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Mini review

Hybrid computational models of multicellular tumour growth considering glucose metabolism

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ABSTRACT

Cancer cells metabolize glucose through metabolic pathways that differ from those used by healthy and differentiated cells. In particular, tumours have been shown to consume more glucose than their healthy counterparts and to use anaerobic metabolic pathways, even under aerobic conditions. Nevertheless, scientists have still not been able to explain why cancer cells evolved to present an altered metabolism and what evolutionary advantage this might provide them. Experimental and computational models have been increasingly used in recent years to understand some of these biological questions. Multicellular tumour spheroids are effective experimental models as they replicate the initial stages of avascular solid tumour growth. Furthermore, these experiments generate data which can be used to calibrate and validate computational studies that aim to simulate tumour growth. Hybrid models are of particular relevance in this field of research because they model cells as individual agents while also incorporating continuum representations of the substances present in the surrounding microenvironment that may participate in intracellular metabolic networks as concentration or density distributions. Henceforth, in this review, we explore the potential of computational modelling to reveal the role of metabolic reprogramming in tumour growth.

Contents

1. Introduction

Cell metabolism can be defined as the series of biochemical reactions that enable cells to produce the energy required for their survival and maintenance. Under some circumstances, metabolism may be altered to fit the cells' energy requirements, for instance, in

Abbreviations: MCTS, multicellular tumour spheroids; PDEs, partial differential equations; ODEs, ordinary differential equations; ABM, agent-based model; ATP, adenosine triphosphate; ECM, extracellular matrix; CPM, cellular Potts model; CA, cellular automata; FDG-PET, [18F]-fluorodeoxyglucose-positron emission tomography; FBA, Flux Balance Analysis; SBML, Systems Biology Markup Language

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proliferating cells, which have high energy demands [1,2]. Tumour cells are characterized by their ability to resist cell death and sustain abnormally high proliferation rates [3,4]. Henceforth, metabolism plays a crucial role in cancer progression since it supports the aberrant proliferation and survival dynamics of tumours. Studies have shown that cancer cells can reprogram their metabolism and favour metabolic pathways that enable cell division at faster rates but are less efficient, such as aerobic glycolysis [5,6,7]. In fact, altered metabolism has been recognized as one of the hallmarks of cancer, and it serves as the foundation for [18 F]-fluorodeoxyglucose-positron emission tomography (FDG-PET), a well-established scanning technique employed to identify and diagnose tumours [8,9]. Specifically, FDG-PET quantifies how much FDG, a glucose analogue, is consumed by cells under the assumption that most cancer cells consume more glucose [10].

Even though metabolic reprogramming has been studied more in recent years, there are still many unanswered questions regarding why tumour cells evolved to metabolize glucose through energetically inefficient pathways [11]. Hence, there is a need for models that can provide new insights into cancer metabolism and how it affects tumour progression. New experimental techniques such as multicellular 3D tumour spheroids (MCTS) provide a realistic representation of the avascular growth states of tumour growth [12]. In addition, mathematical and computational models have emerged as tools to test biological hypotheses, understand the mechanisms that drive cancer progression and accelerate the discovery of new therapies [13]. Biological systems can be modelled through distinct mathematical approaches, including continuum, discrete and hybrid frameworks [15,16]. When considering tumour growth, the spatial resolution at which tumours are reproduced differs between these implementations, with models ranging from microscopic, individual cell-based to more macroscopic, cell population-based representations [17]. Continuum approaches, such as ordinary differential equations (ODEs) and partial differential equations (PDEs), usually consider tumours at a large scale [18,19]. In other words, tumours are generally represented as a single cell population whose size changes over time or as a group of different cell populations to account for heterogeneous subregions in the tumour [20]. Nonetheless, the behaviour of individual cells is not taken into account, and thus continuum approaches lack the ability to model heterogeneous behaviour at the cell level [18]. Conversely, a higher level of detail can be achieved through discrete modelling techniques, also known as agent-based models (ABMs), which simulate tumours as a group of individual cells acting as agents that follow a set of rules and interact with each other and the environment [21,22]. In turn, these approaches enable the modelling of heterogeneous behaviour, although there is an increased computational cost.

Hybrid modelling is a technique that can be used to couple detailed discrete descriptions of cellular systems at the cell level with continuum models of the surrounding microenvironment [16]. Specifically, hybrid modelling is commonly used to study tumour growth as the result of the response of individual cells to the concentration of substances such as nutrients, metabolic waste and therapeutic agents that diffuse and are consumed/produced in the system [17,23]. The mathematical biology community has developed several frameworks that combine discrete representations of cells with PDE-based descriptions of the microenvironment, such as BioDynaMo [24], Chaste [25], CompuCell3D [26], Hybrid Automata Library (HAL) [27], iDynoMiCs [28], Morpheus [29] and PhysiCell [30]. Most of these software options are optimized to take advantage of the increasingly available computational power. Besides, they are accessible and extensible, meaning that new users can build on previous model iterations and focus on creating new extensions to solve specific questions [13,31].

Moreover, hybrid models can be extended to incorporate subcellular models of intracellular pathways and study cell metabolism [16,32] and how it is influenced by the local concentrations of oxygen and glucose [33,34]. In fact, some of the aforementioned hybrid modelling frameworks enable the integration of intracellular metabolic models written in the Systems Biology Markup Language (SBML) [35]. In addition, additional cell rules can be defined to account for stochastic and cancer-specific effects, including the increased glucose consumption rates in aerobic glycolysis [36]. Therefore, in this review, we aim to present how hybrid computational models that integrate tumour growth dynamics and intracellular metabolic pathways have been employed over the years to investigate metabolic reprogramming in tumour spheroids.

2. Glucose metabolism in cancer cells

Glucose is a nutrient used by both healthy and tumour cells to produce energy in the form of adenosine triphosphate (ATP) [9,37]. Generally, glucose can be catabolized via two main metabolic pathways: glycolysis and oxidative phosphorylation. The former is a less efficient but faster process that can be performed under anaerobic conditions, producing lactate and 2 ATP molecules per glucose molecule. The latter is a more complex, oxygen-dependent pathway that can generate large amounts of energy (approximately 32 ATP molecules for each glucose molecule), producing water and carbon dioxide molecules as a result. In healthy tissues, differentiated cells tend to generate energy through oxidative phosphorylation and resort to glycolysis only under anaerobic conditions. Yet, in the 1920 s, studies performed by Warburg [6] showed that tumour cells rely on glycolysis, even when oxygen was available, originating a theory commonly known as the "Warburg effect" or "aerobic glycolysis". Currently, it is well accepted that tumour cells reprogram their metabolism and consume glucose at high rates, as glycolysis requires more glucose molecules to produce large amounts of energy [5,38]. Nevertheless, it is still unclear why cancer cells perform aerobic glycolysis instead of the more effective process of oxidative phosphorylation.

The findings proposed by Warburg suggesting that cancer cells undergo aerobic glycolysis were firstly attributed to defects in their mitochondria that might impair the process of oxidative phosphorylation [6,39]. Later studies have shown that cancer cells are still able to oxidize glucose, though [40]. Furthermore, aerobic glycolysis and oxidative phosphorylation were proven to simultaneously occur at high rates in some tumour types [9,41], unlike what is normally observed in normal cells, which prioritize one of these metabolic pathways [42]. This phenomenon is illustrated in Fig. 1. Consequently, based on these results, scientists started to postulate that there might be an evolutionary advantage to this metabolic adaptation.

Glucose is commonly associated with energy production, which makes the Warburg effect seem paradoxical in the sense that glycolysis results in significantly fewer ATP molecules than aerobic respiration [11]. Nonetheless, previous studies have shown that aerobic glycolysis enables ATP generation at faster rates than oxidative phosphorylation [41,43]. Also, cancer cells can increase their glucose uptake through the upregulation of glucose transporter 1 (GLUT1) expression. Henceforth, the energetical inefficiency of glycolysis does not compromise cell growth and survival when nutrients and oxygen are abundant, since it is balanced by the ability to produce ATP rapidly [37]. In turn, this reveals that, under physiological conditions, the Warburg effect does not interfere with energy production. Furthermore, other studies have shown that aerobic glycolysis benefits proliferating cells as it enables biomass creation, which is essential to duplicate the cells' internal contents [44], it plays a role in maintaining the redox balance [45], and it promotes invasion and metastasis [46,47].

In addition to the Warburg effect, cancer metabolism is a complex phenomenon and there are other mechanisms still being

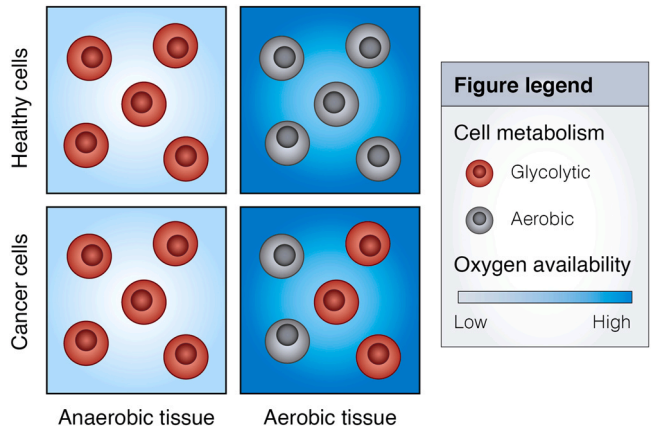

Fig. 1. Cell metabolism differences in healthy and cancer cells. Healthy cells are known to metabolize glucose through glycolysis when they are in anaerobic conditions, i.e., when oxygen is not available. Conversely, healthy cells undergo aerobic respiration when they are in the presence of oxygen. On the other hand, although cancer cells also perform glycolysis in anaerobic conditions, their metabolism shifts in the presence of oxygen. When oxygen is available, some cancer cells perform glycolysis, which is not as energetically efficient but enables energy production at faster rates. Different tumour types have been shown to differ in their preference to shift towards glycolysis. Thus, some tumours may have a glycolytic cell population, whereas other tumour types may also present cells that still perform aerobic phosphorylation.

discovered. For instance, it has been shown that cancer cells can modulate the metabolism of fibroblasts, which undergo aerobic glycolysis and produce lactate [48]. Subsequently, the surrounding cancer cells reuptake the metabolites produced by fibroblasts and further catabolize them in the aerobic respiration cycle, which allows them to generate high energy amounts. This process is commonly termed as the "reverse Warburg effect" and it can also occur between distinct tumour cell populations, one of which presents a glycolytic phenotype while the other catabolizes lactate. Moreover, cancer cells metabolize more glutamine than healthy cells to use as a carbon source for macromolecule biosynthesis [49,50]. Consequently, “glutamine addiction” is also recognized as one of the reprogrammed metabolic pathways in tumour cells [51].

3. Multicellular tumour spheroids

MCTS are spherical aggregates of malignant cells commonly employed as experimental approximations of the early stages of growth during which tumours are still not vascularized [52]. Compared to more traditional cell culturing techniques, e.g., cultures grown in 2D or in suspension, MCTS provide a more realistic histological and functional depiction of solid tumours and their surrounding microenvironment as observed in in vivo [12]. MCTS have been used extensively in research since the 1970 s when Sutherland et al. [53] first described this experimental model. Specifically, scientists have relied on this model to assess the effect of nutrients on cancer progression and test the effectiveness of new anti-cancer therapies [54,55]. Therefore, understanding how glucose modulates the evolution of MCTS is also crucial.

At initial stages of growth, MCTS have small diameters.Consequently, cells rely on diffusion to obtain oxygen and glucose from the microenvironment. However, once a critical diameter of 400–500 µm is reached, diffusion alone is insufficient for nutrients to reach the spheroid core. In addition, metabolic waste that originates from cell metabolism starts accumulating in the spheroid centre [54,56]. Consequently, large avascular MCTS present a layered distribution of cells similar to that observed in in vivo solid tumours [52,57] with three concentric regions. At the spheroid core, cells become necrotic since they do not receive enough nutrients to

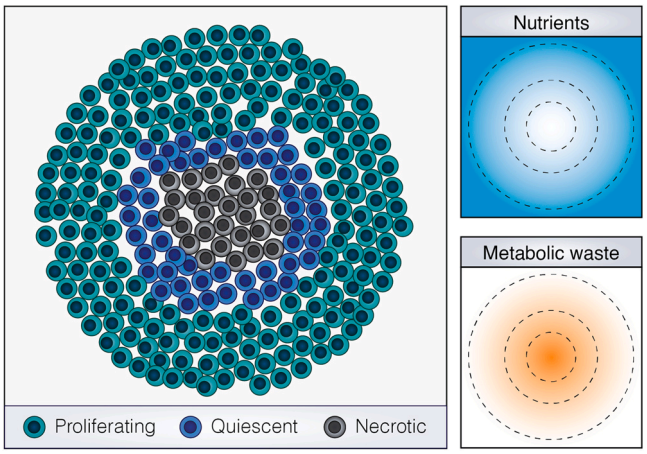

Fig. 2. Internal organization of a tumour spheroid. When tumour spheroids reach a critical size, nutrient diffusion becomes limited and the cells that are in the tumour core start to respond to nutrient shortage by becoming quiescent (represented in blue) or dying (represented in black). Consequently, spheroids present a well-defined internal structure formed by three concentric areas: proliferating, quiescent and necrotic cells. The distribution of nutrients and metabolic waste in tumour spheroids is also characteristic in these structures. Specifically, they are characterized by nutrient shortage as well as an accumulation of metabolic waste at their core.

survive. Besides, it is possible to distinguish two cell populations in the spheroid rim: proliferating cells in the periphery, where there are more nutrients and oxygen, and quiescent cells in the internal region close to the necrotic core. The internal structure of a tumour spheroid and the internal distribution of nutrients and metabolic substances is shown in Fig. 2. Certainly, cell metabolism is also affected by the distribution of the chemical substances that dictate cell survival and death.

Several experimental studies have tried to characterize the internal distribution of chemical substances in tumour spheroids [58,59,60]. Additionally, several of these models relied on mathematical models to predict the distribution of substances such as glucose, oxygen and lactate, as well as their consumption and secretion rates. However, computational models can be used in more advanced studies to provide more information and test hypotheses about the role of glucose in tumour growth, as explained in the section to follow.

4. Computational models

4.1. Classical models of solid tumour growth

For several decades, scientists have relied on mathematical and computational models to understand and reproduce tumour growth and several frameworks have been developed to describe the spatial dynamics of tumours and their microenvironment at different complexity levels [16,17,18,20,61,62]. Some of the simplest models developed were based on continuum approaches that aimed to replicate the evolution of the number of cells or the size of a tumour spheroid over time, using ODEs and PDEs [63]. ODEs can be employed to model macroscopic tumour growth curves under the assumption that tumours are composed of a single, spatially homogeneous cell population [64]. Several growth laws have been used to this aim, as illustrated in Fig. 3 A. For example, tumour growth can be modelled through an exponential law that describes growth as being proportional to tumour size, represented by its volume, V, as written in Eq. (1).

$$\frac{dV}{dt} = \alpha V, \text{ where} V(t=0) = V_o \tag{1}$$

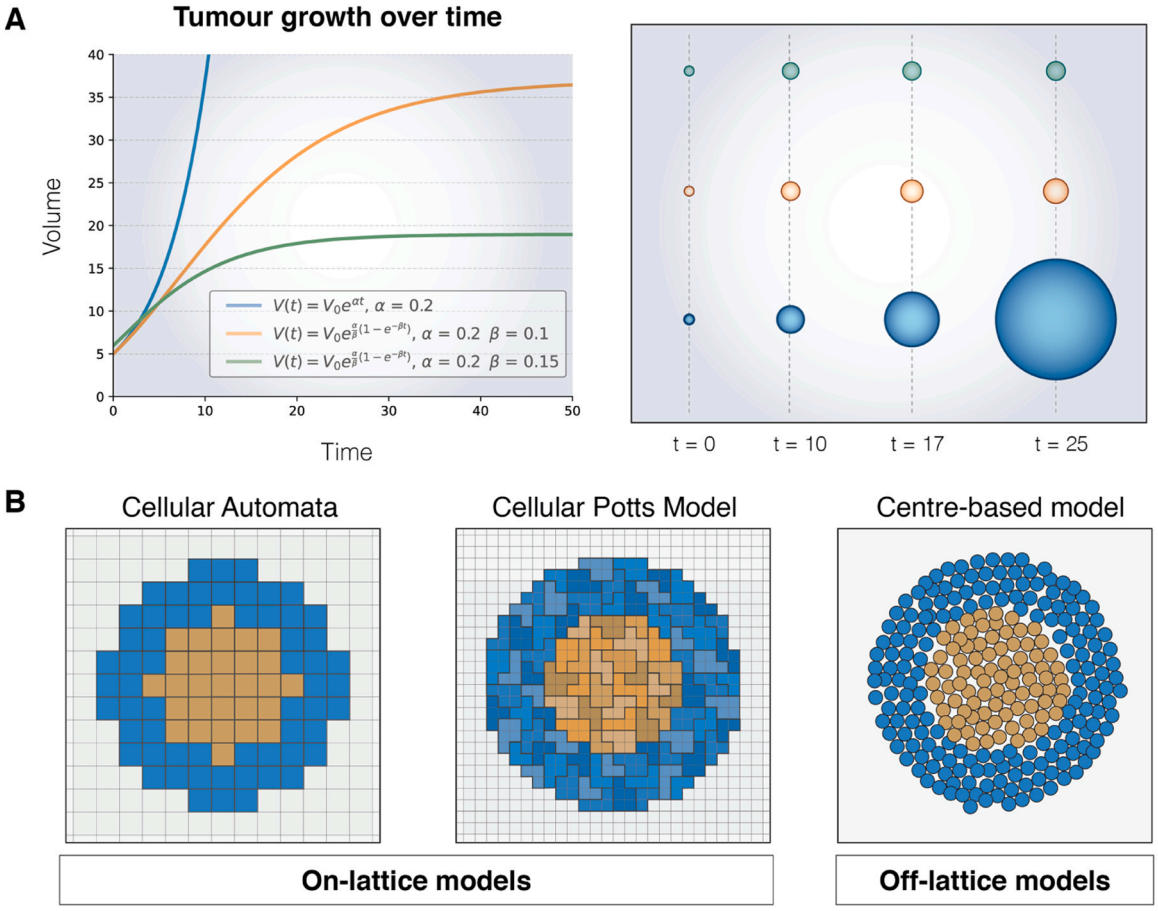

Fig. 3. Continuum and discrete models of tumour growth. (A) Representation of simulated growth curves of avascular models obtained with classical continuum models based on ODEs, namely the exponential (blue) and Gompertzian (green/orange). Although these models provide similar results at early stages of growth, only the Gompertzian model is able to reproduce the saturation in tumour size that is commonly attributed to limited nutrient diffusion once a tumour reaches a critical size. (B) Examples of discrete, or agent-based, models, which, unlike continuum approaches, model tumours as a group of individual agents that follow a set of rules that characterize biological phenomena such as proliferation and death. These models can generally be categorized into two main categories, i.e., on-lattice and off-lattice models, based on whether the cells are bound to occupy fixed positions defined by a lattice or if they are able to freely move through the domain. Proliferative cells are shown in cells while yellow cells represent the necrotic core. In the CPM subfigure, different shades of the same colour represent distinct cells since a single cell may occupy more than one voxel.

Here, α is a growth constant that can be fitted to match a given cell population using experimental data and V_0 is the initial tumour volume. Exponential growth is an adequate model to reproduce the initial stages of growth in a tumour spheroid, when a single cell originates two daughter cells [65]. Nonetheless, it fails to capture the subsequent stages where growth becomes arrested due to the limited amount of nutrients and the increased concentrations of metabolic waste that induce cell arrest and death [56,59].

The inhibitory effect caused by the limited diffusion can be modelled by modifying the exponential growth law and considering logistic or Gompertzian growth instead [65,64,66]. In the 1960 s, Laird [67] showed that the growth curves of several tumour types could be described by the Gompertzian equation, a generalization of the logistic growth law that reproduces an initial fast growth phase, followed by an exponential decrease in the tumour's growth rate that results in tumour size saturation. This model can be defined by defined by Eq. (2):

$$\frac{dV}{dt} = \alpha e^{-\beta t} V \text{where} V(t=0) = V_o \tag{2}$$

where β defines the rate at which growth decays [66,68]. It has been shown to fit experimental data better than exponential and logistic models [69]. Nevertheless, growth laws modelled as ODEs are not able to capture the complex tumour internal spatial organization and structure [18,70]. Consequently, more sophisticated models were adapted to capture the internal spatial organization of tumours and describe growth as a result of insufficient nutrient diffusion that leads to cell death and quiescence [71,72].

PDEs have been used to simulate the effect of the spatial distribution of diffusing factors that promote or inhibit cell growth and how they modulate the growth rate of tumour cells locally. In the 1970 s, Greenspan [71] developed a model of tumour growth that took into account how a single diffusing factor, here assumed to be glucose, influences tumour size. Assuming radial symmetry and that $V(t) = \frac{4}{3}\pi R^3(t)$ where R defines the tumour radius, the Greenspan model can be defined by Eq. (3):

$$\frac{dR}{dt} = \frac{1}{R^2}\int_0^R f(c) r^2 dr \tag{3}$$

where c is the local concentration of glucose and $f(c)$ is a function that describes how the cells' doubling rate changes in function of glucose concentration. Given that glucose is a growth-promoting factor, $f(c)$ should consider that the local concentration of glucose should increase the cells' doubling rate, until a maximum value is reached, where an increase in glucose concentration no longer has an effect on the doubling rate [32]. The spatial distribution of glucose can be modelled as a reaction-diffusion equation and it is assumed that glucose concentration decreases from the tumour surface to its core. Furthermore, the glucose consumption rate can be adjusted to consider different phenotypes, such as proliferating, quiescent and

necrotic [71,72]. In addition, the Greenspan model can be extended to consider other substances and reproduce differential behaviours accordingly [64].

The aforementioned continuum-based models have proven to provide realistic descriptions of tumour growth kinetics at the avascular stages. Nevertheless, these mathematical approaches fail to undisclosed how tumour growth arises from single-cell behaviour. On the other hand, discrete models describe cells at the individual level and are thus more suited to reproduce the heterogeneous behaviour of biological systems [21] and the interactions between cells and the microenvironment [73,74,75]. These models simulate cells as individual agents that follow a set of rules that define their cellular behaviour (e.g., death, proliferation, migration) and how they interact with other cells and the surrounding microenvironment [76]. ABMs can be grouped into on-lattice and off-lattice models. Fig. 3B shows an illustration of some of the most commonly used on-lattice and off-lattice models to simulate tumour growth. On-lattice approaches divide the domain into a grid of cells or voxels, and cells are bound to occupy these specific positions, which makes them computationally efficient [64]. For example, Cellular Automata (CA) models consider that each cell is represented by a single voxel, whereas Cellular Potts Models (CPM) assume that a single cell can be defined by more than one voxel. Thereofore, CPMs take into account an approximate morphology of the cells and their mechanical interactions with the surrounding neighbours [74]. Off-lattice approaches do not consider that the domain is divided into a grid, enabling cells to move freely through the microenvironment based on the forces exerted on them [21]. Centre-based models (CBMs) are an example of the off-lattice approach, and they consider that cells are characterized by their central position and a simplified geometry, such as a sphere. More sophisticated implementations that describe cell shape and allow for cell deformation (e.g., vertex-based and discrete element models) have also been developed, yet they can be considered to be computationally expensive to simulate large tumours [16,77]. All of the aforementioned approaches have been used to simulate tumour growth, as reviewed in more detail in [64,76,74].

ABMs are commonly coupled with continuum approaches that simulate the chemical substances of the cellular microenvironment (e.g., oxygen, glucose, growth factors, lactate and metabolic waste) [16,78]. Accordingly, these frameworks are frequently referred to as hybrid models since they integrate both discrete and continuum representations of biological systems. Generally, the spatial distribution of the chemical species present in the microenvironment is modelled as a set of reaction-diffusion equations written as PDEs where discrete agents act as sources and sinks [32]. Besides, models can be formulated so that the rules that define the ABM are updated based on oxygen and nutrient availability, which is essential to reproduce systems that consider glucose metabolism and how it regulates solid tumour growth.

4.2. Modelling intracellular metabolic networks

Metabolism, like other biological behaviours, can be modelled at different scales. One of the simplest and most commonly employed approaches to incorporate glucose metabolism in hybrid models of tumour growth is to account for the main metabolic processes in the models' continuum component [79,80]. As previously stated, glucose metabolism relies on two main pathways: glycolysis and oxidative phosphorylation. Glycolysis is characterized by being less energetically efficient than oxidative phosphorylation, since it requires glucose consumption at faster rates and produces fewer ATP molecules. Robertson-Tessi et al. [81] developed a hybrid model that takes into account oxygen, glucose, ATP and lactate and their effect on tumour cells. Several previous studies have been designed where cell death was deterministically induced when a critically low concentration of glucose was reached to simulate necrosis. In addition, glucose consumption rates may increase in low-oxygen regions to simulate the metabolic switch between aerobic and anaerobic pathways, while also accounting for the Warburg effect [80].

In the last decades, though multiple mathematical descriptions of intracellular networks at the subcellular scale have been developed, applying distinct mathematical formalisms to simulate signalling and metabolic pathways [82]. Metabolic reaction network models aim to create mechanistic representations of the metabolites that take part in a given pathway and how they interact [15]. These representations can differ on their assumptions regarding not only whether a system is continuous or discrete in time and space but also if it is deterministic or stochastic. Furthermore, network models can be generally classified into two main groups: stoichiometric and kinetic models [83]. The former take into account the stoichiometry of the metabolic reactions and their time-independent characteristics, while the latter introduces additional information on metabolite kinetics [84]. In addition, new techniques have been developed to combine kinetic and stoichiometric modelling and provide new frameworks that combine the comprehensiveness of constraint-based approaches with the detailed mechanisms of kinetic models [85,86,87].

On the one hand, stoichiometric approaches define metabolic networks as stochiometric matrices based on the number of metabolites, which are characterized as reactants and products, and reactions in a pathway [15]. Specifically, the stoichiometric matrices, commonly designed as S, are composed of the metabolites' stoichiometric coefficients and the rows represent the metabolites while the columns define the reactions. Overall, these models define the mass balance over the metabolic network and they are particularly convenient because they can take into account genome-scale metabolic data, without requiring information on the kinetic parameters of the modelled pathways, which can be difficult to measure experimentally [88,89]. Using constraint-based approaches, for example, Flux Balance Analysis (FBA), it is possible to find the metabolic pathways that optimize cellular growth and energy production [15]. To achieve this, it is assumed that the system has reached a steady-state. Besides, additional constraints, such as the bounds of the flux rates, may be imposed.

On the other hand, kinetic models aim to capture detailed and realistic representations of metabolic system dynamics. Henceforth, metabolite concentrations are modelled over time and they are usually represented by a set of ODEs that take into account specific metabolic reactions and detailed kinetic parameters [90]. The general expression for the evolution of a metabolite concentration (c) over time (t) is given by Eq. (4):

$$\frac{dc}{dt} = \sum_{i=1}^{n} k_i r_i \tag{4}$$

where n is the number of reactions in which the metabolite takes part, k represents the stoichiometric coefficients and r is the rate of the reaction. The equation rates can be measured experimentally and mathematically represented by different laws based on the complexity of the interactions between the agents in a given reaction. For example, mass action and Michaelis-Menten kinetics are some of the most used mathematical laws when modelling cell metabolism [91]. Nonetheless, experimentally measuring the intracellular concentration of metabolites and the corresponding reaction rates can be an arduous task, making kinetic models more difficult to calibrate than stoichiometric approaches.

Recently, researchers have developed several biochemical network models to analyse the Warburg effect and other aspects of metabolic reprogramming [92,93,94,95,96,97]. Nonetheless, only a few models have explicitly taken into account the effect of glucose availability and its metabolism at a larger scale

Table 1
Summary of the reviewed multiscale models.

Design	Intracellular models	Chemical species	Metabolism	Cell type	Validation	Reference
2D Cellular Potts Model	PDEs	Glucose, oxygen, waste, growth and inhibitory factors	Warburg	EMT6/Ro	Experimental	Jiang et al.[98]
2D Lattice-gas Cellular Automaton	ODEs	Glucose, oxygen, H+ ions	Not considered	EMT6/Ro	Literature	Piotrowska & Angus[99]
3D Cellular Automaton	ODEs	Glucose, oxygen, ATP, lactate, waste	Warburg	NSCLC	Experimental	Jagiella et al.[33]
2D Centre-based model	FBA	Glucose, oxygen, ATP, lactate, glutamine…	Warburg, reverse Warburg and glutamine addiction	Not specified	None	Shan et al.[100]
2D Cellular Potts Model	ODEs	Glucose, oxygen, ATP, lactate…	Not considered	PaTu8988T	Literature	Roy & Finley[36]
3D Cellular Automaton	PDEs	Glucose, oxygen, ATP	Not considered	EMT6/Ro	Literature	Cleri[101]

[98,99,33,100,36,101,14]. Specifically, there is still a need for models that combine different aspects of cellular behaviour, such as motility, mechanics and cell-cell interactions, into a fully integrated and multiscale model. In the section to follow, we explore some research works that aim to bridge this gap and their implementation.

4.3. Multiscale models

One of the most relevant advances that has emerged in recent years due to the increase in computational power is the ability to couple models that describe different spatial and temporal scales [102,103,104]. Frameworks that integrate phenomena that occur over distinct scales are usually called multiscale models. The idea that cells require some kind of nutrient to survive and proliferate has been incorporated into several models [23,105,106,107,108] yet only a few have integrated explicit models of glucose metabolism [13]. Multiscale hybrid models are particularly relevant in this research field as they are able to integrate intracellular models of glucose metabolism, enabling scientists to understand how changes at the metabolic level affect cell behaviour. A summary of hybrid models that consider glucose metabolism explicitly can be found in Table 1. Fig. 4 shows some illustrative results of on-lattice and off-lattice hybrid models.

Several of these models were formulated with on-lattice implementations. Starting with models developed with CPMs, Jiang et al. [98] proposed a model that was calibrated with experimental results obtained for EMT6/Ro tumour spheroids, a mammary carcinoma cell line. The authors explicitly modelled the Warburg effect using PDEs and defined that necrosis was induced when the glucose and oxygen concentrations went below a given threshold and lactate levels surpassed a maximum value. Furthermore, at the subcellular scale, the model considered a Boolean regulatory network of the cell cycle, which was modulated by growth and inhibitory factors. Using the CompuCell3D [26] modelling framework, Roy et al. [36] also implemented a CPM but incorporated a much more complex intracellular model of cell metabolism, written as a set of ODEs that captured all the reactions in both glycolysis and the aerobic respiration cycle.

Cellular automata models have also been used in this field of research. For example, Cleri [101] extended a previous agent-based model of cancer growth originally built to account for the effect of cytotoxic agents [109] to investigate the impact of metabolism on spheroid growth. In his work, the author introduced and implemented a simplified model of glucose metabolism and tested the effect of different nutrient sources, such as constant and sinusoidal glucose supply mechanisms. The model results were qualitatively compared with data from the literature and were found to be relevant. In addition, Piotrowska & Angus [99] calibrated a lattice-gas cellular automaton model with experimental data available from the literature [110]. Glucose metabolism was modelled through a set of ODEs as done previously by Venkatasubramanian et al. [111]. Furthermore, Jagiella et al. [33] implemented an intracellular model of glucose metabolism based on ODEs considering the aerobic and anaerobic pathways effect and investigated which metabolic conditions increased the similarity between the computational and experimental datasets.

Regarding the off-lattice approach, one previous work has employed a CBM to study MCTS and the role of glucose metabolism on their growth dynamics. Specifically, Shan et al. [100] used the iDynoMiCS [28] framework to model cell behaviour and integrated a complex intracellular network based on FBA and explicitly reproduced the Warburg effect, the reverse Warburg effect and glutamine addiction. In their work, the authors tested how growth dynamics changed according to the metabolic reprogramming strategy that was adopted by the cells.

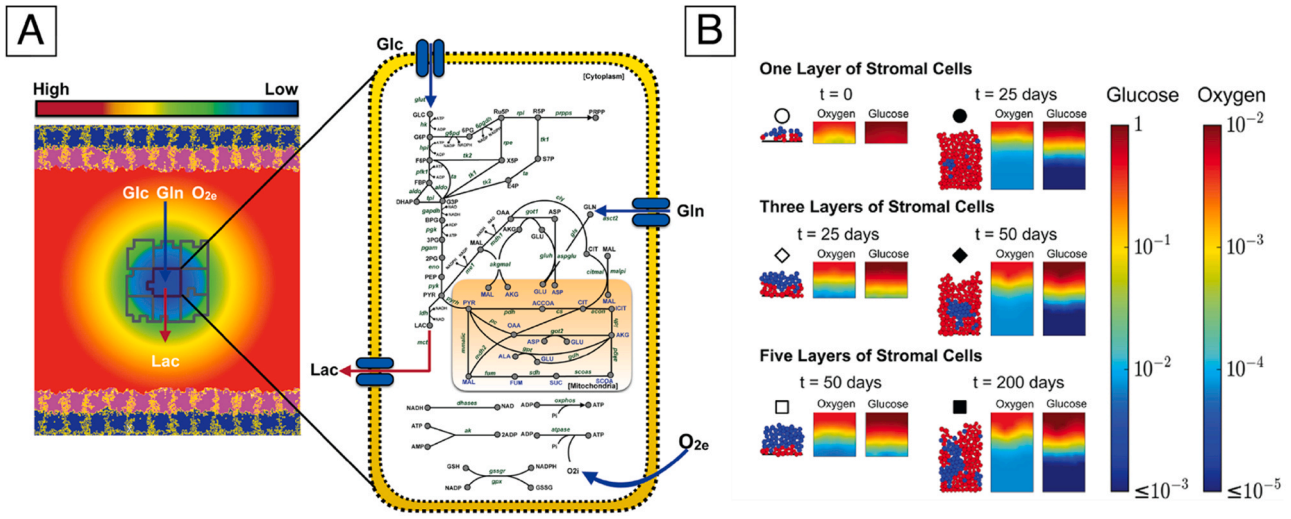

Fig. 4. Examples of multiscale hybrid model results. (A) Illustration of a hybrid model where cells (outlined in grey) are represented by an on-lattice Cellular Potts model and the microenvironment consist of PDE-based descriptions of glucose, oxygen, lactate and glutamine. Single tumour cells consume glucose, glutamine and oxygen and produce lactate based on an intracellular metabolic network represented in the figure which considers both aerobic and anaerobic metabolism. (B) Model results for an off-lattice centre-based model that simulates tumour cells as spherical particles represented by their central point and radius. Reaction-diffusion equations are considered to study the spatial distribution of glucose and oxygen, represented as the colour gradients shown in the figure. Moreover, cell metabolism is introduced through a flux-balance analysis model that simulates the Warburg effect, the reverse Warburg effect and glutamine addiction. SubFigs. A and B were taken from [36] and [100], respectively.

5. Conclusions and future perspectives

In the last decades, computational modelling of solid tumour growth has evolved to consider biological phenomena that occur over different time and spatial scales. Moreover, cell metabolism has been increasingly recognized as one of the main hallmarks of tumour growth and progression, and it has been accordingly integrated into computational frameworks to be better understood. Overall, these models have been able to simulate experimental data and reveal which type of metabolic response best fits the available results. Furthermore, with the constant increase in data availability, models are evolving to become patient-specific [112,113]. However, many of the models developed until now are focused on a single scale and there is still a need for fully coupled models that integrate biochemical networks with cellular and extracellular behaviour.

We highlight that, although we focus our review on the avascular stages of MCTS growth, models that take into account neovascularization have also been developed [114,79,115,116,117]. Some of these models also investigate invasion since tumour cells are able to metastasize by entering the circulatory system through vascularization [118,119,81]. Nonetheless, these implementations were developed with on-lattice frameworks, which do not capture cell mechanics as well as centre-based and off-lattice models. Biomechanical models of tumour growth may be of particular interest to investigate the interplay between glucose consumption and the mechanical properties of the extracellular matrix (ECM) [120,121,122,123,75]. The ECM is the non-cellular component of tissues that provides support and structure to the cells. Previous studies have shown that the ECM stiffness influences multiple cellular processes, such as, proliferation, migration and death [124], and it also modulates tumour growth [125]. Furthermore, recent studies have highlighted that changes in the mechanical properties of the ECM modulate cancer metabolism, specifically glucose metabolism [120]. For instance, it has been shown that cells detached from the ECM change their metabolism and decrease their glucose uptake and that migrating cells regulate their glucose uptake in response to the ECM's mechanical properties [122,126]. With this in mind, it is highly relevant to develop models that allow for the study of cell motility and cell mechanics at the individual level, and how cell-cell and cell-matrix interactions can also play a role in modulating these dynamics.

Moreover, cell-based multiscale models offer an advantage over population-based models since they are able to capture heterogeneity at the individual cell level. This is of particular interest when scaling from tumour spheroid to tumour organoid models. Tumour organoids are 3D self-organized structures grown from patient-derived cancer stem cells [127,128]. These models enable a higher level of personalization since tumours of the same type, e.g., lung, brain, pancreas..., can differ between patients. Henceforth, when developing patient-specific models, it is crucial to be able to calibrate these models with this level of detail. Besides, the internal structure of organoids can be more complex than that of tumour spheroids, thus making it necessary to introduce stochasticity and heterogeneity at the cell level.

Lastly, multiscale models can be further expanded to consider phenomena at the tissue-level. The number of cells in a tissue makes it unfeasible to create a tissue of a model at the individual cell level. Hence, tissue-scale modelling can be achieved by coupling intracellular and cellular models with continuum representations that capture the tissue's mechanics [129]. This strategy is traditionally based on treating the tissue as a continuous material, thus eliminating the heterogeneity that can arise when a tumour is present. Nonetheless, more recent approaches have solved this issue by selecting a region of interest for which a cell-based model is used to evaluate tumour growth dynamics. Subsequently, this detailed description can be integrated into a continuum approach [130],reducing the computational power required to study the effect of tumour growth at this level.Certainly, it would be invaluable to use these approaches to recognize how metabolic reprogramming may influence the evolution of a tumour at the tissue level.

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CRediT authorship contribution statement

I. G. Gonçalves: Conceptualization, Investigation, Writing – original draft, Writing – review & editing, Visualization. **J. M. García-Aznar:** Conceptualization, Writing – review & editing.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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