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A SHORT OVERVIEW OF CELLULAR AUTOMATA IN MATHEMATICAL ONCOLOGY

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ABSTRACT. Mathematical oncology has developed into an increasingly active interdisciplinary field, providing quantitative tools for the study of tumor growth, invasion, metastasis, treatment response, and therapy optimization. Within this field, cellular automata form an important class of models. This overview focuses on cellular automata and their extensions in the context of mathematical oncology. We first introduce the necessary mathematical preliminaries and then present the basic formalism of cellular automata, beginning with deterministic models and elementary cellular automata. We continue with a presentation of biologically motivated extensions, including probabilistic cellular automata, lattice-gas cellular automata, Cellular Potts models, and hybrid cellular automata. Particular attention is given to focusing this survey on the reader with some background in mathematics or computer science, who is interested in first discovering the biological applications of the model. Finally, we review selected works from the recent literature.

1. Introduction

The integration of mathematical techniques into oncology has gained remarkable momentum, highlighting its usefulness in improving cancer detection, treatment planning, and the overall understanding of tumor dynamics. This field, referred to as mathematical oncology, encompasses various models and methodologies aimed at addressing several biological questions in oncology. One of the key

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areas of innovation in mathematical oncology is the modeling of tumor growth and response to various therapeutic interventions. For example, mathematical models can help simulate tumor behavior under different treatment regimens, thereby enabling the optimization of personalized therapy. More recently, the development of mathematical research methods in oncology is mapped in detail in Pradelli et al. [33]. Its content consists of overview statistics covering approximately 75 years of publications focused on this field. These publications are organized into two groups. The first consists of a manually curated corpus of approximately 1,500 papers collected through the newsletter "This Week in Mathematical Oncology (TWIMO)". The second corpus, consisting of approximately 19,000 documents from the period 1951–2024, was obtained by querying the Scopus database using relevant keywords. By analyzing these datasets, an overview of topics and investigated subfields was obtained. Figure 1 shows the range of years on the x-axis and the number of publications on the y-axis within the extracted Scopus publications based on keywords related to mathematical oncology. This demonstrates a growing trend and increasing research interest in this field.

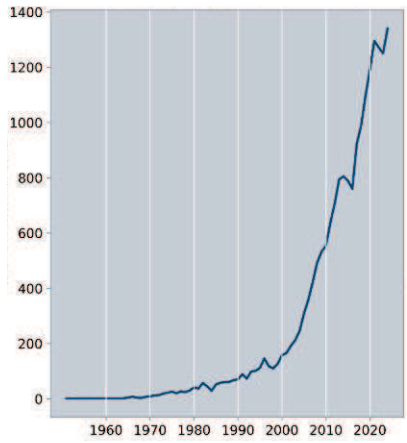

FIGURE 1. Number of publications in the field of mathematical research in oncology published annually from 1951 to 2024. [33]

In [33], the journals most represented in the Scopus corpus were also analyzed. Below we present a table of the ten journals with the highest occurrence, together with their current H-index and quartile (2025) according to the website scimagojr.com.

Based on these data, it is possible to identify several mathematical methods and models of frequent use. These models are often grouped into continuum,

TABLE 1. Journals with the highest occurrence in the Scopus corpus, together with their current H-index and quartile according to the website scimagojr.com (accessed: 27.05.2026).

	Quartile	H-index
Journal of Theoretical Biology	Q2	184
PLOS ONE	Q1	500
Bulletin of Mathematical Biology	Q1	106
Scientific Reports	Q1	382
PLOS Computational Biology	Q1	237
Mathematical Biosciences	Q1	118
Medical Physics	Q1	229
Cancer Research	Q1	522
Physics in Medicine and Biology	Q2	231
Mathematical Biosciences and Engineering	Q2	68

discrete, and hybrid approaches. Continuum models, usually written as ordinary differential equations or partial differential equations, are well suited for population-level or density-level descriptions. Discrete models, including cellular automata, represent individual cells or predetermined grid sites explicitly. Hybrid models combine the mentioned approaches in some way, often by enhancing the transitions of the cellular automaton by modeling the presence of oxygen, glucose, lactate, drugs, or immune mediators [1, 17, 27, 34]. Modern open-source platforms such as CompuCell3D, PhysiCell, and HAL have also made multicellular and hybrid modeling more accessible and reproducible [6, 15, 40].

In this survey, we focus on the cellular automaton approach. We begin with some necessary definitions and notions in the Preliminaries section. Next, we introduce cellular automata. We build on the formalism of basic models and work towards various extensions. We try to emphasize some of the biological motivations in an appropriate measure, assuming the reader has a background in mathematics and computer science. We finish the section with some basic examples in order to demonstrate the connections to oncology. Finally, a survey of selected recent works in the field is presented.

2. Preliminaries

The set of *natural numbers* is denoted by $\mathbb{N}$. The number 0 belongs to $\mathbb{N}$, consequently one can proclaim that $\mathbb{N}$ represents the set of non-negative integers. We denote the set of *integers* as $\mathbb{Z}$ and the set of real numbers as $\mathbb{R}$. The *power set* of a given finite set S is the set of all possible subsets of S denoted by 2^S and

the *number of elements* of S is denoted $|S|$. Given a positive $d \in \mathbb{N}$ the set $\mathbb{Z}^d$ denotes *d-tuples* over integers. As a shorthand, given two integers i and k with $i < k$, we denote $[i, k]$ as the set $\{j \in \mathbb{N} \mid i \leq j \leq k\}$.

Denote y as a function of x, $y' = dy/dx$ as the first derivative of y with respect to x, and $y^{(n)} = d^n y/dx^n$ as the n-th derivative with respect to x. An *ordinary differential equation of order n* (ODE) is an equality of the form given below.

$$F(x, y, y', \ldots, y^{(n)}) = 0$$

Most often the independent variable represents time t with the first order equation written as below.

$$\frac{dx}{dt} = f(t, x(t))$$

Models derived from ODE models are often used useful for fitting tumor-volume data, estimating growth rates, and describing treatment response in certain scenarios [1, 4, 17]. They are also useful as reduced-order components inside larger treatment-optimization frameworks, for example when modeling adaptive therapy or radiotherapy response [5, 12, 25, 26]. Next, let $y(x_1, x_2, \ldots, x_n)$ be a function over variables $x_1, x_2, \ldots, x_n$, and let $\partial y/\partial x_i$ denote the partial derivative of y with respect to x_i, where $i \in [1, n]$. A *first-order partial differential equation* is an equality of the form given below.

$$F\left(x_1, x_2, \ldots, x_n, w, \frac{\partial w}{\partial x_1}, \frac{\partial w}{\partial x_2}, \ldots, \frac{\partial w}{\partial x_n}\right) = 0$$

Let f be a twice-differentiable real-valued function in an n-dimensional Euclidean space. We use the *Laplace operator* denoted Δ in order to express the Laplacian of f as

$$\Delta f = \sum_{i=1}^{n} \frac{\partial^2 f}{\partial x_i^2}.$$

The formalism of PDEs in our context is used for describing spatially distributed quantities, i.e. oxygen concentration, glucose concentration, drug concentration, tumor-cell density, or immune-cell density. They provide additional useful information to the considered cellular automaton models when they are employed in some hybrid format [2, 3].

3. Cellular automata

Cellular automata (CA) are discrete dynamical systems used to model how complex spatial patterns can emerge from simple local rules [29,44]. Space is represented by a grid. Each grid site has a state. Time advances in steps. The state of each site is updated according to a transition function depending on the states of

nearby sites. In biological and oncological modeling, CA are useful because many tissue-level phenomena arise from local cell–cell and cell–microenvironment interactions [7, 10, 43].

3.1. The basic model

A *cellular automaton* is a quadruple (G, Q, N, f) consisting of a non-empty set of positions (often called a *lattice* or a *grid*) G, a non-empty set of *states* Q, a *neighborhood* $N \subseteq G$, and a *transition function* $f : Q^N \to Q$. An assignment of states to each position $c : G \to Q$ is called a *configuration*. A *computation* is a series of configurations that are consecutively valid with respect to the transition function. The *elementary cellular automaton* is a CA with

$$G = \mathbb{Z}, \qquad Q = \{0, 1\}, \qquad N = \{-1, 0, 1\}, \qquad f : \{0, 1\}^3 \to \{0, 1\}.$$

Since there are $2^3 = 8$ possible neighborhood patterns and two possible outputs

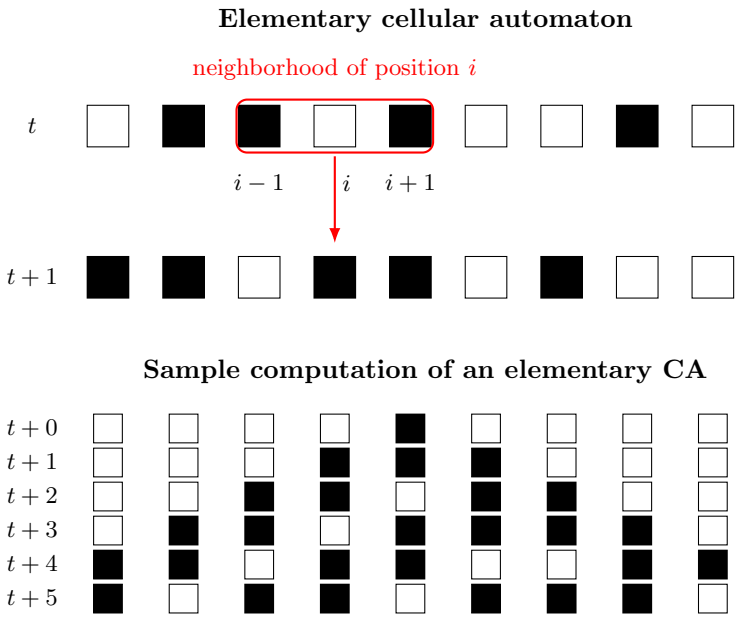

FIGURE 2. Illustration of an elementary cellular automaton. Each position has a binary state, the neighborhood has radius one, and the next state is determined by a local rule applied simultaneously to all positions.

for each pattern of the transition function f, there are $2^8 = 256$ elementary cellular automata. The eight neighborhood patterns are

$$111, 110, 101, 100, 011, 010, 001, 000.$$

A *rule* is specified by assigning an output bit to each pattern, thus defining the transition function. The resulting eight-bit binary number is often used as the rule number. See Figure 2 for the elementary CA with rule 110. An element $i \in G$ was named differently in several publications. Common names include cell, site, or position. In biological applications, a site may represent a spatial location that is empty, occupied by one cell, or associated with local tissue properties. In some models a site is called a cell, but one should distinguish between a lattice cell and a biological cell. A common choice for the grid is $\mathbb{Z}^d$ with subsequent depictions as follows:

- $d = 1$: sites arranged on a line;
- $d = 2$: sites arranged on a rectangular rows and columns;
- $d = 3$: sites arranged in a three-dimensional plane.

The chosen set of states often carries a meaning in the context of mathematical oncology. Some examples include the following:

- binary states $\{0, 1\}$, where 0 may mean empty and 1 occupied;
- tumor-growth states $\{E, P, Q_u, N_e\}$, where E is empty, P proliferating, Q_u quiescent, and N_e necrotic;
- treatment-response states $\{E, S_e, R, D\}$, where E is empty, S_e is sensitive, R resistant, and D dead.

For a site $i \in G$, the neighborhood of i is $\{i + n \mid n \in N\}$. There are several commonly used neighborhoods. In one dimension, the *radius-r neighborhood* is $N = \{-r, -r + 1, \ldots, -1, 0, 1, \ldots, r - 1, r\}$. For $r = 1$, the state of site i at the next time step depends on sites $i - 1$, i, and $i + 1$. In two dimensions, the *von Neumann neighborhood* is $N_N = \{(0, 0), (1, 0), (-1, 0), (0, 1), (0, -1)\}$. It contains the central site and its four nearest neighbors to the left, right, up, and down. The *Moore neighborhood* is $N_M = \{(a, b) : a, b \in \{-1, 0, 1\}\}$. It contains the central site and the eight surrounding sites in a 3×3 block. Moore neighborhoods are common in tumor-growth CA models because they allow local proliferation or migration into surrounding lattice sites [32, 37]. Often when considering configurations, it is useful to focus on a restriction of sites or to specify a configuration at a given time. Given $t \in \mathbb{N}$ and $i \in G$, we denote $c_t|_{i+N}$ as the *configuration at time t of the neighborhood of i*. For the purposes of practical simulation finite grids are utilized. For finite grids there exist sites that have incomplete neighborhoods. Boundary conditions specify how these sites are treated. A *boundary condition* is a rule specifying how neighborhood values outside a finite computational domain are handled. Common boundary conditions include:

- *periodic*: the domain wraps around, so opposite edges are identified;
- *fixed*: outside sites are assigned a fixed state;

- *reflecting*: values outside the domain mirror values inside the domain;
- *absorbing*: migrating cells that leave the domain are removed.

3.2. Extensions of the basic model

There are several extensions to the basic model that take into account domain knowledge. Probabilistic cellular automata replace the deterministic local rule by transition probabilities, making them useful when local events are intrinsically random [42, 44]. Lattice-gas cellular automata enrich the state of a site by discrete particle velocities and typically use propagation and collision steps; biological lattice-gas cellular automata adapt this velocity-based framework to collective cell migration and related biological processes [8,11,19]. Cellular Potts models represent a biological cell as a connected cluster of lattice sites whose dynamics are governed by an energy functional, making them suitable for modeling cell adhesion, motility, and tissue mechanics [18, 41]. Hybrid CA couple discrete cell states to continuous fields such as oxygen, nutrients, extracellular matrix, or drug concentration, and have become important in mathematical oncology because they connect individual-cell behavior with tissue-scale microenvironmental properties [1,34,43]. Below, we outline some simplified illustrative examples from the literature.

EXAMPLE. Consider the grind $\mathbb{Z}^2$ with states $\{E, P, Q_u, N_e\}$. Let the Moore-neighborhood rule be described as follows:

(1) If a proliferating cell has at least one empty neighbor, it divides with some non-zero probability.
(2) If a proliferating cell has no empty neighbor for a specified given time, it becomes quiescent.
(3) If a quiescent cell remains nutrient-deprived, it becomes necrotic.
(4) Necrotic cells remain necrotic.

This relatively simple rule set can simulate some basic structural characteristics of a specific tumor: an outer proliferative rim, an intermediate quiescent layer, and a necrotic core, resembling avascular spheroid organization [17].

EXAMPLE. In a hybrid CA model for tumor growth, the transition function can be enhanced by various parameters, whose values are governed by a set of PDEs along time. The cell state evolves discretely while variables affecting tumor development, like oxygen, glucose, or hydrogen levels, evolve continuously:

$$\begin{aligned} c_{t+1}(i) &= f\left(c_t|_{i+N}, O(t,i), G(t,i)\right), \\ \frac{\partial O}{\partial t} &= D_O \Delta O - \lambda_O(C_t(x))O + s_O(x), \\ \frac{\partial G}{\partial t} &= D_G \Delta G - \lambda_G(C_t(x))G + s_G(x). \end{aligned}$$

Here O represents oxygen, and G represents glucose concentration. The non-negative coefficients D_O and D_G influence the rate of diffusion of these resources. The terms s_O and s_G represent oxygen and glucose supply, respectively. The terms λ_O and λ_G represent oxygen and glucose consumption rate depending on the states of the CA. [1, 17, 32].

4. A survey of some recent literature

Mathematical modeling of solid tumor growth has a long history. Araujo and McElwain review the development of solid tumor growth modeling, including early diffusion-limited concepts, avascular spheroids, invasion, necrosis, vascularization, mechanics, and tumor–host interactions [4]. This historical perspective highlights CA and hybrid CA models as alternatives and complements to ODE and PDE approaches. Altrock, Liu, and Michor provide a broad synthesis of mathematical cancer modeling, covering branching processes, Moran processes, clonal evolution, microenvironmental models, hybrid models, metastasis, immunotherapy, and treatment resistance [1]. McDonald et al. extend this perspective into modern treatment modeling and optimization, reviewing computational approaches for ODE/PDE models, stochastic models, agent-based models, hybrid models, optimal control, reinforcement learning, and adaptive therapy [26].

A foundational oncology-specific review is Moreira and Deutsch's CA models of tumor development [28]. Earlier and related CA applications include brain tumor growth simulations, acid-mediated invasion models, and self-organized avascular tumor growth models [9, 23, 30]. The reviews reinforce the insight that tumor morphology can be studied as an emergent pattern generated by local cell-level rules. The monograph by Deutsch and Dormann provides a broader theoretical foundation for CA and lattice-gas CA modeling of biological pattern formation [7]. It introduces deterministic, probabilistic, and lattice-gas cellular automata; discusses lattice geometry, state spaces, neighborhoods, and transition rules. Several authors emphasize that CA models gained importance in mathematical oncology because they can represent local heterogeneity and spatial structure with relatively simple rules. Unlike ODE models, they do not assume a well-mixed tumor. Unlike purely continuum PDE models, they can represent individual cell states and stochastic cell fate. This makes them attractive for tumors where local crowding, nutrient gradients, phenotype switching, and invasion fronts matter [7, 27, 28, 43].

Sabzpoushan and Pourhasanzade introduced a two-dimensional stochastic agent-based model of avascular tumor growth using cellular automata formalism [37]. Their model includes non-immune and immune agents, proliferating tumor

cells, quiescent tumor cells, necrotic cells, normal or empty sites, natural killer cells, and cytotoxic T lymphocytes. A Moore neighborhood is used, and tumor–immune interactions are probabilistic. A key contribution of Sabzpoushan and Pourhasanzade is the introduction of a critical point at which the growth fraction and necrotic fraction become equal. They interpret this point as a possible temporal marker for growth-rate change and treatment scheduling. Valentim, Rabi, and David later developed a stochastic CA model for tumor growth dynamics that simulates multiple scenarios including dormancy, stem-cell-driven growth, apoptosis-driven instability, migration-driven cluster formation, and invasive-like morphologies [43]. The paper also discusses implementation issues that are of interest from an applied computational standpoint.

Hybrid models are among the most influential approaches in contemporary mathematical oncology. Early hybrid work showed that discrete tumor cells coupled to continuous oxygen, extracellular matrix, and matrix-degrading enzyme fields can reproduce invasive morphology and microenvironmental selection [2, 3]. Evolutionary hybrid cellular automata subsequently connected local microenvironmental conditions with clonal evolution, phenotype selection, and the emergence of glycolytic phenotypes [13, 14]. Rejniak and Anderson define hybrid tumor models as frameworks that combine discrete variables, often individual cells, with continuous variables such as oxygen, nutrients, growth factors, extracellular matrix, or drug concentration [34]. Altrock et al. similarly describe hybrid models as combinations of continuous reaction–diffusion fields with discrete cell dynamics, where movement, proliferation, apoptosis, and mutation probabilities depend on local concentrations of nutrients, extracellular matrix, enzymes, or oxygen [1]. Analogous approaches can be found in the following works [21, 22, 31, 38]. Goncalves and Garcia-Aznar provide a modern review of hybrid computational models of multicellular tumor growth considering glucose metabolism [17]. Their review discusses metabolic hybrid models including cellular Potts, lattice-gas, cellular automaton, and center-based formulations, with examples that couple glucose, oxygen, ATP, lactate, acidity, and intracellular metabolic networks [21, 22, 30, 31, 35, 36].

tumor invasion is a spatial process, and therefore CA and hybrid models are especially relevant. Moreira and Deutsch identified invasion and angiogenesis as major application areas for CA tumor models [28]. Deutsch and Dormann later developed detailed LGCA models of cell migration, chemotaxis, haptotaxis, adhesion, contact guidance, tissue growth, glioma invasion, and go-or-grow phenotype switching [7]. The go-or-grow hypothesis states that cells may switch between proliferative and migratory phenotypes, with migration and proliferation being partially mutually exclusive [20]. This idea is particularly important in glioma modeling, where invasion may be driven less by uniformly high proliferation and more by phenotype switching and local density effects [1, 7].

Valentim et al. also show how migration potential and stem-cell symmetric division probability shape simulated tumor size and morphology [43]. Low migration can generate compact masses, while high migration can generate dispersed clusters or invasive-like morphologies. This is consistent with the broader idea that CA models are useful not merely for reproducing tumor volume curves but for investigating morphology, spatial heterogeneity, and invasion pattern.

Immune interactions add another layer of complexity. Shinde and Kurhekar review agent-based models in immune-system systems biology, including tumor–immune dynamics and cancer vaccination [39]. Sabzpoushan and Pourhasanzade explicitly include immune cells in their stochastic avascular tumor model [37]. Immune cells move toward tumor regions, interact probabilistically with tumor cells, and can be recruited depending on previous immune success or failure. This kind of model is not a full immunological simulation, but it demonstrates how local tumor–immune contact rules can be incorporated into a CA framework.

Bekker et al. review mathematical modeling of radiotherapy and tumor–immune interactions [5]. Although many radio-immunotherapy models are ODE-based, the review emphasizes that CA models become important when some of the data have spatial granularity, such as multiplex immunofluorescence images or spatial immune microenvironment data. This suggests a natural future role for CA models in radio-immunotherapy: modeling how local irradiation, immune infiltration, antigen release, and spatial immune reservoirs interact. Treatment modeling has traditionally used ODEs, stochastic processes, and optimization methods. Classical resistance models motivated later stochastic and evolutionary descriptions of preexisting and acquired resistance [16, 24]. Altrock et al. review models of treatment response and resistance, branching models, drug resistance, adaptive therapy, radiotherapy, and patient-specific response metrics [1]. More specific examples include adaptive therapy as an ecological control strategy and optimized radiation dosing in glioblastoma [12, 25]. McDonald et al. broaden this perspective by reviewing computational approaches to cancer-treatment modeling and optimization, including ODE/PDE models, stochastic models, hybrid models, optimal control, reinforcement learning, adaptive therapy, and machine learning [26].

5. Conclusions

Cellular automata provide a natural and flexible modeling framework for mathematical oncology because they combine spatial explicitness, local interaction rules, and computational tractability. The basic deterministic cellular automaton formalism already captures the essential idea of local rules generating global patterns. However, biological systems often require richer model variants.

Probabilistic cellular automata allow events such as mitosis, apoptosis, mutation, immune killing, and drug-induced death to be represented as stochastic processes. Lattice-gas cellular automata and biological lattice-gas cellular automata incorporate particle-like movement and are useful for migration-dominated processes. Cellular Potts models extend the lattice-based idea by representing a biological cell as a connected set of lattice sites, making them suitable for modeling adhesion, deformation, motility, and tissue mechanics. Hybrid cellular automata further extend the approach by coupling discrete cell states to continuous quantities such as oxygen, glucose, lactate, extracellular matrix, drug concentration, or immune mediators. This hybridization is particularly important in oncology, where the tumor microenvironment strongly influences proliferation, invasion, dormancy, and therapeutic response. The literature reviewed in this survey shows that CA models and hybrid CA models have been used to investigate a broad range of cancer-related phenomena, including avascular growth, tumor invasion, metabolic heterogeneity, immune interactions, radiotherapy response, drug resistance, and treatment scheduling. At the same time, several limitations remain. CA models can be sensitive to the choice of grid geometry, neighborhood structure, update scheme, boundary conditions, and transition functions. Overall, CA models occupy an important position between simple analytical models and highly detailed mechanistic simulations. They offer a somewhat mathematically transparent and computationally accessible way to explore certain phenomena in the oncological setting.

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