

75 Years of Mathematical Oncology

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Conflicts of Interest

The authors declare no conflicts of interest.

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Abstract

Mathematics has long provided a quantitative framework to interpret cancer biology and treatment. Driven by richer biological and clinical data, the field has evolved into a multidisciplinary and translational endeavor - giving rise to Mathematical Oncology. Yet, the field's strong interdisciplinarity obscures a comprehensive view of its evolution, as well as the boundaries between Mathematical Oncology and adjacent domains. Here, we address this gap through a comprehensive bibliometric analysis spanning 75 years of mathematical research in oncology. Using a manually curated corpus (~1,500 papers) and a large query-based dataset (~19,000 papers), we map the field's conceptual and collaborative development over time. Independent analyses reveal sustained growth, high impact, and pronounced interdisciplinarity, together with a gradual shift from fundamental cancer biology toward therapeutic modeling. This reorientation underpins the emergence of Mathematical Oncology as a distinct field, separate from Systems Biology and Pharmacokinetics / Pharmacodynamics. We show how diverse concepts interlace within Mathematical Oncology, bridging applied mathematics, optimal control, evolutionary theory, and imaging. Collectively, we demonstrate that Mathematical Oncology is not merely the application of mathematics to cancer, but the use of interpretable models integrating clinical, biological, and physical knowledge to improve screening, understand disease evolution, guide therapy, and strengthen forecasting.

Introduction

Mathematical modeling has shaped oncology since at least the mid-20th century, enabling scientists to address fundamental questions such as the role of mutations¹⁻³, and therapeutic intervention^{4,5}. It has provided both mechanistic⁶⁻⁸ and predictive⁹⁻¹¹ insights into cancer progression and treatment, evolving from initial pioneering investigations into an interdisciplinary, data-driven, and translational scientific landscape¹²⁻¹⁵. Indeed, cancer originates from genetic alterations whose evolutionary trajectories are driven by intricate interactions across molecular, cellular, tissue, and systemic levels, ultimately leading to metastatic dissemination¹⁶. Each scale offers unique entry points for mathematical exploration, with distinct methods suited to different biological questions.

Among the most established methodologies, deterministic differential equations represent a cornerstone of the field¹⁷. These are broadly classified into ordinary (ODEs) and partial differential equations (PDEs). ODEs characterize a system through continuous functions in time (e.g. tumor burden, drug concentration, clonal frequency), with classical applications including modeling tumor growth laws¹⁸, the identification of optimal treatment schedules^{10,19}, and the emergence of resistance^{20,21}. Historical developments in pharmacokinetics and pharmacodynamics (PK/PD) modeling, which formalize drug-body interactions²², date back to the 1960s²³, and remain central to drug development, personalized medicine, and therapeutic monitoring²⁴. By contrast, PDEs explicitly incorporate spatial dimensions into cancer dynamics²⁵⁻²⁷, which are often calibrated and validated against preclinical²⁸ and clinical^{25,29,30} imaging. In parallel (and often in combination) with PDEs, Agent-Based Models (ABMs) capture spatial heterogeneity by simulating individual agents—often cells or molecules—each governed by unique behaviors and interactions³¹. Despite often restricting the analysis to smaller spatial and temporal scales, ABMs excel in capturing spatial heterogeneity³², stochasticity³³, and multiscale³⁴ or emergent phenomena³⁵ that are difficult to study via differential equations.

The growing focus on heterogeneity and evolutionary dynamics in cancer biology³⁶ has further expanded the methodological repertoire to directly address tumor evolution and selection between distinct populations. Probabilistic modelling (e.g. branching and Moran processes)³⁷, originally applied to study the effect of mutations¹⁻³, currently underpin investigations into tumor plasticity and resistance³⁸. While these modeling techniques characterize clonal dynamics and phenotypic switching, evolutionary game theory (EGT) focuses on ecological interactions between different populations³⁹. Although EGT applications are relatively recent⁴⁰, the framework has proven pivotal for designing therapeutic strategies that mitigate drug resistance and exploit evolutionary trade-offs⁴¹.

Mathematical modeling in oncology has also benefited from integration with machine learning (ML) methods, leveraging the increasing availability of multiscale, multi-modal data. One of the most relevant advancements is the emergence of Mechanistic Learning⁴², which integrates data-driven methods with classical mathematical approaches. Although still in their infancy⁴³, these techniques hold promise for clinical translation⁴⁴ and reflect a broader emphasis on clinical applications of mathematical models⁴⁵. A particularly compelling vision is the concept of Digital Twins, whereby patient-specific models—calibrated with longitudinal biological and clinical data—could ultimately forecast therapeutic responses at the individual level^{13,44,46}.

This increasingly complex landscape has been periodically surveyed through reviews and perspectives^{11–13,15,38,47–49}. Nevertheless, important gaps remain. First, the broader field of mathematical models in oncology (hereafter “mathematical research in oncology”) is fragmented across subareas—such as Mathematical Oncology, Systems Biology, and PK/PD—whose boundaries are often unclear. Second, reviews necessarily limit their scope to a few hundred publications, often focusing on specific modeling paradigms or emerging trends. Moreover, although centered on quantitative methodologies, these reviews ironically rarely apply quantitative analyses to their own bibliographic corpora. Bibliometrics, by contrast, provides a systematic and data-driven framework for evaluating the evolution of scientific domains, mapping thematic structures, and uncovering emerging trends across large bodies of literature^{50,51}.

Here, we apply bibliometric analyses to provide a comprehensive perspective on the role of mathematics in cancer research and clinical management, with particular emphasis on the emergence of Mathematical Oncology. Although rapidly expanding, the field still lacks clear disciplinary boundaries and a unified identity. A central aim of our analysis is therefore to delineate these blurred contours and address the foundational question: “What constitutes Mathematical Oncology?”

To this end, we analyze two complementary bibliographic datasets with distinct, unique advantages. The first is a manually curated corpus of more than 1,500 publications, compiled from *This Week in Mathematical Oncology* (TWIMO), a scientific email newsletter highlighting key contributions in the field. To combat editorial bias, we complement the analysis with a second, query-based dataset which encompasses nearly 20,000 documents spanning 75 years (1951–2024), retrieved from Scopus using a set of carefully designed keywords (see **Methods**). Through these datasets, we show the translational nature of mathematical research in oncology (**Fig. 1**) and its expansion as a translational, impactful, and multidisciplinary field (**Fig. 2** and **3**). We identify the dominant themes that have shaped the discipline and delineate Mathematical Oncology as distinct from two other closely related fields—Systems Biology and PK/PD (**Fig. 4**). We examine the research interests of influential and prolific contributors and, through bibliographic coupling, reveal distinct research lines shaping the current scientific landscape and its temporal evolution (**Fig. 5**). We show that key drivers of the field’s evolution include, but are not limited to, the integration of spatial imaging, evolutionary and ecological dynamics, applied mathematics, optimal control, and multiscale modeling (**Fig. 5**). Collectively, our analysis highlights an ongoing conceptual shift in mathematical research in oncology, from fundamental cancer biology toward translational clinical applications. This evolution has placed increasing emphasis on therapeutic modeling and its relevance for clinical decision-making, coinciding with the rise in prominence of Mathematical Oncology. In conclusion, our findings indicate that Mathematical Oncology is more than the application of mathematics to cancer research, as previously reported⁴⁹. It should be defined as the use of interpretable mathematical models—integrating clinical, biological and physical knowledge— to enhance cancer screening, understand disease evolution, guide therapy, and strengthen forecasting.

Results

Hand-curated bibliographic dataset highlights the interdisciplinary, translational nature of Mathematical Oncology

TWIMO is a free weekly email newsletter for investigators in Mathematical Oncology, highlighting notable blog posts, conferences, job opportunities, and selected papers of community interest. From 2017 to 2025, TWIMO has featured more than 1,500 publications, constituting the curated dataset analyzed in this section. The most represented journals (**Fig. 1a**) span cancer biology, theoretical/computational biology, and multidisciplinary science, reflecting the field's high interdisciplinarity. As TWIMO highlights major recent contributions, most journals are ranked in the top quartile (see Methods) of their respective area, evidencing the field's reach into impactful scientific outlets. The most represented institutions (**Fig. 1b**) are largely U.S.-based, particularly leading cancer centers such as Moffitt Cancer Center, MD Anderson, and Memorial Sloan Kettering, underscoring the close link between Mathematical Oncology and recognized clinical institutions. Similarly, while many frequently featured authors (**Fig. 1c**) have U.S. affiliations, the presence of contributors from the U.K., India, Spain, and Italy suggests the field's growing international reach.

Author keywords (AKs) and text-mining (**Fig. 1d–f**) further illustrate the field's thematic composition. Frequently occurring AKs include general terms (e.g. “*Mathematical Model*”, “*Cancer*”, “*Mathematical Oncology*”), but also tumor-specific (“*Prostate Cancer*”, “*Glioblastoma*”) and therapy-related (“*Adaptive Therapy*”, “*Drug Resistance*”) terms, confirming the field's translational orientation. The recurrence of evolutionary terms (“*Evolution*”, “*Cancer Evolution*”) highlights sustained interest in integrating evolutionary principles with cancer biology. Using regular expressions (regexes) we quantified the occurrences of specific text patterns in the titles, abstracts, and keywords of the TWIMO dataset (see **Methods**). The regexes distribution for mathematical modeling approaches (**Fig 1e**) reveals a prominence of terms related to differential equations in the TWIMO dataset, which are among the earliest tools employed in mathematical oncology¹⁸. However, other approaches—including PK/PD, ABMs, EGT, and ML—also rank highly, reflecting the methodological diversity of current research. Text mining of cancer types (**Fig. 1f**) shows *Breast*, *Prostate*, and *Brain* tumors as the most frequently studied. This focus likely reflects both their high incidence (*Breast* and *Prostate*)⁵² and aggressiveness (*Glioblastoma*, *Glioma*)⁵³.

The TWIMO dataset highlights the interdisciplinary nature of Mathematical Oncology, its strong connections to clinical cancer centers, and its sustained focus on both methodological innovation and translational applications. However, the primary strength of the dataset (manual curation) is also its main limitation, because it comprises a relatively small number of documents, possibly subjected to editorial bias. This is particularly evident in the distribution of institutions (**Fig. 1b**) and authors (**Fig. 1c**), where Moffitt and its Integrated Mathematical Oncology department are disproportionately represented (likely amplified by their status as the founding institution of TWIMO). We address this potential bias in the following sections through analyses of a substantially larger, query-based corpus, enabling a more general perspective on the field.

Query-based bibliographic dataset reveals the international and translational scope of mathematical research in oncology

The query-based dataset was assembled from Scopus by retrieving documents matching a curated list of terms encompassing cancer biology, oncology, and mathematical applications (see **Methods**). Its broader scope enables the delineation of the global landscape of mathematical research in oncology, revealing a considerably broader distribution than suggested by TWIMO (**Fig. 2**). The data confirms a marked predominance of the United States (**Fig. 2a–d**): of the 20 leading institutions (**Fig 2e**), 13 are U.S.-based, including major cancer centers such as Moffitt, MD Anderson, Memorial Sloan-Kettering, and The National Cancer Institute. Within the U.S., California,

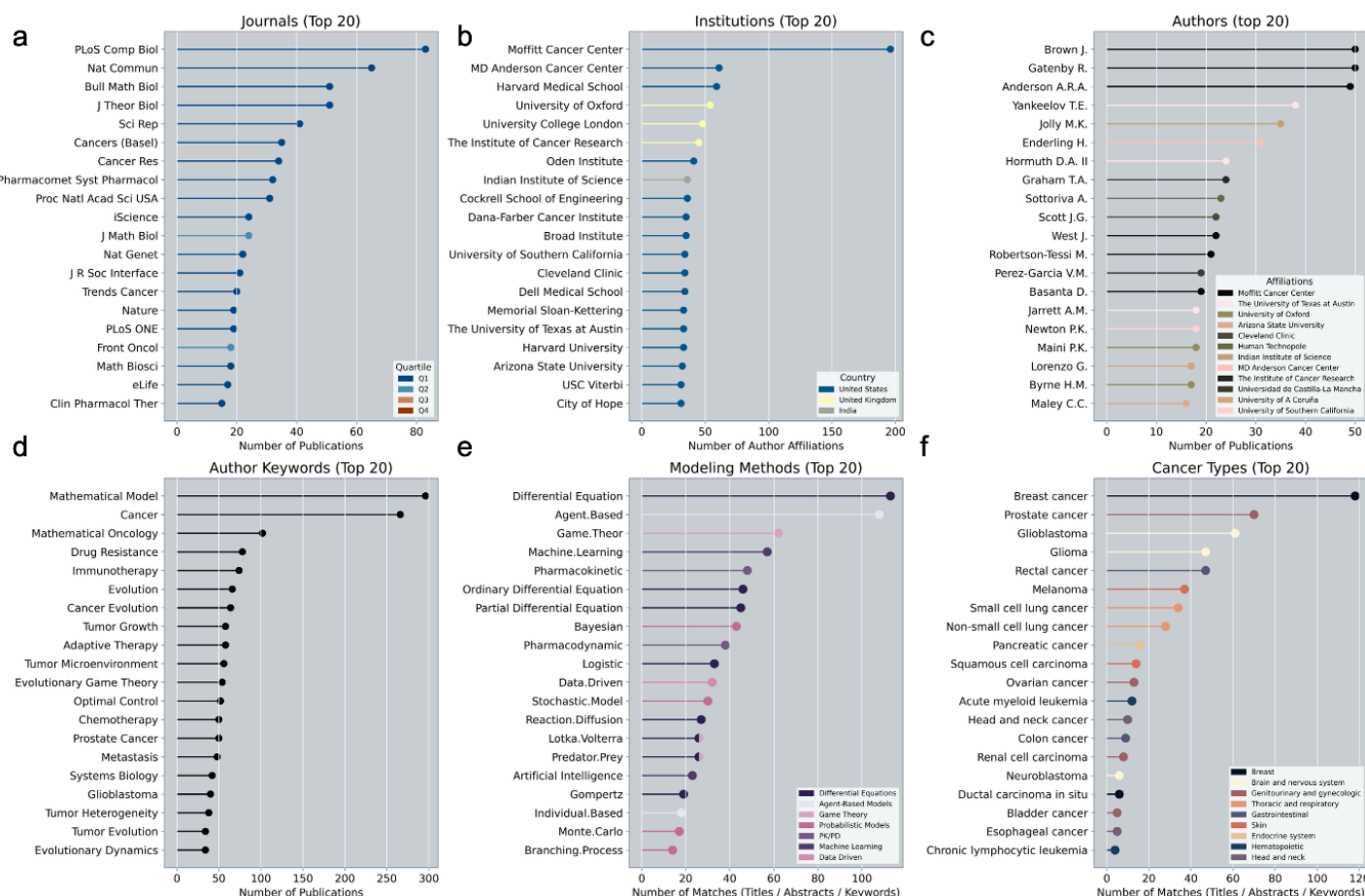


Fig. 1. Main journals, institutions, topics, and authors in TWIMO. **a)** Most represented journals in the TWIMO dataset. The list include five journals in computational biology (*PLoS Comp Biol*, *Bull Math Biol*, *J Theor Biol*, *J Math Biol*, *Math Biosci*), eight multidisciplinary (*Nat Commun*, *Sci Rep*, *PNAS*, *iScience*, *J R Soc Interface*, *Nature*, *PLoS ONE*, *eLife*), and seven biomedical/clinical (*Cancers (Basel)*, *Cancer Res*, *CPT Pharmacometric Syst Pharmacology*, *Nat Genetics*, *Trends Cancer*, *Front Oncology*, *Clin Pharmacol Ther*). **b)** Most represented institutions. The U.S. dominates with 16 of the top 20, many being recognized cancer centers (e.g., Moffitt, MD Anderson, Harvard Medical School, Dana-Farber, Memorial Sloan Kettering). Notably, Moffitt has almost four times the number of publications of the second institute (MD Anderson), suggesting an editorial bias. **c)** The most represented authors. The list includes six currently at Moffitt Cancer Center (Brown J., Gatenby R., Anderson A.R.A., West J., Robertson-Tessi M., Basanta D.). Overall, leading authors are predominantly affiliated with U.S. (e.g., University of Texas at Austin, Arizona State, Cleveland Clinic, MD Anderson) and U.K. institutions (University of Oxford, Institute of Cancer Research), but also with the Human Technopole (Italy), Indian Institute of Science, and universities in Spain (Castilla-La Mancha, A Coruña). **d)** Popular AKs. The list includes therapy-related terms (*Drug Resistance*, *Immunotherapy*, *Adaptive Therapy*, *Chemotherapy*) and tumor types (*Prostate Cancer*, *Glioblastoma*). **e–f)** Most frequent regular expressions. The analysis highlights prevalent modeling techniques and cancer types, categorized by methodological and clinical domains (see **Methods**).

Massachusetts, Texas, New York, and Florida lead in publication output. Although Florida hosts the single most prolific institution (Moffitt), the cumulative contributions of multiple institutions make other states more productive overall. The United Kingdom ranks second, with four institutions, followed by institutions from Italy (Politecnico di Torino), Germany (German Cancer Research Center), and Canada (University of Waterloo).

The analysis of the funding data (**Fig. 2f**) suggests a link between institutional strength and access to dedicated cancer research funding. All the clinically oriented sponsors (e.g. NCI, NIH, Medical Research Council) are concentrated in the U.S. and the U.K., which lead the institutional ranking (**Fig. 2e**). The U.S. and the European Union stand out as the primary sponsors, with five and four major agencies respectively. The National Natural Science Foundation of China also ranks prominently, reflecting increasing national investment. Although relatively few individual institutions from non-Western countries appear among the top contributors, **Fig. 2c** highlights substantial activity across Asia, the Middle East, and South America, attesting to the increasingly global diffusion

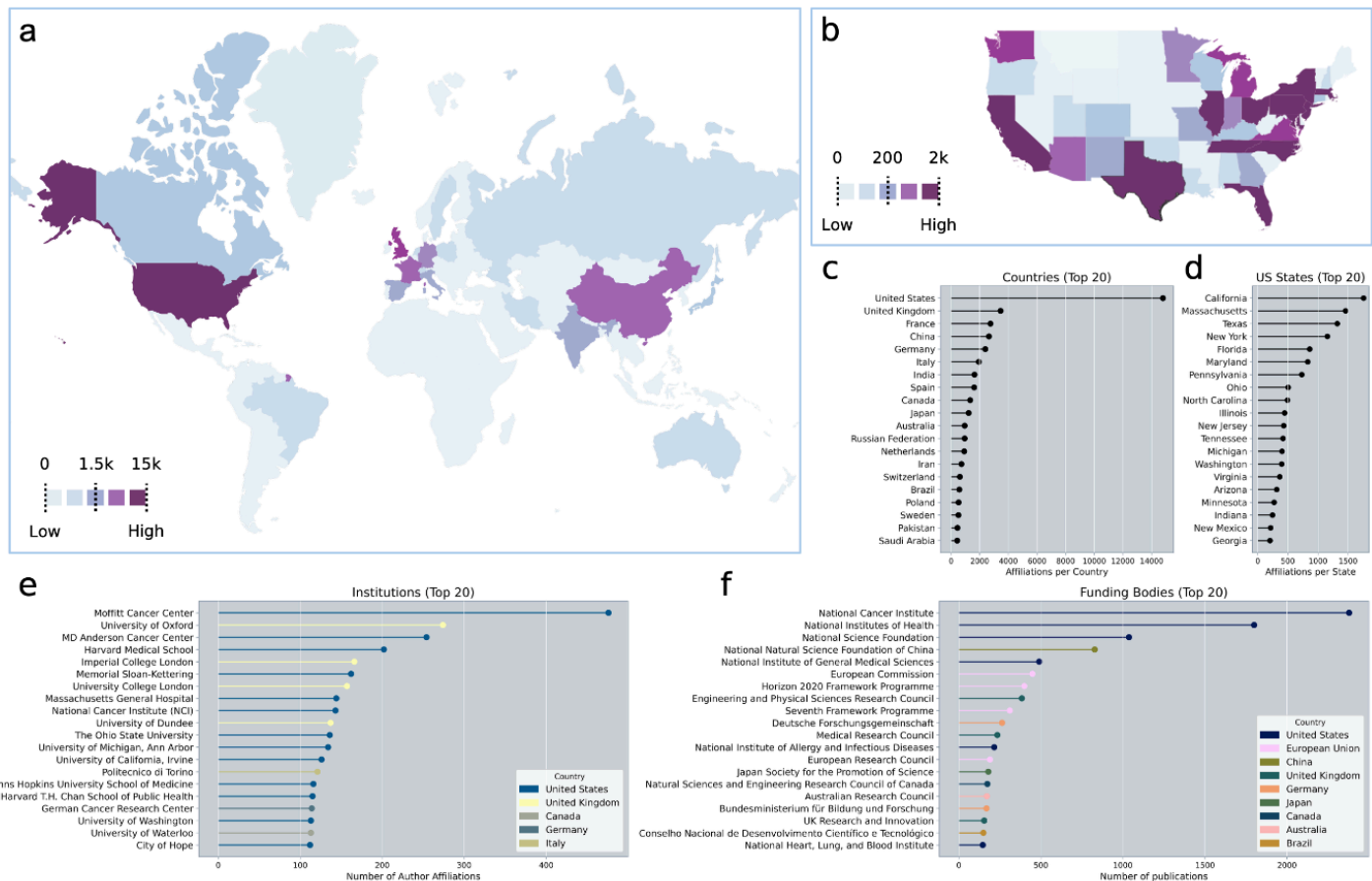


Fig 2. Geographic distribution of mathematical research in oncology. **a)** Heatmap showing the number of documents of each country and **b)** of each state in the U.S (the scale is logarithmic). **c)** Number of documents per each country and **d)** each state in the U.S. Despite the prominence of western countries, the distribution shows relevant contributions from Asia (China, India, Japan, Pakistan), Middle-East (Iran, Saudi Arabia), and South America (Brazil). **e)** Most represented institutions in the query-based dataset, colored for their country. The U.S. is the single most represented country with 13 institutions, including major cancer centres such as Moffitt, MD Anderson, Memorial Sloan-Kettering, and The National Cancer Institute. The second are the U.K., with four institutions: Oxford, Imperial College, University College London, and Dundee. **f)** Most represented funding sponsors in the query-based dataset, colored for their country. Five sponsors are located in the U.S. (NCI, NIH, NSF, National Institute of General Medical Sciences, and the National Institute of Allergy and Infectious Diseases) and four in the European Union (European Commission, Horizon 2020 Framework Programme, Seventh Framework Programme, European Research Council).

of the field. This trend is further corroborated by temporal analyses (**Fig. S1**), which depict a clear expansion of mathematical approaches to cancer research over time.

Mathematical research in oncology reveals continued expansion and interdisciplinary impact (479 words)

The geographic expansion of Mathematical Oncology has been accompanied by a marked increase in publication output (**Fig. 3a**). The trend is steadily positive, with a sharp acceleration beginning in the late 1990s (also noted by others¹⁵), and peaked in 2024 (the most recent year included) with more than 1300 documents. While a large share of these articles appear in journals within computational and mathematical biology, a substantial fraction are published in multidisciplinary (e.g. *PNAS*) or clinical oncology (e.g. *Cancer Research*) journals, underscoring the translational and interdisciplinary focus of the field already evident in TWIMO (**Fig. 3b**).

The analysis of the Journal quartiles further demonstrates that this expansion is paralleled by consistent quality and influence (**Fig. 3c**). Fourteen of the twenty most frequent journals (including all of the top ten) are classified in

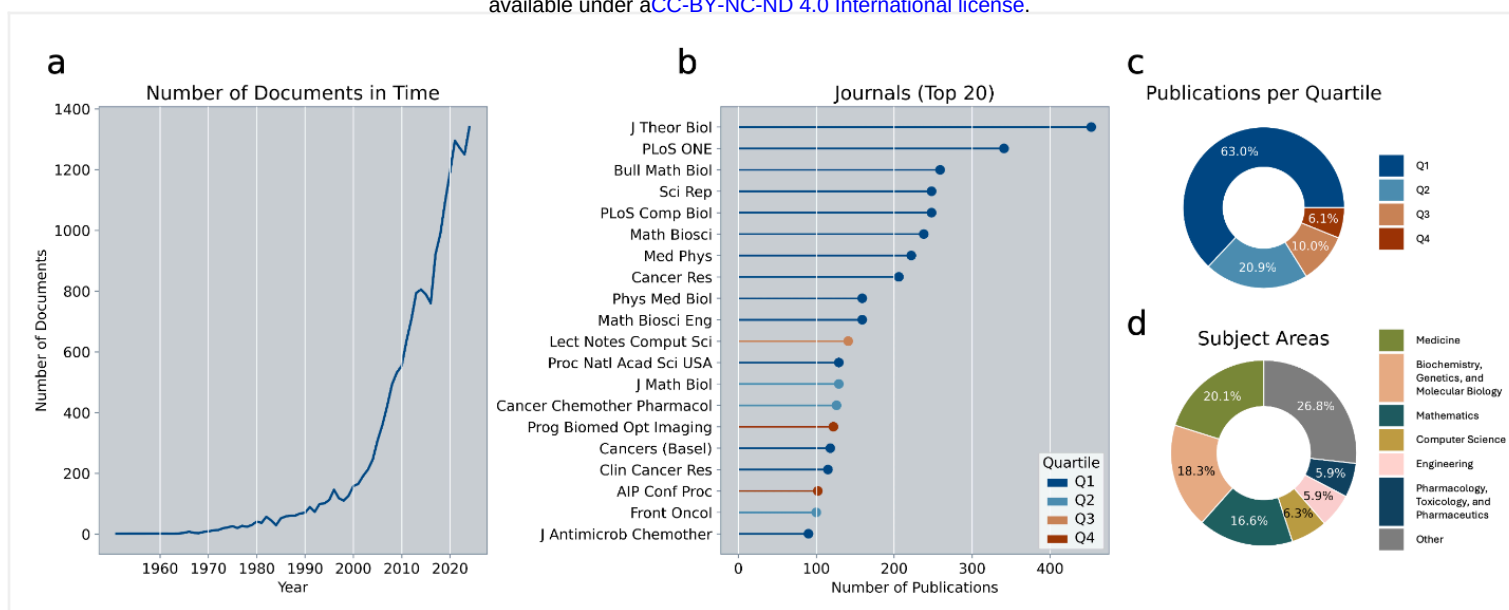


Fig 3. The expansion and impact of mathematical research in oncology. a) Number of documents published in the area in time (first entry in the query-based dataset: 1951). b) Most represented journals in the query-based dataset (top 20), colored by quartile. Most of the listed journals belong to the fields of Computational and Mathematical Biology (e.g., *The Journal of Theoretical Biology*, *The Bulletin of Mathematical Biology*, *PLoS Computational Biology*), but three multidisciplinary (*PLoS ONE*, *Scientific Reports*, *PNAS*) and four oncological journals (*Cancer Research*, *Cancers (Basel)*, *Cancer Chemotherapy and Pharmacology*, *Frontiers in Oncology*) are also present in the ranking. Journal quartile for each publication in the query-based dataset. d) Journal subject areas for each publication in the query-based dataset. The group “Other” includes all ASJC areas representing less than 5% of the publications in the query-based dataset.

the first quartile of their area (Q1), and 63% of all articles in the query-based dataset appear in Q1 journals (i.e. the most cited journals in their relative area; see **Methods**). This proportion is striking when compared to independent reports estimating the average Q1 publication rate at approximately 30%⁵⁴, and highlights the wide-spread interest and impact of Mathematical Oncology research.

The interdisciplinary scope of the field is further reflected by the distribution of the journals’ subject areas (**Fig. 3d**). Each journal in Scopus is classified in one of more scientific areas following the All Science Journal Classification (ASJC), allowing us to map each document to its scientific areas (ASJC areas; see **Methods**). Publications are primarily classified under “Medicine,” followed by “Biochemistry, Genetics, and Molecular Biology,” “Mathematics,” “Computer Science,” “Engineering,” and “Pharmacology, Toxicology, and Pharmaceuticals,” illustrating how Mathematical Oncology bridges computational and mathematical methodologies with biological and clinical sciences. This cross-disciplinary role has remained consistent over time (**Fig. S2**), with more than 50% of publications persistently clustered in “Medicine,” “Biochemistry, Genetics, and Molecular Biology,” and “Mathematics.” Longstanding venues such as *Journal of Theoretical Biology*, *Bulletin of Mathematical Biology*, and *Cancer Research* have played central roles in mathematical research in oncology, while more recent journals—including *PLoS ONE*, *Scientific Reports*, and *PLoS Computational Biology*—have expanded the field’s reach.

Open-Access publications and preprints also appear to impact the field’s influence. Citation analysis of the query-based dataset reveals an average of 28.1 citations per article (median: 10; **Fig. S3a**), with an average annual rate of 2.88 (median: 1.28; **Fig. S3d**). Open Access (OA) publications exhibit higher citation counts overall (**Fig. S3b, S3e**), with significant differences observed among the four OA modalities considered in Scopus (Gold OA, Hybrid Gold OA, Bronze OA, and Green OA; see **Methods**). While journals offering temporary OA tend to achieve the highest total citation numbers, deposition in preprint repositories is associated with the greatest citation rate per year (**Fig. S3c, S3f**, and **Table S1**). These findings indicate that unrestricted accessibility—especially temporary or via repositories—consistently enhances the visibility and impact of research.

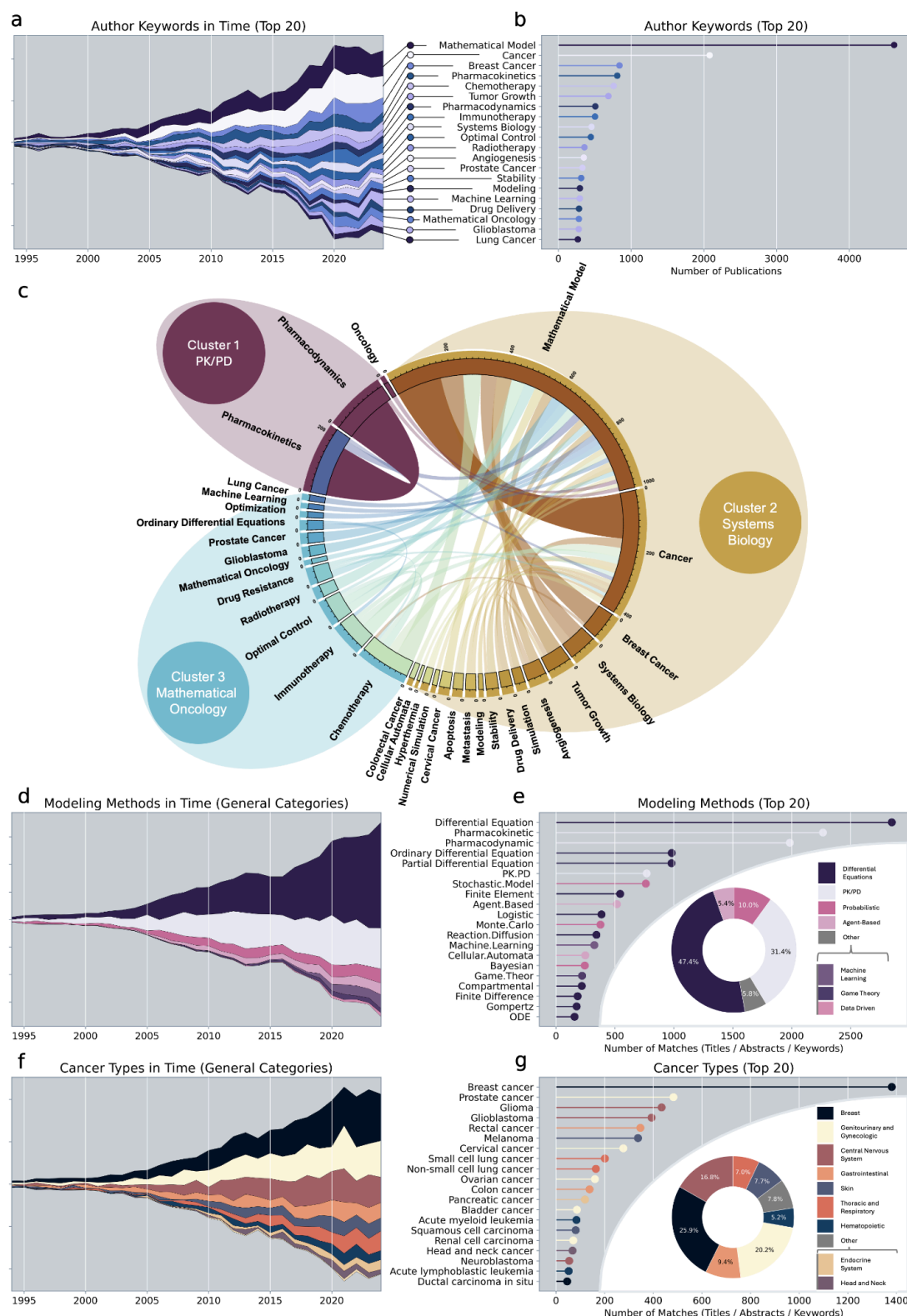


Fig. 4 Primary research topics and areas in the query-based dataset.

a) Utilization in time of the 20 most common AKs in the dataset in the last 30 years (1994-2024) and **b)** their representation in the dataset. **c)** Co-occurrence network between the most popular author keywords (i.e., with more than 100 occurrences (32 terms in total). The color of the outer circle represents the thematic cluster of each AK (3 in total, also evidenced in shade). The width of each chord in the chart is proportional to the co-occurrence between each pair of terms (see **Methods**). **d)** Representation of major modeling categories in the last 30 years (1994-2024), and **e)** 20 most represented regexes associated with specific modeling methods. The coloring in **d)** and **e)** reflects the major modeling category (see legend on the right), and the pie chart shows the distribution of each major modeling category in the dataset. **f)** Representation of cancer types (by location) in the last 30 years (1994-2024), and **g)** the 20 most represented regexes associated with specific cancer types. The coloring in **f)** and **g)** reflects the tumor location (see legend on the right), and the pie chart shows the distribution of each location in the dataset.

Evolution of scientific terminology traces the rise of Mathematical Oncology

The strong impact and expansion of mathematical research in oncology must rely on compelling research questions and investigations. To have further insights into the primary topics in the field, we analyzed the usage of the AKs (**Fig. 4a-c**), and the frequency of terms (see **Methods**) related to mathematical modeling techniques (**Fig. 4d-e**) and cancer types (**Fig. 4f-g**).

The translational orientation of the field is reflected in the prominence of disease- and therapy-related keywords (**Fig. 4a, b**). Beyond the expected prevalence of “*Mathematical Model*” and “*Cancer*,” the third most frequent AK is “*Breast Cancer*,” indicating a strong interest for this tumor type. Other prominent tumor types in the ranking are “*Prostate Cancer*” and “*Glioblastoma*” (in agreement with the findings for TWIMO), and “*Lung Cancer*”. Treatment modalities such as “*Chemotherapy*,” “*Immunotherapy*,” and “*Radiotherapy*” also appear prominently, underscoring the field’s strong clinical focus. The temporal trends (**Fig. 4a**) reveal a shift from cancer biology toward therapy: while usage of “*Tumor Growth*,” “*Angiogenesis*,” “*Apoptosis*,” and others (see also **Fig. S4**) has declined in the past five years, terms linked to therapy—along with “*Optimal Control*” and “*Machine Learning*”—have increased, reflecting growing interest in treatment optimization and data-driven approaches (as also noted by others⁴²).

This conceptual transition toward therapy-related applications is closely tied to the rise of Mathematical Oncology as a distinct subfield. While the AK “*Mathematical Oncology*” has gained traction, “*Systems Biology*,” “*Pharmacokinetics*,” and “*Pharmacodynamics*” have decreased (**Fig. 4a, S4**), suggesting that the emergence of Mathematical Oncology is driven by its focus on therapeutic applications and integration of data-intensive methods.

The co-occurrence network of AKs reinforces this picture (**Fig. 4c**). In the chord diagram, arc length reflects the total frequency of each AK, while link thickness indicates the frequency of co-occurrence across documents (see **Methods**). Clustering by co-occurrence patterns revealed three distinct groups, with “*Mathematical Oncology*,” “*Systems Biology*,” and “*Pharmacokinetics*”/“*Pharmacodynamics*”—each representing a broader domain—emerging in separate clusters (hereafter “thematic clusters”). This separation also motivated the thematic cluster names. Thematic cluster 1 (“PK/PD”, purple) contains the term “*Oncology*”, suggesting that oncological research frequently incorporates PK/PD modeling approaches. Thematic cluster 2 (“Systems Biology”, gold) includes several terms related to the mathematical modeling and fundamental cancer biology (e.g. “*Cancer*,” “*Tumor Growth*,” “*Angiogenesis*,” “*Metastasis*,” “*Numerical Simulation*,” “*Modeling*,” “*Stability*,” “*Simulation*”), suggesting that publications in this group typically (but not exclusively) use mathematical modeling and simulation to investigate foundational or systemic aspects of cancer biology. Finally, thematic cluster 3 (“Mathematical Oncology”, light blue), includes the various treatment modalities—“*Chemotherapy*,” “*Immunotherapy*,” and “*Radiotherapy*”—as well as terms like “*Drug Resistance*,” “*Optimal Control*,” and “*Optimization*.” This structure confirms that Mathematical Oncology is increasingly defined by its therapeutic focus and clinical applications.

To complement keyword analysis, we performed text mining of titles, abstracts, and keywords, quantifying occurrences of a curated set of regexes (see **Methods**). Regexes enable the identification of specific character patterns within a corpus, allowing flexible matching (for example, the regex “*X.ray*” matches both “*X ray*” and “*X-ray*”). Analysis of modeling approaches highlights the historical predominance of differential equations, pharmacokinetic/pharmacodynamic models, and probabilistic approaches (**Fig. 4d-e**). Coherently with the established relevance of differential equations in the field, this group is the most represented in the last 30 years (**Fig. 4d**). Of note, terms related to classic differential equations such as “*Logistic*,” “*Compartmental*,” and “*Gompertz*,” appear in the top 20. Over the past three decades, ABMs, EGT, and ML have emerged strongly, with regexes such as “*Agent.Based*,” “*Cellular.Automata*,” “*Game Theory*,” “*Machine Learning*,” and “*Artificial Intelligence*” appearing among the 20 most frequent terms, reflecting the rise of multi-scale and data-driven paradigms.

Tumor-type analysis confirms the prominence of breast, prostate, and brain cancers—particularly gliomas and glioblastomas—as the most frequently studied tumors (**Fig. 4f–g**), accounting for over half of all publications in the past 30 years. This focus is likely motivated by the high incidence of breast and prostate cancer⁵², and the marked aggressiveness and poor prognosis of gliomas and glioblastomas⁵³, which have historically motivated substantial research efforts. Additional focus areas include rectal cancer, melanoma, cervical cancer, and lung cancers, while head and neck and endocrine tumors remain comparatively underexplored (compared to their respective cancer incidence⁵²), representing opportunities for future research.

Regex co-occurrence analysis provides further insight into methodological development. Related terms, such as “PDE” and “Reaction–Diffusion” or “Pharmacokinetics,” “Pharmacodynamics,” and “PK/PD,” frequently cluster, reflecting natural methodological groupings (**Fig. S5**). Importantly, the co-occurrence patterns of tumor-related and modelling-related regexes suggest that cancers are typically modeled first with differential equations or PK/PD, and subsequently with more modern methods, like ABMs, game theory, and machine learning (**Fig. S6**). This trajectory suggests that the evolution of mathematical oncology is structured less around individual methodologies than around tumor-specific research programs, in which increasing biological insight and data availability enable progressively more sophisticated modeling frameworks.

Bibliographic coupling reveals the historical trajectory of Mathematical Oncology

While terminology analysis reveals how researchers frame their own work, examining the output of leading contributors shows how distinct groups have shaped the landscape of mathematics in oncology. This section highlights the most represented authors (**Fig. 5a**) and the temporal evolution of their contributions (**Fig. 5b**). As the analysis is limited to publications within the query-based dataset, it captures contributions specific to mathematical applications in cancer rather than each author’s broader output outside of mathematics and cancer. To explore relationships beyond individual outputs, we constructed a chord diagram of bibliographic coupling among the top 20 authors (**Fig. 5c**; see **Methods**). Link thickness indicates the degree of shared citations, providing an unbiased measure of proximity in scientific interests⁵¹ (see **Methods**). Clustering by connectivity similarity revealed six groups with distinct research themes and terminologies (hereafter, author clusters), reflected in their use of AKs (**Fig. 5d**).

The “MRI Mathematical Oncology” cluster (maroon, 5 authors) is characterized by the interest in integrating magnetic resonance imaging (MRI) with mathematical modeling, particularly in studies of breast and brain tumors (**Fig. 5d**). Prominent contributors—including T.E. Yankeelov, R.C. Rockne, K.R. Swanson, V.M. Pérez-García, and M. Soltani—are well known for bridging medical imaging and mathematical modeling^{25,55,56}. The recurrent use of the terms “*Mathematical Oncology*” and “*Computational Oncology*” further characterizes this group and motivated its naming.

The “Evolutionary Mathematical Oncology” cluster (yellow, 4 authors) centers on evolutionary and cancer biology concepts applied to modeling tumor growth and therapy. Its key contributors—A.R.A. Anderson, R.A. Gatenby, J.S. Brown, and D. Basanta—have made seminal advances linking evolutionary dynamics to clinical outcomes^{40,57}. A prominent outcome of this work is adaptive therapy (AT)⁵⁸, which leverages tumor heterogeneity and cell–cell competition to control disease progression through flexible treatment schedules. Mathematical modeling has been pivotal in evaluating these schedules. Additionally, AT has demonstrated encouraging results in preclinical studies across multiple tumor types¹¹ and proved successful for metastatic castrate-resistant prostate cancer⁵⁹. Notably, this cluster includes three of the four most represented authors in the query-based dataset (**Fig. 5a**), underscoring the central influence of this research line. Again, the cluster’s designation reflects the frequent use of the term *Mathematical Oncology* among its publications.

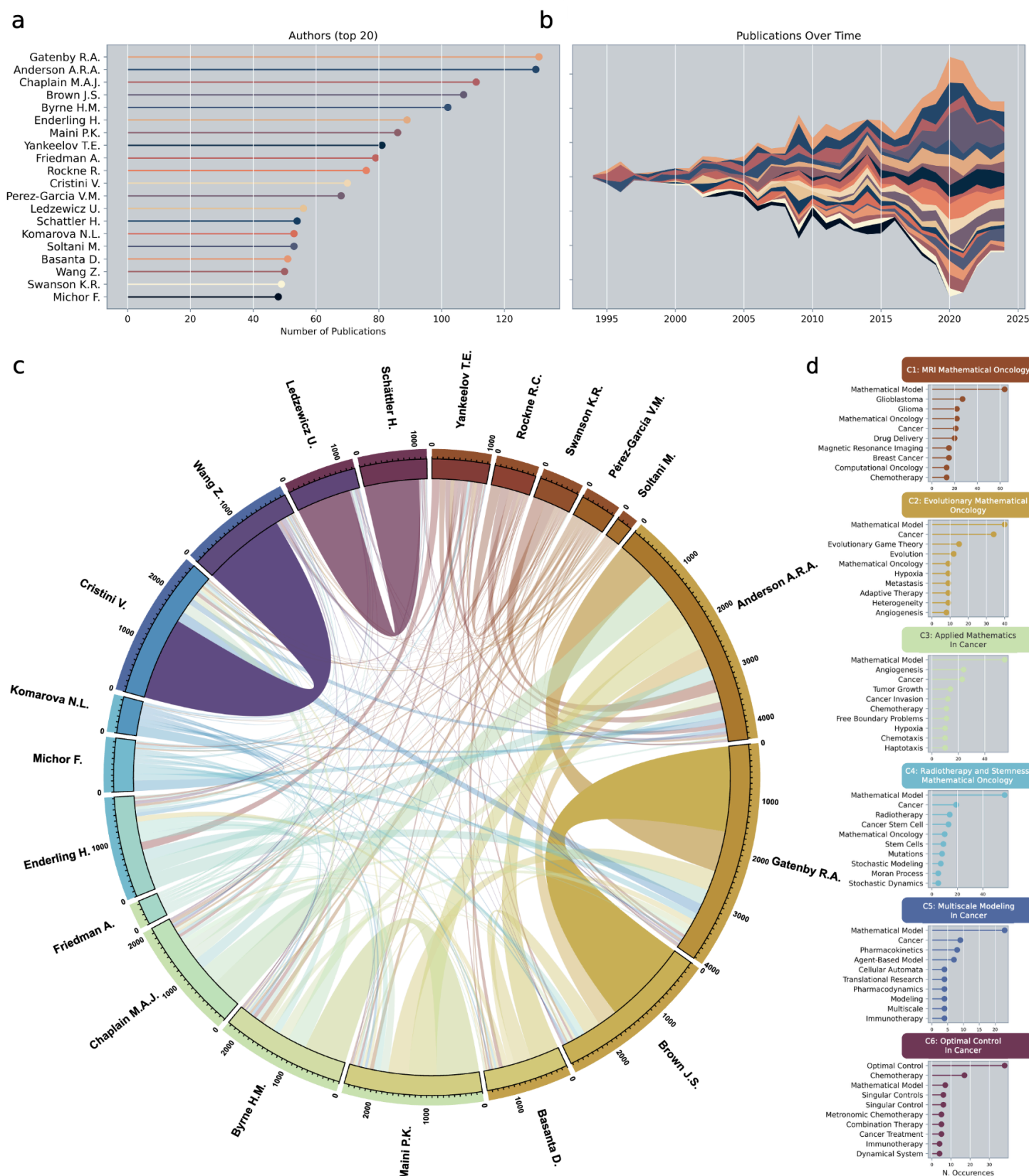


Fig 5. Key contributions in Mathematical Oncology. **a**) Most represented authors in the query-based dataset (Top 20) and **b**) the number of documents they contributed to in time (note: includes only the documents in the query-based dataset). **c**) Bibliographic coupling showing the relationship among the first 20 authors. The width of each chord is proportional to the tendency for each couple of authors to cite the same references (so, to work on the same concepts; see **Methods**). The color of the outer circle corresponds to the cluster of each author (6 clusters in total). **d**) Most common AKs within each cluster, showing the pivotal concepts shared by the authors in each cluster.

The “Applied Mathematics in Cancer” cluster (mint green, 4 authors) comprises the earliest contributors to the field (**Fig. 5b**), including P.K. Maini, H.M. Byrne, M.A.J. Chaplain, and A. Friedman. Consistently with the terminology analysis, the prominent AKs (**Fig. 5d**) reveal an interest in the fundamental biological processes involved in tumor development, such as angiogenesis and invasion. Of note, Maini, together with Gatenby, authored the first paper explicitly introducing the term “*Mathematical Oncology*”⁶⁰. Chaplain and Byrne pioneered the field with an extensive publication record dating back to the early 1990s, spanning from theoretical tumor growth models^{47,61} to predictive cancer therapy models^{62,63}. Finally, Friedman is a leading expert in PDEs and their applications, including tumor growth⁶⁴. These authors are further characterized by a common background in applied mathematics, which motivated the cluster designation.

The authors in the “Radiotherapy and Stemness Mathematical Oncology” (light blue, 3 authors) cluster - H. Enderling, F. Michor, and N.L. Komarova - focus on mathematical modeling of radiotherapy^{65,66} and cancer stem cell dynamics⁶⁷. They maintain substantial connection with other influential authors and they consistently describe their research within the framework of “*Mathematical Oncology*”, motivating the naming of the cluster.

The “Multiscale Modeling in Cancer” (blue, 2 authors) cluster centers on developing multiscale models of tumor progression³⁴ and integrating them with machine learning for predictive medicine⁶⁸. The cluster AKs (**Fig. 5d**) highlight the use of PK/PD and ABMs, bridging systemic and cellular perspectives. The cluster’s authors, V. Cristini and Z. Wang, exhibit strong mutual collaboration but limited links with other influential contributors and rarely describe their work using the term “*Mathematical Oncology*”. Similarly, the “Optimal Control in Cancer” cluster (purple, 2 authors), comprising U. Ledzewicz and H. Schättler, is characterized by the application of optimal control theory to cancer treatment¹⁹, with limited connections with other research groups. This cluster also seldom employs the term “*Mathematical Oncology*”, suggesting that despite the field’s growing recognition, its adoption remains uneven across research communities.

Expanding the analysis to more than 20 authors provides additional insights into the development of mathematics in oncology. The ranking of the most represented 100 authors in the query-based dataset (**Fig S7**) reveals the contributions of early pioneers such as M. Kimmel (Rice University), R.K. Jain (Harvard Medical School), and M. Nowak (Harvard University), who have been active since the 1980s. Bibliographic coupling of the 50 most represented authors (**Fig. S8**) further refines the field’s conceptual structure. Some clusters simply expand (e.g., Applied Mathematics in Cancer, Evolutionary Mathematical Oncology, Multiscale Modeling), while others subdivide, revealing distinct subfields. For example, the “MRI Mathematical Oncology” cluster splits into two. One is more focused on brain cancer, and the other on breast cancer and surgery, suggesting untapped synergies between them.

The analysis of the research groups also supports a historical reading of the discipline’s evolution over time. Early contributors emphasized fundamental cancer biology (see “Applied Mathematics in Cancer” cluster), whereas later work shifted toward imaging, therapies, and evolutionary perspectives. To test this interpretation, we generated bibliographic couplings for the top 20 authors across different time spans (**Fig. S9**). With the exception of the persistent “Optimal Control in Cancer” cluster, results confirm a gradual transition from biological foundations to therapeutic applications, underscoring growing translational engagement. **Fig. S9** highlights the enduring influence of spatial deterministic models (e.g., PDEs) in Mathematical Oncology, suggesting that at least three of the contemporary clusters—*Evolutionary Mathematical Oncology*, *Applied Math in Cancer*, and *Multiscale Modeling in Cancer*—trace their origins to early work in spatial mathematical modeling. **Fig. S9** also shows a narrowing divide between statistical models (e.g., Moran Processes) and deterministic approaches (e.g., differential equations, ABMs). Evolutionary concepts have long been present, but whereas they were once confined to genomics and probabilistic modeling, they are now widely applied to spatial modeling, therapy, and tumor heterogeneity. Notably, in multiple clusters, rising interest in therapy coincides with increased use of the term “*Mathematical Oncology*”, reinforcing its link to therapeutic approaches suggested in terminology analysis.

Discussion

In this work, we presented a comprehensive analysis of mathematical research in oncology using two complementary datasets: a manually curated collection from *This Week in Mathematical Oncology* (TWIMO, >1,500 papers) and a broader, query-based dataset retrieved from Scopus (>19,000 papers). Although smaller and subject to some editorial bias toward Moffitt (TWIMO's founding institution), TWIMO remains broadly representative of the field. Its strong overlap with the query-based dataset—across prevalent topics (**Fig. 1d–f** vs. **Fig. 4**), leading institutions (seven shared; **Fig. 1b** vs. **Fig. 2e**), and authors (eight shared; **Fig. 1c** vs. **Fig. 5a**)—supports its consistency and reliability.

The query-based dataset provides a broader view of the geographic and thematic landscape of mathematical research in oncology. Geographic patterns (**Fig. 2, Fig. S1**) confirm the leading role of U.S. and U.K. institutions while revealing increasing contributions from Europe, the Middle East, and Asia, particularly China. The comparison between institutional (**Fig. 2e**) and sponsor (**Fig. 2f**) rankings suggests a close link between institutional strength and targeted funding. Notably, the U.S. and the U.K. are the only countries reporting to provide clinically oriented funding, which likely contributes to their prominence among leading institutions. This observation, however, should be interpreted with caution, as detailed funding information was available for only 54% of the entries, limiting the completeness of the analysis.

The broader international reach is mirrored by a steady rise in publications on mathematical research in oncology (**Fig. 3a**). Earlier reports attributed this growth to advances in Systems Biology and new modeling approaches¹⁵. The analysis of terminology and key contributors (**Figs. 4–5, S9**) indicates that it also reflects increasing attention to therapy, integration of evolutionary concepts, and stronger coupling with imaging data.

These trends indicate that multidisciplinary and a growing focus on clinical applications have been major drivers of the field's expansion. Journal subject areas corroborate this view: over half of the publications fall within Medicine, Biochemistry/Genetics, and Mathematics (**Fig. 3d**), with a stable distribution over time (**Fig. S2**). An independent bibliometric study on a smaller sample⁶⁹ similarly highlighted the field's interdisciplinarity, reinforcing its central role in shaping mathematical research in oncology.

The journal analysis reveals the strong scientific impact of mathematical research in oncology, with 63% of the papers published in Q1 - more than double the expected 30%⁵⁴ (**Fig. 3c**). Citation patterns also indicate that publicly available publications (**Fig. S3**) achieve greater impact, with Bronze OA (see **Methods**) showing the highest total citations and Green OA (see **Methods**) the highest annual citation rate (**Table S1**). The strong performance of Green OA underscores the value of preprint-based accessibility in increasing research visibility.

Analysis of the most represented AKs (**Fig. 4a, b, S4**) reveals a clear shift in mathematical research in oncology from tumor-biology themes toward therapy-focused topics. Terms related to specific tumors and cancer therapies are strongly represented in the query-based dataset (**Fig. 4b**) and temporal trends show declining use of terms related to tumor biology (e.g. “*Tumor Growth*”, “*Angiogenesis*”, “*Apoptosis*”). The popular AKs in the author clusters (**Fig. 5, S9**), show a similar trend, with a strong relevance of terms related to therapy (e.g. “*Chemotherapy*”, “*Radiotherapy*”, “*Adaptive Therapy*” in **Fig. 5d**) and an increase of their use in time across multiple research groups in parallel (**Fig. S9**).

This trend reflects the growing integration of mathematical and quantitative approaches into clinical oncology, which, despite some limitations, are increasingly offering mechanistic insights to improve cancer treatment¹¹. This shift appears to focus on breast cancer and tumors of the genitourinary, gynecologic, and central nervous systems, indicating uneven attention across cancer types (**Fig. 4f, g, S6**). While traditional modeling approaches—differential equations, PK/PD, and probabilistic models—remain dominant in mathematical research in oncology, temporal trends reveal growing contributions from other techniques, including ABMs and EGT (**Fig.**

4d). The most pronounced increase is observed for publications incorporating ML (**Fig. 4a, d**), likely driven by the emergence of Mechanistic Learning⁴².

Independent bibliographic analyses indicate that the reorientation toward clinical applications is a key factor in the emergence of Mathematical Oncology as a distinct subfield. Thematic clusters (**Fig. 4c**) show that “PK/PD,” “Systems Biology,” and “Mathematical Oncology” occupy separate semantic domains, with the latter focused on therapy, optimization, and data-driven approaches. Temporal trends reveal that declining usage of cancer biology terms parallels decreases in “Systems Biology,” “Pharmacokinetics,” and “Pharmacodynamics,” whereas “Mathematical Oncology” continues to gain traction. Author clusters (**Fig. 5c**; see **Methods**) show that the term “Mathematical Oncology” appears in half of the groups and is used by the majority of authors. Furthermore, the evolution of bibliographic coupling over time (**Fig. S9**) indicates that increasing use of therapy-related keywords frequently coincides with greater adoption of the term “Mathematical Oncology.”

In conclusion, this work comes with some limitations that must be acknowledged. The TWIMO dataset, while curated by experts, is too small to fully capture the field and exhibits editorial bias toward the Moffitt Cancer Center. Conversely, the query-based dataset is broader but imperfect, as its reliance on a keyword-based search introduces false positives (see **Methods**). For example, *The Journal of Antimicrobial Chemotherapy* appears in the top 20 journals (**Fig. 2b**), largely due to PK/PD modeling studies on infection control, sometimes linked to cancer but often unrelated. Such issues illustrate the challenges of bibliometric searches and highlight the importance of combining curated and automated approaches. Future advances in bibliometric tools and search engines may enable more precise document selection, further improving analyses of the growth, trends, and global distribution of scientific fields. Nevertheless, our analysis addresses fundamental gaps in interpretation of mathematical research in oncology, offering a comprehensive, data-driven perspective on its current status and evolution over 75 years. It further clarifies the scope of subfields, highlighting the central role of therapy and clinical data in Mathematical Oncology. Based on these findings, we propose a more precise definition of the field, which is not merely the application of mathematics to study cancer. Mathematical Oncology is the use of interpretable mathematical models—integrating clinical, biological and physical knowledge—to enhance cancer screening, understand disease evolution, guide therapy, and strengthen forecasting.

Methods

Datasets

This Week in Mathematical Oncology dataset (TWIMO dataset)

The complete list of papers featured in *This Week in Mathematical Oncology* (TWIMO) is maintained and updated weekly by the editors on GitHub (**Table S2**). From this list, we retrieved the digital object identifiers (DOIs) of all entries and extracted the corresponding bibliographic information from Scopus for analysis (**Table S3**).

Query-based dataset

To broaden the scope of our study, we constructed a second dataset through a keyword-based search in Scopus. As with most scientific databases, Scopus enables the use of logical operators to combine search terms. We therefore designed a comprehensive query integrating terminology commonly used in both cancer research (e.g., “Cancer,” “Tumor,” “Radiotherapy”) and mathematical modeling (e.g., “Mathematical Model,” “Mathematical Oncology,” “Computational Oncology,” “PK/PD”) (**Table 1**). To ensure inclusiveness, we considered all citable document types (articles, books, and conference papers) published in complete years up to 2024, since the analysis was conducted in 2025. Additionally, all documents explicitly containing the term “Mathematical

This search yielded a dataset comprising over 19,000 publications. To evaluate its relevance, we randomly sampled 200 records and manually assessed their alignment with the scope of mathematical oncology. Of these, 73.5% (147 items) were deemed relevant, with a margin of error below 5% (4.8%) for the estimation of true positive rate⁷⁰. Moreover, 41% of the manually curated TWIMO dataset overlapped with the query-based dataset. Inspection of the non-overlapping items indicated that discrepancies primarily arose from publications related to Mathematical Oncology in a broader sense—such as works focusing on mathematical methods, cancer evolution, or clinical data—without explicitly presenting mathematical models of cancer.

Table 1. Query used for deriving the query-based dataset. Notice that the search is not case-sensitive and the character “*” represent every possible group of characters (e.g. “Moran Proces*” matches both “Moran Process” and “Moran Processes”). We also show the number of results, the percentage of the papers in TWIMO that are present in the query-based dataset, and the estimated percentage of true positives.

Data Analysis

Rankings

We generated multiple rankings and distributions of bibliographic features across both datasets, including authors, countries, journals, and author keywords (AKs). All rankings were programmatically produced and the code is publicly available on GitHub. Whenever possible, unique identifiers were used to prevent duplication or spelling inconsistencies. Specifically, authors, journals, and institutions identifiers were matched via Scopus IDs, which ensured unambiguous aggregation of entities. Since AKs lack unique identifiers, terms were standardized by capitalization, and eventual synonymous terms were merged together (see **Table S4** for the list of synonyms). For example, “Mathematical Model,” “Mathematical Modeling,” and “Mathematical Modelling” were considered under a single keyword entry.

All Science Journal Classification (ASJC) areas

To measure the multidisciplinary of the publications in the query-based dataset, we leveraged the distribution of the ASJC areas. In Scopus, each journal is associated with one or more scientific areas following the ASJC. Since each document in the query-based dataset has been published in a journal, this allowed us to map each individual publication to one or more scientific areas, and to observe the overall distribution in the dataset (**Fig. 3**, **Fig. S2**).

Citations, quartile, and open access

Citation data were obtained directly from Scopus (**Table S3**). To calculate citation rates per year, total citations were divided by the number of years since publication (e.g., a paper with 100 citations published in 2015 has 10 citations per year in 2025). Scopus also reports Open Access (OA) status, classifying publications into five categories: Not OA (N/A), Gold OA (published in an OA-only journal), Hybrid Gold OA (journal allows OA or non-OA publishing), Green OA (journal publication plus deposition in a public repository such as arXiv or bioRxiv), and Bronze OA (journal provides temporary OA). These classifications enabled stratified analyses of citation distributions by OA type (**Fig. S3**). Kolmogorov-Smirnoff test with Bonferroni correction (when comparing more than two groups) was used to establish statistical significance between different OA modalities (**Table S1**).

Journal quartiles were derived from Elsevier’s Scival database (**Table S5**), as Scopus does not directly provide this information. Quartiles are defined using the distribution of Scopus CiteScore™, which reflects the average citations per document over the preceding four years. Journals are assigned to subject fields and classified into quartiles accordingly, with Q1 representing the highest-performing journals. Since quartile data are available only from 2014 onward, analyses were limited to publications from 2014–2024.

Text mining and regular expression analysis

Regular expressions (regexes) were designed to identify key modeling approaches and cancer types within publication titles, abstracts, and keywords. Regexes representing modeling methods (45 total, **Table S6**) were grouped into seven categories: Differential Equations (22 terms), Agent-Based Models (3), Probabilistic Models (9), Game Theory (10), Machine Learning (3), Data-Driven Models (3), and PK/PD (3).

To capture cancer-specific research topics, we compiled a list of 197 regexes based on cancer types listed in *Wikipedia* (**Table S7**), organized into 13 categories: Bone and Muscle Sarcomas (10), Brain and Nervous System (26), Breast (13), Endocrine System (15), Eye (5), Gastrointestinal (16), Genitourinary and Gynecologic (30), Head and Neck (9), Hematopoietic (41), Skin (9), Soft Tissue Sarcomas (6), Thoracic and Respiratory (15), and HIV/AIDS-related (2).

For each regex, all titles, abstracts, and keywords were programmatically scanned. A publication was counted once per regex if at least one match was found, regardless of multiple occurrences within the same record.

Bibliometric Networks

Two types of bibliometric networks were analyzed: (1) a co-occurrence network of AKs (**Fig. 4c**) and (2) bibliographic coupling networks of authors (**Figs. 5c, S9**). Both were generated using VOSviewer⁵¹ and visualized as chord diagrams via the **D3.js** JavaScript library.

In the co-occurrence network, link width represents the frequency with which two AKs appear together in the same publication, and node size corresponds to the total occurrences of each AK. In the bibliographic coupling network, link strength reflects the extent to which two authors cite common documents, thus highlighting shared research trajectories or collaborations⁵¹. Node size is proportional to an author's overall connectivity within the network.

Both networks were clustered using VOSviewer's internal similarity-based algorithm (see **Appendix S1**). The clustering granularity is controlled by the "resolution" parameter, where higher values yield finer partitions. For the AK co-occurrence network (**Fig. 4c**), a resolution of **0.7** was used; for author coupling networks, **1.1**

Data Availability Statement

The bibliometric data generated during the study are permanently available on Zenodo (DOI: <https://doi.org/10.5281/zenodo.18207986>). The code used for the analysis is available on GitHub (link: <https://github.com/fpradelli94/MathOnco-Bibliometrics>)

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