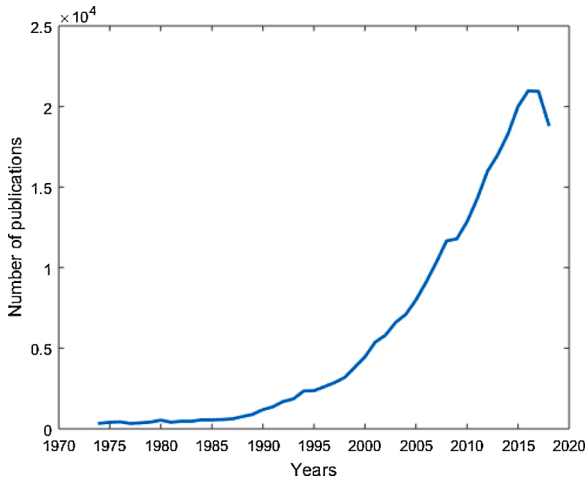

Fig. 1. PubMed query for ((mathematical model) OR (in silico)) AND ((cancer) OR (tumor)). The number of publications about cancer mathematical modeling is steadily increasing since 1974.

When classifying mathematical models, they are usually sorted based on specific aspects. Beyond their scopes of application, they can be described according to the kind of information used to build the model (from hypothesis-driven to data-driven), the way they represent the system (continuous *versus* discrete), and the length and time scales (from the gene/protein level to the population level). Depending on the question to be answered, one kind of model is preferentially considered. The models can also be coupled, leading to hybrid or multiscale modeling.

In the context of cancer research, mathematical modeling studies usually focus on one or two "hallmarks" of cancer cells [74,75]. These hallmarks are a small number of common traits and characteristics that normal cells have to acquire to become malignant - whatever their origin and phenotype:

1) (cancer) cells sustain proliferative signaling and encourage their own growth;
2) cells evade growth suppressors and maintain their proliferative profile;
3) cells avoid the immune destruction;
4) cells have a limitless replicative potential and can reproduce indefinitely;
5) inflammation is considered to promote cancer;
6) cells are able to invade neighboring tissues and form metastases in distant body parts;
7) cells induce angiogenesis;
8) cancer development is linked to genome instabilities;
9) cells resist to cell death;
10) cells deregulate their energetic metabolism.

Whereas only a few components of each feature can be studied at any one time with *in vitro* and *in vivo* experiments, *in silico* models enable a better understanding of the different actors individually as well as their interactions.

In vitro and *in vivo* models are the dominant forms in current biomedical practice, but the incorporation of *in silico* techniques, called the symbiotic approach, is increasingly perceived as beneficial [197,84]. The computational model is constructed, validated, and iteratively refined through *in vitro* and *in vivo* experiments. When it is sufficiently precise, it confirms or invalidates some biological hypotheses, looks at alternative mechanisms, and makes predictions that are to be tested experimentally. Besides being used as a method for discovering novel insights in basic research, *in silico* models can generate valid preclinical evidence or be included as a verification tool in other phases of (pre) clinical research [140]. *In silico* approaches are important to realize the 3R's (reduction, refinement, replacement) [84], allowing to reduce the animal experiments required to confirm a hypothesis or generate digital evidence. Competent authorities have already developed pipelines for the approval of *in silico* methods in other fields of medicine (*e.g.* medical devices, cardiology, diabetes or toxicology) [92,142,11] and they are progressively being applied in mathematical oncology. Unfortunately, even if *in silico* models are currently applied in basic cancer research (academia and industry), their use in clinical practice is still limited. Only a few therapeutic strategies based on mathematical modeling are currently under investigation in phase I or II clinical trials[1] .

This paper aims at reviewing the published literature about cancer modeling and mathematical oncology. First, the different mathematical modeling approaches that may be applied to biology and particularly cancer biology are stated. The modeling techniques are sorted based on some of their mathematical/computational features: from mechanistic to data-driven approaches, from continuous to discrete models, and from gene to population levels. Second, examples of models used in basic cancer research are given and classified according to the cancer trait they relate to. Indeed, models can address questions about tumor growth, metabolism, vasculature, microenvironment, immunity, invasion, treatment and resistance. Subsequently, the mathematical models developed specifically for clinical applications are discussed. Clarifications about the existing guidelines for the use of *in silico* modeling in clinical practice are provided. Finally, the underlying challenges for the establishment of such regulations and further perspectives about *in silico* medicine are discussed.

This review is by no means an exhaustive listing of all available *in silico* models in cancer; it merely aims to provide an introduction to the vocabulary and potential applications of this rapidly evolving and promising field of research.

2. Brief overview of mathematical modeling techniques

Mathematical modeling is the art of using mathematical tools and concepts, usually supported by computing power, to represent natural systems, properties and phenomena. Mathematical and computational models are exploited in a variety of fields, such as social sciences, economy, engineering, physics, chemistry, biology, *etc.* Beyond their scope of application, these models can be described and sorted in many ways, according to the kind of information feeding them, their intrinsic features and/or the mathematical tools applied to construct them. This section aims at reviewing non-exhaustively the various classifications of *in silico* models and tools in the context of biological processes. In the following, if not specified otherwise, the term model will be used interchangeably with mathematical model.

Table 1 brings together the most used types of *in silico* model technologies and provides a small explanation for each. The models explained in this table are referred with an * in the following text.

2.1. White, grey and black box modeling

Information about the real system one wants to mathematically represent is essential to build the model. Two sorts of information are accessible: qualitative knowledge and quantitative data. In line with the information used to feed and implement the models, they can be labeled as white-box, grey-box or black-box [76]. Hypotheses on and simplifications of the biological system are a third kind of information needed when building a model. Yet, because assumptions are required for every modeling approach, they are not regarded as a classifier.

On one extreme side, white-box models, also called mechanistic, hypothesis-driven or physics-based models, are constructed based on

[1] https://clinicaltrials.gov/ct2/results?cond=Cancer&term=Mathematical+model, https://clinicaltrials.gov/ct2/results?cond=Cancer&term=in+silico

Table 1
Explanations about a non-exhaustive list of specific *in silico* models.

Modeling techniques	Explanations
Differential equation	Differential equations are equations that unknowns are functions and they imply these functions but also their derivative. In the case of dynamic systems, ordinary differential equations (ODEs) are used and the independent variable, or the one in respect to the derivation is performed, is time. For dynamic systems involving more than one independent variable (e.g. time and space), partial differential equations (PDEs) are exploited.
Neural network	A neural network in computational science is a network of artificial neurons or nodes. The nodes and their relationships are found with the integration of different algorithms that copy the way the brain operates. They identify the best network according to the provided input and output experimental data.
Agent-based modeling	Agent-based model is a class of discrete mathematical and computational models that are able to represent the behavior (actions and interactions) of different autonomous agents and to highlight the whole system as the integration of its different actors. They differ from rule-based models especially because of their notion of space and their incorporation of the microenvironment.
Neuro-fuzzy models	The fuzzy logic is a kind of polyvalent logic in which the truth values are ranged between 0 and 1 and not 'true' or 'false". Neuro-fuzzy models are a hybrid combination of neural network and fuzzy logic.
Cellular automaton	Cellular automaton (CA) is a kind of discrete modeling composed of a grid of cells with different possible states. At each discrete time step, a new generation of states is produced according to a set of rules based on the current cell state and the state of the neighboring cells. Usually, the update rules are the same for each cells, except for stochastic CA. When the update times are different for various grid positions, asynchronous CA is referred.
Petri net	Petri net is a very graphical discrete modeling technique in which the network nodes are not biological entities but conditions and events. Directed interactions connect the different conditions, going through one or several event(s) or transition(s).
Cellular Potts model	Computational cellular Potts models are cell-based models that represent the comportment of cellular structures by using the principle of free energy minimisation.

physiological knowledge or first principles in physics. Differential equations* and rule-based models are typically used in such white-box strategy. In this case, most parameters have a purely physical and/or physiological significance such as reaction kinetics, mass transfer coefficient, *etc.*

On the other side, black-box or data-driven empirical models are established purely based on experimental data. They determine operational connections between system inputs and outputs. Parameters do not have here any physical significance and they are set to match as closely as possible with the provided data, without any knowledge of the model's internal functioning. Deep learning and neural network* models are a good illustration of data-driven methods. Even though machine learning is becoming increasingly interpretable, to date it is still mostly categorized as a black-box approach.

However, both aforementioned approaches rely in some way on previous knowledge and experimental records. Furthermore, almost no mechanistic model is purely theoretical and more and more black-box models try to include prior knowledge. This meeting-in-the-middle of both approaches is indicated by the term grey-box modeling, merging exploratory data with theoretical structures. For example, a white-grey-box model could be a system of partial differential equations (PDEs) where some boundary conditions group a multitude of physiological processes that are not described in the model and have therefore no real physiological meaning themselves, which means they can only be estimated through a data fitting strategy. On the other hand, the shape of the elementary functions used in black-box modeling could be adjusted on the basis of prior knowledge. Other examples are agent-based modeling* [136], neuro-fuzzy systems* [20], cellular automata* [128], Petri net models* [17], *etc.*

2.2. Continuous, discrete and hybrid modeling

Another classification method differentiates between continuous and discrete models. In continuous modeling, if we aim to model a process at the cell/tissue level, cells of interest will be considered as concentrations of cells or, in other words, as a population. This continuous approach often use ordinary (ODEs) or partial differential equations. In discrete models, each cell is considered as a discrete element and a set of rules governs the interactions with other cells, implemented through *e.g.* agent-based models. Hybrid approaches combine both continuous and discrete modeling. In many hybrid models, cells of interest are discretely modeled and continuous methods are used for the other molecular species, such as environmental variables (growth factor concentrations, oxygen, nutrients, *etc.*) and the remaining cell types.

2.3. From gene to population modeling

Another classification widely used for *in silico* models is based on the length and time scales of the process described [195]. Fig. 2 highlights the different scales that might be considered in cancer studies, from the gene level to the population level.

At very small scales, gene expression is inferred from mRNA measurements. Comparison between control and pathological expressions provides indications about *e.g.* genetic mutations related to the disease. Cancer is well known for being a genetic disease, caused by changes in genes essential for a normal cell functioning [82]. A lot of bioinformatics and mathematical tools have been therefore developed, and continue to be refined, for discovering cancer driving mutations, improving diagnosis and promoting personalized treatments [174]. At the same spatiotemporal scale, protein profiles are also interesting to study. Genetic and protein interactions are modeled and analyzed through regulatory networks, bringing out the interplay between the main biological pathways. The key actors, druggable targets and the robustness of a given network can also be deduced by mathematical approaches.

The mathematical models developed at the cell level focus on the biological and mechanistic behavior of a single cell [125]. The interactions between a set of cells subjected to external clues are also considered. For example, growth dynamics is usually analyzed *in silico* through a single cell-based modeling framework such as agent-based modeling.

At the tissue level, extracellular matrix, vasculature, growth factors and other types of cells influence the behavior of a single cell and all of these aspects are therefore added to the cell-based models. Tissue level models are often used as the baseline for hybrid approaches. Cells of interest and their interactions are discretely modeled based on a set of rules, taking into account the internal and external clues of the tissue level model. Continuous modeling is used for environmental variables and other cell types.

The organ level looks the whole organ, allowing to study, for example, the influence of the tumor on healthy tissues or the effect of external mechanical loading on the tumor.

A level higher on the spatiotemporal scale is the patient level and, collecting multiple patients, the population level. A cohort of virtual patients, modeled individually with patient-specific parameters, can be used to execute *in silico* clinical trials prior to the physical trials, allowing *e.g.* for a better patient stratification, leading higher success rates in the physical trials [141]. *In silico* clinical trials can also be used to augment physical trials for *e.g.* pediatric cancers or rare cancer types – cases where the execution of physical trials is ethically more difficult or where patient numbers are insufficient to execute a full physical trial [33].

Even though a detailed discussion falls outside the scope of this review, it should be mentioned that the model construction is just the first step of a long procedure [65]. Indeed, processes such as parameter

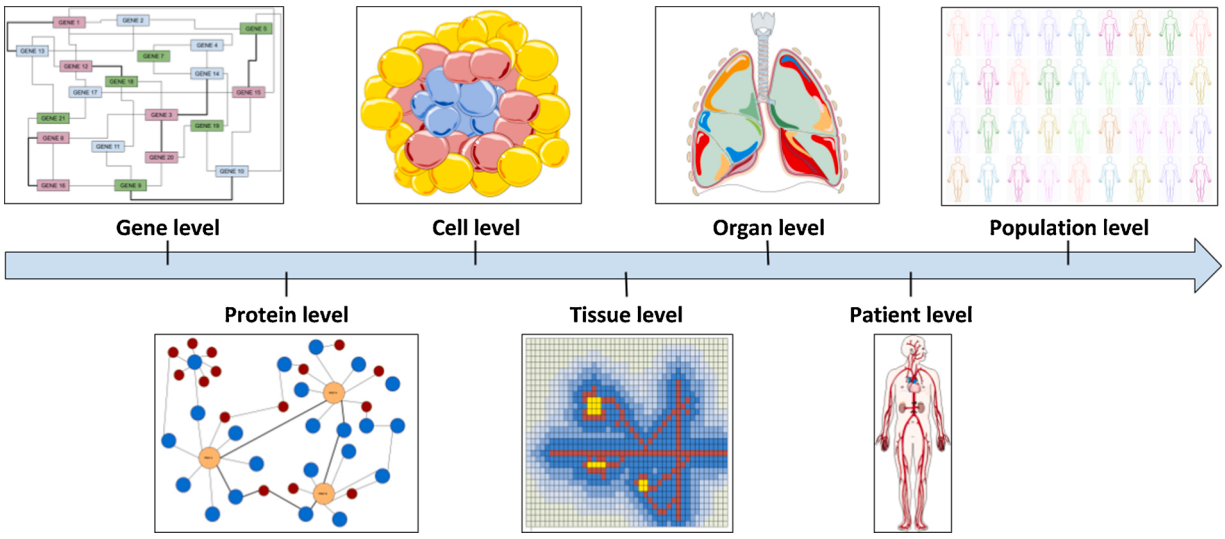

Fig. 2. Classification of *in silico* models by spatiotemporal length scale (gene, protein, cell, tissue, organ, patient and population levels).

optimization and model reduction are performed by using the existing experimental data. Subsequently, a validation step confronts *in silico* produced hypotheses with newly generated experimental data. Only at this point the model can be used to better understand the disease, generate new predictions, and guide scientists towards the most impactful experiments

3. Mathematical modeling in basic cancer research

Cancer is a multiscale and heterogeneous disease, involving a lot of different components and processes (Fig. 3) [42,176]. Traditional *in vitro* and *in vivo* techniques do not consider this integrated aspect and usually analyze the several mechanisms one by one. These reductionist methods are therefore limited in their capacity to provide significant insights in and perspectives on cancer pathogenesis. This disease really needs strategies able to highlight the interactions between individual components rather than to understand only the individual components [203].

Because of the rising amount of generated data and because of their accessibility, computational and mathematical approaches are becoming more and more prevalent to study complex systems of interacting components, such as cancer in this case [85]. Moreover, *in silico* models are less restricted by financial, timing or ethical constraints. They allow performing large-scale screening tests, making predictions, guiding scientists towards more informative experiments to carry on and generating novel biological and clinical discoveries. *In silico* cancer models, in parallel with biological experimental data, are currently increasingly implemented. They have the potential to capture more of the complexity of this disease by integrating the interactions between the various actors at different spatial and temporal scales. Improvements are obviously still needed to integrate an increasing amount of cancer aspects in a single model, but the developed methods are already reliable for hypothesis generation and testing in the context of basic research.

Considerable amount of mathematical and computational models of cancer have been implemented so far, each focusing on different specific aspects of the disease. Notice that, in the following, the term mathematical model refers to both mathematical and computational models

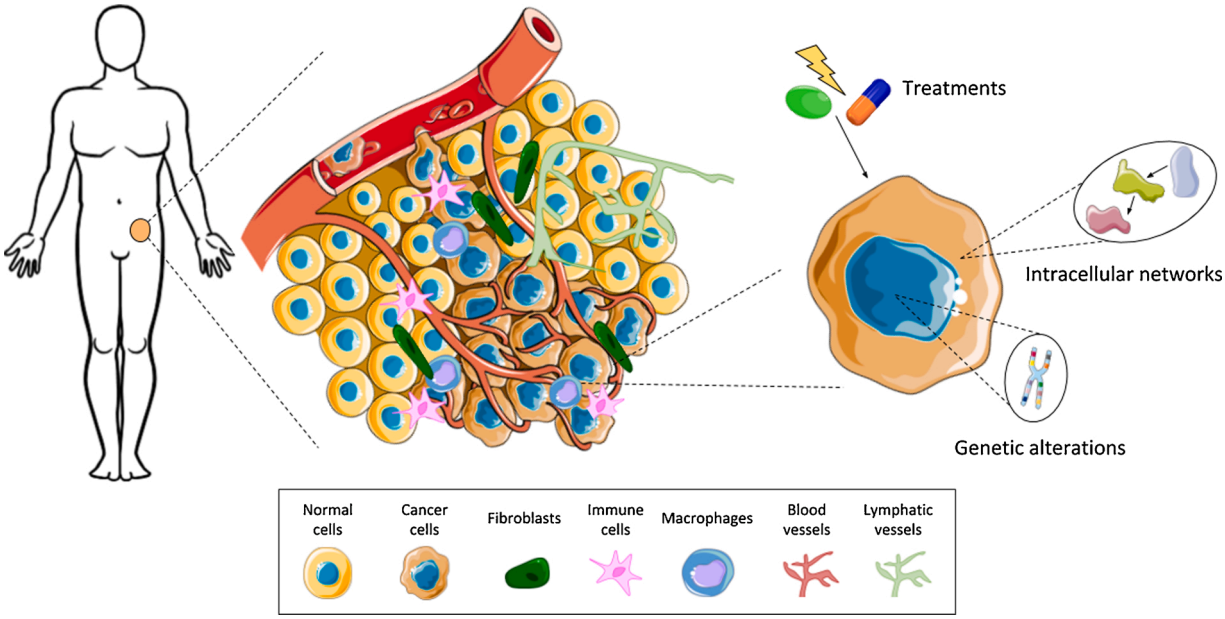

Fig. 3. Multiscale and heterogeneity of cancer.

or, more globally, to *in silico* models. This section reviews the different mathematical models developed for basic cancer research in a non-exhaustive manner. It will be divided in different parts according to the main cancer features captured by the model, being tumor growth, cancer metabolism, vasculature, heterogeneity, microenvironment, immunity, metastases and treatment. In contrast, models about cancer stem cells, epidemiology, apoptosis evasion, *etc.* fall outside the scope of this review. The cancer genomics and bioinformatics tools will not be discussed either. For these, we refer the readers to [115,174] and references within.

3.1. Tumor growth

Given their sustained proliferative signaling, their limitless replicative potential, and their capacity to avoid growth suppressors and immune destruction, cancer cells have the ability to grow indefinitely, unlike healthy cells [74,75]. Mathematical models have focused on representing this particular growth dynamics.

Deterministic mathematical laws, based on general growth laws, were developed to represent the tumor growth kinetics in terms of the number of cancer cells over time (reviewed in [22,83,190,206]). Ordinary differential equations are suitable for modeling scalar data of longitudinal tumor volume. The Gompertz curve [68], the most widely accepted approach, is a time serie model and is based on the sigmoid function, meaning that the growth is slow at the beginning, becomes fast, and stagnates at the end. However, the large number of variables in this model makes it complicated to manipulate. West [204] took into consideration the energy conservation and proposed the Universal Law. This model was adapted from the biological growth model of von Bertalanffy [200] in the case of cancer [72]. It seems to fit the *in vitro* and *in vivo* experimental conditions, as well as the patient data. Because of the complexity of this disease, all of these deterministic models can be switched into their stochastic counterparts, by adding a randomness perturbation.

The model complexity increases when the spatial evolution, the nutrient influence, the vasculature (see the section 'vasculature' below) and/or the microenvironment are investigated. For instance, Greenspan [71] was a pioneer in the field of avascular tumor growth modeling. He was one of the first to mathematically describe the growth and movement of solid tumors in response to an arbitrary distribution of nutrients. Avascular tumor growth was also intensively modeled by Byrne, Chaplain and later on by Lowengrub and Cristini [25–28,38,86,100,173,41,29,30]. Ferreira [60] represented cell proliferation, motility and death in an environment with nutrients, by combining Gompertz curves with reaction-diffusion partial differential equations. Vermolen et al. [196] also used PDEs combined with cell-based modeling and a stochastic approach for studying tumor growth and initiation. The influence of growth factors, such as epidermal growth factor receptor (EGFR) here, on tumor cell proliferation and migration was investigated by Deisboeck through a hybrid multiscale model [110,111,11]. Ordinary differential equations describe the intracellular molecular network affecting the tumor evolution and an agent-based approach is used to model the interactions between the cells. They improved this model by adding the impact of the cell cycle and the hypoxia, and by extending the representation in three dimensions through PDEs [12]. Mallet and de Pillis [109] relied on a hybrid cellular automata–partial differential equation model to describe the immune system impact on the tumor growth in a nutrient source. Hybrid models of tumor growth are gathered in Rejniak and Anderson [157]. Szabo and Merks [189] reviewed the use of cellular Potts modeling (CPM) for representing tumor growth, tumor invasion and tumor progression. It is worth reminding that this work was inspired by the article of Graner and Glazier [69], using CPM to have a more visual and discrete representation of cell sorting.

3.2. Cancer metabolism

Cancer cells have high metabolic needs to sustain proliferation and migration [74,75]. Compared to normal cells, cancer cells therefore require changes in the metabolic network [43]. *In silico* models of cancer metabolism identify the key alterations in metabolic pathways that are critical for the switch between the healthy and diseased phenotypes.

The Warburg effect is one key example of cancer metabolism [202]. Indeed, even in presence of oxygen, cancer cells promote the glycolysis as a source of energy, instead of the conventional and more efficient path of oxidative phosphorylation. Mathematical approaches have been implemented to better understand this effect (reviewed by Schuster et al. [166]). A more recent model developed by Shamsi and collaborators [172] uses a hybrid four compartment model, combining PDEs with CA, to identify which advantages the Warburg effect imparts on cancer cells. The selective advantages of other cancer metabolic phenotypes and the finding of metabolic biomarkers have been extensively investigated through systems biology approaches and computational modeling (reviewed in [67,116,158,133,135,124]). For example, Roy and Finley [162] used simple ODEs to determine the impact of targeting metabolic actors. Ghadiri and colleagues [66] developed a multiscale agent-based framework coupled with a constraint-based metabolic network model to stimulate the tumour growth. Even if metabolism modeling already led to interesting discoveries about potential therapeutic biomarkers, its future really lies in the development of multiscale models incorporating signaling and metabolic pathways with cell-cell interactions [161].

3.3. Vasculature (blood and lymphatic)

Cancer promotes the formation of new blood and lymphatic vessels through the secretion of pro-(lymph)angiogenic growth factors [171,52,103]. Tumor-induced vasculature enables cancer cells to have access to nutrients and oxygen, to dispose of their waste, and to spread to distant organs through the circulatory system. The growth of tumors is therefore limited without access to vasculature. Excessive angiogenesis and lymphangiogenesis are associated with cancer progression, metastasis formation and an overall bad prognosis. Mathematical models of tumor angiogenesis are well developed, in contrast to those of cancer-induced lymphangiogenesis which is a less investigated – but for a number of cancer types very important – process. In their review, Scianna et al. [167] made the distinction between the formation of all vascular networks, meaning vasculogenesis, angiogenesis and lymphangiogenesis.

Mathematical modeling of tumor-induced angiogenesis begun with Balding and McElwain [13] and their PDE model of sprout formation and new capillary development. Chaplain is one of the pioneers in angiogenesis modeling and developed with his team a plethora of mathematical models in this field, using different modeling strategies encompassing continuous, discrete and hybrid approaches [35,31,138,5,36,6,120,179,180,121,37]. Mathematical models of cancer angiogenesis focusing especially on the behaviour of endothelial cells are reviewed in the papers of Mantzaris et al. [112], Pamuk [139], Levine and Sleeman [97], Levine and Nilsen-Hamilton [98], Peirce [140], Qutub et al. [153], Lowengrub, Cristini et al. [100] and Suzuki et al. [182]. Lowengrub, Cristini et al. [100] also used mathematical approaches to model the flow aspect related to angiogenesis. Vilanova et al. [198] developed a mathematical framework of cancer angiogenesis including capillary growth, regression and regrowth after a stimulation with tumour angiogenic factors (TAFs). Their model combines diffusion-reaction equations (PDEs) for TAF dynamics, phase field theory for capillaries and their morphology, and agent-based modeling for tip cells activity. The CPM framework is often used to model angiogenesis: Bentley and colleagues [21] used it to capture early stages of new vessel growth, and Bauer et al. [16] used it for vascular branching. For hybrid modeling of tumor-induced angiogenesis, we refer the reader to the work of Chamseddine and Rejniak [34]. Regarding the process of lymphangiogenesis, the work of Lolas et al., mainly based on parabolic

partial differential equations, should be highlighted [62,147,102].

3.4. Tumor immunity

In case of immunodeficiency is existent, tumors develop more frequently and their growth is increased [75]. For some cancers, the immune system fights against this disease and it provides a better survival prognosis. However, the immune system is also involved in cancer growth and progression [75]. Indeed, cancer cells have the ability to evade immune detection or to avoid immunological killing [199]. Because the interactions between immunity and tumor cells can both be favorable and adverse for cancer development, mathematical models have been used to generate new insights into this tumor immunity and to elaborate more efficient immunotherapies.

Bellomo and Preziosi [19] wrote one of the first reviews about the modeling of tumor interactions with the immune system. They sorted the different mathematical approaches according to their spatiotemporal scales. Mathematical models of tumor-immune interactions are also reviewed in Eftimie et al. [54], Adam and Nicola [2], Eladdadi et al. [55], de Pillis et al. [48] and Altrock et al. [4]. The studies published by de Pillis and colleagues [44–47] are all centered around immune resistance modeling. The T cell response to a tumor was modeled by Robertson-Tessi et al. [160] through an ODE model, subsequently simplified by Dritschel et al. [51]. The acquired resistance to immune cells was modeled with a system of non-linear ODEs by Mahasa et al. [106]. Tumor-immune continuum models were resumed in Mahlbacher et al. [107], focusing on the modeling of different immune cell types. Cooper and Kim [39] used a PDE cellular automaton model to represent the tumor-immune dynamics. Norton et al. [137] reviewed multiscale agent-based and hybrid modeling of the tumor immune microenvironment. Successful immunosurveillance was modeled by Kather et al. [87] with a cellular automaton model. The mathematical models underlying immunotherapy usually exploit the previously mentioned frameworks of tumor-immune interactions. Models of other immunotherapies, are discussed in the 'Cancer treatment' section below.

3.5. Tumor microenvironment and heterogeneity

The tumor microenvironment is very heterogeneous and not only composed of cancer cells, but also of immune cells, fibroblasts, vessels, growth factors, signaling molecules and the extracellular matrix (ECM). All these components interact together and the interplay between these different elements is often more significant than the behaviour of a single component [118,14]. Tumor cells can influence their surrounding environment to support their own needs. The dynamics emerging from the interactions between tumor cells and their microenvironment is an important factor in cancer progression.

Overall, the microenvironmental mathematical models use multiscale hybrid approaches, combining continuous and discrete modeling. The continuous deterministic part describes the dynamics of environmental factors and extracellular matrix whereas the discrete stochastic part models the migration and proliferation of cancer cells based on a set of rules, taking into account the extracellular and intracellular cues. For example, Anderson [7] developed such a hybrid mathematical framework: tumor cells are described discretely while the ECM, the degradation enzymes and the oxygen are modeled continuously. Macklin and Lowengrub [104] reformulated previously developed tumor growth models by incorporating the effects of the microenvironment. The role of exosomes in pancreatic cancer microenvironment was investigated in 2017 by Friedman and Hao [63] through PDEs with free boundary conditions. An overview of current trends in mathematical modeling of tumor microenvironment interactions can be found in Rejniak and McCawley [156], Konstorum [91], and Crespo et al. [40]. The comprehension of intratumor heterogeneity with a combination of genome analysis and mathematical modeling, through a cellular automaton model of the branching evolution process, is detailed in Niida et al. [134]. Tumor heterogeneity can be linked to treatment resistance [42], see section 'Treatment resistance'.

3.6. Tumor invasion and metastases

Cancer cells have the ability to seed distant metastases and therefore to invade organs other than the primary location [74,75]. Metastases are linked to a bad prognosis and cancer mortality. This process is unfortunately poorly understood and mathematical modeling could lead to the identification of key actors in the metastatic dynamics. Prevention of the metastatic spread is of paramount importance for patient survival, and a reliable estimation of the risk of metastases is crucial for providing better patient care.

Liotta and his coworkers were the first to investigate the metastatic spread with mathematical approaches [164,99]. Inter alea, they used a stochastic model of Markov chains combined with ODEs in parallel with an experimental set-up to investigate the different steps of the metastatic spread. Through a dynamical model, Iwata et al. [80] investigated the density of metastatic tumors with respect to the size of metastases in order to estimate the potential number of other metastatic tumors below the detectability limit. Anderson et al. [6,7] linked the invasiveness with matrix-degradative enzymes in their PDEs and discrete biased random-walk models, both of which subsequently forming a hybrid model. It has been proven that metastatic cancer cells have a more aggressive and invasive phenotype than primary cancer cells. The behavior and phenotype of malignant invasive cells were modeled by Byrne and co-workers through continuous differential equations [29,30,113,148,149]. This invasiveness feature is often due to gene mutations, such as the epithelial-mesenchymal transition (EMT), giving cancer cells their metastatic potential [96]. The signaling pathways involved in the EMT were dynamically modeled through the network theory in Steinway et al. [178] who discovered the feedback motifs that stabilize this process. Michor and colleagues [49,126] developed a mathematical model based on the Moran process [127] to describe the dynamics of mutations leading to metastatic cells, allowing for a calculation of the number of metastatic cells formed by a tumor. Ramis-Conde et al. [154,155] used an individual force-based multiscale approach to model the cancer cell intravasation (the way cancer cells reach the circulation). Araujo et al. [9] elaborated a hybrid model, combining PDEs for signaling molecules and CA for cells, for investigating the metastatic spread in prostate cancer. Franssen et al. [61] developed a multigrid, hybrid, individual-based model to capture the key steps of the invasion-metastasis cascade. Newton et al. [130,131] established a network of potential locations for lung cancer metastases and used a stochastic Markov chain model to identify the preferred sites for receiving metastases. Scott et al. [168,170] also highlighted the probability of each organ to receive metastases by adding to his model the vasculature and the infiltration capacity of each organ. The model of Niculescu et al. [132], based on cellular Potts modeling [69] and originally representing shape-driven cell migration, was extended to study the migration of cancer cells during metastases. An overview of mathematical models of the tumor invasion and the metastatic process can be found in [6,169,15], and [105].

3.7. Cancer treatment

Oncological treatments are diverse and include, among others, surgery, radiotherapy, chemotherapy, immunotherapy, targeted therapy and virotherapy. The choice of the optimal treatment strategy is always challenging because of therapy specificity and patient diversity. Mathematical models are therefore widely used to predict prognostic and therapeutic biomarkers, treatment effect, schedule, drug toxicity and the best treatment combination.

Brady and Enderling [24] and Chamseddine and Rejniak [34] provided a very good review of mathematical models used for different cancer treatments. Moreira and Deutsch [128], Araujo and McElwain

[8] and Lowengrub, Cristini et al. [100] reviewed tumor growth models and radiation effects. Lewin et al. [101] investigated the effect of radiation on the spatiotemporal distribution of oxygen inside the tumor. They extended the model of Greenspan [70] for tumor growth and hypoxia with a linear-quadratic model representing cell death due to radiotherapy. Benzekry et al. [23] assessed the impact of surgery on metastatic potential through mathematical analyses. Enderling et al. [57,58] developed a mathematical approach for surgery and radiation treatment in early breast cancer, based on PDEs and a linear quadratic model. This linear quadratic relation appears in many studies modeling the radiobiological reaction rate and is based on the kinetics of damage reported in Sachs et al. [163,119,88]. Belfatto et al. [18] proposed an *in silico* approach to personalize radiotherapy and to provide an irradiation regimen. Personalised treatment prediction in radiotherapy using a Monte Carlo technique has also been suggested by Marcu et Marcu [114]. Powathil and co-workers [151] used reaction-diffusion partial differential equations to model the effects of radiotherapy and chemotherapy on brain tumors, determining the optimal sequence of the postoperative treatments. Actually, they developed several multiscale *in silico* models to investigate multi-modality treatments [73,123,152]. Williams et al. [205] developed different additive damage models to characterize the *in vitro* response to radiochemotherapy with a fixed schedule and variable dose. Alfonso et al. [3] used a cellular automaton model to investigate the dose effect in radiotherapy. Gardner [64] developed a kinetically tailored treatment model of ODEs to predict the best chemotherapeutic drug combinations (6 drugs analyzed), doses, and schedule. Usher [193], Hinow et al. [78], Pinho et al. [150], Wang and Schättler [201], and Kozlowska et al. [93] are other examples of mathematical models simulating chemotherapy. Optimization of chemotherapy protocols for grade II oligodendrogliomas was realised by Perez-Garcia et al. [144] through the creation of an ODE model. It should be noted that Perez and co-workers also developed other mathematical models to better investigate therapeutic responses of brain tumors [117,145,146]. Arakelyan et al. [1] reviewed some multi-scale models of angiogenesis and their potential for studying anti-angiogenic therapies. Ribba et al. [159] used a pharmacokinetic differential equation model to predict the optimal dosing regimen for immunotherapy. Kather et al. [87] established an agent-based model of tumor, immune and stromal cell interactions to propose recommendations for immunotherapies. Kiran and Lakshminarayanan [89] developed a pharmacokinetic/pharmacodynamic ODE model to optimise the combination of chemotherapy and immunotherapy. Isaeva and Osipov [81] also developed a mathematical model to understand the combined effect of chemotherapy and immunotherapy. The PDE model of Stein et al. [177] provided a way to find the optimum dosing schedule for the drug lapatinib in the context of glioblastoma. Concerning brain tumors, Swanson and co-workers developed mathematical models to study glioma growth, invasion and treatment [183–188]. Many systems biology tools can be used to discover *in silico* specific new drugs [165]. Mathematical models of cancer treatments with small molecule inhibitors and virus therapy are reviewed in Komarova and Wodarz [90]. Malinzi [108] studied the chemovirotherapy with delay differential equations to determine the efficacy of several drug interventions. Nanotechnologies could be of great interest for improving the delivery of cytotoxic agents selectively to cancer cells. A review about mathematical modeling in cancer nanomedicine was written by Dogra et al. [50]. Behinaein et al. [17] implemented a physiochemical and Petri net model of the EGFR-Ras-MAPK signaling pathway, which is implicated in the development and progression of cancer and is often targeted in combination therapies. With specific analyses and structural properties of Petri nets, drug-targetable nodes were identified.

Cancer cells are able to elude treatment, either through normal resistance coming from intrinsic variation between patients, or through acquired resistance which develops during the initially working treatment. Sun and Hu [181], as well as Yin et al. [206], have reviewed the mathematical modeling of cancer treatment resistance.

4. Mathematical modeling in clinical cancer applications

Even if the application of *in silico* tools is current increasing in research and industry, the uptake of mathematical and computational methods in clinical practice is in its infancy. Most of the commonly used computational approaches in clinical practice are related to the computational analysis of medical images. One example is that of surgical planning software that, based on medical images, provides the exact anatomy of a patient and the tumor location in order to plan and prepare a complex surgery. Image-based *in silico* models are also implemented as detection tools: more and more AI systems are developed to detect cancer. In breast cancer, several studies show the systems being able to surpass the radiologists' ability in identifying possible cancerous lesions [122]. Computational models are also directly responsible for the development of novel treatment strategies which are currently being tested in phase I and II clinical trials[2] . For example, Tanguturi (NCT03557372) proposed a mathematical model-based schedule of radiation therapy for recurrent glioblastoma that is currently in phase I clinical trial. Traina et al. [191] proposed a mathematical model for a better dosing schedule of the drug capecitabine in metastatic breast cancer. Based on a previously developed tumor growth kinetics [175,136], they optimized the chemotherapy delivery and reduced the toxicity at the same time. The hypotheses were successfully confirmed during a preclinical study and the phase I and II trials, a phase III trial is currently being launched [192]. Hénin et al. [77] developed MODEL 1, a pharmacodynamic/pharmacokinetic (PD/PK) mathematical model able to identify the best schedule and the combined toxicity of several chemotherapy drugs in metastatic breast cancer. Even if PD/PK models are widely used in drug development and accepted in regulatory filings, they are often incomplete and should be supplemented with other mechanistic modeling approaches to really identify new and innovative therapeutic targets.

5. Limitations and perspectives

Many mathematical and computational challenges need to be addressed when dealing with *in silico* models for biological processes.

- Similar to *in vitro* and *in vivo* models, *in silico* models are a representation of specific aspects of the reality and are not able to capture all the intrinsic characteristics of a biological system. The entire system is sometimes not known exactly and simplifying assumptions have to be made. Moreover, besides the inherent uncertainties, the more details are included in a model, the more parameters need to be estimated accurately which increases the risk of overparameterization.
- Models comprise more or less parameters depending on the model type. These parameters are sometimes impossible to measure with *in vitro* or *in vivo* experiments and have to be estimated through fittings technique between the *in silico* generated data and the observed ones. Parameter identification techniques are becoming more widely spread and more accurate. Sensitivity analyses, in which parameter values are changed in a physiological range to investigate their impact on the system output, are usually performed to ensure the model robustness. Parameter estimation is of critical importance because it is linked to the model reliability and robustness.
- Model performances strongly depend on the quality of experimental data as model construction, calibration and validation both all rely on biological data. The experimental inaccuracies are directly transmitted in model outcomes. Pipelines for data sharing are developed and it allows interactions between the different communities and an easier detection of model issues [32,56,59].

[2] https://clinicaltrials.gov/ct2/results?cond=Cancer&term=Mathematical+model, https://clinicaltrials.gov/ct2/results?cond=Cancer&term=in+silico

- Computational limitations have to be considered for all model types, but can vary depending on the model technology. An example of a compute-intensive technology are the agent-based models. Because this kind of approach tracks individual agents in time and space, it requires high computational power. A trade-off between the accuracy of cell-based models and the low computational cost of continuous approaches capturing mean behavior can be found in hybrid modeling.

The vast majority of the models discussed in this review, are theoretical models that are currently not used in preclinical tracks or clinical practice. In order for a model to be used in such setting, it needs to undergo regulatory scrutiny. This starts by the definition of a precise Context of Use, in which the model will be operated and in which it will generate reliable, robust and reproducible results. Subsequently, models need to undergo VVUQ: verification, validation and uncertainty quantification. Verification refers to the agreement between the theoretical concept and the resulting computer simulations; validation refers to the agreement between computer simulations and physical reality (using high-quality and reliable experimental data). Finally, uncertainty quantification needs to be performed to show that the model results remain reliable within the context of use, even when uncertainty on parameter values and assumptions are taking into account. There is a recent worldwide effort, accompanied by the necessary policy initiatives, focused on providing the correct regulatory setting that allows to evaluate computational models and the digital evidence they generate. In 2018, the V&V40 standard for computer models in the medical device domain [10] was published by the American Society for Mechanical Engineers (ASME), after a process that saw the active participation of industry and regulators [143]. These same principles can be used for the context of drug development [94,129]. With these standards available, the different stakeholders are now working on Good Simulation Practices (in analogy to Good Clinical Practices and Good Manufacturing Practices), a body of guidelines that helps the *in silico* modeling community to develop models that are set-up in such a way that compliance with regulatory guidelines will be more straightforward. Several academic societies, including the virtual physiological human (VPH) institute, play an active role in bringing the academic world closer to the regulatory and policy world, in order to simulate the use of computer simulations and modeling, to answer questions related to prevention, diagnosis, treatment of a disease, and development of biomedical product [194].

In conclusion, the symbiotic approach, mixing *in vitro*, *in vivo* and *in silico* models, is of great interest in the oncology domain. In basic cancer research, a plethora of mathematical and computational tools is available. They have shown to be able to contribute to achieving a better understanding of several aspects related to cancer, to the generation of new hypotheses and predictions, and to guiding scientists towards the most (more) impactful experiments. To date, this has not yet resulted in many models used in clinical practice. However, current joint efforts within the scientific, industrial and regulatory communities will lead to guidelines for the proper verification and validation of *in silico* models, a prerequisite to regulatory approval and industrial/clinical uptake. This uptake could be situated in all phases of the drug development pipeline, from the generation to preclinical evidence to *in silico* clinical trials, and from drug development to clinical decision support. Daily improvements of computational performances and data sharing can only support the development and the reliability of these *in silico* techniques.

Author statement

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Declaration of Competing Interest

The authors report no declarations of interest.

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