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Fractional Mathematical Oncology: On the potential of non-integer order calculus applied to interdisciplinary models

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ABSTRACT

Mathematical Oncology investigates cancer-related phenomena through mathematical models as comprehensive as possible. Accordingly, an interdisciplinary approach involving concepts from biology to materials science can provide a deeper understanding of biological systems pertaining the disease. In this context, fractional calculus (also referred to as non-integer order) is a branch in mathematical analysis whose tools can describe complex phenomena comprising different time and space scales. Fractional-order models may allow a better description and understanding of oncological particularities, potentially contributing to decision-making in areas of interest such as tumor evolution, early diagnosis techniques and personalized treatment therapies. By following a phenomenological (i.e. mechanistic) approach, the present study surveys and explores different aspects of Fractional Mathematical Oncology, reviewing and discussing recent developments in view of their prospective applications.

1. Introduction

Cancer embodies a group of diseases that emerge from abnormally mutated cells and can appear in almost any body organ or tissue. It is the second leading cause of death worldwide and survival rates are profoundly related to timely access to quality diagnosis and treatment (World Health Organization, 2020). Experimental oncology and techniques involving molecular biology and, more recently, genetics have dominated most research projects on the subject, increasing the knowledge on malignancies characterization, diagnostic and treatment (Gatenby and Maini, 2003). In the last few decades, physics and mathematics have been increasingly applied to cancer-related problems, thus giving rise to a new research area (Byrne, 2010; Rockne and Scott, 2019).

Mathematical Oncology broadens the development and application of models to manifold phenomena including tumor growth dynamics, anticancer therapies and personalized treatment (Jackson et al., 2014; D'Onofrio and Gandolfi, 2014). While this research field has rapidly evolved in the wake of increasing data availability from the recent expansion of bioinformatics (Khoury and Ioannidis, 2014; Meyer et al., 2014), it still lacks theoretical models to understand, organize and apply clinical data (Gatenby and Maini, 2003). As strategic advantage, the often called in silico models can test and reproduce several scenarios, which could be unfeasible or even impossible through in vitro experiments. It then becomes a powerful analysis tool as clinical tests in humans are time and resource consuming. Furthermore, in research activities 'know-why' has been progressively desired over 'know-how', contributing to the development of models that suitably combine data-oriented and phenomenological approaches (Sam Saguy, 2016).

Also called physics-based or mechanistic modeling, the phenomenological approach to oncological processes is a complex and interdisciplinary task, mainly because governing equations are generally formulated by invoking concepts from different areas. Accordingly, Mathematical Oncology under phenomenological approaches remains largely an underexplored research niche (Anderson and Quaranta, 2008) as a result of complex aspects such as variable compositions, heterogeneity and moving borders.

In this context, the present paper reviews and discusses cancer-related models under an interdisciplinary viewpoint. As Fig. 1 illustrates, Mathematical Oncology can benefit from approaches conveying engineering, physics, biosystems and nanothecnology. For instance, population dynamics and computational biology can be employed to analyze tumor growth (Wodarz and Komarova, 2014), fluid mechanics and reaction-diffusion phenomena can determine nutrient availability around cells, material science can characterize external forces and stresses on tissue surrounding neoplasms (Matoz-Fernandez et al.,

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2017), and nanomedicine can enhance clinical translation of oncology (Moradi Kashkooli et al., 2021).

The idea is to follow mathematical approaches able to maintain deductive-reducionist model features without mischaracterizing eventual complexities. One promising alternative is modeling via fractional calculus – an area of mathematical analysis that employs non-integer order differential and integral calculus (Oldham and Spanier, 1974; David et al., 2011; Teodoro et al., 2017; Luchko and Kochubei, 2019). Fractional models are characterized by the presence of an arbitrary order (i.e. not necessarily integer) of differentiation (or integration). This feature widely amplifies the application scope since it enables the model to present distinct behavior according to such fractional order, enhancing its ability to deal with properties from different scales regarding both fractal structure and memory of biological tissue (Magin et al., 2008; West, 2014). For this and other remarkable attributes, fractional models may be optimal to model biological phenomena (Craiem and Armentano, 2007) and have been successfully applied towards Mathematical Oncology (Sweilam et al., 2020; Akman Yildiz et al., 2018; Ionescu et al., 2017).

Therefore, besides reviewing Mathematical Oncology and surveying some recent well-succeeded implementations of fractional models, the present study prospectively explores approaches to reductionist models that could help understand and describe cancer-related phenomena and predictive oncology. In theory, an interdisciplinary approach symbiotically combining physics, material science, biology and fractional calculus, could offer unpaired developments and distinct views on oncology phenomena. In fact, Byrne (2010) supports that it is the collaboration between theoreticians and modelers, i.e. the interplay among different areas, that could start improving Mathematical Oncology towards its effective application to real problems and personalized care. As different mathematical approaches can reproduce the same experimental results, Byrne (2010) also claims that it might be suitable to apply Occam's razor concept in order to develop an oncology-applied model. In other words, a model should contain sufficient detail to describe the phenomenon of interest but not excessively to obscure it. Accordingly, preference should be given to reductionist approaches.

Overall, this paper is organized as follows: section 2 provides a brief contextualization on Mathematical Oncology; section 3 surveys some of the most relevant continuum cancer-related models; on the other hand, section 4 presents cell-based and stochastic models; fractional calculus main aspects and oncology models are explored in section 5; finally, section 6 delves into hybrid approaches, discussing prospect investigations.

2. An introduction to Mathematical Oncology

Cancer is the collective name given for a large group of over 100 diseases related to abnormal cell reproduction (Jackson et al., 2014). World Health Organization (2020) states that cancer is the second major cause of death worldwide, responsible for about 1 in 6 deaths. It is a disease that generally compromises health care systems mainly as a result of its lingering effects along with usually severe side-effects from lasting treatments. Whether combined or separately administered, chemotherapy, immunotherapy and radiation therapy are usually the most common interventions. Considering how cancer might develop very differently in each case while dose adaptation or fractionation are both subject to individual clinical responses, personalized therapy may require the support from mathematical models to optimize treatment strategies (Enderling et al., 2019; Rockne and Scott, 2019).

In that context, Mathematical Oncology develops and applies models to cancer-related phenomena, ranging from tumor dynamics analysis to personalized treatment (Jackson et al., 2014; Abernathy et al., 2017; Cristini et al., 2017). It is a research field that has been benefiting from recent increase in data availability from quickly evolving biosensors and bioinformatics techniques (Khoury and Ioannidis, 2014). Predictive

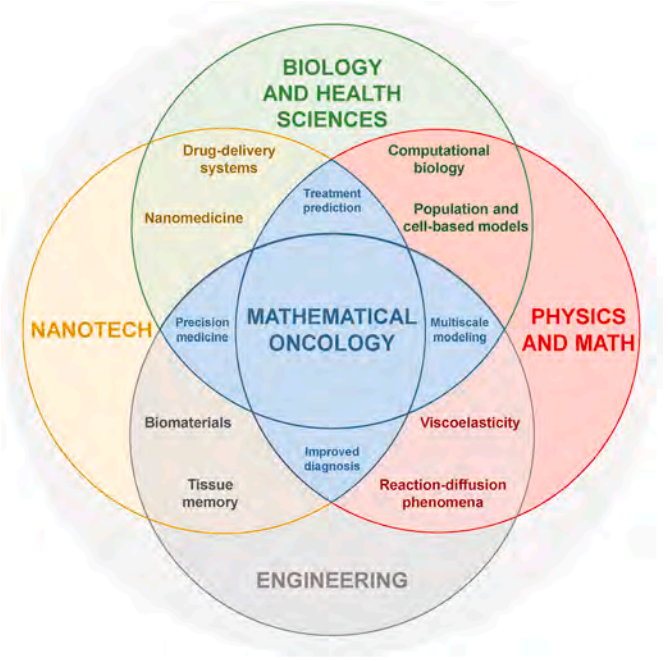

Fig. 1. Sketch of possible interdisciplinary approaches to Mathematical Oncology and related keywords.

oncology may contribute to personalized treatment procedures by means of numerically virtualized scenarios based on tumor dynamics and individual gene expression.

As all-inclusive modeling prospectively enhances creating and carrying out innovative cancer treatments, research endeavors have been concerned to apply mathematics and physics towards cancer onset and early growth as well as tumor and intercellular interactions (D'Onofrio and Gandolfi, 2014). Mathematical Oncology indeed rises as a scientific area relying on the notion that '(1) mathematics can be applied to improve biomedical knowledge of the disease and (2) that biology proposes new mathematical challenges, which generates enhanced mathematical tools' (Chauviere et al., 2010). Accordingly, Mathematical Oncology claims for comprehensive theoretical models to understand, coordinate and employ clinical data in view of aiding decision-making in oncology (Gatenby and Maini, 2003).

On that matter and to different extents and perspectives, Mathematical Oncology can encompass the so-called translational research, which bridges the gap between basic research and its final application in health systems (Barreto et al., 2019; Doroshow & Kummar, 2014). Also referred to as 'blackboard-to-bedside' or 'bench-to-bedside' research, in the present case it concerns how mathematical models can go from complex theoretical frameworks to comprehensive personalized strategies to identify and treat specific cancers. Applications of interest refer to early diagnosis improvement, such as decision-making support systems based on prediction algorithms (Chakraborty et al., 2020) or molecular testing through real-time tissue acquisition and analysis (Mitri et al., 2018), and personalized medicine. On the latter, information combined from mathematical models and corresponding in silico experiments can build patient-specific tumor profiles and be implemented into preclinical and clinical use (Hamis et al., 2019). Overall, Mathematical Oncology can provide the necessary theory to connect the unique biology of patient's tumor to tailored treatment routine or drug dosage, enabling true precision-guided therapy (Hormuth et al., 2021; Nenoff et al., 2020; Sarhaddi and Yaghoobi, 2020).

3. Deterministic and continuum models: Tumor growth described by differential equations

In spite of usually evolving differently, solid cancers have a common inception on the progenitor mutated cell that originates a primary tumor. Aiming at this mutual point may help grasp important characteristics of early tumor dynamics. Recently, gene sequencing and molecular biology have progressively explored paths and signals leading to cancerous cell arise (Golub et al., 1999; Easton et al., 2015), yet it is equally important to understand mechanistic basis of tumor cells dynamics.

Population or ecological models are customary approaches in view of grasping phenomenological foundations concerning general avascular tumor growth, being usually modeled in terms of ordinary differential equations (ODE) (Savageau, 1980; Sachs et al., 2001; Sarapata and de Pillis, 2014). Albeit more elementary than oncology models containing partial differential equations (PDEs), ODE-based approaches have advantages motivating their current employment (Wodarz and Komarova, 2014). Their relative simplicity (compared to PDE) enables the derivation of analytical solutions, thus allowing mathematical description of phenomena evolution (de Souza-Santos, 2007). Moreover, ODE-based models free parameters can be usually fine-tuned against clinical data in order to describe different tumor phases (Benzekry et al., 2014; Hartung et al., 2014), favoring their flexibility and consequent use to support clinical advice.

Being tailored towards specific experimental evidence and biological peculiarities, many ODE models have been elaborated to virtualize dynamic tumor growth. Most follow a sigmoidal law relying on two parameters, namely population growth rate and carrying capacity. Aforesaid definition is imposed so that models can capture the particular stages a primary tumor sustains in view of available resources such as neoplasm surface area and tissue heterogeneity (Marušić et al., 1994).

Tumor progression often involves different stages such as random mutations, alterations in tissue biomechanics (Fritsch et al., 2010; Ramião et al., 2016) and epigenetic spontaneous cell changes (Boveri, 2014; Lowengrub et al., 2010). Those features should be considered when modeling tumor development since they interfere with growth behavior, thus enabling a possibly better approach supported by multistage carcinogenesis (Wodarz and Komarova, 2014). Accordingly, some authors proposed models that integrate and express multifactorial or multistep growth patterns (Rodriguez-Brenes et al., 2013; Tracqui, 2009; Spencer et al., 2004) (e.g. alternated dormancy periods modeled as stepwise patterns).

Alternatively, there are other ODE-based approaches in Mathematical Oncology besides ecological models. Kinetic interactions between tumor and immune cells on different cellular and sub-cellular levels can be modeled by means of ODE system (Dolfin et al., 2014). Other models can target the interaction between gene expression and population dynamics concerning different cell classes (La Porta and Zapperi, 2017).

However, Murphy et al. (2016) claim that ODE models may be unable to fully consider the intricate tumor dynamical evolution and need to be carefully employed. For other authors, these models should necessarily be used to describe only general trends concerning neoplasm behavior, being inadequate to characterize specific cases (e.g. in personalized therapy) (Wodarz and Komarova, 2014). Such drawback is often a result of irregular growth patterns and aforementioned genetic instabilities in these organisms (Lowengrub et al., 2010; Fritsch et al., 2010; Ramião et al., 2016).

A subsequent climbing step in the complexity ladder takes cancer models into the significantly more robust PDE domain, describing tumor growth and other related phenomena in terms of not only dynamic variations (i.e. time dependence) but also gradients (i.e. spatial dependence), allowing a far-reaching description of reality. When employing models with PDEs well-established conservation laws can be conveniently applied to incorporate a more mechanistic (i.e. phenomenological) approach to oncology modeling (Wodarz and Komarova, 2014). For that reason, PDE approach is a more comprehensive choice when studying tumor growth into surrounding tissue.

Some models describe tumors as a fluid or a fluidized mixture, thus admissible of being modeled through transport equations. Byrne and Preziosi (2003) proposed an early two-phase model of an avascular tumor comprising cellular (solid) and interstitial (liquid) parts. Along with supplementary constitutive laws mass and momentum equations were applied to investigate time-spatial dependence of cell proliferation rate on cellular stress. Through their findings, the authors related the impact of mechanical effects on tumors equilibrium size, identifying a critical value for proliferation rate influencing on tumors outcome behavior (either growth or elimination). Fasano et al. (2014) proposed other models based on conservation laws and considering a heterogeneous system. They also considered free boundaries, being an important particularity when treating expanding tumors and complex processes in multi-component neoplastic formation. Other models employ the transport equation for metastatic processes and beyond (Hartung et al., 2014; Xu et al., 2016).

In a surrogate approach, the diffusion equation can be used to study the dynamic of cell population density across tissues (Debbouche et al., 2021; Polovinkina et al., 2021). In those studies, one may consider different combinations of population heterogeneity, possibly including stem and regular tumor cells, dead cells, healthy cells and even lymphocytes or similar (Adam and Maggelakis, 1990; Pham et al., 2012; Wong et al., 2015). Stability and possible outcomes are frequently focused in those investigations since they allow the virtualization of general scenarios regarding tumor form such as dormancy, evanescence, or uncontrolled growth and invasion.

Other models (La Porta and Zapperi, 2017) target specific cell behavior such as tumor angiogenic factors or mitosis rates trying to describe the specific interior cell behaviors leading to the accumulation of genetic chances and consequently emerging Hanahan and Weinberg's (2011) hallmarks of cancer. A vast part of Mathematical Oncology also focuses on modeling treatment-related phenomena such as drug delivery, tumor-immune dynamics, optimal chemotherapy and radiotherapy dosage, cycle-specific oncolytic virotherapeutics, and their impacts on tumor and healthy cells (Eladdadi et al., 2014). In those studies, not only PDEs are employed but also ODE systems and control techniques.

As cancer is a systemic disease, some authors argue that it requires an equally systemic model approach. With the help of PDEs, a commonly adopted approach relies on modeling tumor micro-environment (i.e., neoplasm surroundings), considering not only where cancerous cells arise and proliferate but also on how they react to certain environmental conditions. In this context, the concept of dynamic capacity of the tissue bearing the tumor can be better approached by modeling factors such as nutrient availability (Benzekry et al., 2014), invasion tendencies (Rejniak, 2016), biomechanical stresses (Taloni et al., 2014; Ambrosi et al., 2017) and anticancer therapies.

Nevertheless, using PDEs is mathematically more difficult and costly than employing ODEs due to the simultaneous dependence on more than one independent variable and often intricate boundary and initial conditions. Additionally (and quite paradoxically), an inherent limitation of models employing solely differential equations turns out to be exactly their characteristics of being continuous and deterministic. When a model invokes specific cellular structure and probabilistic nature involving cell proliferation, a different mathematical approach is required.

4. Cell-based and stochastic models: tumor growth governed by discrete models

Anderson et al. (2007b) claim that while continuum mathematical models have been successfully employed to describe several portions of matter, they are essentially particles, cells, thus discrete. In the wake of the impressive progress of biochemical and biological concepts on

genetics, sub-cellular levels and their intricate mechanisms, computational-enhanced Mathematical Oncology faces the difficult task of transforming specific portion-sized data into complex information describing emergent higher-level multi-scale cellular phenomena. In recent years, many cell-based models have been proposed to face such challenge (Weerasinghe et al., 2019).

Cell-based or discrete models are organized frameworks that keep track of fully independent individual parameters varying in time and space, reflecting the heterogeneity and complex, emerging, phenomena found in cancer. Computationally, they can rely on different approaches including Monte-Carlo simulations, energy minimization techniques, volume conservation laws, motion rules and others (Anderson et al., 2007b).

If these models follow a structural or grid organization, they are mathematically treated as lattice-based models, which are categorized according to the number of cells that each lattice site can hold (Metzcar et al., 2019). Lattice-gas cellular automata models admit more than one cell per site (being suitable for larger systems). On the other hand, if a single cell allegedly occupies many spots, then it should be modeled as sub-cellular systems (Jamali et al., 2010). Finally, if each cell can occupy a single lattice, it can be modeled as a regular cellular automaton (CA) (Metzcar et al., 2019).

Virtualization (or numerical simulations) involving cell-based models are often referred to as in-silico modeling because of their similarity and logical extension of in vitro experimentation (Jeanquartier et al., 2016). Concerning regular CA models, relatively simple implementations can go a long way in providing emergent complex behavior. Enderling et al. (2009) established only a basic set of rules concerning proliferation and migration rates for each type of tumor cell (regular or stem) in a CA model and investigated the virtualization of very different emergent scenarios when changing these rules, including cell clustering and tumor dormancy. Later, Poleszczuk & Enderling (2014) improved the model by implementing it with high-performance computational techniques.

5. Fractional Mathematical Oncology

5.1. Fractional calculus basic theory

Fractional calculus (FC) or calculus of arbitrary order may be considered an natural extension of traditional integer order calculus since it is a mathematical area of analysis that investigates and applies concepts of non-integer differential and integral calculus. It appeared for the first time in correspondences between L'Hospital and Leibniz in the end of the 17th century (Ross, 1977). Even with an ancient origin, FC had a slow development when compared with its integer counterpart. Only over one hundred years after those letters there was the first formal definition for a fractional derivative, accomplished by Laplace and Lacroix (Domingues, 2005).

Later, Riemann's and Liouville's definitions became two of the most known and popular formulations for fractional integrals and derivatives (Oldham and Spanier, 1974). Nevertheless, the scenario changed when Caputo (1967) suggested a new approach from Riemann definition by incorporating initial conditions of integer order in the resolution of fractional differential equations. Such change allowed a greater fidelity to physical phenomena modeled with fractional calculus, which widely disseminated Caputo's approach in applications ranging from physics to life sciences. Many other definitions have surfaced ever since, with different interpretations and particularities addressed to each one (Sales Teodoro et al., 2019; Ortigueira and Tenreiro Machado, 2017). Main publications on the theme have only appeared in the beginning of the 20th century (Machado et al., 2010a, b), whose major history and grounding concepts can be found in classical materials from Oldham and Spanier (1974), Ross (1977) and, more recently, in works by David et al. (2011), Capelas de Oliveira and Tenreiro Machado (2014), Luchko and Kochubei (2019).

Considering that FC is a generalization of integer order calculus, its fundamental concepts can be introduced by relying on simpler conjectures. Therefore, just as it is possible to state that real numbers are generalizations of natural and integer numbers, the same can be applied to some mathematical tools (Herrmann, 2014). Factorials, for instance, comprise only natural numbers, thus restricting its application domain. As factorial generalization, gamma function is introduced for any $\Re(z) > 0$ as

$$\Gamma(z) = \int_0^\infty t^{z-1} e^{-t} dt. \tag{1}$$

On the same line of thought, exponential Euler function

$$e^z = \sum_{n=0}^{\infty} \frac{z^n}{n!} \tag{2}$$

can also be generalized by replacing its factorial component with a gamma function, yielding

$$e^z = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(1+n)} \tag{3}$$

and thus introducing the so-called Mittag-Leffler (ML) function for $\Re(\alpha) > 0$ (Mittag-Leffler, 1903)

$$E_\alpha(z) = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(1+n\alpha)}, \tag{4}$$

which was extended to admit two parameters for $\Re(\alpha) > 0$ by Wiman (1905).

$$E_{\alpha,\beta}(z) = \sum_{n=0}^{\infty} \frac{z^n}{\Gamma(n\alpha+\beta)}. \tag{5}$$

ML function is as important for FC as are exponential functions for integer calculus since it is commonly employed to represent the solution of several fractional mathematical and physical problems. This is due to the fact that many simple and popular functions are particular cases of this generalization. Therefore, several researchers have long explored its uses and particularities (Camargo, 2009; Valério et al., 2013; Gorenflo et al., 2014).

Considering the basic notation of conventional (i.e. integer order) derivative, one writes

$$g(x) = \frac{d}{dx} f(x). \tag{6}$$

If, for instance, it is assumed $f(x) = x^k$ then

$$\frac{d}{dx} x^k = k x^{k-1}, \tag{7}$$

whose generalization for $n \in \mathbb{N}$ is

$$\frac{d^n}{dx^n} x^k = \frac{k!}{(k-n)!} x^{k-n}. \tag{8}$$

By considering that order n may be arbitrary to the point of including non-integer values, one may apply gamma function (as previously introduced) to extend Eq. (8) as

$$\frac{d^\alpha}{dx^\alpha} x^k = \frac{\Gamma(1+k)}{\Gamma(1+k-\alpha)} x^{k-\alpha} \quad x \geq 0, k \neq -1, -2, \ldots, \tag{9}$$

in which $x \geq 0$ and k is positive to assure the singularity of fractional derivative definition in view of the convergence of the integral in Eq. (1) for any integer $z > 0$.

This intuitive approach has been long applied to several types of functions. Before formally defining fractional derivatives, it is more intuitive to present the definitions regarding fractional integrals in line with Herrmann (2014). An integration of a function is considered as the

inverse operation of its differentiation

$$\left(\frac{d}{dx}\right)({}_{a}I)f = f. \tag{10}$$

In turn, one defines the conventional integrator ${}_{a}I$ operator in a domain as

$${}_{a}If = \int_{a}^{x} f(\xi)d\xi. \tag{11}$$

The definition of fractional integrals start with a multiple integral as

$${}_{a}I^{n}f = \int_{a}^{x_n}\int_{a}^{x_{n-1}}\dots\int_{a}^{x_1} f(x_0)dx_0\dots dx_{n-1}, \tag{12}$$

which represents the successive anti-differentiation of a continuous function $f(x)$. From Cauchy's Integral Theorem and the Fundamental Theorem of Calculus it is possible (Folland, 2002) to represent Eq. (12) in a more convenient way, thus writing integral Cauchy formulation:

$${}_{a}I^{n}f(x) = \frac{1}{(n-1)!}\int_{a}^{x}(x-\xi)^{n-1}f(\xi)d\xi. \tag{13}$$

By employing gamma functions, Eq. (13) can be extended for the fractional case as

$${}_{RL}I_{+}^{\alpha}f(x) = \frac{1}{\Gamma(\alpha)}\int_{a}^{x}(x-\xi)^{\alpha-1}f(\xi)d\xi, \tag{14}$$

$${}_{RL}I_{-}^{\alpha}f(x) = \frac{1}{\Gamma(\alpha)}\int_{x}^{b}(\xi-x)^{\alpha-1}f(\xi)d\xi. \tag{15}$$

In those equations, a and b respectively determine the lower and upper limits of the integral domain. While Eq. (14) is called "left-handed" and valid for $x > a$ since it collects function values for $\xi < x$, Eq. (15) is called "right-handed" and applies for $x < b$, collecting function values where $\xi > x$. The choice of a and b fundamentally sets apart two of the most used definitions of fractional calculus, namely Liouville's and Riemann's fractional integrals for $a = -\infty$ and $b = +\infty$, and $a = 0$ and $b = 0$, respectively. Pragmatically, the distinction between those definitions may be observed from the differentiation of some specific functions that will result in significantly different solutions, depending on the chosen approach.

From the definition of fractional integrals one can obtain fractional derivatives. Thus, the fractional derivative operator

$$\frac{d^{\alpha}}{dx^{\alpha}} = D^{\alpha} \tag{16}$$

is used to introduce the concept of operation sequence between integrals and derivatives. For instance, one can consider the following operation:

$$D^{\alpha} = D^{m}D^{\alpha-m} = \frac{d^{m}}{dx^{m}}\,{}_{a}I^{m-\alpha} \quad m \in \mathbb{N}. \tag{17}$$

Such notation determines that a fractional derivative may be interpreted as a fractional integral followed by a conventional integral. Therefore, once non-integer integral is defined, so is the corresponding fractional derivative. Another possibility regards an inverse sequence of operators as

$$D^{\alpha} = D^{\alpha-m}D^{m} = {}_{a}I^{m-\alpha}\frac{d^{m}}{dx^{m}} \quad m \in \mathbb{N}, \tag{18}$$

leading to an alternative decomposition of the fractional derivative into a conventional derivative followed by a non-integer order integral. One must note that each decomposition can lead to a different result.

From these definitions, it is possible to understand the non-locality mechanism in FC. The conventional derivative is the local operator and the fractional derivative can be interpreted as the inversion of the fractional integration, i.e. a non-local operation. As a result, both Liouville and Riemann approaches lead to different definitions of fractional derivatives depending on the adopted decomposition sequence. Therefore, for $0 < \alpha \leq 1$ one obtains Riemann-Liouville fractional derivatives by employing equations for integral operators in the sequence given in Eq. (17):

$${}_{RL}D_{+}^{\alpha}f(x) = \frac{d}{dx}\,{}_{RL}I_{+}^{1-\alpha}f(x) = \frac{d}{dx}\frac{1}{\Gamma(1-\alpha)}\int_{a}^{x}(x-\xi)^{-\alpha}f(\xi)d\xi, \tag{19}$$

$${}_{RL}D_{-}^{\alpha}f(x) = \frac{d}{dx}\,{}_{RL}I_{-}^{1-\alpha}f(x) = \frac{d}{dx}\frac{1}{\Gamma(1-\alpha)}\int_{x}^{b}(\xi-x)^{-\alpha}f(\xi)d\xi. \tag{20}$$

If the operators sequence is inverted, as in Eq. (18), one obtains Caputo-Liouville or Caputo-Riemann derivatives:

$${}_{RLC}D_{+}^{\alpha}f(x) = {}_{RL}I_{+}^{1-\alpha}\frac{d}{dx}f(x) = \frac{1}{\Gamma(1-\alpha)}\int_{a}^{x}(x-\xi)^{-\alpha}\frac{df(\xi)}{d\xi}d\xi, \tag{21}$$

$${}_{RLC}D_{-}^{\alpha}f(x) = {}_{RL}I_{-}^{1-\alpha}\frac{d}{dx}f(x) = \frac{1}{\Gamma(1-\alpha)}\int_{x}^{b}(\xi-x)^{-\alpha}\frac{df(\xi)}{d\xi}d\xi. \tag{22}$$

The fractional operator can also be written by stating the independent variable as subscript, i.e. D_{x}^{α}. It is worth mentioning that when the independent variable is time t, the definition given by Eq. (21) is also called "causal derivative". Such name stems from the integral in the definition considering values smaller than t, i.e., considering what happened before that instant while defining time flow as causal (Ortigueira and Tenreiro Machado, 2017). In this case, the non-locality feature is called memory effect, being very important to model nonlinear phenomena history such as cancer-related phenomena as addressed in next section.

For the sake of simplicity, the "left-handed" Caputo-Riemann operator can be written as either D_{x}^{α} or D_{t}^{α}, depending on the independent variable, and given by the definition

$$D_{x}^{\alpha}f(x) = \frac{1}{\Gamma(1-\alpha)}\int_{0}^{x}(x-\xi)^{-\alpha}\frac{df(\xi)}{d\xi}d\xi, \tag{23}$$

which is widely known as Caputo's derivative (Caputo, 1967). Its usefulness to model physical problems and solve generalized differential equations is recurrent because, if $f(x)$ is a constant, by applying Riemann's definition one obtains

$${}_{R}D_{+}^{\alpha}const = \frac{const}{\Gamma(1-\alpha)}x^{-\alpha}, \tag{24}$$

while in case of Caputo's definition

$$D_{+}^{\alpha}const = 0, \tag{25}$$

which adheres to integer-order models with constant initial or boundary conditions, thus justifying its widespread use.

For their many remarkable characteristics, fractional models have been increasingly chosen and successfully applied in many other areas such as signal processing (Miljković et al., 2017), thermoacoustics (Valentim et al., 2018), economy (David et al., 2016, 2021), robotics (Leyden and Goodwine, 2016), food science (David and Katayama, 2013), chemical kinetics (Singh et al., 2017), electromagnetism (Mescia et al., 2019), traffic control (Kumar et al., 2018), among others (Valentim et al., 2020b; David et al., 2020; David and Rabi, 2020; Mainardi, 2018; Hernandez et al., 2010).

5.2. Cancer-related fractional models

One may refer to Fractional Mathematical Oncology as the intersection between FC and Mathematical Oncology, wherein there are already many fields of application. For instance, concerning population or ecological models, the elevation of cancer cells may be interpreted as a population increase subjected to restrictions concerning substrate availability and competition (with healthy cells). Some works have

applied FC as an attempt to generalize the main models for tumor growth. Effectively, arbitrary orders in differential equations might refine cell growth dynamics description, allowing a deeper understanding of investigated phenomena (Varalta et al., 2014).

On that note, Valentim et al. (2020a) generalized and analytically solved relevant ODE models for tumor growth towards fractional order extensions. The solutions were then fitted to an extent clinical data set of breast cancer evolution in mice. Resulting best-fitted models perform better as predictors compared to their traditional counterparts, suggesting that inclusion of fractional models could avoid misdirection when choosing potential predictors. Moreover Bolton et al. (2015) suggested that fractional models with a specific arbitrary order (in case 0.68) would better fit to experimental curves obtained from tumor growth in mice.

Stemming from ODE frameworks, Valentim et al. (2021) proposed fractional variable-order models to describe multi-stage tumor characteristics. Exploring the memory effect in non-integer order models, the authors interpreted the variable order as indicative of tumor memory. Clinical data were employed to fit and analyze different mathematical behaviors relating to tumor particularities. Results suggested that variable order $\alpha(t)$ modeled as a periodic function can better describe tumor evolution regarding the fitted data, potentially capturing dormancy periods.

Within the viscoelastic scope, Magin (2010) developed a fractional rheological model that is not limited to particular definitions of Maxwell, Voigt and Kelvin. Thus the author managed to obtain better results when identifying benign and malign tumors in elastography data from MRI scans. Magin et al. (2008) also claim that "fractional operators encode information about molecular interactions regarding the spin of water that is built in polymer structures and in the extracellular matrix of cells and tissues", being able to store extra information on the physical phenomena being modeled when compared to traditional integer order models.

Another featured application of FC in Mathematical Oncology refers to modeling the invasion of healthy systems by tumors as well as cancer cells transport throughout the organism, characterizing metastasis onset. Such processes are often modeled as diffusion phenomena in which several parameters must be taken into account in order to maintain the accuracy of the phenomenological description. In a non-integer order model, one can adjust the arbitrary order so that the system acquires sub-diffusive or super-diffusive behaviors, visualizing complex aspects that traditional (i.e. integer-order) counterparts cannot reproduce, as shown in a tumor diffusion model by Iyiola and Zaman (2014).

In continuous transport models, FC also allows to incorporate statistical randomness by combining a probability distribution function with a dynamic (i.e. time-dependent) random-walk model. Therefore, it is possible to simultaneously consider stochastic and deterministic natures when simulating tumor evolution, whose random-related mutations can suddenly lead to pivoting features favoring growth, movement or invasion of healthy tissue (Iomin, 2006).

Regarding treatment therapies, Iomin (2014) investigated the effects of different mathematical functions to represent chemotherapeutic treatments in scenarios modeled through fractional kinetics. Namazi et al. (2015) proposed a new prediction method based on Hurst coefficient and fractional-diffusion equation aiming at modeling the effect of a specific drug in lung-cancer patients' DNA. The authors found that the new model could simulate drug effects with 3.21% mean difference from real sick patients' DNA. FC has also gained strength in exploring ideal combinations of chemotherapy and immunotherapy through optimal control to minimize cancerous cells with the lowest possible impact on healthy cells (Akman Yildiz et al., 2018).

Other studies embrace treatment optimization methods (Ucar et al., 2019; Khajanchi and Nieto, 2019), control in invasion systems (Manimaran et al., 2019; Dai and Liu, 2019), bioengineering (Ionescu et al., 2017), and general tumor growth (Ren et al., 2018; Sowndarrajan et al., 2019; Farayola et al., 2020). From aforementioned studies, one can note the contemporary interest of the scientific community towards mathematical tools that suitably describe oncological models, improve the understanding of tumor mechanics and evolution, and expand diagnostic options and treatment routines. In this context, fractional oncology may play a promising and strategic role to allow more accurate and reliable virtualization devices.

6. On the prospective fractional hybrid models

Hybrid models are a recent category in which continuum characteristics are incorporated into discrete frameworks. Advantages of such approach are very clear for modeling multi-scale phenomena since the discrete part can focus on cell movements scale while the continuum methods can model events on larger scales (Rejniak and Anderson, 2011). This capacity to bridge scale gaps while communicating aspects of very different magnitudes across the model makes hybrid approaches very interesting to describe several aspects of cancer phenomena (Anderson et al., 2007a).

Accordingly, Anderson et al. (2007b) proposed a hybrid model comprising discrete methods to deal with tumor cells while considering continuous methods to model micro-environment factors such as host tissue, matrix-degradative enzymes and oxygens. Their model focused on micro-scale level to simulate tumor at tissue-scale and could be easily implemented to incorporate other scales (e.g. sub-cellular).

In the following years, many other hybrid models were proposed, each with their own characteristics and often involving either discrete or continuum tools (Chamseddine and Rejniak, 2019). Zangooei and Habibi (2017) combined CA and machine learning methods to develop a vascular multi-scale framework capable of predicting cell phenotypes. In silico results indicate that their model can represent key cancer features, such as angiogenesis, while presenting good agreement with biological behavior. Phillips et al. (2020) also proposed a hybrid model capable of describing the physical interaction between tumor and surrounding blood vessels, but focused on complementing cells' discrete behavior with a mathematical description of vascular endothelial growth factor (VEGF).

Additionally, Norton et al. (2019) reviewed agent-based and hybrid models that specifically handle the interplay between tumor immune micro-environment and cancer immune response, thoroughly discussing the importance of modeling tumor heterogeneity. Alemani et al. (2012) combined CA with lattice Boltzmann method to model multi-scale tumor dynamics considering nutrient diffusion and immune competition. The authors replaced PDEs with a statistic and stochastic approach claiming that such system combination could successfully capture cellular, molecular and continuum complexities.

On that context, coupled differential equations can help purely stochastic models cover some shortcomings. For instance, integrating a diffusion PDE to a hybrid model could tackle at least two problems at once. Firstly, if a CA disregards dead cells, it also dismisses their remains, which could cause some sort of toxicity in tumor micro-environment. Secondly, it is known that tumors can react very differently depending on oxygen lack or abundance. By its nature, some cells can effectively change biomechanical characteristics in order to migrate from an oxygen-deprived environment. Therefore, a model that does not take tissue nutrient availability into account can overlook important tumor dynamics details.

Accordingly, the diffusion equation could be an important tool to model tumor micro-environment. It could mathematically describe diffusive transport of chemical species (e.g. oxygen and nutrients simultaneously with cell remains) through the tissue in which the tumor grows. By following transport laws (e.g. Fick's law), this part of the model would be completely deterministic while also depending on outcomes from stochastic CA (e.g. if a cell replicates, it will increase nutrient consumption in that lattice area, thus influencing the diffusion equation). On the other hand, at each time step the deterministic portion

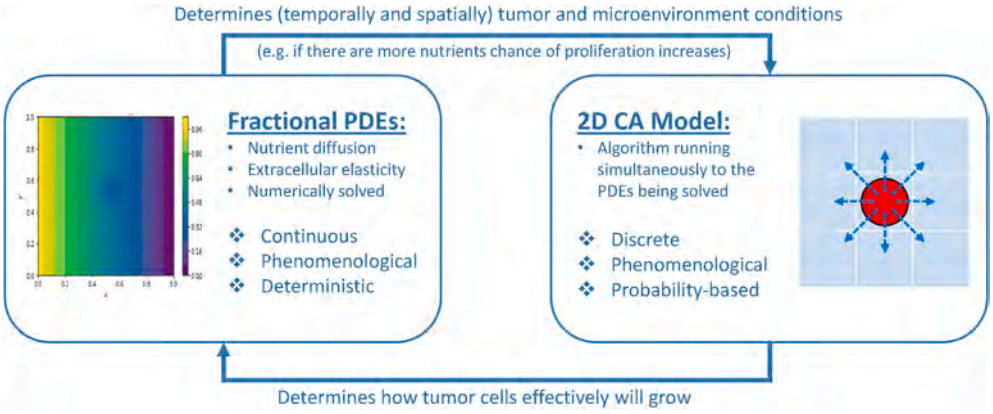

Fig. 2. Conceptual scheme for the hybrid model with fractional differential equations.

of the model would also affect probabilities generated from the CA (e.g. if nutrient availability is very low, the chance for local apoptosis is higher).

Moreover, the literature generally confirms that diffusion processes are better modeled with a time-fractional derivative (Costa and Capelas de Oliveira, 2012; Wu et al., 2015; Agrawal, 2002). These fractional models would be capable of presenting sub-diffusive and super-diffusive phenomena by only varying the arbitrary order of model time derivative. This feature could provide a much powerful tool to represent how nutrients are transported through tissue and affect tumor growth, possibly enhancing accuracy of the hybrid model.

On the other hand, CA models often disregard healthy cells, not establishing any stress relation between cells and their surrounding extracellular matrix. As an attempt to improve this characteristic on a hybrid framework, a differential equation to model viscoelasticity of both tumor and its surrounding tissue may be useful.

Furthermore, external stresses such as pressure and mechanical resistance can strongly affect tumor progression, malignancy and metastasis possibility (Fritsch et al., 2010; Ramião et al., 2016; La Porta and Zapperi, 2017). As a result, it becomes very important to account for these factors by modeling tumor (or its surrounding tissue) as either soft or viscoelastic material. As discussed in (Magin, 2004, 2012; Catania et al., 2008), fractional approaches can generally provide more effective reductionist viscoelastic models, being a viable option to mathematically describe such phenomena.

On that note, a hybrid model could potentially contain at least two equations modeling tumor micro-environment, namely one dealing with nutrient diffusivity and the other tackling tissue stresses. A conceptual scheme of a prospective hybrid model as previously described is illustrated in Fig. 2. Although there are other hybrid CA models developed in the literature, there are few that profoundly consider such aspects through an interdisciplinary view. Moreover, even fewer (if any) rely on improved capabilities of fractional models to describe natural phenomena in differential equations constituting the deterministic part of these models. This could be a prospective research field in Mathematical Oncology that could potentially contribute to areas of interest such as understanding tumor evolution, early diagnosis techniques and personalized treatment therapies.

7. Concluding remarks

There are tools in Mathematics still waiting to establish their way in Theoretical Biology and such is the case of fractional (i.e. non-integer order) calculus, whose historical and philosophical aspects have attracted growing interest. As addressed and discussed in the present review work, the application of fractional calculus indeed arises as powerful and strategic modeling approach in view of prospective challenges and opportunities in Mathematical Oncology. Besides well-known advantages of either testing or reproducing different in silico scenarios (which could be impractical or even impossible via corresponding in vitro experimentation), Fractional Mathematical Oncology can straightforwardly deal with heterogeneous scales, memory effects and/or dormancy periods related to tumor onset and development.

Declaration of competing interest

The authors have no affiliation with any organization with a direct or indirect financial interest in the subject matter discussed in the manuscript

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