

Review Article

Artificial Intelligence Is Driving Cell Kinetics Studies in Cancer: A Narrative Review on the Evolution of Cancer Kinetics Studies

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Quantitative descriptions of how tumors grow over time, from the interpretation of screening intervals to the design of chemotherapy schedules, underlie much of modern oncology.

Tumor doubling time (TDT) is a fundamental kinetic descriptor of neoplastic growth, defined as the time required for a tumor to double in volume, mass, or cell number. As a deceptively simple metric, TDT occupies a pivotal place in oncology because it links microscopic cellular proliferation to macroscopic disease evolution, informs screening and surveillance strategies, and contributes to prognostic modeling. However, TDT is not a fixed biological constant; rather, it is an estimate shaped by tumor histology, microenvironmental constraints, vascular supply, immune surveillance, treatment exposure, and the assumptions embedded in mathematical growth models.

In practice, most clinical applications rely on volume doubling time (VDT), particularly when serial imaging is available. Yet VDT estimates are sensitive to measurement interval, segmentation method, imaging modality, and whether growth is modeled as exponential, Gompertzian, logistic, or otherwise non-linear.

On the other hand, the efficacy of cytotoxic chemotherapy depends not only on the intrinsic sensitivity of malignant cells to a given agent but also on the kinetic behavior of the tumor cell population before, during, and after treatment. Tumor growth is governed by dynamic parameters including the growth fraction, cell cycle transit time, and rates of cell loss, all of which are non-static and are themselves perturbed by cytotoxic exposure.

TDT is not purely an intrinsic feature of the malignant cell. It is strongly influenced by the proportion of stem cells, oxygen supply, vascularity, and other environmental characteristics.

Cell kinetics — the quantitative study of how individual cells and cell populations grow, divide, move, differentiate, and die over time — has traditionally relied on manual microscopy scoring and mechanistic mathematical models such as ordinary differential equation systems describing exponential or logistic growth. Over the past decade, artificial intelligence (AI), and deep learning in particular, have transformed this field by enabling automated, high-throughput, and single-cell-resolution analysis of dynamic cellular behavior.

This paper reviews the conceptual basis of TDT, analytical methods for estimating it, determinants of intertumoral variability, and its clinical significance across cancer types. It also highlights limitations that complicate direct comparison across studies and argues for standardized reporting to improve reproducibility and translational utility.

It also reviews the theoretical and experimental basis of chemotherapy-induced cell kinetic change, beginning with classical cell cycle kinetics and the log-kill hypothesis of Skipper, Schabel, and Wilcox, and extending through Gompertzian growth models, von Bertalanffy-type formulations, cytotoxic synchronization and recruitment phenomena, accelerated repopulation after cell killing, the Norton-Simon hypothesis, and the Goldie-Coldman model of kinetic drug resistance.

Finally, it reviews the principal Artificial Intelligence (AI) methodologies applied to cell kinetics, including convolutional neural networks for segmentation, recurrent and transformer-based architectures for temporal modeling, variational autoencoders for latent cell-state representation, generative adversarial networks for data synthesis, and hybrid mechanistic-machine-learning frameworks. Four major application domains are examined: cell-cycle phase prediction and proliferation modeling, image-based cell segmentation and tracking, tumor growth kinetics and treatment-response forecasting, and stem-cell fate and differentiation prediction.

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Introduction

Tumors grow. And there is no doubt that this growth was the first symptom/sign observed more than three thousand years ago, even if the early physicians did not know what a tumor was about. Furthermore, tumor means “a mass”, that is, something that has grown.

Tumor growth is rarely a simple matter of unconstrained proliferation. From the moment a malignant clone first arises, its expansion is shaped by nutrient and oxygen availability, the surrounding stroma and

vasculature, immune surveillance, and the accumulation of further genetic and epigenetic alterations.

Cancer growth at the molecular and cellular level is best understood as a breakdown of the normal, multi-layered systems that restrain proliferation, maintain tissue architecture, and eliminate damaged cells with the full cooperation and participation of the tumor microenvironment. It is not just faster mitosis, but an evolutionary process where cells acquire, select, and stabilize traits that collectively create autonomous, invasive, therapy-resistant populations. Therefore, the concept of tumor growth cannot be clearly separated from tumor evolution.

In normal tissues, proliferation is closely tied to differentiation, mechanical constraints, metabolic state, and organismal homeostasis via the extracellular matrix (ECM), stromal cells, and systemic cues. The molecular and cellular concept of cancer growth is that these control layers are progressively disabled or hijacked, so that cell division becomes driven by cell-intrinsic oncogenic circuits and a reprogrammed microenvironment rather than by physiological demand.

At its heart, cancer growth reflects accumulated lesions in (a) growth-promoting pathways (oncogenes), (b) growth-restraining and damage-sensing pathways (tumor suppressors and genome maintenance), and (c) contextual regulators (ECM (extracellular matrix), immune system, vasculature, cytokines), producing a new “supracellular” organization of tissue that favors the expansion of malignant clones.

The tumor microenvironment (TME) supports cancer cell survival by acting as a dynamic, co-evolving “niche” that provides physical shelter, trophic support, stress adaptation, and immune protection to malignant cells. Conceptually, survival is not a purely cell-intrinsic property. It is continuously reinforced by reciprocal interactions between tumor cells, stromal cells, immune cells, vessels, metabolites, and ECM.

The cancer growth process is not only the growth of tumor cells, as it intuitively seems, but the intertwined growth of tumor cells and the surrounding tumor microenvironment. Without the supportive environmental growth, tumor cells would not be able to thrive and proliferate.

Describing the growth process quantitatively serves two related purposes. First, it allows clinicians and researchers to estimate quantities that cannot be observed directly, such as the age of a tumor at diagnosis or the interval before it would have become symptomatic in the absence of intervention.

Second, it provides a framework for reasoning about timing: how often a population should be screened, how long a course of therapy should last, and how treatment cycles should be spaced to avoid both excessive toxicity and re-growth between doses.

The literature on tumor growth modeling spans nearly a century, beginning with early applications of the logistic and Gompertz equations to experimental tumor data and continuing through contemporary agent-based and partial differential equation models of vascularized, heterogeneous tumors. This review focuses on the subset of that literature most relevant to timing: the kinetic laws used to fit clinical and experimental growth curves, the parameters they yield, and the ways those parameters have been used to inform decisions about when to screen, when to treat, and how to space treatment over time.

It is important to establish that classical growth models such as Gompertzian or logistic growth lump everything into a single feature which implicitly mixes cell-intrinsic limits and environmental limits. However, there are intents to separate malignant cell and environmental growth. These equations that include variables such as angiogenesis, hypoxia, immune cells, metabolites, extracellular matrix rigidity and other mechanical cues, are more theoretical than practical. The practicing physician only has access and can only use a “lump growth model” that includes cells and environment.

Artificial intelligence is changing the outlook for the original tumor kinetics studies by incorporating some complex parameters such as tumor heterogeneity, stochastic behavior of individual cells within a population, hypoxia, lack of nutrients, and integrating genomics, proteomics, and treatment in the growth process. All these data would be very difficult to process completely without the help of AI.

This paper is divided in two sections. The first section discusses the classic knowledge of cell dynamics. The second discusses and analyzes how AI can go many steps beyond classic knowledge allowing a more accurate measurement of growth, and also providing reliable prognostic and therapeutic information.

SECTION A: Tumor kinetics

From intuitive versus real growth mechanics in tumors

Tumor growth can feel “intuitive” (more cells → bigger tumor), but real growth is driven by *mechanistic constraints* inside tissue. The following is a bridge from intuition to the actual biological/physical processes that determine whether a tumor shrinks, stalls, or grows.

Intuitive idea

More proliferation → tumor expands

This is directionally right, but real tumors are governed by feedback loops, spatial limits, environmental factors, clonal evolution that leads to heterogeneity, immune facilitation or attack, inflammatory

environment, nutritional constraints, lack of oxygen, excessively acid environment, all of what we can call a very harsh environment. To this we must add intracellular homeostatic issues such as excessive radical oxygen species (ROS), metabolic changes, and altered transduction signaling, among many others.

Real growth mechanics

Even if cells divide, growth may plateau if death rates rise (e.g. due to stress, hypoxia, or poor perfusion). In early tumors, oxygen and nutrients diffuse inward. As tumor size increases,

diffusion becomes limiting,

hypoxic regions form,

cells slow down, become quiescent, or die.

Tumor growth often becomes slower after a critical size. Necrotic cores are common in larger solid tumors. Hypoxia can be a “trigger” that converts a tumor from contained growth to more aggressive expansion. Cell adaptation and clonal evolution strongly influence tumor growth rate according to **which subpopulation “wins”** in a given microenvironment.

Even if biology is “pro-growth,” physical barriers can reduce effective expansion (and can also promote invasion). When a tumor switches from expansion to invasion it can circumvent diffusion limits because dispersed cells can access nutrients in new locations. The immune context can determine whether proliferation dominates or gets suppressed.

In summary

Intuition: tumors grow because cells divide

Reality: tumors grow when:

proliferation exceeds death;

nutrients/oxygen remain sufficient or are complemented with angiogenesis;

immune suppression prevents effective killing;

mechanics don't fully block expansion (or invasion occurs);

evolution selects subclones that thrive under constraints. Summarized in Figure 1.

Cancer cell kinetics refers to the study of the rates and dynamics of cancer cell processes, including their growth, division, and death. Understanding these kinetics is crucial for grasping how tumors develop, progress, and respond to treatments.

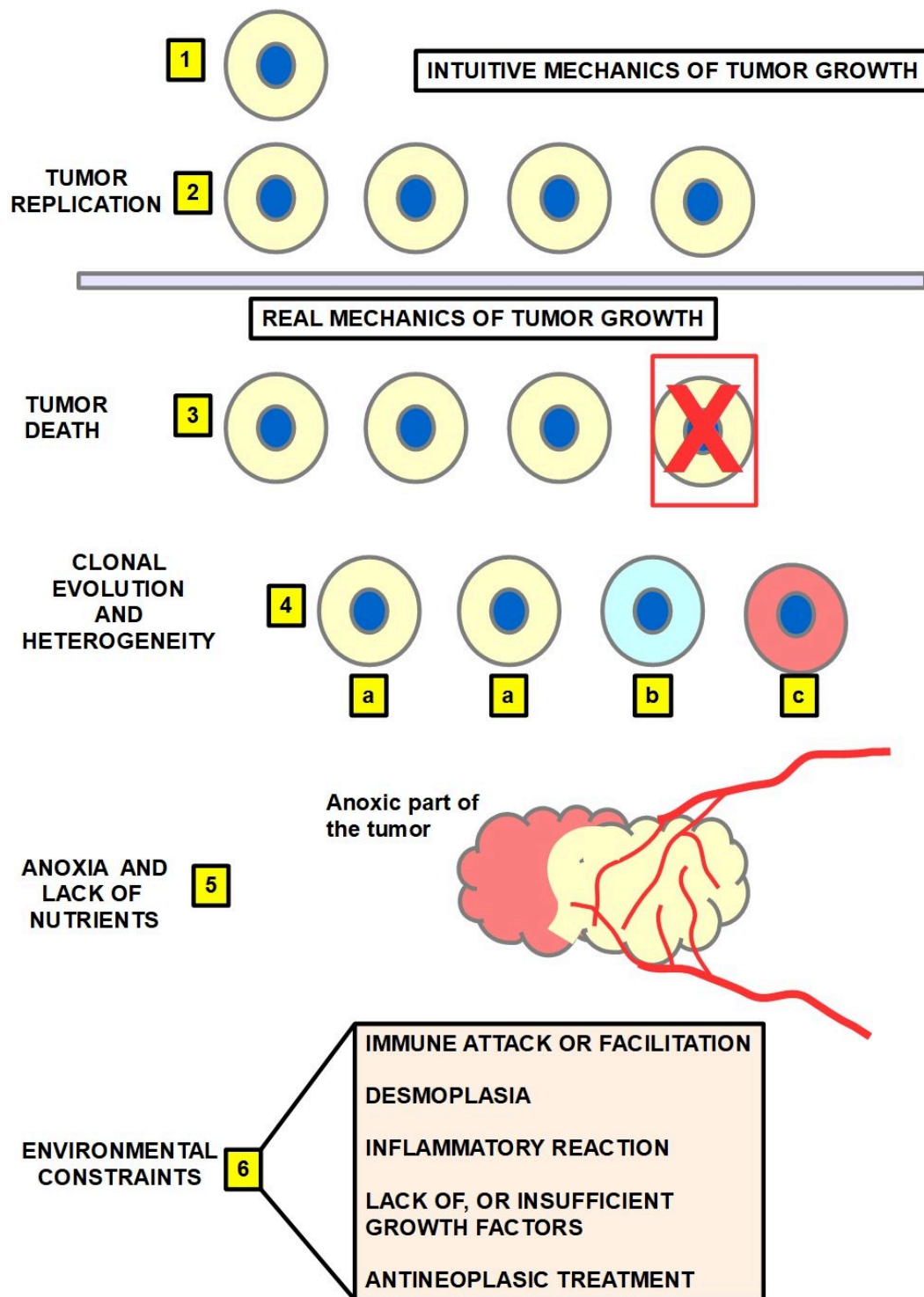


Figure 1. Intuitive versus real mechanics of tumor growth. During cancer proliferation many cells die and many stop proliferating (senescence or quiescence). Therefore, the intuitive concept of permanent growth in cancer is not what really occurs.

Cancer cell kinetics

Key concepts in cancer cell kinetics include:

1. **Cell Proliferation Rate:** The speed at which cancer cells divide and multiply. Cancer cells typically have a higher proliferation rate than normal cells, leading to tumor growth. This means that more cells are in a proliferative stage.
2. **Cell Cycle:** Cancer cells often have altered cell cycle regulation, causing uncontrolled progression through phases (G1, S, G2, M), which increases replication frequency. This does not mean that the time necessary for the cell cycle is always different from that of normal cells.
3. **Growth Fraction:** The proportion of tumor cells actively dividing at a given time. A high growth fraction means more cells are in the replication phase.
4. **Cell Loss Factor:** The rate at which cancer cells die or are lost from the tumor due to mechanisms like apoptosis (programmed cell death), necrosis, or immune system attack. When the number of dying cells is greater than or equal to the replicating cells, the tumor does not grow.
5. **Tumor Doubling Time:** The time it takes for the tumor cell population to double in number, reflecting the balance between cell proliferation and cell loss.
6. **Cell Cycle Time:** The time it takes for a single cell to complete one full cycle and divide into two daughter cells. Usually, cell cycle time can be similar in normal and malignant cells, or shorter in the latter case. Table 1.

Aspect	Normal Cells	Malignant Cells
Overall Cell Cycle Time	Generally longer, often ranging from 12 to 24 hours depending on cell type	Usually shorter, can be as little as 8 to 12 hours or even less in aggressive cancers
Regulation	Strictly controlled by checkpoints that ensure proper DNA replication and repair	Checkpoint controls are often defective, leading to faster progression through the cycle.
Growth Signals	Require external growth factors to proceed with division	Often independent of external growth signals, proliferating autonomously.
Cycle Phases Duration	Balanced length of G1, S, G2, and M phases	Frequently shortened G1 phase, accelerating progression to DNA synthesis (S phase).
Cell Cycle Arrest	Can enter a resting phase (G0) when not needed or damaged	Rarely enter G0; often continue dividing uncontrollably
Apoptosis Sensitivity	More sensitive to damage, allowing repair or cell death	Often resistant to apoptosis, enabling survival despite DNA abnormalities

Table 1. Differences between normal and cancer cell cycle/replication.

This Table is based on references [\[1\]](#)[\[2\]](#)[\[3\]](#)[\[4\]](#)[\[5\]](#)[\[6\]](#)[\[7\]](#)[\[8\]](#)[\[9\]](#)[\[10\]](#)

Therefore, we can consider that the cell cycle is shorter in cancer cells than in most normal cells, enabling faster proliferation, although this has many exceptions. For example, the typical durations are:

- Many normal human cells: ~24 hours (varies widely—e.g. intestinal lining cells ~9-10 hours, much longer for liver cells).
- Cancer cells: Often 12-24 hours or less (e.g. some leukemia cells ~24 hours; certain breast/colon cancer cells ~20 hours). Some solid tumors can be slower, but the trend is accelerated division compared to their tissue of origin.
- Not all cancer cells or tumor types behave identically. Highly aggressive cancers (e.g. some leukemias, small cell lung cancer) proliferate rapidly, while some well-differentiated or slow-growing tumors (e.g. certain prostate cancers) may have cycles closer to normal. Tumor microenvironment, differentiation status, and specific mutations influence it.

- The core hallmark of cancer is uncontrolled division rather than a universally fixed shorter duration, but faster cycling is a common feature that drives tumor growth.

Cancer therapies aim to disrupt cancer cell kinetics by targeting highly proliferative cells, slowing growth, or increasing cell death. Usually, targeting proliferative cells means that many normal cells in the proliferative phase are also targeted. This results in the loss of many normal cells such as those of the intestinal mucosa and bone marrow, with the consequently adverse events such as diarrhea, anemia, low neutrophil and platelet counts.

Mathematical Models of Tumor Growth

A tumor growth model relates tumor size (typically volume, cell number, or a linear diameter used as a proxy) to time. Most models used in oncology come from population-growth equations originally developed in ecology and demography, adapted to account for the resource limitations that constrain a growing mass of cells.

Measuring speed of growth gives an approximate but reliable idea of how malignant a tumor is. A simple method of finding out the growth speed consists of calculating the time required for duplication of the tumor volume. This requires two successive measurements of the tumor's size with a CT scan or MRI. Ultrasound studies can also serve this purpose. Determining growth speed is a useful method for measuring responses to treatment. Therefore, it is an interesting resource for making therapeutic decisions. In certain cases, a tumor's growth can be so slow that it requires no therapy, such as some prostate cancers in old men. However, growth dynamics are still the subject of some controversy because they are not fully exponential as intuition would make us believe. Tumors that reach a large size, usually tend to decrease their growth speed, although this cannot be considered a universal rule. Tumor doubling time is particularly useful in evaluating the efficacy of new chemotherapeutic drugs.

Cell kinetics is the study of cell growth and division. It has led to an understanding of how and when cancer cells increase in number and the speed at which this happens. Cell kinetics has also been useful in developing chemotherapeutic methods. The basis of cell kinetics is the common characteristic of tumors, their positive and uncontrolled growth. This growing process can be explained by some parameters such as volume duplication time. This is the time that a tumor takes to double its volume. It would be logical that the more developed the tumor is, the more quickly it grows. But this is not so. It has been found that the older the cell population is, the slower duplication time becomes.

Tumor growth implies that a cell goes through the cell cycle and results in two daughter cells. If this happens at a regular interval, and all the cells replicate in similar intervals, growth would be exponential. However, replication intervals may vary and then growth would not follow a geometric increase.

The growth rate of a tumor depends mainly on ^[11]:

1. duration of the cell cycle, which for all practical purposes can be considered constant,
2. proportion of proliferating cells (growth fraction), and
3. amount of cell death.

Tumor doubling time has long served as one of the most accessible quantitative descriptors of cancer growth. Its appeal lies in intuitive interpretation: a short doubling time implies rapid expansion, whereas a long doubling time suggests slower progression or greater growth restraint. In oncology, this parameter is used in screening contexts, prognostic modeling, and comparisons of tumor aggressiveness across histological subtypes and disease stages ^{[12][13]}. Despite its apparent simplicity, TDT is not a direct biological measurement but a derived estimate whose meaning depends on the model used to generate it and the temporal window over which the tumor is observed. For example, determining tumor doubling time through ultrasound measurements will probably show different results than with standard X-ray or CT scan.

Artificial intelligence coupled with modern image diagnostics is making a big difference towards TDT accuracy.

Historical background

Tumor doubling time occupies a distinctive place in the history of oncology because it links a biological process that is inherently microscopic—cell division—to a macroscopic clinical phenomenon—tumor enlargement over time. As a concept, it emerged from a broader mid-twentieth-century effort to describe cancer quantitatively rather than impressionistically, when investigators began to treat tumor growth as a measurable kinetic process instead of a purely morphologic event. In this sense, doubling time was not simply a descriptive variable; it became part of an epistemic shift in oncology, helping transform cancer from a static lesion into a dynamic system whose behavior could be modeled mathematically and studied longitudinally.

Historically, one of the most influential milestones was the 1956 paper by Collins, Loeffler, and Tivey ^[14], which articulated the idea that human cancer growth could be approximated by linear exponential

behavior and expressed through a constant growth rate. Their framing was remarkable for its time because it proposed that “doubling time” could serve as a biologically meaningful characteristic of an individual tumor, with implications for tumor duration before diagnosis, the interpretation of dormancy, and the apparent paradox that earlier detection does not necessarily eliminate mortality. The paper’s enduring influence is evident not only in the later citation history but also in the way it helped normalize the idea that tumor growth could be studied with quantitative rigor, using serial measurements and mathematical extrapolation ^{[15][16]}.

This early kinetic perspective was reinforced by subsequent work in radiology and cell kinetics that used serial imaging and clinical follow-up to infer growth rates in vivo. In 1961, Mordecai Schwartz ^[17] introduced a mathematical method for calculating tumor doubling times by assuming exponential tumor growth. It was based on the differences in tumor diameters between two serial measurements using X-ray images. This method has some limitations, for example it is inaccurate when the change is very small, or the measurement is difficult to achieve. CT scan has improved measurement quality; thus, the last limitation is no longer important.

In the decades that followed, investigators applied doubling-time reasoning to pulmonary metastases, primary breast cancers, childhood tumors, and other solid malignancies, often with the hope that growth-rate estimates could illuminate the timing of occult disease and the rationale for treatment scheduling. A 1970s analytical review summarized the field by reviewing clinical doubling times of solid tumors and proposing that growth-rate patterns could help distinguish rapidly proliferating, therapy-responsive tumors from slower-growing diseases that were less likely to yield durable responses. These early studies established a conceptual bridge between tumor kinetics and clinical decision-making that remains visible in contemporary oncology ^[18].

The historical development of tumor doubling time also paralleled the rise of mathematical growth laws in biology. Exponential growth was initially attractive because it captured the intuitive notion that each tumor cell division adds to a growing mass in a multiplicative manner. However, as empirical observations accumulated, it became increasingly difficult to sustain a purely exponential model across all phases of tumor development. Later work introduced Gompertzian and logistic descriptions to account for the empirical reality that tumors often grow rapidly at first and then decelerate as they enlarge, reflecting vascular limitation, nutrient depletion, immune pressure, and spatial constraint. The broader significance of this shift is that tumor doubling time came to be recognized not as a universal constant but as a model-dependent summary of a non-linear biological process ^[19]. Kendal ^[20] proposed

that the Gompertzian growth model was a consequence of tumor heterogeneity, a concept also confirmed by other authors [\[21\]\[22\]\[23\]\[24\]](#).

This conceptual maturation is especially clear in modern studies of breast and lung cancer. In breast cancer, a systematic review found that tumor doubling time has remained broadly stable over approximately 80 years despite changes in screening and diagnostic practice, suggesting that secular changes in detection do not necessarily imply altered intrinsic growth kinetics [\[25\]](#). At the same time, the same literature shows substantial heterogeneity by subtype, with more aggressive molecular phenotypes generally doubling faster than hormone receptor-positive tumors. In lung cancer, CT-based studies and meta-analyses have demonstrated similarly marked heterogeneity, with solid tumors tending to show shorter doubling times than part-solid or nonsolid lesions, and with rapid growth being particularly common in aggressive histologies. These findings underscore the modern view that doubling time is best interpreted as a phenotype-sensitive kinetic marker rather than a fixed property of cancer.

A second historical theme concerns the tension between simplicity and biological realism. Tumor doubling time became influential precisely because it distilled complex growth behavior into a single number that could be communicated easily across disciplines. Clinicians could use it to compare lesions, epidemiologists could use it to estimate preclinical dwell time, and modelers could use it to parameterize simulations of screening and treatment timing [\[26\]\[27\]\[28\]](#). Yet this same simplicity is also its limitation. A single doubling time value can conceal changes in growth phase, treatment effects, spatial heterogeneity, and measurement uncertainty. As later theoretical and clinical studies showed, the doubling time derived from two time points is often only an average over a limited interval, whereas the biologically relevant growth rate may vary continuously with tumor size and environmental context [\[29\]](#). Furthermore, laboratory tumor growth cannot be fully extrapolated to what happens in vivo [\[30\]](#).

The historical literature also reveals that tumor doubling time has been used to connect growth kinetics with prognosis and therapeutic responsiveness. Early reviews suggested that rapidly growing tumors were often more sensitive to cytotoxic therapy, whereas slower-growing tumors tended to be less responsive and more prone to durable residual disease. Although this generalization is too coarse to serve as a clinical rule, it influenced the development of cell-kinetic approaches in oncology and helped motivate treatment schedules designed around proliferative dynamics. Modern studies continue to extend this logic, for example by examining whether tumor volume doubling time predicts prognosis in squamous cell carcinoma of the lung or metastatic adenoid cystic carcinoma. Thus, the historical role of doubling time is not merely archival; it remains embedded in contemporary translational research [\[31\]](#).

From a historiographic standpoint, the evolution of doubling time reflects a broader transition in cancer science from descriptive pathology to quantitative systems thinking. Early investigators were concerned primarily with whether tumors grew “fast” or “slow”; later researchers asked how growth rates should be measured, which mathematical law best captured their behavior, and how these measurements should be interpreted in relation to screening and survival. In this progression, doubling time served as a conceptual anchor. It allowed scientists to compare tumors across patients, across histologies, and across eras, even as the underlying models became more sophisticated. That durability explains why TDT remains central in modern oncology despite the availability of genomic, radiomic, and multi-omic data [\[32\]\[33\]\[34\]\[35\]](#).

In current research, the historical legacy of tumor doubling time is evident in ongoing debates about model choice, reporting standards, and clinical utility. Contemporary reviews emphasize the need to state clearly whether a reported doubling time is volume-based, mass-based, interval-based, or model-derived, because different methods may produce materially different values. They also highlight the increasing recognition that indolent cancers exist even within traditionally aggressive disease categories, complicating older assumptions of uniformly exponential growth [\[36\]\[37\]](#). In this sense, the history of TDT is a history of refinement: an initially elegant simplification that has gradually been embedded in a more nuanced framework of tumor heterogeneity, measurement uncertainty, and model dependence. It is particularly important to mention that modern diagnostic imaging tools have substantially improved calculations of tumor doubling volume time [\[38\]\[39\]\[40\]](#) as compared with the original methods based only on two dimensional radiology.

Accordingly, an academically rigorous introduction to tumor doubling time should present it not merely as a metric of tumor growth, but as a historically situated concept that emerged from the convergence of radiology, cell kinetics, and mathematical oncology. Its enduring relevance lies in the fact that it offers a bridge between biological mechanism and clinical observability. Its equally important limitations arise from the reality that tumor growth is shaped by non-linear, context-dependent processes that a single numerical value can only partially represent. This dual character—simplicity on the one hand, biological complexity on the other—explains why doubling time remains both useful and contested, and why it continues to occupy a central place in the study of cancer growth kinetics

Clinical significance

The clinical significance of TDT is perhaps most evident in lung cancer, where CT-based volumetric analysis has enabled systematic examination of growth rates in primary tumors. A 2024 systematic review and meta-analysis found a pooled mean VDT of approximately 207 days for solid lung cancers, with much longer values for part-solid and nonsolid lesions, indicating profound heterogeneity by radiographic phenotype ^[12]. Earlier meta-analytic work reported a pooled mean VDT of 213 days and similarly emphasized that nodule solidity and histological subtype are among the most consistent correlates of rapid growth ^[13]. In breast cancer, serial ultrasound studies have shown substantial variability as well, with median TVDT around 141 days and significantly shorter values in triple-negative tumors than in ER-positive tumors ^[41]. Together, these findings suggest that TDT is best understood as a contextual descriptor rather than a universal property of malignancy ^{[12][13][14]}.

Conceptual Basis

At its core, TDT reflects the net balance between proliferation and cell loss. A tumor may divide rapidly at the cellular level yet still exhibit a modest increase in measurable volume if apoptosis, necrosis, immune-mediated killing, or poor vascular support offset proliferation. Conversely, a tumor with a relatively low proliferative fraction may still demonstrate a short doubling time if cell loss is minimal. This distinction is crucial because TDT is often interpreted as synonymous with proliferation, although it is actually a composite outcome of multiple processes occurring simultaneously ^[12].

Although tumor doubling time is intuitively appealing, it should be interpreted as a **summary statistic** rather than a direct biological constant. Its most fundamental limitation is that real tumors rarely grow at a fixed rate ^{[42][43]}. Growth often changes over time as vascular supply, immune pressure, stromal constraints, metabolic adaptation, and treatment exposure alter the balance between proliferation and cell loss ^[44]. Under these conditions, a single doubling time can obscure important phase-specific changes in tumor behavior and may therefore misrepresent the underlying biology ^{[45][46][47][48][49]}.

Mathematical approach to tumor growth rate

A major limitation for calculating tumor volume doubling time (TVDT) is that it is strongly **model dependent**. The estimated value can differ substantially depending on whether growth is assumed to be exponential, logistic, Gompertzian, or another functional form. In a cautionary analysis of seven ordinary

differential equation models, predicted doubling times differed by as much as 12-fold depending on model choice, demonstrating that the same dataset can yield very different clinical inferences if the growth law is altered. This means that doubling time is not an invariant property of the tumor itself; it is partly an output of the mathematical framework used to estimate it ^[50].

Measurement error further limits interpretability. Imaging-derived volume doubling time depends on scan interval, segmentation quality, reconstruction settings, lesion shape, and partial-volume effects. Small inaccuracies in the measured volume can produce large changes after logarithmic transformation, especially when serial measurements are close together or the lesion is small. These sources of error are not trivial technical nuisances; they can dominate the estimate and make short-term doubling times unstable or irreproducible ^[51].

Tumor heterogeneity is another major problem. A biopsy or a single imaging-derived estimate may not capture regional differences in proliferation, necrosis, vascularity, or clonal composition within the same tumor. Even in studies of proliferative biomarkers, tumor heterogeneity has been identified as a major cause of variability that cannot be fully eliminated by standardization. The same applies to doubling time: a rapidly expanding peripheral rim and a necrotic or quiescent core may coexist, yet the model returns only one number ^{[52][53]}. In this regard, Turnquist et al. ^[54] suggest that tumor heterogeneity should somehow be introduced in the calculation of tumor growth. However, this has not been achieved as yet. AI assisted measurements are changing this.

One of the major limitations for determining tumor growth is that any model we choose is also weakened by its limited ability to incorporate treatment effects. Once therapy begins, growth kinetics may shift abruptly, and post-treatment volume changes can reflect necrosis, edema, fibrosis, or cavitation rather than viable tumor expansion. In such cases, a calculated doubling time may be biologically misleading unless the timing relative to therapy is explicitly controlled for. This is one reason doubling time is most defensible in untreated lesions or in carefully designed natural-history studies. AI is also modifying these inaccuracies.

Finally, there are inferential limitations. Doubling time is often derived from only two time points, which makes it highly sensitive to noise and does not allow robust discrimination among competing growth models. Even when multiple time points are available, parameter identifiability can remain weak, particularly for slowly growing lesions or heterogeneous datasets. For this reason, modern modeling

studies emphasize that doubling time should be accompanied by confidence intervals, model-fit statistics, and explicit reporting of assumptions ^[55].

After describing all these limitations of any mathematical method used, let's take a look at possible mathematical approaches.

The simplest biologic framework would be

TDT is the direct consequence of proliferation rate/time – cell death

This biologic approach is flawed by the fact that tumor size can be importantly modified by edema, extracellular substance increase (e.g. desmoplastic stroma such as found in pancreatic ductal adenocarcinoma), and measurement method. However, it is acceptable as an initial elementary approach.

In mathematical terms, the simplest framework assumes exponential growth, in which

Tumor size N at time t follows $N(t) = N_0 e^{kt}$

This is the standard exponential tumor growth model where N_0 is the initial tumor size, $N(t)$ is the tumor size at time t, e the natural exponential base and k how fast the tumor grows per unit of time.

This model assumes that the growth rate is proportional to the current tumor size, so larger tumors add more cells per unit time than smaller ones. That is why the curve rises faster and faster over time ^{[56][57]}. This exponential scheme was the accepted tumor growth model until the 1980s.

Under this assumption, the doubling time is given by $TDT = \ln(2)/k$. This formula is attractive because it yields a closed-form estimate from two measurements and can be applied to imaging-derived volumes. However, exponential behavior is usually only a local approximation, especially in untreated tumors observed over longer intervals. As tumors enlarge, nutrient limitation, hypoxia, structural constraints, and altered perfusion often decelerate the net growth rate, making a single constant TDT increasingly inadequate ^{[12][13]}. Figure 2.

Exponential growth can be expressed mathematically with a differential equation:

$$\frac{dV(t)}{d(t)} = rV(t)$$

In which the rate of increase in volume $dV(t)/d(t)$ is equal to the current volume $V(t)$ multiplied by a constant rate r which is the growth rate. The "constancy" of r is what determines the exponential growth

behavior. However, the growth rate is not constant in many tumors and this casts doubts about the exponential model.

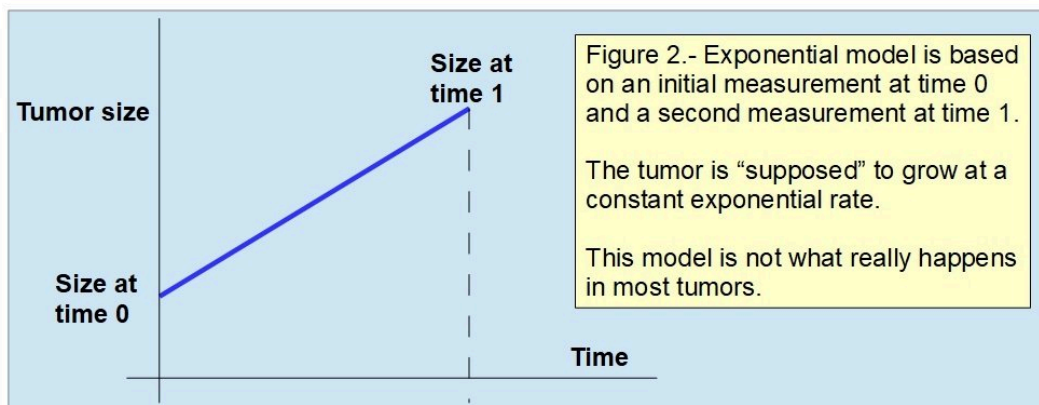


Figure 2.

More elaborate models, including Gompertzian (Figure 3) and logistic growth, attempt to capture this deceleration. In these frameworks, the apparent doubling time increases as the tumor approaches an effective carrying capacity. Consequently, TDT is no longer a fixed constant but a time-dependent property influenced by tumor size and the phase of growth under observation. This matters methodologically because two studies can report identical “doubling times” while referring to fundamentally different estimates derived from different models or time intervals [\[12\]\[13\]](#).

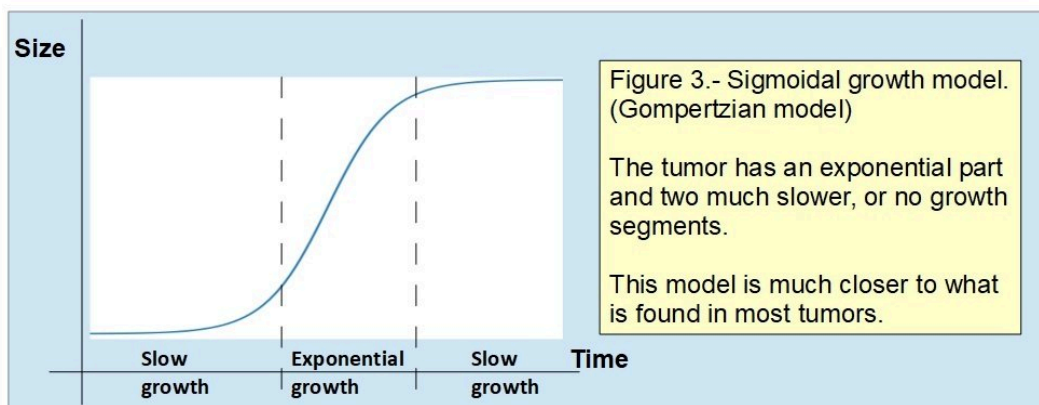


Figure 3.

The Gompertzian model of tumor growth describes tumor growth as **initially rapid but progressively slowing over time**, which makes it a better fit than simple exponential growth for many solid tumors. In practical terms, it assumes that the relative growth rate decreases exponentially as the tumor enlarges, reflecting constraints such as nutrient limitation, hypoxia, vascular insufficiency, and increasing microenvironmental resistance [58].

The model is widely used because many tumors do not keep growing at a fixed proportional rate. Early growth may appear close to exponential, but as the lesion becomes larger, the growth rate tends to decelerate, producing the sigmoidal pattern that Gompertzian kinetics capture well. This is especially useful in reconstructing natural history, estimating time of onset, and modeling metastasis or treatment effects [59].

The Gompertzian model

Described by the English actuary Benjamin Gompertz (1779-1865). The Gompertzian equation was originally conceived for population growth, not for tumor growth. However, the Gompertzian model:

- fits many empirical tumor growth datasets better than pure exponential models;
- provides a biologically plausible representation of growth deceleration;
- is useful for estimating latent growth histories and for simulating treatment timing effects. Figure 4.

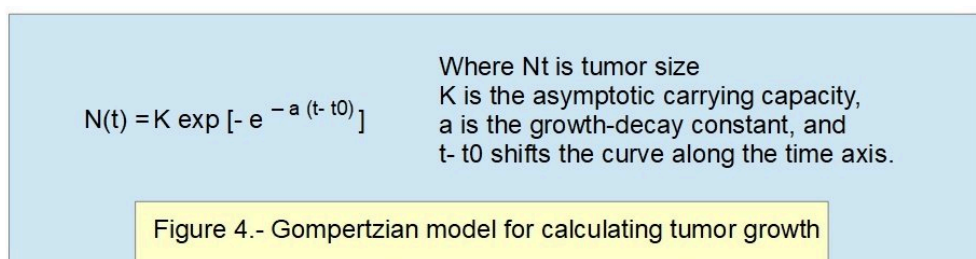


Figure 4.

However, it is still a simplified model and may not capture spatial heterogeneity, clonal evolution, immune effects, or abrupt therapy-induced changes. Parameter estimation can be unstable when data are sparse, and different tumors, or even different phases of the same tumor, may deviate substantially from Gompertzian behavior.

The initial low growth in the Gompertzian model is usually attributed to the tumor's **small effective growth fraction** and the way the model represents early constraints on proliferation. In biological terms, as solid tumors begin to expand, not all cells remain actively cycling; some become quiescent, and the fraction of proliferating cells can be low even before strong macroscopic limitation appears.

A common interpretation is that early growth is limited by the transition of cells into a non-proliferative state. As the tumor increases in size, more cells may become quiescent because of local nutrient gradients, oxygen limitation, and emerging microenvironmental constraints; this reduces the proportion of cells that contribute to net expansion. In the quiescence-based explanation, the Gompertz curve emerges because the probability of a proliferating cell remaining proliferative decreases with tumor size, so the growth fraction falls over time ^[60].

The Gompertzian model is often interpreted as reflecting a transition from early unconstrained proliferation to later constraint-dominated growth. Experimental work has suggested a shift from exponential to Gompertzian behavior when tumor size reaches roughly $10^{[2]}$ to $10^{[4]}$ cells, depending on the cell line and conditions. This transition is one reason the model is attractive in oncology: it connects a mathematical curve to plausible biological mechanisms.

The initial low growth is not usually explained as “slow division because the tumor is small,” but rather as an early manifestation of **declining growth fraction and increasing quiescence**, driven by microenvironmental constraints and the intrinsic structure of the model. When these initial limitations are “solved” by tumor adaptation, rapid growth ensues (exponential growth) that finally is also limited by environmental factors (lack of nutrients, lack of oxygen, necrosis or apoptosis of parts of the tumor, and quiescence of some cells).

The main difference between the Gompertzian and the logarithmic model is that the **latter** assumes that growth slows in a symmetrical way around its midpoint, while the **Gompertzian** model assumes growth slows earlier and more gradually and asymmetrically. In tumor biology, that usually means the Gompertz curve is often considered more realistic for solid tumors because its relative growth rate declines continuously as the tumor enlarges. Figure 5.

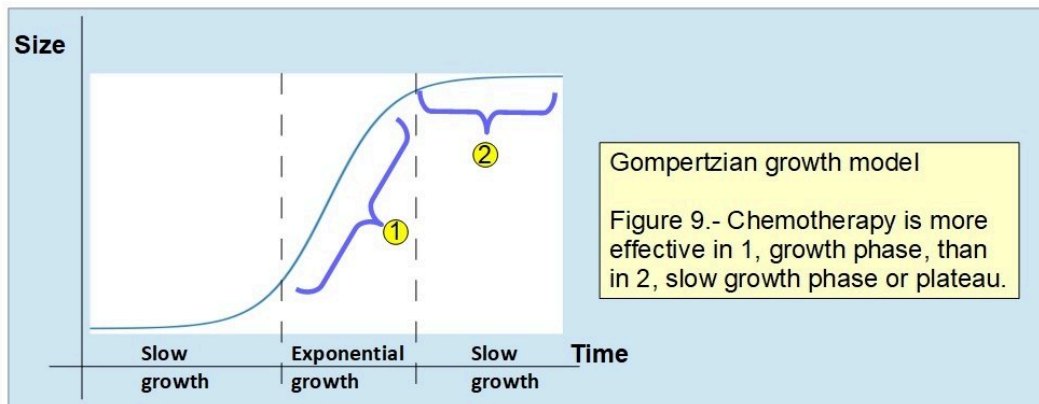


Figure 5.

Many other formulas have been proposed to calculate tumor growth, such as Mendelsohn's formula ^[61], and Dethlefsen et al. ^[62]. We believe that the Gompertzian model is the most accurate.

There is an online simulator for calculating TVDT in pulmonary nodules that can be found at <https://www.radiology.no/vdt/>. We cannot establish its accuracy. It is based on a modified version of Schwartz formula:

$$\text{TVDT} = [\ln_2 \times \Delta T] / [\ln(X_2/X_1)]$$

Where ΔT is the number of days between the two measurements, X_1 is the initial volume, X_2 the final volume and $\ln$ is natural logarithm ^[63].

Regarding lung nodules, a TVDT of 232 days was established as the cutoff to determine lung cancer diagnosis ^[64]. Another report found that duplication times of malignant nodules can take up to 318 days, while for benign nodules it was 389 days ^[65]. We believe that a 400 day cutoff is a more reliable figure. This means that a nodule with a TVDT of 400 days or more is probably not a lung cancer. Another important issue is that diagnosis should not only be based on TVDT ^[66].

It has been postulated that all metastatic lesions in an individual have a similar growth rate. This is not what we have found in practice. We frequently found important differences in the growth rate of metastasis in the same individual (unpublished data regarding only renal cell carcinoma).

Sudden changes in the growth rate of tumors have not been adequately investigated in the literature. According to our experience these changes occur occasionally, thus growth rate constancy is in doubt.

Furthermore, growth rate changes have also been found in patient-derived xenograft experiments ^[67].

According to Shackney et al. ^[18] tumors with a short doubling time respond better to chemotherapy. This type of rule is logical because the shorter the doubling time, the more intensive the growth and cell replication. The more frequent mitosis is the target of classic chemotherapy. They completed their observations with the comment *"Slowly growing tumors respond less favorably to therapy, and responses are generally not durable. Rapidly growing tumors in advanced stages are similar in their response behavior to the slowly growing tumors"*. Gompertzian growth of tumors will explain why, in advanced stages, the response is similar to slowly growing tumors.

Measurement Methods

The most common clinical implementation of TDT is volume doubling time, calculated from serial imaging. Computed tomography is particularly important in lung cancer, where nodule volumetry can be derived from contiguous scans and used to estimate growth rate before intervention. The 2024 systematic review of CT-based VDT in primary lung cancer included 33 studies and 3959 patients, demonstrating a pooled mean VDT of 207 days for solid tumors and much longer values for part-solid and nonsolid lesions ^[12]. Earlier pooled analyses similarly estimated a mean VDT of 213 days, with median ranges spanning 139 to 357 days across studies ^[13].

Ultrasonography has also been used for breast cancer, especially in longitudinal observational cohorts. In one study of molecular breast cancer subtypes, serial ultrasound revealed broad TVDT variation, with mean values of 241 days in ER-positive tumors, 162 days in HER2-positive tumors, and 103 days in triple-negative tumors ^[14]. These data reinforce the point that TDT is not merely a technical measurement but a phenotype-sensitive index with potential biological and clinical meaning ^[14].

Methodological rigor is essential because imaging-derived TDT is vulnerable to several sources of error. Small changes in lesion size can be obscured by segmentation variability, slice thickness, motion artifact, and differences in reconstruction algorithms. The problem is especially pronounced when the two scans are separated by a short interval or when the lesion is near the lower limit of reliable volumetric detection ^{[12][13]}. For this reason, many authors recommend reporting the exact measurement technique, time interval, and mathematical formula used to derive doubling time, rather than presenting TDT as a self-evident quantity.

The importance of the measurement methodology can be understood with the following example of breast cancer.

Breast tumor volume duplication time measured by ultrasound ^[41]

ER positive breast cancer: 241 ± 166 days

Her 2 positive breast cancer: 162 ± 60 days

Triple negative breast cancer: 103 ± 43 days

Breast cancer volume duplication time measured by MRI ^[68].

The median VDT was 540 days (range: 68-2424 days).

Invasive ductal carcinoma non-luminal the median VDT 178 days.

Invasive ductal carcinoma luminal type 478 days.

Breast cancer measured by digital mammogram

Volume duplication time for malignant lesions was less than 250 days while benign lesions averaged 2.5 years ^[69].

Biological Determinants

Tumor doubling time varies across cancers because growth is regulated by many interacting biological factors. Histological subtype is one of the strongest correlates of TDT. In lung cancer, pooled VDT differs substantially by subtype, with small cell carcinoma and squamous cell carcinoma generally exhibiting shorter doubling times than adenocarcinoma and nonsolid lesions ^{[12][13]}. This pattern reflects differences in proliferative capacity, differentiation state, stromal architecture, and likely microenvironmental dependence. The following list (Table 2) shows this variability.

Tumor	TDT in days or months	Reference
Poorly differentiated hepatocarcinoma	20-78 days	[70]
Hepatocarcinoma	70 days	[71]
Stage I Lung cancer prior to treatment	180 days	[72]
Lung squamous cell carcinoma	115 days	55
Lung adenocarcinoma	222 days	55
Lung large cell carcinoma	67 days	55
Lung small cell carcinoma	86 days	[73]
Pulmonary metastasis of different origins	118 ± 134 days	[74]
Untreated pancreatic adenocarcinoma	144 days	[75]
Thymoma	468 days	[76]
Thymic carcinoma	164 days	59
Metastatic uveal melanoma	63 days	[77]
Renal cell carcinoma	~ 500-600 days	[78]
Tumor metastasis in lung measurement based on radiology	42 (range 11 to 164)	
Basal carcinoma of skin, head and neck	147 days	[79]
IDH-mutant low-grade glioma	3.5 years	[80]
Malignant gliomas overall measured by CT scan	19.5 days	[81]
Glioblastoma, preoperative, untreated, MRI	21.1 days	[82]
Glioblastoma, untreated growth dynamics, MRI	50 days	[83]
Gastric cancer stage T1 (not treated)	11.8 months	[84]
Gastric cancer stage T4 (not treated)	6.2 months	84
Colorectal cancer	211 days	[85]

Tumor	TDT in days or months	Reference
Calcitonin doubling time in medullary thyroid carcinoma (MTC) High grade tumors	8.5 months	[86]
Calcitonin doubling time in MTC Low grade tumors	> 2 years	86

Table 2. TDT of different tumors

The highly variable biology of prostate cancer – from latent to extremely aggressive – makes it impossible to establish a “universal” average doubling time [87].

Glioblastoma estimates vary markedly because they come from different imaging modalities, time intervals, and mathematical conversions, so a single universal average is not defensible. For diffuse gliomas, especially IDH-mutant tumors, recent studies increasingly report longitudinal growth rates and molecular-grade associations rather than a single stable doubling-time value [65].

Molecular subtypes also matter. In breast cancer, triple-negative tumors have substantially shorter TVDT than ER-positive tumors, while HER2-positive tumors occupy an intermediate position. These differences are consistent with the more aggressive natural history of triple-negative disease and likely reflect altered cell-cycle control, genomic instability, and reduced dependence on endocrine signaling. Tumor grade, invasiveness, and architectural pattern further contribute to variations in growth kinetics.

Breast cancer TDT according to molecular subtype
Triple negative BC < Her2 positive < ER positive tumors

The tumor microenvironment imposes an additional level of regulation. Angiogenesis determines whether a growing lesion can maintain oxygen and nutrient supply; if not, growth slows and necrosis may increase. Immune surveillance can also suppress net expansion, while desmoplasia and extracellular matrix remodeling may either limit or facilitate progression depending on context. These factors help explain why TDT derived from serial imaging may diverge from proliferation indices such as Ki-67, which measure a different biological construct [12].

However, despite methodological inaccuracies the doubling time measurement approach, may serve as a guide for comparative visualization of the differences among different tumors and establish the fact that

cancer cannot be considered one disease but as different diseases that share common traits.

Using a different methodology, Kay et al. ^[88] determined the following doubling times:

Pancreatic cancer	5.3 months
Melanoma	3.78 months
Hepatocarcinoma	3.06 months
Renal cell carcinoma	2.67 months
Triple negative breast cancer	2.38 months
Non-small cell lung cancer	2.40 months
Hormone positive breast cancer	4.31 months
Her 2 positive breast cancer	4.12 months
Gastric cancer	3.82 months
Glioblastoma	2.55 months
Prostate cancer	4.10 months

Kay et al. determined doubling time by extracting data from progression-free survival (PFS) plots. Interestingly, pancreatic ductal adenocarcinoma (PDAC) that has the reputation of being one of the most malignant tumors shows the slowest doubling time in the Kay et al. paper.

It is evident that data regarding tumor volume duplication time is quite variable. For example, in pancreatic cancer, Ahn et al. ^[89] studied duplication time with CT scan in 110 patients with proven PDAC. They found a very wide range that went from 20 to 977 days (mean 132 days): *"The growth rate was significantly associated with the initial diameter and volume. The development of distant metastasis was significantly associated with initial diameter, volume, and volume growth rate"*. Although Furukawa et al. ^[75] found a much narrower range between 64 and 255 days, the average of 144 days was similar to Kay's.

The average volume duplication time of a malignant tumor is between 100 and 120 days ^[90] (average of all tumors 105 days). This differs from tumor to tumor. In general, the shorter the duplication time is, the

more malignant the tumor.

The time it takes to a cell to double its DNA content is called T_s or synthesis time and it is usually 10-18 hours. This value is more or less constant, notwithstanding whether if it is a normal or malignant cell, though tumors tend to have a shorter cell cycle time (See Table 1).

The reason for such a big difference between volume doubling time and T_s is based on many factors:

1. Not all the cells of a tumor replicate at the same time.
2. There are many cells that do not replicate at all.
3. Many cells die.
4. As tumors grow, less and less oxygen and nutrients are available, thus a smaller proportion of cells can replicate.
5. There is a considerable heterogeneity of growth parameters in each tumor ^[91].
6. Some tumor marker doubling times reflects tumor volume doubling time. This is the case of CA 19-9. According to Nishida et al. CA 19-9 doubling time is clearly associated with the tumor volume doubling time and prognosis ^[92].

Some authors believe that the tumor's proliferation rate is less significant than decreased cell loss in order to produce accelerated volume doubling.

TDT in breast cancer

TDT in breast cancer is a fundamental biophysical parameter that reflects intrinsic growth kinetics and informs screening intervals, prognostic stratification, and treatment timing. Across eight decades of studies, mean TDT in breast cancer has remained remarkably stable at approximately 180 days, despite shifting epidemiology and the adoption of widespread screening [25]^[93].

Breast cancer presents a very particular problem regarding growth estimates: breast imaging modalities correctly estimated pathological tumor size in less than half of the tumors ^[94]. Small changes in diameter translate into large uncertainties in volume and TDT, especially with mammography. Most clinical studies assume exponential growth over short intervals, whereas long-term growth often follows Gompertzian kinetics and modern studies exclude many locally advanced or metastatic cases due to neoadjuvant therapy, potentially skewing TDT estimates toward earlier-stage, slower-growing tumors. Future work leveraging MRI-based volumetry, standardized intervals, and molecular annotation could

refine TDT estimates and enable subtype-specific growth modeling. AI can be an important player in improving this issue.

However, growth is highly variable and not purely exponential over the long-term. It depends on subtype, grade, receptor status, Ki-67 proliferation index, age, and other factors. Many tumors show periods of stability or slower growth.

Population-level estimates of breast cancer TDT show wide inter-tumor variability but with a consistent central tendency. Most studies report averages or medians between ~50-200+ days, with wide individual variation (e.g. 46-2424 days in some cohorts). This stability supports current screening interval recommendations, as substantially faster growth would necessitate shorter intervals to detect tumors before they progress.

- **By subtype** (strongest predictor):
 - **Triple-negative (TNBC):** Fastest growth — often ~100-130 days (e.g. means of 103 ± 43 days or around 124 days) ^[41].
 - **HER2-positive:** Intermediate — e.g. $\sim 162 \pm 60$ days ^[41].
 - **ER-positive / Luminal (especially Luminal A):** Slowest — often 200-1000+ days (e.g. medians of 241 days, 478 days, or up to 1126 days / ~3 years in some MRI-based studies) ^[95].

These differences align with clinical behavior: TN and HER2+ cancers present more often at younger ages, grow rapidly, and require prompt systemic therapy, whereas many ER+ tumors are indolent.

Beyond molecular subtype, DT correlates with conventional pathologic features:

- **Histological grade:** Grade 3 tumors consistently show shorter TDT than grade 1-2. For instance, Fornvik et al. found mean TDT of **105 days** for grade 3 vs. **296-352 days** for grade 1-2 ($p = 0.002$) ^[96].
- **Ki-67 index:** Elevated Ki-67 ($\geq 14\%$) is associated with significantly shorter TDT. Ryu et al. reported TDT of 114 ± 78 days for Ki-67 $\geq 14\%$ vs. 205 ± 146 days for Ki-67 $< 14\%$ ($p = 0.004$) ^[41].
- **“Inactive” tumors:** A notable fraction ($\sim 28-36\%$) of screen-detected tumors show no measurable growth between serial imaging, raising concerns about over-diagnosis.

These findings suggest that TDT combines information from both genotype (subtype) and phenotype (proliferation, grade).

Other factors:

- Higher grade (Grade 3) and elevated Ki-67: Shorter TDT.
- Mass or focus lesions on imaging: Often shorter TDT than non-mass enhancement.
- Older age: Sometimes associated with longer TDT.

This heterogeneity underscores the need of personalized approaches to screening, diagnosis, and treatment.

TDT is a central biophysical parameter that directly shapes screening interval guidelines: intervals are chosen to be short enough that most clinically relevant tumors will not progress from a detectable but treatable size to an advanced stage between screenings, yet long enough to avoid excessive false positives, costs, and over-diagnosis. In practice, population mean TDT, its variability, and the distribution of fast-growing subtypes jointly determine the “safe” maximum interval for a given screening modality and risk group.

For establishing adequate screening time intervals in breast cancer the following guidelines should be considered:

- The **mean and distribution of TDT** in the target population.
- The **size threshold** at which the screening test can reliably detect tumors.
- The **clinical consequences** of a tumor growing from that threshold to a more advanced stage before the next screening.

Evidence that TDT varies by age and tumor biology has been explicitly used to justify different screening intervals:

Age-dependent TDT: Primary breast cancers in women <50 years have significantly shorter median TDT (~80 days) than in women aged 50-70 (~157 days) or >70 (~188 days). Because younger women’s tumors grow faster, a 2-year interval is less likely to catch them early; this has been used to argue for **more frequent screening** (or earlier initiation with adjunct modalities) if any mortality benefit is to be observed in this age group ^[97].

Stability of TDT over time: Despite major epidemiological changes and widespread screening, mean breast cancer TDT has remained stable (~180 days) over the past 80 years. This stability supports the **validity of current screening intervals** (e.g. biennial mammography for average-risk women aged 50-74) because the underlying growth kinetics have not accelerated.

Heterogeneity and over-diagnosis: Modern studies identify both “fast-growing” tumors (grade 3, HER2+, triple-negative, high Ki-67) and “inactive” tumors with very long or effectively infinite TDT. This heterogeneity implies that:

A **single fixed interval** will be too long for some aggressive subtypes and too short (contributing to over-diagnosis) for indolent ones.

Risk-adapted strategies (e.g. shorter intervals or MRI for high-risk, genetically predisposed, or dense-breast populations) are conceptually aligned with TDT heterogeneity, even if guidelines do not explicitly reference TDT values.

TDT in lung cancer

Lung cancer remains the leading cause of cancer mortality worldwide, and the rate at which an individual tumor grows is one of the most direct in vivo reflections of its underlying proliferative and metastatic potential. Lung cancer growth approximates an exponential model over clinically relevant intervals, VDT provides a reproducible index of biological aggressiveness that complements static measures such as histology, stage, and molecular profile.

Because malignant pulmonary nodules are approximately spherical over short growth intervals, small changes in diameter correspond to disproportionately large changes in volume, making volumetric doubling time (VDT) a far more sensitive index of growth than linear diameter change alone.

With the advent of thin-section computed tomography (CT) and semiautomated volumetric segmentation software, VDT can now be estimated with far greater precision, and it has become a formal component of nodule management protocols in lung cancer screening [98].

Data from the Dutch–Belgian NELSON lung cancer screening trial provided the first robust in vivo confirmation that early, screen-detected lung cancers follow the exponential model closely, with growth curves fitted to a single exponential function yielding an excellent fit ($R^2 = 0.98$) across 47 lung cancers followed with three or more sequential CT examinations]. In that cohort the median overall VDT was 348 days, with an interquartile range of 222–492 days [99].

In practice, VDT is most often estimated from only two imaging time points rather than a full growth curve. When volumes are approximated from bidimensional diameters, the modified Schwartz formula is commonly applied: $DT = t \cdot \log(2) / \log(V_t/V_0)$, where V_0 and V_t are tumor volumes calculated from the maximum diameter and its largest perpendicular diameter at the initial and follow-up scan, and t is the

interval between scans in days ^[100]. This two-point approach assumes constant exponential growth between measurements and is the method underlying most clinical and screening-based VDT estimates, including those used in nodule management algorithms.

Because volume scales with the cube of diameter, small errors in linear diameter measurements are amplified substantially when converted to volume, and manual diameter-based estimates are subject to considerable inter-reader variability. Semiautomated volumetric segmentation software, as used in the NELSON trial, markedly improves reproducibility and is now considered the preferred approach for CT-based VDT determination in screening contexts. Nonetheless, diameter-based thresholds remain in widespread clinical use — for example, the American College of Radiology's Lung-RADS algorithm defines nodule growth as an increase in mean diameter of 1.5 mm, in contrast to the NELSON algorithm's volumetric definition of growth as a 25% increase in nodule volume ^[101].

Numerous cohort studies spanning six decades, from early plain-film follow-up series to contemporary volumetric CT studies, have consistently demonstrated that VDT varies substantially by histological subtype. In one of the more extensively cited chest-radiograph cohorts from the Japanese Lung Cancer Screening Research Group, doubling time was calculated in 237 patients from two serial chest radiographs. The mean doubling time was 166.3 days overall, with substantial variation by histology: 221.6 days for adenocarcinoma; 115.2 days for squamous cell carcinoma; 86.3 days for small cell carcinoma; and 67.5 days for large cell carcinoma ^[96].

More recent systematic reviews using volumetric CT measurement corroborate this histology-dependent pattern on a larger scale. A 2023 systematic review and meta-analysis of 26 studies comprising 2,275 patients with primary lung cancer reported a pooled overall mean VDT of 213 days (95% CI, 171-256 days), with pooled mean VDT of 241 days for solid adenocarcinoma, 731 days for subsolid (ground-glass or part-solid) adenocarcinoma, 136 days for squamous cell carcinoma, and only 71 days for small cell carcinoma ^[102]. Rapid growth, defined as $VDT \leq 400$ days, characterized 64.8% of lung cancers overall but only 23.7% of adenocarcinomas, underscoring how strongly nodule composition and histology modulate growth kinetics ^[98]. A subsequent 2024 meta-analysis of 33 studies and 3,959 patients similarly found that pooled mean VDT differed significantly by radiologic nodule type: 207 days for solid nodules, 536 days for part-solid nodules, and 669 days for pure nonsolid (ground-glass) nodules ^[10]. Table 3 summarizes representative pooled values.

Histological subtype	Pooled mean VDT (days)	Range reported	Growth pattern
Overall (all lung cancer)	213	139-408	64.8% rapid (≤ 400 d)
Adenocarcinoma (solid)	241	—	Intermediate
Adenocarcinoma (subsolid/GGN)	731	536-669	Indolent
Squamous cell carcinoma	136	115-150	Rapid
Small cell carcinoma	71	67-86	Very rapid
Large cell carcinoma	—	~68	Very rapid

Table 3. Representative pooled tumor volume doubling times in lung cancer by histological subtype and growth pattern.

Molecular features also modulate growth kinetics within a single histological subtype. In a retrospective CT-based cohort of 102 surgically resected non-small-cell lung cancers, tumors harboring activating EGFR mutations were compared with EGFR-wild-type tumors. The median VDT across the full cohort was 188 days ^[103], and EGFR mutation status was examined as a determinant of growth rate, illustrating how oncogenic driver alterations can be studied through the lens of imaging-derived growth kinetics rather than histology alone.

Lung cancer screening

Low-dose CT screening programs must distinguish the large number of indeterminate, mostly benign pulmonary nodules from the minority that represent early lung cancer. The NELSON trial pioneered a volumetric nodule-management protocol in which nodule growth is defined as a relative volume increase greater than 25%, and a positive (referral-triggering) result is defined by a VDT below a specified threshold, historically 400 days, with some protocol refinements using tiered thresholds around 400 and 600 days to stratify follow-up intensity ^[104].

Optimization studies within the NELSON cohort have further refined these thresholds. One analysis of nodules referred because of fast growth found that, for nodules reassessed on a 3-month follow-up CT after baseline, an optimized VDT cutoff of 232 days reduced false-positive referrals by 33% while

maintaining diagnostic sensitivity, whereas for nodules identified at the regular one-year screening round, VDT values among malignant nodules varied significantly to safely lower the conventional 400-day cutoff [105]. This illustrates that the optimal VDT threshold is not fixed but depends on the interval between scans and the point in the screening protocol at which growth is assessed.

Comparative work on benign versus malignant nodules detected during CT screening found that a substantial minority of benign nodules also grow on follow-up. In one retrospective series of 153 persistent nodules (44 malignant, 109 benign), 68% of malignant and 33% of benign nodules met volumetric growth criteria, reinforcing that growth alone is not fully specific for malignancy and that the growth rate, captured by VDT, is what carries the greatest discriminatory value [97].

Radiomic and machine-learning approaches are increasingly being combined with VDT to further stratify risk in screen-detected nodules. In an analysis of National Lung Screening Trial data, a decision-tree model combining VDT with a peritumoral radiomic compactness feature identified a high-risk subgroup with markedly poorer five-year overall survival (25%) compared with a low-risk subgroup (83.3%), and VDT alone, using a data-derived cut point of 279 days, distinguished aggressive from indolent cancers with five-year survival rates of 45% versus 82.8%, respectively [106].

Beyond its diagnostic utility in nodule triage, VDT is an independent prognostic factor once lung cancer is diagnosed. In the classic Japanese Lung Cancer Screening Research Group cohort, patients were stratified by log-normal distribution into rapid-growing ($DT < 109.6$ days), intermediate-growing, and slow-growing ($DT > 252.4$ days) tumors. Five-year survival was 23.3% in the rapid-growing group compared with 43.3% in the slow-growing group, a statistically significant difference, and the same gradient persisted among patients who underwent curative resection (42.4% versus 70.1% five-year survival) [96]. Multivariable analysis in that cohort confirmed that doubling time was an independent predictor of prognosis, distinct from stage or histology [96].

Contemporary studies extend these findings to the surgical setting. A study of 96 patients undergoing sublobar resection for early-stage non-small-cell lung cancer identified an optimal VDT cutoff of 133 days by receiver-operating-characteristic analysis, below which surgical outcomes were significantly worse, supporting the use of preoperative VDT to inform the extent of resection in early-stage disease [107].

Limitations of the TDT concept

- Measurement variability: manual diameter measurements are subject to inter- and intra-observer variability that is cubed when converted to volume; semiautomated volumetric software substantially reduces, but does not eliminate, this error.
- Non-exponential growth: although the NELSON data support an exponential model for most early lung cancers with excellent statistical fit, individual tumors may show non-uniform growth, plateauing, or transient shrinkage, particularly in the setting of intercurrent inflammation or hemorrhage.
- Dependence on scan interval: VDT estimates derived from short inter-scan intervals are disproportionately sensitive to measurement noise, while very long intervals may obscure clinically important early changes in growth rate.
- Heterogeneity across studies: pooled meta-analytic VDT estimates show substantial statistical heterogeneity (I^2 frequently exceeding 90%), reflecting differences in patient populations, measurement software, nodule composition, and follow-up intervals across the underlying studies.
- Applicability after treatment: doubling-time formulas assume untreated, natural growth and are not directly applicable to assessing response during or after systemic therapy or radiotherapy.

In summary, TDT is a well-validated, quantitative biomarker of lung cancer growth kinetics that bridges radiological observation and tumor biology. It varies systematically by histological subtype and nodule composition, ranging from under 100 days in small cell and large cell carcinoma to several hundred days in subsolid adenocarcinoma, and it carries independent prognostic weight beyond stage and histology. Volumetric VDT thresholds are now embedded in major lung cancer screening algorithms, where they help balance the sensitivity needed to detect aggressive early cancers against the false-positive burden associated with indolent or benign nodules. Continued refinement of measurement methodology, together with integration of VDT into radiomic and machine-learning risk models, is likely to further improve individualized risk stratification in both screening and surgical decision-making.

TDT in prostate cancer

Tumor volume doubling time (TVDT) is particularly important in prostate cancer follow-up and surgical decisions. Sometimes it is difficult to decide with precision which prostate tumors should be operated. This is because in some cases tumor growth is very slow and the patient is in an age range where he will

probably die from some other disease or cause than from prostate cancer. Since PSA measurement is available, many more prostate cancers have been diagnosed at an earlier age. This led to increased radical prostatectomy in many cases in which the tumor had a very slow growth rate. It is still matter of debate if this is justified or not. A prostate cancer without metastasis that doubles its volume in four years in a patient 80-year-old patient, should probably not be operated. Determining volume doubling time could help in the decision. If the tumor doubles its volume in six months, the situation would be different. In the first case it is not infrequent to find an "atypical adenomatous hyperplasia and a moderate degree of prostatic intraepithelial neoplasia in surgical specimens".

Egawa *et al.* [108] found that in prostatic tumors with TVDT:

of 2 years, 4.8% of cases were clinically insignificant;

of 3 years, 10.6% of cases were clinically insignificant;

of 4 years, 15.4% of cases were clinically insignificant;

of 6 years, 26.9 % of cases were clinically insignificant.

This means that one quarter of the patients with a 6 years TVDT were operated on unnecessarily. They concluded that many patients with stage T1c prostate cancer required no treatment. (Stage T1c prostate cancer is defined as nonpalpable disease diagnosed by needle biopsy [109]).

High doubling time in prostate tumors generally suggests **slower biological progression**, which usually supports active surveillance or observation rather than immediate surgery, especially when the cancer is otherwise low risk. By contrast, prostate surgery is more likely to be considered unnecessary when the tumor is indolent, localized, and unlikely to threaten life expectancy within the patient's expected lifespan [72].

Tumor or PSA doubling time is most useful as a risk-stratification tool, not as a standalone trigger for surgery. A long doubling time tends to correlate with more favorable prognoses, whereas very short PSA doubling times after treatment are associated with higher risks of metastasis and prostate cancer-specific mortality. That means a **high** doubling time usually argues against overtreatment, while a low doubling time raises concern for aggressive disease.

In prostate cancer, some patients—particularly older men or those with limited life expectancy—may have cancers that grow so slowly that they are unlikely to become clinically significant. One analysis explicitly concluded that life expectancy and tumor doubling time strongly influence whether radical

prostatectomy is likely to be beneficial, and that many stage T1c cancers may require no treatment. This is the basis for active surveillance in selected low-risk cases ^[110].

PSA doubling time is frequently used as a proxy to prostate cancer doubling time ^{[111][112]}. A high doubling time does **not** automatically mean surgery is unnecessary in every case. Decisions still depend on Gleason grade, PSA level, MRI findings, tumor volume, clinical stage, symptoms, and patient preferences. Some tumors with relatively slow kinetics can still be clinically significant because they are higher grade or already locally advanced ^[113].

TDT in HNSCC

For head and neck squamous cell carcinoma (HNSCC), reported tumor doubling times vary widely, but typical values fall in the range of a few days (for “potential” doubling time based on cell-kinetic measurements) to many months (for clinical volumetric doubling measured on imaging)

Potential doubling time (Tpot): Flow-cytometry and in vitro radiobiological studies in HNSCC report mean/median Tpot values around 2-5 days, with ranges roughly from 1 to 7 days. Example: a cell-kinetic study of mainly HNSCC found calculated potential doubling times from about 19 to 85 hours (mean $\approx$ 47 hours, i.e. $\approx$ 2 days). Another flow cytometry series in head and neck tumors reported a median Tpot of about 5 days, with shorter Tpot ($\leq$ 5 days) associated with poorer local control after radiotherapy. Foster et al. found that the doubling time varied by a factor of 3 from well oxygenated tumors to the most severely hypoxic HNSCC tumors ^[114]. They found that the doubling time decreased with increasing tumor vascularity and increasing blood oxygenation. Tuckwell et al. ^[115] using a modeling system found that:

“The stem cell percentage and the degree of hypoxia are the parameters which most influence the final tumour growth rate. For a tumour with a doubling time of 40 days, the final stem cell percentage is approximately 1% of the total cell population. The effect of hypoxia on the tumour growth rate is significant. Using a hypoxia induced cell quiescence limit which affects 50% of cells with and oxygen levels less than 1 mm Hg, the tumour doubling time increases to over 200 days and the time of tumour growth for a clinically detectable tumour (10^{12} cells) increases from 3 to 8 years.”

Clinical volumetric tumor doubling time (imaging-based):

- A CT-based study of oropharyngeal HNSCC estimated a mean clinical tumor doubling time of about 286 days, with an extremely broad range from 7 to 1,282 days, indicating very heterogeneous growth

patterns between patients and tumors ^[116].

- In that cohort, daily relative growth averaged ~1.8% of initial volume per day, and more than half the patients had >50% volume increase during a mean waiting period of ~42 days before radiotherapy planning, emphasizing that clinically relevant growth can occur even when the formal “doubling time” is long ^{[117][118][119]}.

Cell-kinetic T_{pot} reflects how fast the proliferating compartment could double if all cycling cells contributed effectively and there were no cell loss; it is derived from labeling index and S-phase duration, not from macroscopic volume changes.

Clinical volumetric doubling time on CT or MRI integrates proliferation, cell loss, necrosis, hypoxia, and stromal contributions, which generally slow observed growth, hence longer apparent doubling times.

In vitro studies of established sinonasal SCC cell lines report population doubling times in the order of 21-34 hours, again highlighting that isolated cancer cells can divide much faster than whole tumors appear to grow in patients.

If we assume a T_{pot} of 3 days for a rapidly proliferating HNSCC in a repopulation model, a 30-day treatment delay corresponds to roughly 10 potential doublings of the proliferative compartment, even though the gross tumor volume on imaging may not show 2¹⁰-fold expansion due to cell loss and microenvironmental constraints.

TDT in gliomas, glioblastoma, and meningioma

In gliomas, a diverse group of primary brain tumors, TDT varies according to histological type, molecular characteristics, and individual tumor biology.

Low-Grade Gliomas:

IDH-Mutant Low-Grade Gliomas: These tumors often exhibit a slow growth pattern. A study involving 128 patients found a median TDT of approximately 3.5 years, with high-grade IDH-mutant gliomas (characterized by homozygous deletion of CDKN2A/B) having a faster growth rate compared to low-grade variants ^[120].

High-Grade Gliomas:

Glioblastomas (GBMs): As the most aggressive form of glioma, GBMs have a rapid growth rate. Research indicates that GBMs have a TDT ranging from 48.1 to 50.5 days, depending on the tumor’s enhancement

characteristics on imaging scans [\[121\]\[122\]\[123\]\[124\]](#).

Malignant Astrocytomas: These tumors also demonstrate rapid growth, with TDTs averaging around 65.1 days.

In a multicenter study, De Witt Hamer et al. [\[125\]](#) found a mean volumetric TDT of 22 days in a cohort of 1033 patients with glioblastoma before surgery. The large size of this cohort, and their MRI studies in all cases, make 22 days the more reliable datum regarding glioblastoma VTDT. The vast majority of patients were operated within 1 month of the initial scan. Knowing the short time of glioblastoma VTDT was decisive for resetting the “standard for when these tumors should be operated”. On the other hand when glioblastoma cells (C6 and Y79) were cultured the doubling time was 24 to 48 hours [\[126\]](#). These two examples clearly show the growth difference in vivo and in vitro.

Meningioma: Most meningiomas are benign (WHO grade 1), slow-growing, and often incidental findings. Doubling times vary widely due to tumor heterogeneity, location, patient factors (e.g. age, sex), and growth patterns (linear, exponential, or Gompertzian/plateauing) [\[127\]](#). Tumor doubling time and growth rate are key for management decisions, especially in asymptomatic or incidental meningiomas, where “watchful waiting” with serial imaging is common.¹

Long TDT supports conservative management with extended MRI follow-up intervals (e.g. after initial 5 years of stability). Short TDT may prompt earlier surgery or radiation, even in asymptomatic patients, to prevent future complications.

Benign (grade 1) meningiomas: Often very slow. Studies report medians or means ranging from several years to decades (e.g. median ~1082 days or ~3 years in one surgical cohort; means around 415 days in older data for grade I, with many reports of 10-20+ years in asymptomatic cases) [\[128\]](#).

Atypical (grade 2) or anaplastic (grade 3): Significantly shorter, e.g. means of ~178-205 days [\[129\]](#).

Asymptomatic/incidental meningiomas: Many show no or minimal growth; in growing tumors, volumetric doubling times can be 5-20+ years on average, though a subset grow faster.

Overall medians in mixed cohorts: Vary (e.g. ~51-186 months across risk groups in one study; shorter in high-risk radiographic features).

Growth is not purely exponential long-term; many follow a **Gompertzian model** (initial faster growth that slows/plateaus), supporting longer imaging intervals over time for stable tumors.

Radiographic predictors of faster growth (shorter TDT) include:

- T2-weighted MRI iso-/hyperintensity.
- Absence of calcifications.
- Younger patient age.
- Larger initial size (sometimes).
- Higher proliferation markers (e.g. MIB-1/Ki-67 index).

Meningioma doubling time provides a practical, imaging-based measure of biological aggressiveness that complements histology and helps personalize surveillance or intervention strategies. Most are indolent, but identifying the faster-growing subset improves outcomes by guiding timely treatment while avoiding unnecessary interventions.

TDT in pancreatic ductal adenocarcinoma (PDCA)

PDAC is considered a very aggressive tumor with poor prognosis. Many books and publications say that “The rapid growth rate of PDAC contributes to its tendency to spread before symptoms become noticeable, making early detection difficult”. However, PDAC doubling time is not lower than other aggressive tumors. When we compare PDAC to other common solid tumors (e.g. colorectal, lung, breast, some renal and head-and-neck cancers), PDAC’s **median doubling time is not dramatically shorter**; it often falls in a similar broad range, sometimes even appearing slower than aggressive subtypes of other cancers. **Therefore, it is an error to believe that PDAC aggressiveness is a product of a short TDT.**

So the statement “PDAC has a short doubling time, indicating rapid expansion” can be technically true for a subset of tumors but becomes misleading if it suggests that PDAC as a class grows faster than most other malignancies.

In pancreatic ductal adenocarcinoma (PDAC), “doubling time” is most often reported as **tumor volume doubling time (TVDT)** in patients, and it is highly heterogeneous but typically in the order of **a few months** ^[130].

Retrospective imaging studies in PDAC patients show:

- **Median TVDT ≈ 144-159 days (about 5 months).**
- **Wide range:** from very aggressive tumors with TVDT around **~64 days** up to slower-growing ones near **~255 days**.
- A separate CT-based analysis, assuming spherical geometry, estimated **linear tumor doubling times** ranging from **~20 days to ~3.7 years**, reflecting extreme inter-patient heterogeneity in growth rates.

Why PDAC behaves as if it's "fast" despite moderate doubling times

The clinical aggressiveness of PDAC is not primarily due to an exceptionally high intrinsic proliferation rate, but rather to:

1. Late detection

PDAC usually presents at an advanced stage because early lesions are asymptomatic and hard to image. By the time it is detected, the tumor has already undergone many doublings over years ^[131].

Mathematical models suggest that it takes many years for an initiating cell to evolve into a clinically detectable, advanced PDAC, consistent with a long preclinical phase rather than hyper-rapid growth ^[132] ^[133] ^[134].

2. Early dissemination and metastatic competence

PDAC can seed metastases relatively early in its natural history, sometimes before the primary is large enough to be noticed. This makes the disease appear "fast" in terms of progression and lethality, even if the primary's volume doubling time is moderate.

3. Dense, therapy-resistant microenvironment

The desmoplastic stroma, hypovascularity, and immunosuppressive TME limit drug delivery and foster resistance, so once PDAC is clinically apparent, it progresses rapidly under standard therapy.

This treatment resistance, not unusually rapid cell division, is a major driver of poor outcomes.

4. Selection bias in perceived growth

The PDAC cases we see clinically are often the biologically aggressive ones that have already disseminated; slower-growing, more indolent variants may be under-represented in symptomatic cohorts, biasing our intuition toward "fast" disease.

Many solid tumors have median TVDTs in the ~1-6 **month** range, with wide overlaps between histologies. PDAC's reported median TVDT of ~144-159 days sits comfortably within this range. Some cancers (e.g. certain small-cell lung cancers, high-grade lymphomas, germ cell tumors) clearly have **shorter** doubling times; others (e.g. some prostate, low-grade renal, certain thyroid cancers) have **longer** ones.

Thus, PDAC is better characterized as **moderately proliferative but profoundly lethal due to late presentation, early metastasis, and therapy resistance**, rather than as a uniquely fast-doubling tumor.

TDT in renal cell carcinoma

Renal cell carcinoma (RCC) usually has a slow primary-tumor doubling time, commonly in the order of ~500–600 days in imaging-based studies. One classic series reported a mean tumor doubling time of 603.1 ± 510.1 days, and another found a mean volume doubling time of 505 days [135].

Primary RCC often grows more slowly than its reputation suggests, which is why some small renal masses can be observed for a period in selected patients. However, growth is highly variable, and the large standard deviations in these studies show that some tumors expand much faster than the average.

A key nuance is that metastatic RCC can grow much faster than the primary kidney tumor. In one older series, primary-site RCC had doubling times of **372–579 days**, while pulmonary metastases had doubling times of 20–154 days [136].

Therefore in localized primary RCC, a reasonable TDT is about 1.5 years, but for metastatic disease, the doubling time can be far shorter and is much less predictable.

Hematologic cancer

Tumor doubling time (or equivalent measures like potential doubling time, lymphocyte doubling time, or marker doubling time) varies widely in hematological cancers. These are primarily "liquid" tumors (leukemias, lymphomas, myelomas) without solid masses, so growth is often tracked via blood counts, bone marrow burden, or molecular markers (e.g. BCR-ABL in CML, MRD in CLL) rather than imaging-based volume doubling time used for solid tumors.

Data come from kinetic studies, clinical observations, and prognostic models. Actual observed doubling times are typically longer than "potential" ones due to high cell loss (apoptosis, immune clearance). Values are approximate ranges/medians; significant patient-to-patient and subtype variability exists, influenced by genetics (e.g., IGHV status, mutations), stage, and prior treatment.

Potential vs. Actual: Potential doubling time (based on proliferation kinetics like the labeling index) assumes no cell loss and is much shorter. Real-world/clinical doubling accounts for cell death and is longer.

Prognostic Value: Shorter doubling times generally indicate more aggressive disease and worse outcomes (e.g. short LDT in CLL, rapid BCR-ABL rise in CML). They help guide "watch and wait" vs. treatment decisions.

Variability: Influenced by genetics (e.g. TP53, FLT3-ITD shorten times), patient factors, and treatment. Post-treatment MRD kinetics differ (e.g., slower after venetoclax-based regimens in CLL).

Measurement: For leukemias, often calculated from serial blood/marrow counts or qPCR for transcripts. Solid tumor-style volume doubling is less applicable.

- Unlike solid tumors, where doubling time is usually measured by imaging (tumor volume on CT/MRI), hematological cancers are typically tracked using cell counts in blood or bone marrow — for example, lymphocyte doubling time in CLL, or blast percentage in acute leukemias — rather than a discrete measurable mass.
- General tumor doubling time for malignant solid tumors is often cited as 50-100 days, but this benchmark does not map well for hematologic cancers, which range from under 48 hours (Burkitt lymphoma) to years (indolent lymphomas, CLL).
- Doubling time in CLL has direct clinical significance: a lymphocyte doubling time under 6 months is a recognized signal of biologically active, progressive disease and is a factor considered when evaluating treatment initiation.

Values in this table are approximate ranges drawn from clinical literature. Actual growth kinetics vary substantially by individual patient, molecular/cytogenetic subtype, and disease phase, and should not be used alone for clinical decision-making. Table 4.

Malignancy	Typical Doubling Time	Notes	Refer.
Burkitt lymphoma	24-48 hours (~1-3 days)	One of the fastest-growing human tumors; hallmark of an extremely high proliferative index (Ki-67 near 100%)	[137] [138] [139] [140] [141]
Acute lymphoblastic leukemia (ALL)	Days to ~1 week	Rapid blast expansion; varies by cytogenetic subtype	[142] [143] [144]
Acute myeloid leukemia (AML)	~Days to 2 weeks	Blast doubling times vary; often estimated indirectly from serial blast count kinetics	[145] [146]
Diffuse large B-cell lymphoma (DLBCL)	~1-3 weeks (reported range 1.4-70 days)	Wide range depending on stage and molecular subtype	[147] [148]
Hodgkin lymphoma	Weeks to a few months	Generally slower-growing than aggressive non-Hodgkin lymphoma	[149] [150]
Follicular lymphoma (indolent NHL)	Months to >1 year	Classic “indolent” growth pattern	[151] [152] [153] [154]
Multiple myeloma	Months (often tracked via plasma cell labeling index)	Growth is more often assessed via M-protein kinetics than classic doubling time	[155] [156] [157]
Chronic lymphocytic leukemia (CLL)	Months (lymphocyte doubling time, LDT)	LDT is a key prognostic factor for time to first treatment; defined as the time for peripheral blood lymphocyte count to double	[158] [159] [160] [161] [162]
Chronic myeloid leukemia (CML, chronic phase)	Months	Much slower than blast-phase disease	[163] [164]
Waldenström macroglobulinemia	Months to years	Very indolent course	[165]

Table 4. TDT in hematological malignancies

Growth Models

The choice of growth model has major implications for interpretation. Exponential growth is mathematically simple and often useful for early lesions, but it implicitly assumes constant net growth rate. This assumption is rarely justified over longer observation windows ^{[12][13]}. In contrast, Gompertzian growth captures the common observation that tumors expand rapidly at first and then slow as they enlarge. Logistic models similarly incorporate a ceiling effect through a carrying-capacity term.

Model selection is not just a technical preference; it changes the meaning of doubling time itself. Under exponential assumptions, TDT is constant. Under Gompertzian or logistic growth, the instantaneous doubling time lengthens over time. Therefore, a study reporting “doubling time” should specify whether it refers to an interval-based average or a model-derived instantaneous estimate ^{[12][13]}. Without this distinction, direct comparison across studies becomes problematic.

These issues are especially relevant in meta-analytic work. The 2024 lung cancer review showed that pooled mean VDTs differ according to nodule solidity and histological subtype, but it also underscored substantial heterogeneity across the included studies ^[12]. Earlier summaries similarly reported very high heterogeneity, with I^2 near 90 percent in overall lung cancer analyses. Such variability is not a flaw of the field; rather, it reflects genuine biological diversity and the limitations of compressing complex growth trajectories into a single summary statistic.

Clinical Relevance

Clinically, TDT has value in screening, surveillance, and prognostication. In lung cancer, VDT is particularly useful for risk stratification of pulmonary nodules and for estimating whether lesions are likely to represent clinically significant malignancies. The 2024 meta-analysis concluded that the pooled mean VDT of solid lung cancer remained below the commonly used 400-day referral threshold, supporting the continued clinical relevance of volumetric growth assessment in nodule management. Earlier works likewise found that around two-thirds of lung cancers exhibit rapid growth, emphasizing that VDT can help differentiate indolent from aggressive disease.

TDT also has prognostic implications in selected settings. In lung metastases from adenoid cystic carcinoma, tumor volume doubling time was associated with survival and appeared to outperform time to progression as a predictor in one recent study. In stage I lung squamous cell carcinoma, shorter tumor

VDT was also reported to be a useful prognostic indicator. These findings suggest that, in some contexts, TDT may reflect intrinsic biology more effectively than conventional response metrics.

In breast cancer, knowledge of doubling time has practical implications for screening interval design and estimation of sojourn time. The observation that triple-negative and HER2-positive tumors tend to grow faster than ER-positive tumors suggests that a single screening schedule may not be equally effective across all molecular subtypes. This reinforces the broader principle that TDT should be interpreted in conjunction with tumor biology rather than alone.

Cell kinetics and radiotherapy

In 1906, Bergonie and Tribondeau established that the radiotherapy-responsiveness of a tissue was directly related to its mitotic index. This should not be confused with radiotherapy-sensitivity^[166]. The first concept implies time, the second quantity. A radiotherapy-responsive tumor is a tumor that quickly responds quickly to radiation. Sensitivity, on the other hand, refers to the amount of cells killed by radiation therapy.

Radiotherapy targets DNA. This damage will not be clearly evident until the cell replicates. Therefore, the effects of radiotherapy will be dependent on the cell's proliferative characteristics. The time required to find apoptosis in a tissue after radiotherapy will be short in highly proliferative cells such as those in the intestinal mucosa, while it will be quite long in less proliferative cells of the kidney.

Radiotherapy-sensitivity also varies with the stage of the cell cycle and the kinetics of sensitivity follow a few simple rules that were established in 1963 by the works of Terasima and Tolmach^{[167][168]}. As can be expected, mitotic cells are the most radiosensitive. Within the mitotic cycle the initial part of the S phase is the most radiotherapy-sensitive and it diminishes by the end of this phase. G1 is probably the most radiotherapy-resistant phase.

Cell kinetics in the evaluation of response to treatment

Response Evaluation Criteria in Solid Tumors (RECIST) is the most popular standardized system for evaluating the response to treatment and has been adopted by most clinical trials since 2000^[169]. Table 5.

COMPLETE RESPONSE	Complete disappearance of lesions
PARTIAL RESPONSE	30% decrease of lesion diameter
STABLE DISEASE	No change
PROGRESSION	20% increase of diameter and/or new lesions

Table 5. RECIST

RECIST is not a perfect method, because it uses unidimensional measurements. CT scan allows the measurement of tumor size and density. A decrease in CT density does not necessarily means a decrease in size ^[170]. Furthermore, apparent non-response according to RECIST criteria may be inaccurate and needs to be complemented with CT density studies. For example, sunitinib treatment of 26 patients with hepatocellular carcinoma showed one patient achieving a partial response and 22 having stable disease. However, when tumor density was studied, it was discovered that ten patients had major tumor necrosis. Therefore, tumor size alone was underestimating the rate of response ^[171].

To this we must add that measurement variables cannot be excluded ^[172]. In another group of patients with hepatocellular carcinoma treated with sunitinib, tumor density and size showed no significant correlations with PFS (progression free survival) ^[173].

However, it is and probably will soon be, a very practical and reliable method. We believe that changing from unidimensional to tridimensional measurement would enhance RECIST's precision.

Another consideration is that tumors can continue growing after/during treatment (progression according to RECIST) but at a much slower growth rate. Should treatment continue? We think it should, because overall patient survival may improve by slowing down growth rate ^[174]. However, this needs experimental validation. In cases of tumor progression, RECIST should be complemented with TVDT, so that two different groups of progression can be defined:

- a. progression with no change in growth rate;
- b. progression with slower growth rate.

In case b) continuing treatment would be justified.

Overall survival and molecular oncology

Pishvaian *et al.* ^[175] examined the intermingling of survival and molecular oncology. They studied the outcomes of 1856 patients with pancreatic cancer. 58% of patients underwent molecular testing. 26% of patients had actionable molecular alterations. Those patients that received a specific treatment targeting their molecular profile had significantly longer median overall survival than those patients who only received unspecific therapies (2.58 years vs 1.51 years). This publication shows the importance of performing molecular profiling in tumors and the importance of the OS for research purposes ^[176].

OS is probably the most reliable parameter when investigating the efficacy of a cancer treatment because survival is objective and easily measured. On the other hand, PFS (progression free survival) may have confounding factors including bias introduced by different researchers and their ability to determine when progression takes place ^[177].

Limitations

Despite its utility, TDT has several important limitations. First, it is highly sensitive to measurement error, especially when derived from only two imaging time points. Second, it conflates proliferation with cell loss, vascular limitation, and treatment effects, and therefore does not serve as a pure measure of cell division. Third, different studies may use different thresholds, imaging modalities, segmentation methods, or mathematical assumptions, making pooled estimates difficult to compare directly.

Another limitation is that TDT can be misleading when applied to non-spherical or heterogeneous tumors. Irregularly shaped lesions may change in volume without proportional changes in linear dimensions, and necrotic or cavitory components may distort growth estimates. Furthermore, some tumors may exhibit non-monotonic behavior, including transient shrinkage or stabilization, which complicates the interpretation of a single doubling time value. These issues are particularly important in the era of personalized oncology, where biological heterogeneity is increasingly recognized as the rule rather than the exception.

Reporting Recommendations

To improve interpretability, at minimum, studies reporting tumor doubling time should specify the following: tumor site, histology, molecular subtype if relevant, imaging modality, segmentation method, number of observations, interscan interval, mathematical model used, and confidence intervals for the

estimate. When possible, authors should report both the raw volumetric measurements and the derived doubling time. If the tumor does not show exponential behavior, the modeling strategy should be made explicit so that readers can understand whether the reported value is an average interval-based TDT or a model-dependent instantaneous estimate.

Where feasible, investigators should also consider reporting model fit statistics for alternative growth functions. This would allow readers to assess whether exponential, Gompertzian, or logistic assumptions are most appropriate for a given dataset. Such transparency would improve reproducibility and facilitate cross-study..

Cancer kinetics: maintaining a high tumor burden theory (adaptive therapy)

Traditional cancer chemotherapy often administers maximum tolerated doses (MTD) with the goal of maximal tumor cell kill. While initially effective, this approach frequently leads to rapid emergence of drug-resistant clones through strong selective pressure and "competitive release," where resistant cells proliferate unchecked once sensitive cells are eradicated. Adaptive therapy (AT), pioneered by researchers such as Robert Gatenby ^{[178][179]}, represents an evolutionarily informed alternative. It uses lower or intermittent doses of chemotherapeutics to maintain a stable, tolerable tumor burden, preserving a population of drug-sensitive cells that competitively suppress less-fit resistant subclones.

Cancer is an evolutionary disease characterized by genetic and phenotypic heterogeneity within tumors. Conventional therapies aim for eradication but often fail due to pre-existing or rapidly evolving resistant subpopulations. Adaptive therapy, rather than pursuing complete tumor elimination, treats cancer as a manageable chronic condition by exploiting eco-evolutionary dynamics: sensitive cells, which retain higher fitness in the absence of drug, outcompete resistant cells that incur a fitness cost for resistance mechanisms.

This paradigm shift draws from principles in ecology and pest management, where complete eradication is often impractical, and sustainable control is achieved by managing population dynamics.

Tumors are heterogeneous ecosystems. Resistance can arise via genetic mutations, epigenetic changes, or microenvironmental adaptations. Under MTD, therapy eradicates sensitive cells, freeing resources (nutrients, space) for resistant clones—a phenomenon called competitive release.

Resistant cells often pay a fitness cost (e.g. slower proliferation due to energy diverted to efflux pumps or altered metabolism). In the absence of the drugs, sensitive cells proliferate faster and suppress resistant

ones through competition. Adaptive therapy deliberately maintains this competition by modulating treatment based on tumor burden (typically measured via imaging, PSA levels, or circulating tumor DNA).

Key protocols include:

Intermittent (dose-skipping): Treat with fixed dose until tumor shrinks to a threshold (e.g. 50% of baseline), then pause until it regrows to a higher threshold.

Continuous dose modulation: Adjust dose dynamically to keep tumor volume stable.

Mathematical models (e.g. Lotka-Volterra competition, agent-based simulations) predict that AT can significantly extend time to progression (TTP) compared to MTD, especially when resistance costs are present, cell turnover is high, and initial resistant fractions are low. The Lotka-Volterra competition model is a mathematical framework used in ecology to describe the population dynamics of two (or more) species that compete for shared limited resources, such as food, space, or nutrients. It extends the single-species **logistic growth model** by incorporating the negative effects of interspecific competition (among different species).

These models simulate sensitive (S) and resistant (R) subpopulations, with treatment reducing S fitness more than R. By allowing S to rebound during treatment holidays or low doses, R growth is curtailed. Extensions explore multidrug cycling to create "evolutionary traps" or double binds.

Preclinical studies in breast, ovarian, and prostate cancer models show that adaptive therapy maintains stable tumor volumes longer, with reduced overall drug use. For example, adaptive carboplatin in ovarian models exploited fitness deficits in resistant cells, prolonging control.

A pilot trial in metastatic castrate-resistant prostate cancer at Moffitt Cancer Center, using adaptive abiraterone showed median TTP of 33.5 months vs. 14.3 months with standard care, and overall survival of 58.5 vs. 31.3 months (updated follow-up). Patients were off treatment ~46% of the time, reducing costs and toxicity. Four patients remained progression-free long-term ^[180].

AT's most important characteristics are delayed resistance, reduced toxicity and improved quality of life. On the other hand, it is not suitable for curative intent and requires frequent monitoring of tumor size.

The theory of using moderated chemotherapy to maintain a controlled tumor burden, grounded in Darwinian evolution, offers a promising departure from MTD dogma ^[181]. By harnessing intratumoral competition, adaptive therapy can extend the utility of existing drugs, improve patient outcomes, and reduce burdens on healthcare systems. While challenges remain, accumulating evidence supports its potential to transform incurable metastatic cancers into manageable chronic conditions.

Importantly, adaptive theory is based on theoretical and mathematical models that have been experimentally confirmed. Figure 6.

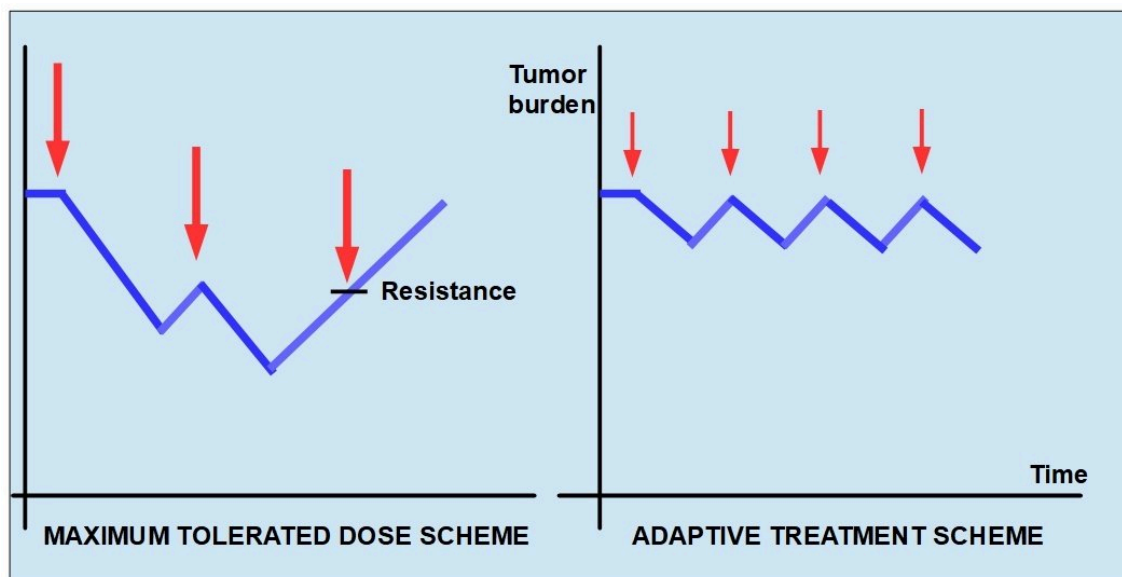


Figure 6. The usual chemotherapeutic protocols use the maximum tolerated dose (MTD) scheme. This means that the dose is defined by the patient tolerance to the dose (left panel). Protocols designed with an MTD scheme (almost all the protocols used by oncologists), hover near toxicity and sometimes even beyond it. The goal is to kill as many malignant cells as possible.

This leads to the destruction of most chemo-sensitive cells while chemo-resistant cells survive and slowly replace the other cells. After MTD medication the tumor shrinks but then it relapses with chemo-resistant cells. Adaptive chemotherapy (right panel) proposes the use of much lower doses of drug, which should be enough to block growth but insufficient to significantly shrink the tumor. The tumor mass would not shrink, but resistant cells would not replace sensitive cells. The dose needs to be permanently adapted in order to avoid further growth or excessive shrinkage.

Cancer kinetics: metronomic treatment

Metronomic treatment consists of using small doses of chemotherapeutic drugs in a permanent schedule, without interruptions. Metronomic chemotherapy can alter tumor kinetics by changing the **effective growth rate** of the tumor rather than simply producing abrupt cytoreduction. It does this

through continuous, low-dose exposure that can suppress endothelial cells, impair angiogenesis, reduce proliferative capacity, and reshape the balance between tumor cell birth and death ^[182].

This approach, first conceptualized in the early 2000s, was initially explored as a way to overcome resistance and reduce toxicity while maintaining or improving efficacy. Instead of primarily targeting rapidly dividing tumor cells in a "hit hard and rest" manner, metronomic scheduling exerts sustained, multi-targeted pressure on the tumor ecosystem. It preferentially damages tumor-associated endothelial cells (anti-angiogenic effect), modulates the immune microenvironment (e.g. reducing regulatory T cells and enhancing anti-tumor immunity), and limits the emergence of resistant clones in heterogeneous tumor populations.

Unlike maximum tolerated dose regimens, which often cause a sharp initial decline followed by regrowth of resistant clones, metronomic therapy tends to produce a slower, more sustained kinetic effect. In practical terms, this may flatten the growth curve, prolong time to progression, and sometimes convert an otherwise exponential trajectory into a more constrained one. Because the treatment is continuous, the tumor's apparent doubling time may lengthen during therapy if the regimen remains biologically active ^[183].

Metronomic chemotherapy does not necessarily produce a uniform or permanent shift in tumor doubling time. The kinetic effect depends on tumor type, drug, dose, schedule, and baseline biology, and some tumors may mainly show disease stabilization rather than measurable shrinkage. Therefore, metronomic chemotherapy can modify cancer kinetics but the magnitude and direction of the kinetic change are context dependent ^[184]. Figure 7.

Mathematical and computational models (including Neural ODEs and hybrid mechanistic-AI frameworks) are particularly valuable for optimizing metronomic regimens. They help simulate tumor growth vs. destruction dynamics, account for intratumoral heterogeneity and polyclonal evolution, and predict optimal dosing intervals that maximize therapeutic index while minimizing resistance.

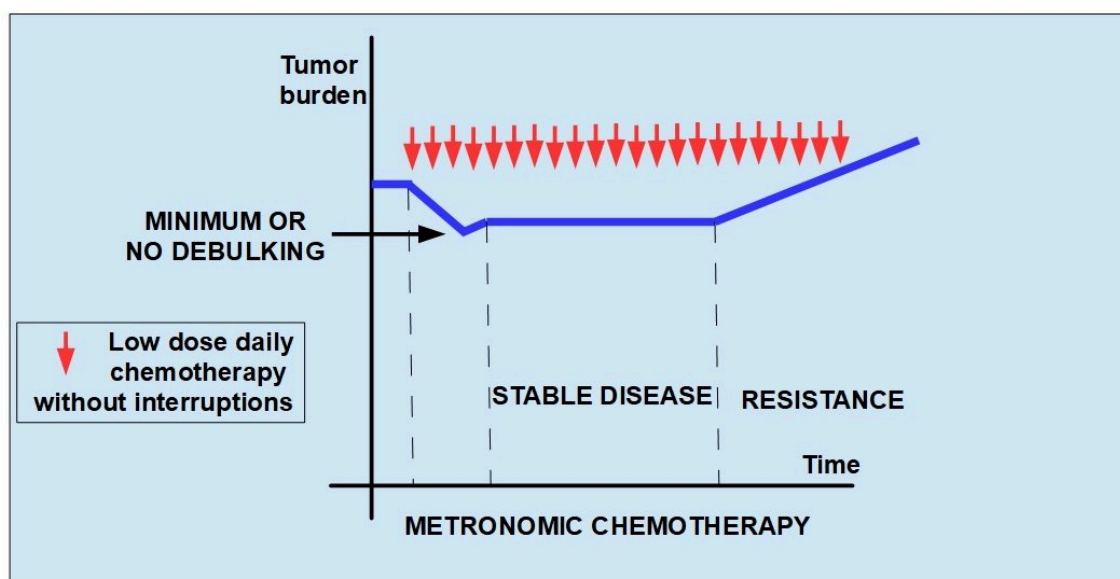


Figure 7. Cell kinetics in metronomic chemotherapy

While results vary by cancer type, drug, and patient (with strong evidence in breast, prostate, and pediatric cancers), metronomic chemotherapy exemplifies how rethinking **drug administration schedules** can profoundly influence outcomes in precision oncology. Ongoing trials continue to refine its role alongside modern biomarkers like PSA-DT and advanced imaging.

Biomarkers as proxies to cell kinetics

In oncology and endocrinology, directly measuring cell proliferation, death, and tissue turn-over often requires invasive tissue biopsies or complex laboratory assays. To bypass these limitations, clinicians and researchers frequently rely on circulating biochemical markers as functional proxies for cell kinetics.

Among the most widely studied and clinically utilized proxies are Prostate-Specific Antigen (PSA) in prostate cancer and thyroid hormones (along with Thyroid-Stimulating Hormone, or TSH) in thyroid pathophysiology.

Velocity & Doubling Time: The rate at which a marker rises (Velocity) or doubles (PSA Doubling Time - PSADT) serves as a direct mathematical surrogate for cellular doubling time and tumor growth kinetics.

Rapid drops in marker levels typically signify therapeutic cell kill or suppression of cellular activity. On the other hand, an increase of biomarkers usually indicates relapse or tumor growth.

a) PSA (prostate-specific antigen) as a guide to prostate cancer growth

PSA doubling time (PSA-DT or PSADT) has become a cornerstone kinetic biomarker in prostate cancer management. It serves as a practical, non-invasive tool for estimating tumor growth rate by quantifying how quickly serum prostate-specific antigen (PSA) levels rise over time, assuming exponential growth [185][186].

Clinicians use it widely to stratify risk, predict biochemical recurrence, metastasis-free survival, prostate cancer-specific mortality, and overall response to therapies — particularly in settings such as post-radical prostatectomy biochemical recurrence, active surveillance, or advanced/castration-resistant disease. Shorter PSA-DT (e.g. <3–6 months) typically signals more aggressive biology and poorer prognosis, while longer values (e.g. >12–24 months) often indicate more indolent behavior [187].

A key study from researchers at the National Cancer Institute (including Stein, Gulley, Fojo, and colleagues [184]) analyzed data from five intramural NCI prostate cancer trials. It highlighted the growth rate constant derived from PSA kinetics as a robust indicator of therapeutic efficacy. The work underscored how PSA-DT and related metrics provide valuable insights into tumor regression and progression dynamics, helping evaluate treatment impact beyond traditional endpoints.

For handy clinical use, the **Memorial Sloan Kettering Cancer Center (MSKCC)** offers a free, user-friendly online nomogram at: <https://nomograms.mskcc.org/Prostate/PsaDoublingTime.aspx> (or the updated path: https://www.mskcc.org/nomograms/prostate/psa_doubling_time).

How it works: Users enter the dates and corresponding PSA values (in ng/mL) from at least two (ideally more) consecutive measurements, preferably within the last 12 months or post-treatment nadir. The tool computes:

- **PSA Doubling Time** — expressed in months or years.
- **PSA Velocity** — the rate of change in ng/mL per year.

It supports comma-delimited batch entry for multiple values and includes guidance on handling post-prostatectomy or post-radiation scenarios (e.g. starting from the lowest PSA value and disregarding values after hormonal therapy begins). The calculator draws on established methodologies and is accompanied by supporting literature on the natural history of PSA progression.

This accessible resource empowers both patients and physicians to make informed, data-driven decisions. When integrated with other factors — such as Gleason score, absolute PSA levels, imaging, and

genomic markers — PSA-DT enhances risk stratification and helps guide choices around salvage therapy, clinical trial enrollment, or watchful waiting.

In the broader context of **tumor cell kinetics modeling** (e.g. with Neural ODEs or hybrid mathematical frameworks), PSA-DT provides real-world longitudinal data for calibrating patient-specific simulations of tumor burden under cytotoxic, hormonal, or targeted therapies. These models can then explore optimized dosing schedules while accounting for heterogeneity and resistance.

b) Thyroid hormones and thyroglobulin

The thyroid gland operates on a tightly regulated feedback loop, making thyroid function markers excellent proxies for both normal cell turnover and neoplastic activity [\[188\]\[189\]](#).

Thyroglobulin (differentiated thyroid cancer, post-thyroidectomy): Reflects residual/recurrent tumor burden kinetics. Shorter DT (e.g. <5-14 months) predicts progression and poorer survival, especially with high tumor load [\[190\]](#).

Calcitonin / Procalcitonin DT in Medullary Thyroid Carcinoma): Strong prognostic tool. Short DT indicates aggressive disease. Procalcitonin DT mirrors calcitonin DT as a complementary proxy [\[191\]](#).

While biochemical proxies offer a non-invasive window into cell kinetics, interpreting them requires caution. Proxies like PSA and thyroid hormones bridge the gap between microscopic cellular behavior and macro-level clinical decision-making. By applying mathematical kinetic models—such as velocity and doubling times—to routine blood tests, clinicians can dynamically monitor cell proliferation, assess treatment response, and anticipate disease trajectory without needing frequent, invasive tissue sampling.

Kinetics of tumor cell destruction with chemotherapy

So far, we have analyzed how tumors grow. Now we will briefly see how chemotherapy stops growth and destroys tumor cells.

Drug administration schedules are pivotal determinants of therapeutic success in oncology. The timing, dosage, frequency, and sequencing of cytotoxic agents can dramatically influence how effectively a treatment eradicates tumor cells while minimizing damage to healthy tissues. Optimal scheduling exploits the differential sensitivities between rapidly dividing cancer cells and slower-recovering normal cells, turning a blunt instrument into a precisely tuned strategy.

Mathematical and computational models play a transformative role here. By simulating the intricate population dynamics of tumors under various treatment regimens, these models — ranging from

traditional ordinary differential equations to advanced approaches like Neural ODEs — allow researchers and clinicians to predict responses, identify synergies, and optimize protocols *in silico* before costly clinical trials. They integrate growth kinetics, drug pharmacokinetics/ pharmacodynamics, resistance emergence, and immune interactions to forecast outcomes and refine "what-if" scenarios, ultimately improving efficacy, reducing toxicity, and personalizing therapy.

Unlike tumor growth kinetics, which can often be approximated by relatively straightforward models (e.g. exponential, logistic, or Gompertzian curves), the kinetics of tumor destruction under cytotoxic therapy are far more complex and multifaceted. Destruction involves not just cell killing but also compensatory proliferation of surviving cells, drug-induced stress responses, spatial gradients within the tumor microenvironment, and evolving resistance mechanisms. These processes unfold across multiple scales — from molecular signaling to tissue-level heterogeneity — making purely empirical approaches insufficient.

At the heart of this complexity lies tumor heterogeneity — one of the most formidable challenges in cancer treatment. Malignant cells are not uniform. Within a single tumor mass, there is in fact, a diverse ecosystem of coexisting subpopulations. Although these cells may trace their origins to a common ancestral clone, rapid genetic instability and frequent mutations quickly generate genetic and phenotypic diversity. The tumor evolves into a **polyclonal** entity, harboring subclones with distinct traits: some highly proliferative, others dormant or stem-like; some exquisitely sensitive to a given drug, others inherently resistant due to efflux pumps, altered targets, or DNA repair proficiency.

Additional layers of heterogeneity arise from the microenvironment — variations in oxygen and nutrient availability create hypoxic niches that protect certain cells, while immune infiltration and stromal interactions further modulate drug response. This intratumoral diversity explains why a seemingly effective treatment may shrink the tumor bulk yet allow resistant subclones to dominate and drive relapse.

By embracing these realities through data-driven modeling (including patient-specific parameters from longitudinal biomarkers like calcitonin in medullary thyroid carcinoma or imaging-derived volumes), researchers can design adaptive, evolutionary-informed schedules — such as intermittent dosing, sequential combinations, or metronomic therapies — that better anticipate and counter clonal evolution. This approach shifts cancer treatment from a static "one-size-fits-all" paradigm toward dynamic, precision strategies that account for the living, ever-changing nature of tumors. Figure 8.

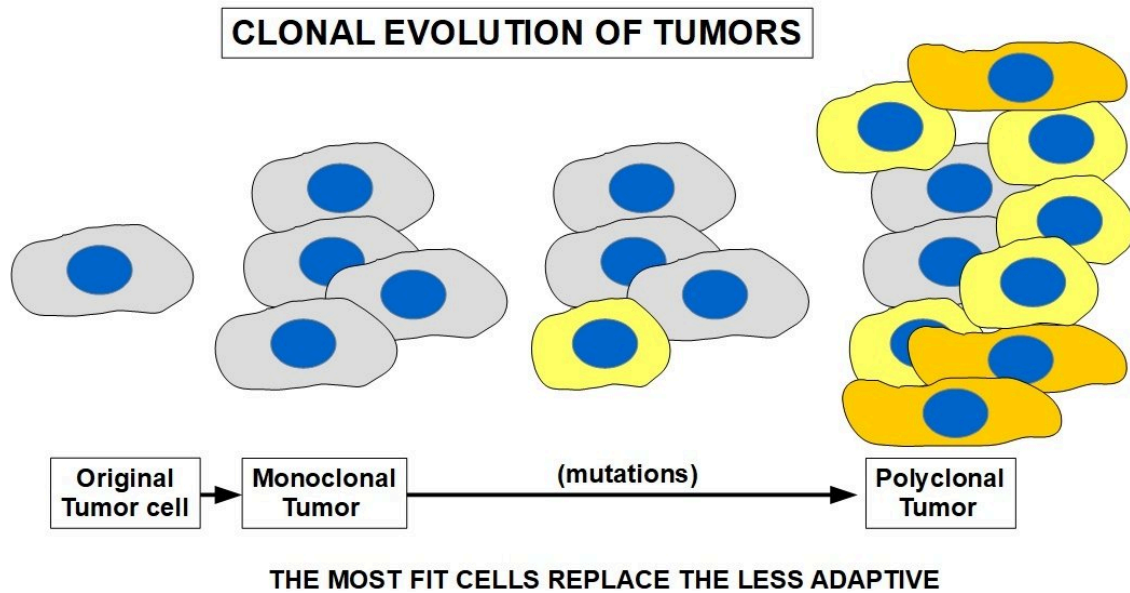


Figure 8. Development of a polyclonal tumor from a monoclonal initiator. Mutations are the cause of these events. Clonal evolution follows the Darwinian concept of survival of the fittest, while non well-adapted cells die (not shown).

Fundamental kinetic parameters

The eukaryotic cell cycle proceeds through four principal phases: G1 (post-mitotic growth and preparation for DNA synthesis), S (DNA synthesis), G2 (premitotic growth and repair checkpoint), and M (mitosis). Cells that are not actively cycling go into a quiescent state, G0, from which they may later re-enter the cycle in response to appropriate stimuli. In a tumor, only a fraction of the total cell population is cycling at any given time; this fraction is termed the growth fraction (GF). The remaining cells are either in G0, terminally differentiated, or in the process of dying.

Several kinetic parameters together determine the net growth rate of a tumor:

- Potential doubling time (T_{pot}) — the time required for the tumor to double in size if no cell loss occurs, determined by the cell cycle time and the growth fraction.
- Cell cycle time (T_c) — the duration required for a cycling cell to complete one full division cycle, typically ranging from about 18 to 40 hours in human tumors, with S phase generally the longest component.

- Growth fraction (GF) — the proportion of clonogenic tumor cells actively traversing the cell cycle rather than resting in G0.
- Cell loss factor (ϕ) — the proportion of newly produced cells that die or are shed rather than contributing to net tumor growth; in many solid tumors this factor is very high, often exceeding 90 percent, which explains why the actual volume doubling time (T_d) of a tumor is typically many-fold longer than its potential doubling time.

The relationship among these parameters can be expressed approximately as $T_d \approx T_{pot} / (1 - \phi)$, underscoring that observed tumor growth rate is the net result of proliferation partially offset by ongoing cell death — a balance that chemotherapy directly perturbs by increasing the cell loss factor, at least temporarily.

Cell Cycle Specificity of Cytotoxic Agents

Chemotherapeutic agents are traditionally classified according to their dependence on cell cycle phase for cytotoxic action, a distinction with direct kinetic consequences for scheduling.

Cell-Cycle-Phase-Specific Agents

Phase-specific agents exert maximal lethality on cells traversing a particular phase of the cycle and are relatively sparing of quiescent (G0) cells. Antimetabolites such as methotrexate, cytarabine, and 5-fluorouracil act principally in the S phase by disrupting nucleotide synthesis or incorporating into DNA. Vinca alkaloids and taxanes act in the M phase by disrupting mitotic spindle assembly. Because these agents depend on active cycling, their efficacy is a function of both drug exposure time and the fraction of cells passing through the vulnerable phase during that exposure — prolonged or repeated low-dose exposure (schedule-dependence) is often more effective than a single brief high-dose exposure.

Cell-Cycle-Nonspecific Agents

Nonspecific (or phase-nonspecific) agents, including alkylating agents, platinum compounds, and anthracyclines, can kill cells in any phase of the cycle, including G0, although cycling cells are frequently somewhat more sensitive due to reduced time for DNA repair before the next mitotic checkpoint. These agents tend to show a steeper dose-response relationship and are therefore more amenable to dose-intensification strategies, since their cytotoxicity is less dependent on the temporal distribution of cells across the cycle.

The foundational quantitative model of chemotherapy cell kinetics arose from experiments on murine L1210 leukemia conducted by Skipper, Schabel, and Wilcox in the 1960s. Their central finding was that a given dose of a cytotoxic drug, under first-order kinetics, kills a constant fraction — rather than a constant number — of tumor cells, regardless of the absolute tumor burden at the time of treatment. This is the log-kill hypothesis: a dose producing a 99% kill (2-log kill) reduces $10^{[9]}$ cells to $10^{[7]}$ and would equally reduce $10^{[6]}$ to $10^{[4]}$ cells.

Actually, the Skipper hypothesis has two parts, one of them is probably incorrect.

Skipper Hypothesis

Skipper's hypothesis ^{[192][193][194]}. This publication was an attempt to use models wisely to gain information on treatment failures, designing experiments and interpreting experimental and clinical results. The first hypothesis states that the doubling time of a tumor's volume is constant. This would be true if the tumor followed exponential growth. However, most tumors follow the Gompertzian model. We will leave this part of the hypothesis aside because it is probably inaccurate.

The second hypothesis, that is of particular interest to us, states that chemotherapy works in first-order kinetics. This means that a number of cells are destroyed regardless of the size of the tumor. This theory is known as the logarithmic destruction theory. What Skipper's law says is that since the doubling time of the tumor mass is constant, the percentage of malignant cells that are eliminated with chemotherapy treatment is also a fixed percentage, regardless of the number of original cells in the tumor. However, the doubling time is not constant, therefore, we assume that the Skipper hypothesis is correct for the growth part of the growth curve but not for the late stage in which growth is slowed down.

Several important corollaries follow from this model. First, because cell kill is fractional rather than absolute, repeated cycles of therapy are required to progressively reduce tumor burden to a level compatible with immune clearance or clinical cure; a single log-kill, however large, is unlikely to eradicate a clinically detectable tumor of $10^{[9]}$ to $10^{[12]}$ cells. Second, the model implies that chemotherapy is most effective, in absolute cell-number terms, when the tumor burden is small — providing the rationale for adjuvant chemotherapy given after surgical debulking, when micrometastatic disease represents the smallest attainable tumor burden. Third, the model predicts that early, aggressive treatment initiated close to diagnosis should outperform delayed or reduced-intensity treatment, a principle later formalized in dose-intensity analyses of clinical trial data.

The log-kill model, however, assumes exponential tumor growth and a constant growth fraction, assumptions that hold reasonably well for rapidly proliferating murine leukemias but break down for most human solid tumors, which display markedly different, non-exponential growth kinetics.

Gompertzian Growth Kinetics and Its Implications for Chemotherapy

Human solid tumors typically follow Gompertzian rather than exponential growth kinetics. In a Gompertzian model, the growth rate itself declines progressively as tumor size increases, producing a sigmoid growth curve: rapid early growth followed by progressive deceleration as the tumor approaches a theoretical plateau size. This deceleration is attributed to a shrinking growth fraction and rising cell loss factor as the tumor outgrows its vascular supply, develops central hypoxia and necrosis, and encounters increasing intratumoral competition for nutrients.

Gompertzian kinetics have two major implications for chemotherapy that depart substantially from the log-kill model. First, because larger, more established tumors have a lower growth fraction, they are kinetically less sensitive to cell-cycle-specific agents than smaller, rapidly proliferating tumors — providing an additional kinetic rationale (beyond simple cell number) for treating micrometastatic or minimal residual disease. Second, and paradoxically, when a large Gompertzian tumor is debulked by surgery, radiation, or a cycle of chemotherapy, the surviving cell population is shifted onto a steeper, earlier portion of the Gompertzian growth curve, where the growth fraction is higher and proliferation is faster.

This phenomenon — accelerated repopulation of the residual tumor — is a central and clinically consequential kinetic effect of cytoreductive therapy.

Kinetic Alterations Induced by Chemotherapy: Synchronization, Recruitment, and Redistribution

Beyond simply killing cells, cytotoxic exposure actively reshapes the kinetic state of the surviving tumor cell population through several interrelated mechanisms.

Synchronization

Because phase-specific agents preferentially kill cells in a particular part of the cycle, surviving cells are disproportionately drawn from the remaining phases, producing a transient synchronization of the residual population. For a period after treatment, a larger-than-baseline proportion of surviving cells

traverses subsequent cell cycle phases in unison. This has been exploited clinically and experimentally in sequential scheduling, where a phase-specific agent is used to synchronize the population, followed at a calculated interval by a second agent timed to strike the synchronized cohort as it re-enters the vulnerable phase — a strategy sometimes termed kinetic scheduling or synchrony-based sequential chemotherapy.

Recruitment

Cytotoxic injury, cytorreduction, and the resulting relief of spatial and nutrient constraints can trigger previously quiescent G0 cells to re-enter the active cell cycle, a phenomenon termed recruitment. Recruited cells, having been drawn from a resistant, non-cycling reservoir into an actively dividing (and thus drug-vulnerable) state, recruited cells may become newly sensitive to subsequent cycle-specific therapy, but recruitment also increases the growth fraction of the residual tumor and thereby accelerates regrowth if further treatment is delayed.

Redistribution

Redistribution refers to the movement of surviving cells through the cell cycle following a sublethal insult, such that cells partially blocked at a checkpoint (for example, the G2/M checkpoint after DNA damage) accumulate and later progress through the cycle in a relatively synchronized wave, again creating a window of enhanced vulnerability to subsequently timed treatment.

Together, synchronization, recruitment, and redistribution mean that the kinetic composition of a tumor immediately after a cycle of chemotherapy differs substantially from its pretreatment state, and this altered state — rather than the pretreatment state — determines the tumor's response to the next intervention. This is the essential kinetic rationale for multi-cycle, appropriately spaced treatment regimens rather than single-dose therapy.

Accelerated Repopulation After Cytotoxic Therapy

One of the most clinically important kinetic phenomena in oncology is accelerated repopulation: the observation that surviving tumor (and normal tissue stem) cells often proliferate faster after a course of cytotoxic therapy than the corresponding untreated tissue would have. This phenomenon, first characterized extensively in the radiotherapy literature but equally applicable to chemotherapy, arises from several converging mechanisms: recruitment of quiescent cells into cycle, shortening of cell cycle

transit time, reduction of cell loss through apoptosis in the surviving clone, and relief of Gompertzian growth constraints following cytoreduction, as described above.

Accelerated repopulation has direct implications for treatment scheduling. If the interval between treatment cycles is too long, the kinetic advantage gained by cytoreduction is eroded or reversed by accelerated proliferation of survivors, effectively allowing the tumor to "outrun" the next dose of therapy. This principle underlies the clinical rationale for minimizing unnecessary delays between chemotherapy cycles and for dose-dense regimens. The same phenomenon in normal tissues — for example, accelerated repopulation of mucosal or bone marrow stem cells after cytotoxic injury — is also central to the recovery of normal tissue tolerance between treatment cycles, and the balance between tumor repopulation and normal tissue repopulation kinetics substantially determines the achievable therapeutic index of a given schedule.

The Norton-Simon Hypothesis and Dose-Dense Chemotherapy

In the late 1970s, **Larry Norton and Richard Simon** {m/28/} found experimentally that the proportion of cells killed by an effective therapy was not independent of tumor size, as Skipper's hypothesis states, but was inversely proportional. The Norton-Simon hypothesis stated that "A high fraction of the cells in faster-growing, small tumors could be killed by a given drug at a certain dose level that had very little effect on larger, slowly growing masses of otherwise identical cancer cells."

Therefore, rapidly growing small tumors would be more susceptible to treatment than slow-growing large tumors. Large tumors that would be on the second plateau of the Gompertzian curve and have poor growth and are therefore less affected by chemotherapy ^[195]. Figure 9.

Norton-Simon Hypothesis

Chemotherapy results in a rate of regression in tumor volume that is proportional to the rate of growth of that tumor at that size.

Included in this concept is that growth follows a Gompertzian pattern and that different tumor sizes may have a different growth rate. Small rapidly growing tumors are more susceptible to treatment than large slow growing tumors.

The clinical corollary of the Norton-Simon hypothesis is dose-dense chemotherapy: rather than increasing the dose delivered per cycle, treatment cycles are administered at shorter intervals (for example, every two weeks rather than every three, typically supported by growth factor support to

permit adequate normal tissue recovery), with the goal of minimizing the interval available for accelerated tumor repopulation between doses. Randomized trials in several tumor types, most notably early breast cancer, have demonstrated modest but reproducible improvements in disease-free and overall survival with dose-dense scheduling compared with conventional interval dosing at equivalent cumulative doses, providing clinical validation of the underlying kinetic model, although the magnitude of benefit varies by tumor type and biological subgroup.

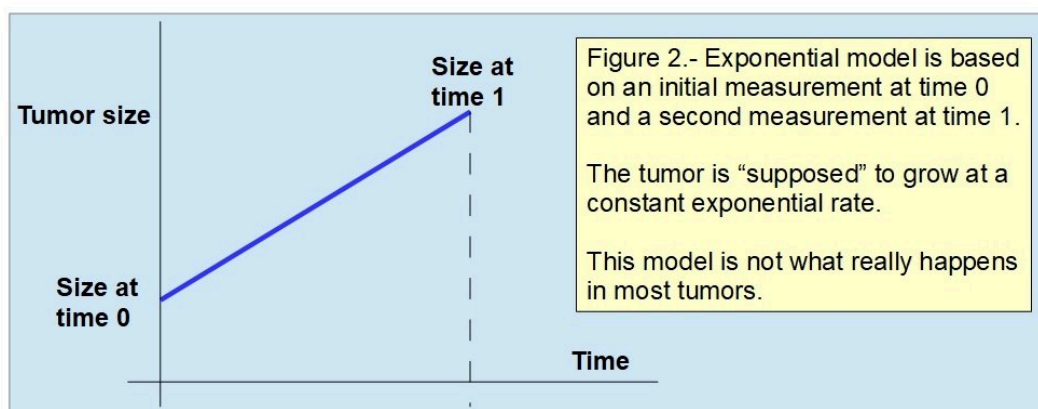


Figure 9.

Kinetic Resistance and the Goldie-Coldman Hypothesis

The Goldie-Coldman hypothesis ^[196] predicts that tumor cells develop phenotypic adaptations that oppose chemotherapy: “Analysis of the model indicates that the probability of the appearance of a resistant phenotype increases with the mutation rate. Furthermore, for any population of tumors with a non-zero mutation rate the likelihood of there being at least one resistant cell will go from a condition of low to high probability over a very short interval in the tumor’s biologic history.”

This resistance is not controlled by the treatment and depends on the number of cell divisions that occur after the initiation of treatment. The larger the tumor or the longer the delay in starting chemotherapy, the lower the possibility of cell destruction. It also implies that two successive cycles of different drugs will produce a greater effect.

The Goldie-Coldman hypothesis establishes the emergence of drug resistance as a function of tumor growth kinetics rather than treatment scheduling per se. The model posits that spontaneous mutation to

drug resistance occurs stochastically at a roughly constant rate per cell division, such that the probability a tumor already harbors a resistant clone at diagnosis increases with the total number of cell divisions that have occurred during its growth history — that is, with tumor size and mutation rate, largely independent of the drug used. A key kinetic implication is that resistant subclones themselves proliferate according to the same Gompertzian and cell-kinetic principles as the sensitive population, and once selected for by exposure to a single agent, a resistant clone may repopulate the tumor with the same accelerated kinetics.

The Goldie-Coldman model provides the theoretical basis for combination chemotherapy and for alternating (rather than purely sequential) non-cross-resistant drug regimens. By exposing the tumor to multiple agents with distinct mechanisms of resistance early and repeatedly, before an established resistant clone has an opportunity to expand kinetically, the probability of achieving durable tumor control is increased respect to sequential single-agent therapy given to the point of progression.

The fractional cell death hypothesis

The fractional cell death hypothesis is based on the Skipper hypothesis, but is not exactly the same. It states that by administering a certain concentration of chemotherapy drug over a period of time to a group of tumor cells, a fixed percentage of the tumor cells will be eradicated. This is because only a certain percentage of the tumor is eradicated with one-drug treatment. Therefore, drugs induce incomplete cell death in a population of cancer cells ^[58]. Drug-tolerant cells can survive treatment. Other susceptible cells can also survive due to differences in drug uptake, stromal protection preventing drug diffusion, stemness ^[59], and other cell characteristics ^[60]. Although not fully understood, variability between cells in chemotherapy- induced cell death, eliminates a constant fraction of cells with each cycle of administration ^[61]. This explains why repeated doses must be administered to reduce the size of the tumor. This also explains why chemotherapy protocols repeat drug administration. In addition, using lower doses prevents drugs toxicity. Figure 8.

The **fractional death hypothesis** says that a given chemotherapy exposure kills a constant **fraction** of the tumor cell population, regardless of how many cells are present. The **Norton-Simon hypothesis** is broader: it proposes that the rate of tumor regression after chemotherapy is proportional to the tumor's **untreated growth rate**, so faster-growing tumors should shrink more quickly and be more chemosensitive.

Main difference

- **Fractional death hypothesis:** focuses on the **drug effect per dose**; the same treatment kills the same proportion of cells.
- **Norton-Simon hypothesis:** focuses on **tumor growth kinetics**; chemotherapy is more effective when the tumor is growing faster, and response depends on the tumor's intrinsic growth rate.

On the other hand the fractional kill hypothesis, or log kill, and Skipper's second law are usually used interchangeably in oncology discussions of chemotherapy kinetics. This removes Skipper's first law which is probably inaccurate, from the discussion.

The **fractional death hypothesis** in chemotherapy is the idea that a given drug dose kills a **constant fraction** of tumor cells, not a constant number. For example, if a regimen produces a 90% kill, it will reduce a tumor from 10 billion cells to 1 billion, and the same 90% kill applied again reduces 1 billion to 100 million ^[197].

This is also called the **fractional kill** or **log kill** hypothesis. The key implication is that repeated cycles are needed because each cycle removes only a proportion of the remaining cells, rather than eradicating all of them at once. That is why chemotherapy is usually delivered in cycles rather than as a single exposure.

The model explains why tumor burden declines in a logarithmic way during effective therapy. It also helps explain why smaller tumors are often easier to eradicate: after each cycle, the same fractional reduction leaves fewer residual cells, so the absolute number remaining becomes progressively smaller. This framework underlies much of classic chemotherapy scheduling.

The hypothesis is often linked to the idea that many cytotoxic drugs act in a **cell-cycle-dependent** manner, so only the fraction of cells in a susceptible state is killed during any given exposure. In solid tumors, poor drug penetration, hypoxia, quiescence, and microenvironmental protection can also reduce the fraction killed. More recent work also suggests that stochastic differences in apoptotic threshold and signaling dynamics contribute to fractional killing even in genetically similar cell populations ^[198].

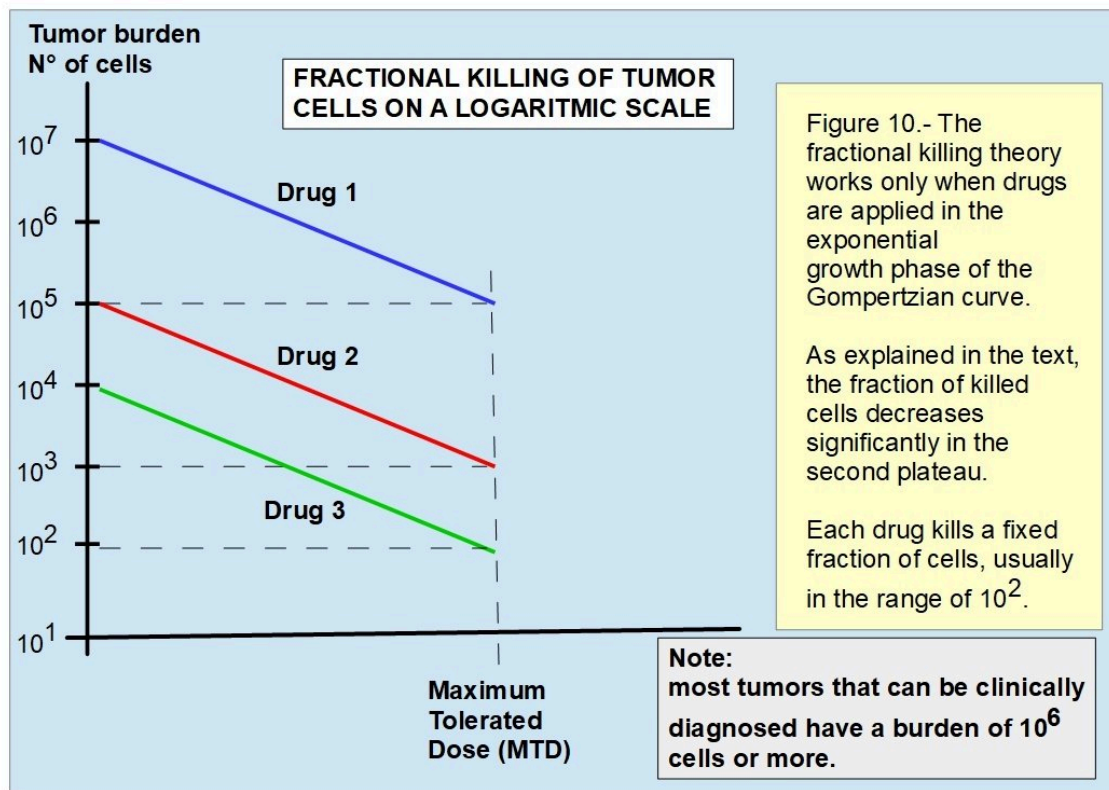


Figure 10.

The hypothesis is useful, but it is not universal. Real tumors do not always respond with a perfectly constant kill fraction because resistance, spatial heterogeneity, drug delivery differences, and regrowth between cycles can all change the apparent effect. So the model is best understood as a practical approximation rather than a strict law of tumor biology.

Although we do not know the exact kinetics of tumor destruction with chemotherapy, we can summarize the concepts that are likely correct:

1. Tumor size influences the result of treatment because large tumors generally have fewer mitosis (second plateau of the Gompertzian curve) and therefore the effectiveness of the attack decreases.
2. Each application of chemotherapy can destroy a fraction of the tumor, but not the entire tumor, since that would require intolerably high doses.
3. The fraction that is destroyed is the one with the greatest growth dynamics, that is, the greatest amount of mitosis.

We must clarify that these precepts apply only to treatments that attack DNA and the mitotic apparatus. They are not applicable to immunotherapy, or to attacks on other cellular mechanisms. **Tumor growth is not just a biological process, but an evolving population dynamic shaped by selection, saturation, and treatment pressure.**

If instead of representing multiple tumors' size/dose, we represent only one tumor size/time with two cycles of chemotherapy the best way to show the fractional tumor killing hypothesis results in Figure 11.

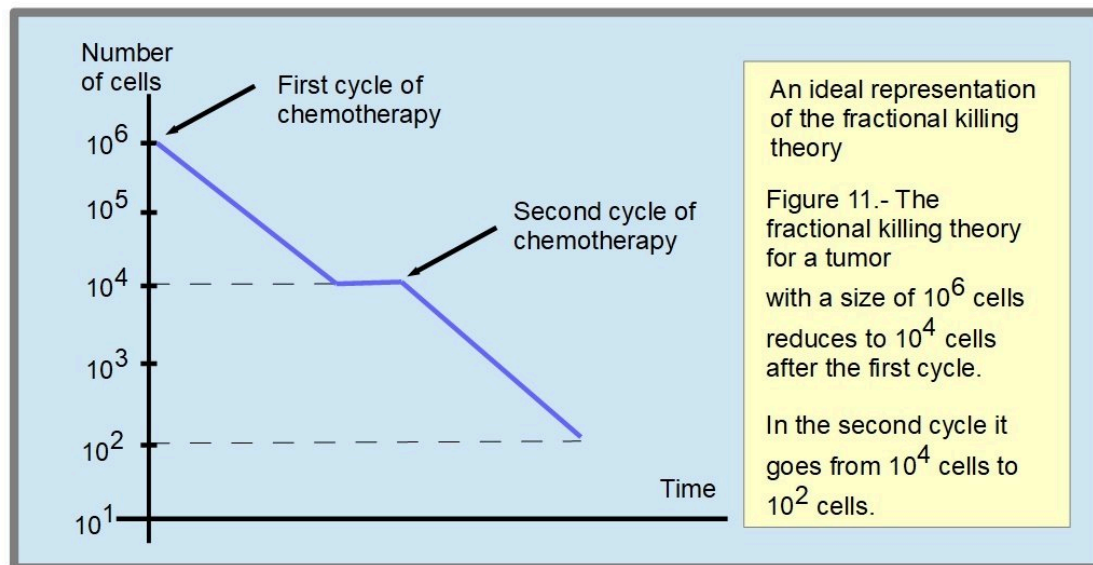


Figure 11. Each cycle kills a proportion of cells in the order of $10^{[6]}$ to $10^{[4]}$ in the first cycle and from $10^{[4]}$ to $10^{[2]}$ in the second cycle (this is only an example, however the $10^{[2]}$ killing seems to be a close approximation to real cell killing).

Links between Gompertzian growth, adaptive therapy and metronomic chemotherapy with the fractional killing theory

Link to Gompertzian growth

The Gompertz model describes a tumor whose **relative growth rate decreases over time** as the mass expands and becomes more constrained by nutrient limitation, hypoxia, and quiescence. That matters for the fractional kill hypothesis because if a therapy eliminates a constant **fraction** of cells, then the absolute number killed is larger in a bigger, faster-growing tumor, while the surviving fraction can

regrow under a slowing-growth regime. This is one reason the Gompertz framework became influential in chemotherapy scheduling: it fits the observation that shrinking tumors often respond better to additional treatment than larger, slower-growing ones ^[199].

Link to adaptive therapy

Adaptive therapy relies on **preserving sensitive cells** so they can suppress resistant clones through competition. The fractional kill idea supports this logic because treatment does not wipe out all cells at once; it removes only a proportion, leaving a residual population that can still influence the tumor's evolutionary ecology. In a Gompertzian model, because growth slows as the tumor gets smaller, treatment breaks can sometimes allow the tumor to remain controllable rather than rapidly rebounding, especially if the sensitive population is maintained ^{[200][201]}.

Link to metronomic chemotherapy

Metronomic chemotherapy also fits naturally with fractional kill because it uses **continuous low-dose exposure** rather than intermittent high-dose pulses. Instead of trying to achieve maximal fractional kill in one cycle, it aims to apply sustained pressure on tumor cells and, importantly, on angiogenesis and the microenvironment. When the tumor follows Gompertzian kinetics, metronomic schedules may be particularly effective at keeping growth in the decelerating phase, where the balance between cell death and limited proliferation favors disease control over rapid expansion.

Shared logic

All three concepts reject the notion that cancer is best managed by a simple one-shot eradication model. The fractional kill hypothesis says chemotherapy removes a proportion, not all cells. Gompertzian growth says tumor expansion slows as the tumor becomes larger and more constrained. Adaptive therapy says treatment should be modulated to maintain competition against resistance. Metronomic chemotherapy says continuous low-dose pressure can reshape kinetics and microenvironmental support. Together, they provide a more ecological and kinetic view of cancer treatment than classical maximum-tolerated-dose approach.

Clinical Implications and Therapeutic Strategies

The kinetic principles reviewed above converge on several practical strategies employed in modern oncology practice ^{[202][203][204][205]}.

- Adjuvant therapy timing: initiating chemotherapy as soon as feasible after surgical resection minimizes the interval available for accelerated repopulation of micrometastatic residual disease.
- Dose-dense scheduling: compressing the interval between cycles, supported by hematopoietic growth factors, to limit tumor repopulation between doses, as predicted by the Norton-Simon model.
- Combination and alternating regimens: using multiple non-cross-resistant agents concurrently or in rapid alternation to reduce the kinetic opportunity for a resistant subclone to expand, per the Goldie-Coldman model.
- Sequential kinetic scheduling: timing a second cycle-specific agent to coincide with the synchronized re-entry of surviving cells into a vulnerable phase following an initial synchronizing agent.
- Maintenance and metronomic therapy: low-dose, frequent (metronomic) dosing schedules that target the tumor vasculature and residual proliferative clones over extended periods, exploiting sustained low-level cytotoxic pressure rather than intermittent maximal cell kill.

These strategies illustrate that optimizing chemotherapy is not solely a matter of selecting the most potent agent or the maximum tolerated dose, but of matching the temporal architecture of treatment to the temporal architecture of tumor cell kinetics, both at baseline and as reshaped by treatment itself.

Furthermore, the kinetic principles make it possible to establish the following:

1. The interval between cycles is bounded by two opposing forces.

- **Floor:** normal tissue (mainly bone marrow) must recover enough to survive the next hit safely.
- **Ceiling:** the tumor must not be given enough time to regrow and “erase” the damage from the last cycle. The “right” interval sits between these two limits — as short as normal tissue allows, not shorter than tumor biology requires. Figure 12.

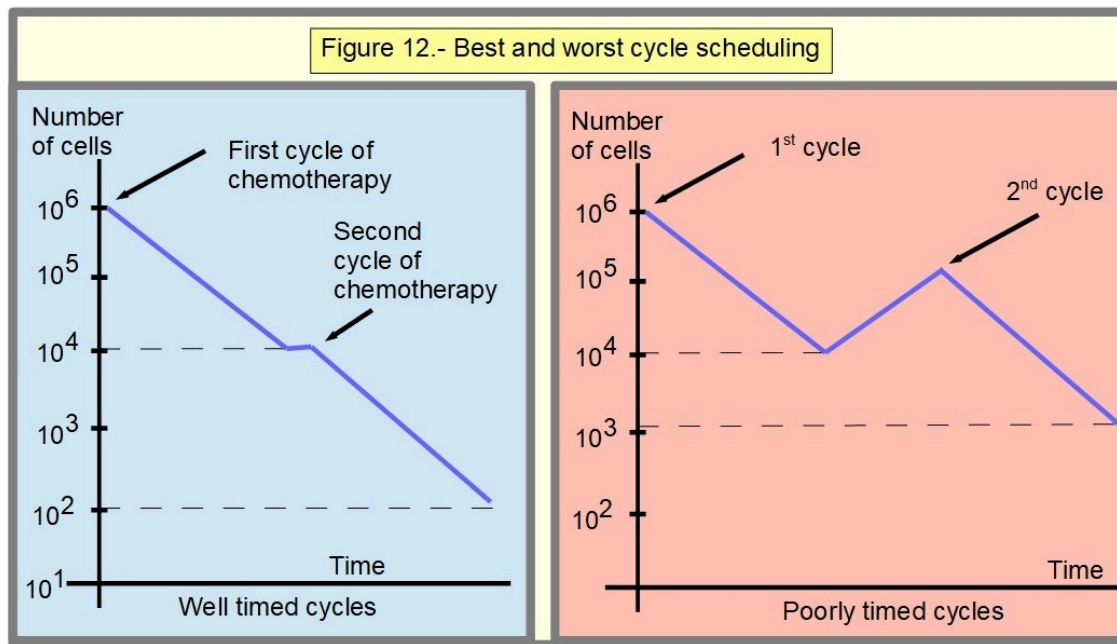


Figure 12.

2. Bone marrow recovery sets the practical floor.

- Neutrophils typically reach their nadir at day 7-14 post-treatment and recover by day 21.
- Platelets usually recover faster than neutrophils, so neutrophil recovery is normally the limiting factor.
- Rule of thumb: do not start the next cycle until neutrophils count $\geq 1,500/\mu\text{L}$ and platelets $\geq 100,000/\mu\text{L}$ (thresholds vary by regimen/protocol).
- G-CSF support artificially raises this floor by speeding neutrophil recovery — this is the mechanism that made shorter intervals (e.g. 2-week "dose-dense") possible without unacceptable infection risk.

3. Tumor regrowth kinetics set the ceiling (Norton-Simon principle).

- After a cycle kills a fraction of cells, the survivors re-enter a faster-growing part of the growth curve.
- The longer you wait, the more that regrowth cancels out the kill from the last cycle. Figure 11.
- Practical translation: shrink the gap, not necessarily the dose. This is why dose-dense (same dose, shorter interval) beats dose-intense (bigger dose, same interval) in several proven regimens.

4. Faster-growing tumors demand shorter intervals; slower ones tolerate longer ones.

- High-proliferation tumors (e.g. aggressive lymphomas, some breast cancers) lose more ground during a delay — compress the schedule.
- Slow-growing or indolent tumors are more forgiving of standard 3-4 week spacing, since regrowth between cycles is minimal.

5. Cumulative, non-marrow toxicity caps how far you can push regardless of blood counts.

- Anthracyclines (cardiac), platinum (renal/neuro), bleomycin (pulmonary) accumulate damage independently of treatment interval.
- Even if counts recover fast enough to go sooner, these agents have a hard lifetime dose ceiling that eventually forces treatment to be stopped or switched — timing cannot out-plan this.

6. Cell-cycle specificity affects within-cycle scheduling, not just the gap between cycles.

- Phase-specific drugs (antimetabolites, taxanes) hit only cells passing through the vulnerable phase at the moment of exposure.
- Because tumor cells cycle asynchronously, repeated or prolonged exposure (weekly dosing, continuous infusion) catches more cells than a single big bolus every three weeks — this is a timing lever independent of the marrow-recovery interval.

7. Practical decision rule clinicians actually use:

Treat as soon as normal-tissue counts have recovered to a safe threshold — with growth factor support if needed to shorten that recovery — unless cumulative organ toxicity or patient fitness forces a delay ^[206]
^{[207][208][209][210][211][212][213]}.

We can build a “decision tree” according to the principles of tumor kinetics we have considered. Figure 13.

Figure 13.- Decision tree

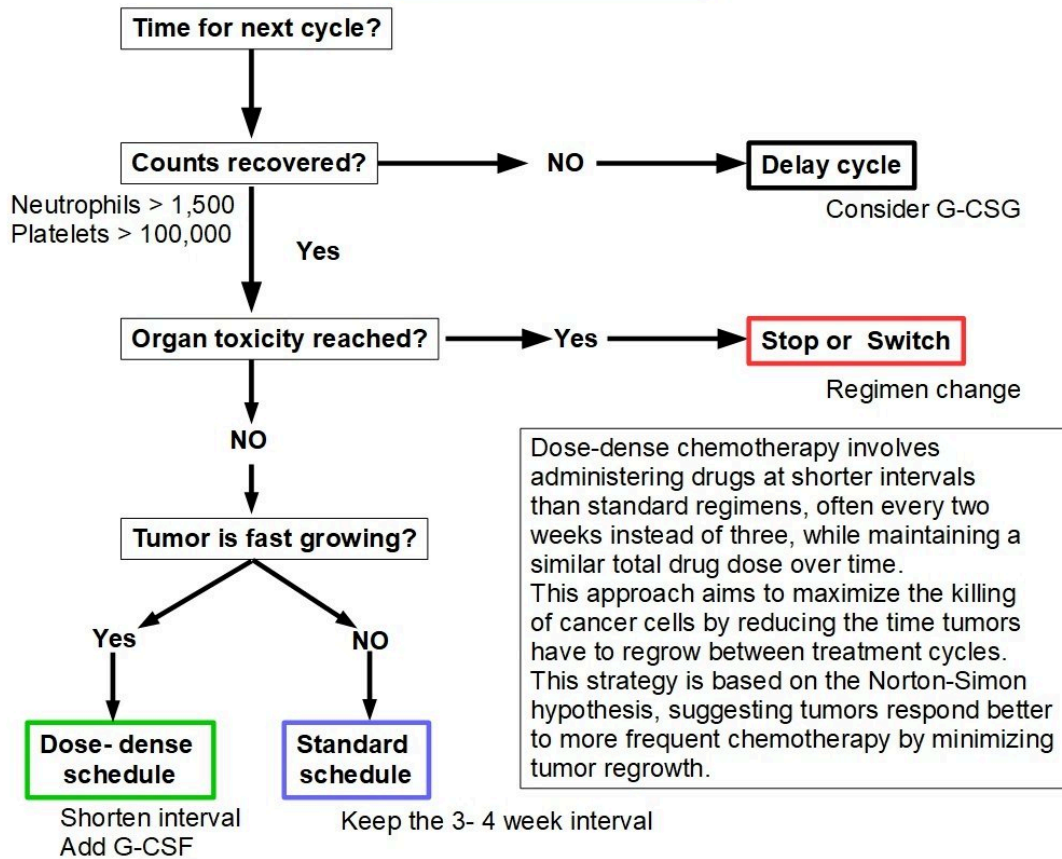


Figure 13.

Dose-dense chemotherapy keeps the same drug doses as standard chemotherapy but delivers them more frequently — shortening the gap between cycles rather than increasing how much drug is given per cycle.

Standard dosing: Cycles every 3 weeks (21 days), at doses close to the maximum a patient can tolerate. The 3-week interval lets bone marrow recover.

Dose-dense dosing: Same per-cycle doses, but cycles every 2 weeks (14 days) instead of 3. This is only possible because granulocyte colony-stimulating factor (G-CSF) is given to accelerate neutrophil recovery — without it, a 2-week interval wouldn't be safe.

Why compress the interval instead of raising the dose? This comes back to the Norton-Simon principle: after a cycle kills off tumor cells, the surviving population re-enters a faster-growing phase. The longer the gap before the next cycle, the more that regrowth erodes the benefit of the last treatment. So

shrinking the *time between* cycles limits the tumor's opportunity to regrow, rather than trying to kill more cells per cycle (which mainly just adds toxicity without much regrowth benefit).

Does it actually work? The key evidence is the CALGB 9741 trial in node-positive breast cancer: patients getting doxorubicin, cyclophosphamide, and paclitaxel every 2 weeks (with G-CSF) had better disease-free and overall survival than patients getting the identical cumulative doses every 3 weeks. Same total drug — just delivered on a tighter schedule. Later meta-analyses confirmed a modest but real survival benefit [\[214\]](#)[\[215\]](#)[\[216\]](#). However, dose-dense treatments do not help with cumulative, non-marrow toxicities (cardiac, renal, neuro), which are dose-dependent but not interval-dependent.

The dose-dense schedule benefit is clearest in fast-growing tumors; slow-growing tumors have little to gain from compressing the schedule, since they are not regrowing much between cycles anyway. In summary, standard dosing asks "how much drug can we give at once," while dose-dense dosing asks "how little time can we safely leave between doses."

The above examples clearly show the strong relationship between tumor kinetics and treatment approach and results.

What Are Von Bertalanffy-Type Models?

Von Bertalanffy-type formulations are mathematical models originally developed by Ludwig von Bertalanffy to describe growth processes in biology. These models are widely used to describe the growth of organisms, populations, as well as tumors in cancer biology.

They are based on the idea that the net growth rate of a system (like a cell population or an organism) is determined by the balance between anabolic processes (which build up or add mass) and catabolic processes (which break down or remove mass). The general form of von Bertalanffy models expresses growth as a difference between these two competing processes.

Basic Form of Von Bertalanffy Growth Equation

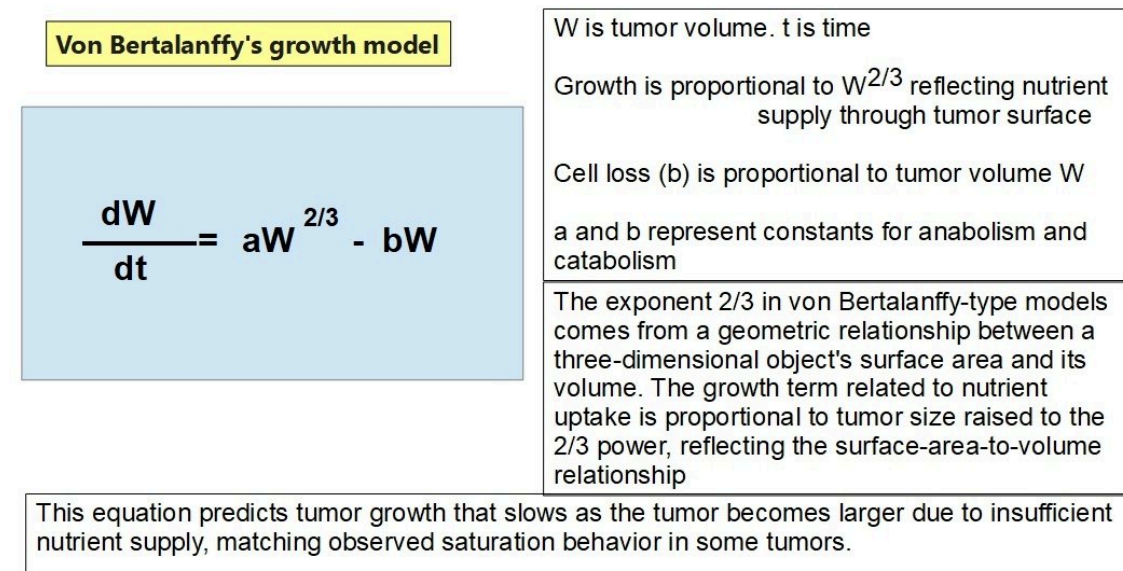


Figure 14. Von Bertalanffy growth equation

Interpretation in Cancer Cell Kinetics

The growing population of cancer cells accumulates through cell division (analogous to aW).

At the same time, cells are lost by death or other mechanisms (analogous to bW).

The model captures how the balance between growth and loss leads to tumor growth dynamics that may slow as tumors reach a certain size.

The geometric principle linking **surface area** and **volume** fundamentally influences biological growth laws by shaping how resources are absorbed and how demands increase as organisms or cell populations grow. Here is how it works:

1. Surface Area-to-Volume Relationship

Surface Area (A) scales as L^2 (square of size).

Volume (V) scales as L^3 (cube of size).

Therefore, surface area relates to volume as $A \propto V^{2/3}$.

2. Impact on Growth

Nutrient and Resource Uptake: Many biological systems (cells, tumors, organs) absorb nutrients or oxygen through their surfaces. The amount absorbed depends on surface area.

Metabolic Demand: The system's total metabolic demand depends on volume (or mass) because it represents the number of cells or biomass needing energy and nutrients.

This difference means:

As the system grows larger, **nutrient uptake (surface area-related)** does not increase as fast as **metabolic needs (volume-related)**. This imbalance imposes a natural limitation on growth rate and maximum size.

3. How It Shapes Growth Laws

The von Bertalanffy Growth Model: Uses the idea that anabolic (building up) processes depend on surface area ($\propto V^{2/3}$), while catabolic (breaking down) processes depend on volume ($\propto V$). This creates a balance that slows growth as size increases.

Other Growth Models Like Gompertz or Logistic: Also reflect slowing growth as size increases due to limits in nutrient supply or space, which is indirectly tied to surface-to-volume constraints.

4. Biological Implications

Small organisms or tumors can grow rapidly because their surface area relative to volume is large.

As size increases, the diminishing ratio of surface area to volume reduces relative resource intake, slowing growth.

This leads to **growth saturation or plateauing**, observed in many biological systems.

5. Example

A small tumor can efficiently receive nutrients through its surface.

A larger tumor faces internal cells far from the surface, possibly causing slower growth or cell death inside due to nutrient shortage.

Overall, the geometric principle explains why growth is not simply exponential and why biological systems show characteristic growth curves where growth rate declines with size.

Uses and Relevance:

It models growth that is not simply exponential but shows saturation or slowing down over time.

It helps understand tumor growth dynamics quantitatively.

It can fit experimental growth data better than simple exponential models.

It is used in cancer research, ecology, and developmental biology for describing growth curves.

Methods for Measuring Tumor Cell Kinetics

Quantifying the kinetic parameters described above requires methods capable of resolving the proliferative state of individual cells within a heterogeneous tumor population.

Thymidine labeling index: historically, tumor cells were pulse-labeled with tritiated thymidine, which is incorporated into DNA during the S phase, and the labeling index (proportion of labeled cells) was determined by autoradiography, providing an estimate of the growth fraction and, through sequential sampling, the duration of the S phase and the overall cell cycle time.

Bromodeoxyuridine (BrdU) / EdU labeling: modern analogues of thymidine labeling use halogenated or click-chemistry nucleoside analogues detected by immunofluorescence or flow cytometry, allowing more precise, higher-throughput determination of the S-phase fraction and cell cycle transit time without radioactivity.

Flow cytometric DNA content analysis: staining cellular DNA with fluorescent dyes (e.g. propidium iodide) permits rapid classification of large cell populations into G0/G1, S, and G2/M compartments based on DNA content, providing a snapshot of cell cycle distribution that can be tracked serially before and after treatment to detect synchronization or arrest.

Ki-67 and PCNA immunohistochemistry: Ki-67 is expressed in all active cell cycle phases (G1, S, G2, M) but not G0, making it a widely used clinical surrogate for the growth fraction in tumor biopsy specimens; PCNA, a DNA polymerase accessory protein, provides a related, though less specific, proliferation marker.

Mitotic index and apoptotic index: direct histological counting of mitotic figures and apoptotic bodies provides complementary measures of the rate of cell production versus cell loss, allowing estimation of the net cell loss factor.

Serial application of these techniques before, during, and after chemotherapy cycles has been essential for establishing the empirical basis for the synchronization, recruitment, and accelerated repopulation phenomena described above, and increasingly informs the design of kinetically-optimized clinical trial schedules.

SECTION B: Artificial intelligence in cell kinetics

Cell kinetics — the quantitative study of how individual cells and cell populations grow, divide, move, differentiate, and die over time — has traditionally relied on manual microscopy scoring and mechanistic mathematical models such as ordinary differential equation systems describing exponential or logistic growth as discussed in SECTION A.

Cell kinetics describe the temporal dynamics of cell populations: rates of proliferation, cell-cycle progression, migration, differentiation, and death. These processes underlie nearly every question in developmental biology, immunology, regenerative medicine, and oncology.

Historically, cell kinetic parameters were inferred from population-averaged measurements — bulk assays such as thymidine incorporation, flow cytometry snapshots, or growth-curve fitting to simple exponential or Gompertzian models. While informative, such approaches average over cellular heterogeneity and cannot easily capture the asynchronous, stochastic behavior of individual cells within a population.

The advent of time-lapse microscopy, live-cell reporters, and high-content imaging platforms has made it possible to observe individual cells continuously over hours or days, generating datasets of a scale and complexity that exceed what manual annotation or classical image-processing pipelines can handle. This data explosion has coincided with rapid advances in artificial intelligence, particularly deep learning, which is well suited to extracting patterns from large, high-dimensional, noisy datasets such as microscopy image sequences. As a result, AI has become an increasingly central tool for quantifying cell kinetics at single-cell resolution, automating tasks that were previously bottlenecked by manual annotation.

Classical cell kinetics rests on a small set of biological processes that are mathematically tractable but biologically complex. The cell cycle itself is divided into four canonical phases — G1 (first gap), S (DNA synthesis), G2 (second gap), and M (mitosis) — each governed by checkpoint proteins such as cyclins and cyclin-dependent kinases (CDKs) that ensure the fidelity of DNA replication and chromosome segregation before division. Dysregulation of these checkpoints is a hallmark of cancer, and cell-cycle dynamics have documented prognostic value across multiple tumor types, motivating substantial interest in accurately profiling cell-cycle state at scale.

Beyond the cell cycle, cell kinetics also encompass population-level growth laws (exponential, logistic, or Gompertzian growth of tumors and tissues), single-cell motility and migration (relevant to wound

healing, immune surveillance, and metastasis), and differentiation trajectories, in which multipotent or pluripotent progenitor cells commit to specific lineages over time. Each of these processes has traditionally been modeled with mechanistic mathematical frameworks — ordinary or partial differential equations, agent-based models, or Markov chain models of state transition — that encode explicit biological assumptions and offer interpretability, but which require prior knowledge of governing parameters and often struggle to capture the full heterogeneity observed in real cell populations.

Markov chain model as a foundational predecessor to modern AI techniques in tumor kinetics

Markov chains are one of the earliest and most influential mathematical tools used to model tumor kinetics and cancer progression. They form a direct conceptual and technical bridge to many of today's AI methods—especially reinforcement learning—applied to adaptive therapy and evolutionary cancer treatment.

Markov chain models of state transition are mathematical frameworks based on probabilistic processes, used to describe systems that move between different states according to certain probabilities. The functional basis of the Markov model is that the present state of a tumor determines the future of the tumor, and disregards the events that preceded it (“memorylessness”).

Interestingly the “Markov paper”, introducing the Markov chains, is from 1906, and it was originally published in Russian: “Extension of the law of large numbers to quantities depending on each other”... and the objective was not tumor kinetics.

Three elements form the fundamentals of the Markov chain:

(1) STATE, (2) STATE TRANSITION, and (3) TRANSITION PROBABILITIES

A **Markov chain** is a type of random process where the future state depends only on the current state and not on the sequence of events that preceded it. For example in the case of tumors the states for tumor kinetics can be:

STATES	TRANSITION	PROBABILITY
Healthy cells (HC)	From normal to small tumor	HC to transition to STS
Small tumor size (STS)	From small tumor to large tumor	STS to transition to LTS
Large tumor size (LTS)	From tumor to metastatic state	STS/LTS transition to metastasis
Dormant tumor	From tumor to dormant state or vice versa	Tumor transition to dormant and vice versa
Metastatic tumor	From one to more metastasis	Tumor to metastasis or metastasis to colonization transitions.
Treated tumor	From tumor to response /lack of response	For positive or negative response.
Death or remission		Prognosis

Future tumor progression depends only on the current state, not on the path taken to get there, simplifying the modeling process. However, real tumor biology can be more complex than states and probabilities. Markov models assume “memorylessness”, which might oversimplify some biological processes where history matters. Furthermore, it requires good data to estimate transition probabilities accurately.

Markov chains provide a structured way to model tumor progression with defined states and probabilities. AI systems, especially earlier or simpler ones, sometimes incorporate these models to predict tumor behavior or treatment outcomes.

Tumor growth and treatment response are inherently stochastic processes involving proliferation, death, mutation, phenotypic switching, and spatial competition. Markov chains provide a natural language for these dynamics:

States can represent:

Discrete cell phenotypes (drug-sensitive, drug-resistant, stem-like, differentiated)

Tumor burden categories (e.g., low / intermediate / high)

Clinical stages or metastatic sites

Biomarker levels (e.g. PSA, or CA19-9)

Transitions capture:

Cell division and cell death rates.

Mutation or epigenetic switching to resistance (often at low probability).

Treatment effects (increased death rate of sensitive cells).

Competitive interactions (e.g. sensitive cells suppressing resistant ones when drug pressure is low in the case of adaptive theory).

Classic examples include:

Markov models of breast tumor progression rates and screening sensitivity (1990s)

Stochastic Markov chain models of metastatic spread (e.g. lung cancer progression across organ sites)

Continuous-time Markov chains describing cell population dynamics under chemotherapy.

The key evolutionary step toward AI occurs when we add:

1) control (e.g. treatment decisions). This produces a Markov Decision Process:

- States = tumor composition / burden / biomarkers
- Actions = treat (dose level or drug choice) or withhold treatment
- Transition probabilities = how the tumor state evolves under each action
- Reward = negative tumor burden, progression-free time, quality of life, cumulative toxicity, etc.

2) Big database that allows to refine probabilities for each transition.

Early tumor kinetics models used Markov chains to describe uncontrolled growth and simple treatment effects. Adding decision-making turned them into Markov Decision Process (MDP). Modern AI (especially reinforcement learning) solves large or partially observable MDPs using neural networks, simulation, and patient data—exactly the tools now being developed in AI.

More advanced AI techniques go well beyond simple Markov models. They may use:

Deep learning to analyze medical images that detect tumors, or probabilities for each type of transition.

Reinforcement learning which can include Markov Decision Processes (an extension of Markov chains) to optimize treatment strategies.

Bayesian networks or other probabilistic graphical models that capture more complex dependencies than Markov chains.

Survival analysis and predictive modeling using large datasets without strictly adhering to Markov assumptions.

Markov chains are sometimes used as a foundation or component within AI models because they provide a clear probabilistic framework for state transitions, which can be very useful for interpreting tumor progression stages. AI sometimes uses or builds upon Markov chain models for tumor kinetics, especially in modeling progression or treatment pathways probabilistically. However, modern AI for tumor analysis frequently employs more complex machine learning or deep learning methods that go beyond traditional Markov chains to better capture tumor complexity and personalized factors.

Over the past decade, artificial intelligence (AI), and deep learning in particular, has transformed this field by enabling automated, high-throughput, and single-cell-resolution analysis of dynamic cellular behavior.

AI-based approaches complement these mechanistic frameworks by learning patterns directly from data rather than requiring an explicit parametric model. This is particularly valuable when the underlying biology is only partially understood, when data are high-dimensional (as with microscopy images), or when the goal is prediction rather than mechanistic explanation. As reviewed below, the most effective recent approaches often combine the two paradigms, using AI for perception and pattern extraction while retaining mechanistic structure for biological plausibility and extrapolation.

AI assists tumor cell kinetics research by handling complex, high-dimensional data, building predictive models, analyzing images, and simulating dynamics that are hard to study experimentally alone [\[217\]\[218\]](#).

An elementary example will help understand the basic concept of AI in cellular kinetics.

Let's imagine tracking a plant's growth in a garden. Traditionally, we would measure its height manually every week and guess its future size with basic math. AI is like having a super-smart assistant that looks at thousands of plants (in our case, thousands of patients), spots hidden patterns (e.g. "this type grows faster in certain soil"), learns from past examples, and predicts growth for a new plant—even with incomplete data. It can also simulate "what if" scenarios, like "what if we add fertilizer?"

How does AI work?

1. **Data Collection:** gathering information like tumor sizes from CT/MRI scans over time, blood markers (e.g. PSA for prostate cancer [\[219\]\[220\]\[221\]\[222\]](#)), or imaging that shows how blood flows in the tumor. This creates "longitudinal data" (measurements across time).

2. Traditional Math Models + AI Boost: Scientists use equations (like differential equations) to model tumor growth—e.g. exponential growth early on, then slowing as the tumor gets bigger (similar to the Gompertz or logistic models). AI improves this by:

- Automatically fitting these models to real patient data ^[223].
- Handling complex factors like drug effects, immune responses, or tumor resistance.

3. Machine Learning Learns Patterns:

Neural Networks / Deep Learning: These are like layered brains that process images or time-series data. For example, they can analyze dynamic contrast-enhanced (DCE) imaging or PET scans to figure out how fast molecules move in and out of the tumor (tracer kinetics) ^{[224][225]}.

Neural-ODEs (a cool hybrid): Combines neural nets with math equations for tumor dynamics. It "discovers" the underlying rules of growth from data and predicts future tumor size or survival, even from early, incomplete measurements.

4. Prediction and Personalization:

AI builds patient-specific models ("digital twins") that simulate how the tumor might grow or respond to treatment ^[226].

It predicts things like: Will this drug shrink the tumor? How long until progression? It factors in variability among patients (age, genetics, tumor type).

Tools like Physics-Informed Neural Networks (PINNs) blend real physics/biology rules with AI learning for more reliable predictions.

5. Other Helpful Roles:

Image Analysis: AI segments tumors in scans automatically and tracks changes.

Tracer Kinetics: In advanced imaging, AI speeds up complex calculations of blood flow, permeability, or cell proliferation in tumors.

Big Data Integration: Combines scans, genetics, and clinical outcomes to find new insights ^[219].

AI Benefits

- Faster analysis than manual methods.
- Better predictions for personalized treatment (e.g. adjusting doses or choosing therapies).

- Handles messy, incomplete real-world data.
- Helps in drug development by simulating tumor responses.

In short, AI supercharges tumor kinetics by learning from massive data, crunching complex math quickly, and turning measurements into actionable predictions—helping move from "one-size-fits-all" to more tailored cancer care. Research is advancing quickly in areas like glioblastoma, lung cancer, and immunotherapy response.

Artificial Intelligence Methods Relevant to Cell Kinetics

Image based inference of progression dynamics

AI models (e.g. deep learning on H&E-stained whole-slide images) classify tumor cell differentiation status using morphology and spatial organization. They infer cell trajectories and derive tumor progression scores. In lung adenocarcinoma cohorts, this approach quantifies intratumor heterogeneity, links fast-progressing tumors to up-regulated cell cycle pathways, and predicts patient survival. It permits large-scale analysis from routine pathology slides without needing dynamic live cell imaging.

Image-based inference consists of deep learning models that “learn” from histological images coupled to patient history and evolution, fed to the program, and then extracting dynamic biological insights like cell states, trajectories, progression scores and heterogeneity that are difficult to obtain directly from static samples ^[227].

It leverages visual features (morphology, spatial organization, texture) as proxies for underlying molecular and kinetic processes, permitting large-scale analysis from routine pathology slides without needing costly single-cell RNA-seq or live imaging for every case.

To achieve this, the program needs to be fed with a large amount of images, whether histology slides or MRI or PET/CT images plus the clinical, molecular and evolution data of each case. It is with these data, the AI program “learns”.

Image-derived features are treated analogously to gene expression data. Dimensionality reduction, clustering, graph construction, and diffusion pseudotime algorithms arrange image patches/cells along a progression axis — from normal-like to highly malignant states. A root (e.g. normal patch) anchors the trajectory.

Then a tumor progression score that combines differentiation predictions, spatial organization (e.g. clustering of cell types), and pseudotime into a composite metric is built. Additional inferences are: proliferation rates, immune interactions, migration/proliferation balance (e.g. in glioblastoma from single time-point images), or treatment response via live-cell imaging analysis.

What can a program like this do?

It can determine pseudotime inference, establish a tumor progression score prognostic of patient survival, and presume the involved transcriptomics. Furthermore, using live cell imaging can track cell-killing kinetics, proliferation, or T-cell tumor interactions in 3D organoids ^[228].

Pseudotime (also called pseudo-time or trajectory inference) is a computational concept used in single-cell analysis and related fields to reconstruct the *continuous progression or developmental trajectory* of cells (or image patches/tissues) from **static, cross-sectional data** — without actual time-series measurements.

It assigns a quantitative “time-like” value (pseudotime score) to each cell or sample, representing its relative position along a biological process, such as differentiation, tumor progression, or response to treatment.

Neural ODEs and Physics-Informed Neural Networks (PINNs) for Tumor Growth Modeling

Neural Ordinary Differential Equations (Neural ODEs or NODEs) are a powerful class of models in scientific machine learning. They parameterize the derivative (right-hand side) of an ODE using a neural network, allowing continuous-time modeling of dynamics from discrete, irregular, or sparse data. This is particularly useful for tumor modeling, where tumor size, growth kinetics, treatment responses, and patient-specific behaviors evolve continuously but are observed at discrete clinical time points (e.g. via imaging)

Tumor Dynamic Neural-ODE (TDNODE) uses an encoder-decoder architecture on longitudinal tumor size data to discover underlying dynamic laws. The encoder outputs interpretable patient-specific kinetic rate parameters (with inverse time units), permitting unbiased predictions from truncated (early) data and better overall survival (OS) prediction via integration with models like XGBoost ^[229].

PINNs infer parameters like proliferation rates and drug effects in tumor models by embedding physics (e.g. ODEs for growth and killing) into neural networks, validated against simulations.

Bernstein polynomial-based neural networks approximate solutions to fractional tumor-immune-chemotherapy models, capturing spatial-temporal dynamics of tumor, immune, and normal cells.

How is data fed into these programs?

Data feeding into an AI program for tumor cell kinetics involves a structured pipeline that transforms raw, often noisy or irregular clinical/preclinical data into formats suitable for training, validation, and inference. The goal is to capture dynamics like proliferation rates, treatment responses, apoptosis, and heterogeneity ^[230].

The source of these data can be:

- Imaging, such as MRI or CT or 3D volumes;
- Longitudinal tumor measurements: Sum of longest diameters (SLD), volumes from CT/MRI (e.g. caliper measurements in preclinical models or RECIST/RANO criteria in clinics). Time-stamped sequences per patient (pre- and post-treatment).
- Multimodal features such as genomics, clinical data (age, treatment, biomarkers), drug concentrations, immune markers, or TME data.
- Other: Patient-derived xenografts (PDX), cell line assays, or high-throughput omics for metabolic/kinetics modeling

These data are loaded in the form of a CSV (Comma-separated values). CSV is a plain-text format used to store and exchange tabular structured data. We can represent it as a spreadsheet or a database.

An example of a CSV:

```
PatientID, Time_Days, Tumor_size_mm, Treatment, Tumor_volume_mm3
```

The CSV file is simple, human-readable, and compatible with almost any tool such as Excel, or other spreadsheets or databases. However it is not ideal for very large or complex hierarchical data.

In the case of our example, the PatientID can be a number, name or any other text that identifies the patient. Time_Days are the observation times. Tumor_size refers to tumor measurements that can be lineal or volumetric.

The AI pipeline reads the CSV, preprocesses it (normalization, augmentation, splitting sequences), and feeds tensors/sequences into encoders or models.

CSV is often the bridge between raw clinical data (exported from trial databases) and AI workflows. It can be opened/edited in any text editor or spreadsheet software.

How does it work?

Traditional mathematical models of tumor growth (e.g. exponential, logistic, or Gompertz equations) use fixed formulas with a few parameters. A **Neural ODE** replaces (or augments) the right-hand side of an ordinary differential equation with a **neural network**. This allows the model to learn flexible, data-driven dynamics directly from observations while maintaining a continuous-time framework. Mathematically, Figure 15.

$$\frac{dz(t)}{dt} = f_{\theta}(z(t), t, p)$$

Figure 15. The equation that AI solves

where:

- $z(t)$ is the hidden state (e.g. representing tumor burden or cell populations),
- f_{θ} is a neural network parameterized by weights θ ,
- p are patient-specific parameters (e.g. kinetic rates),
- An ODE solver (like Runge-Kutta or adjoint method) projects this forward in time.

How It Works for Tumor Dynamics (e.g. TDNODE)

The most prominent example is **TDNODE (Tumor Dynamic Neural-ODE)**, developed for clinical oncology:

Encoder-Decoder Architecture:

Initial Condition Encoder: Takes pre-treatment tumor size measurements (e.g. sum of longest diameters (SLD), at different times) and outputs an initial latent state $z(0)$.

Parameter Encoder: Processes post-treatment longitudinal data to learn patient-specific kinetic parameters (interpretable as rates with inverse-time units due to built-in homogeneity constraints).

Neural ODE Decoder: Uses the learned dynamics to generate continuous tumor size trajectories.

Reducer: Maps the latent state back to observable tumor measurements.

Flow of information and process

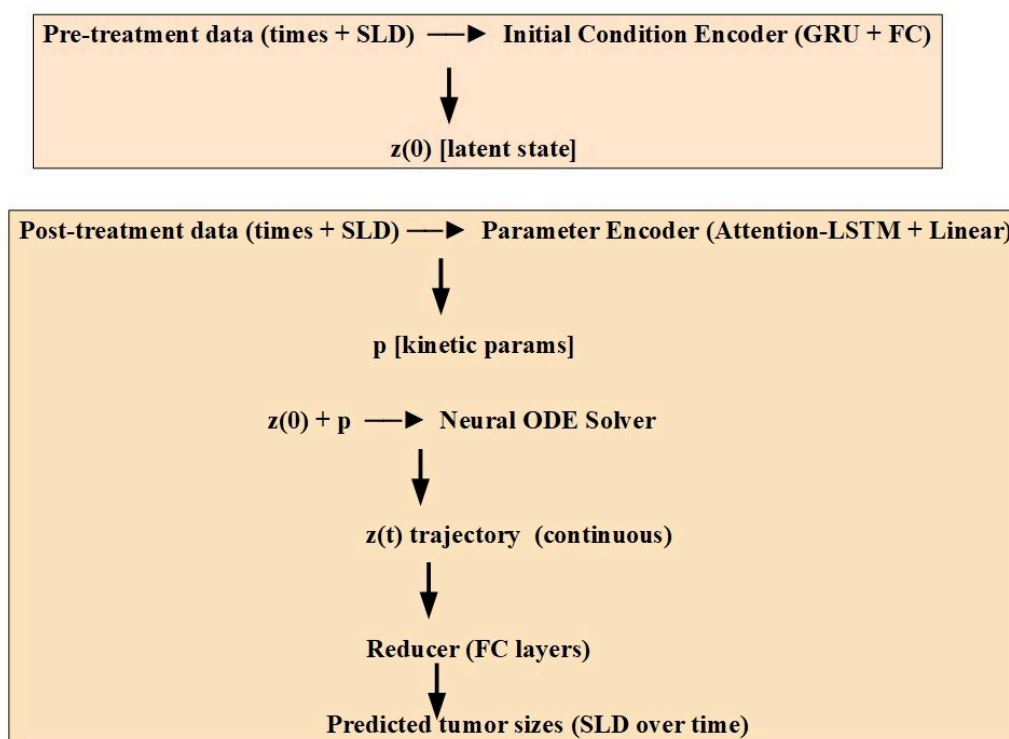


Figure 16.

GRU (gated recurrent unit): is a processor of sequential data such as time series. It controls information flow. Imagine feeding tumor size measurements one by one over time. The GRU "remembers" important past trends (e.g. how fast the tumor was growing before treatment) and forgets irrelevant noise, producing a compact summary of the patient's starting condition.

FC (fully connected layer) is an FC layer that learns arbitrary linear (or non-linear, when stacked/activated) transformations — it mixes and projects features into a new space.

In summary:

- **GRU** → Handles the sequential nature of tumor measurements over time.
- **FC** → Performs final transformations, dimensionality reduction, or mapping to outputs.

Together they help turn raw, irregular clinical data (tumor sizes at different times) into useful latent states and parameters that feed into the Neural ODE solver.

Neural ODE solvers are the computational engines that make Neural Ordinary Differential Equations (Neural ODEs), such as the equation shown in Figure 15, work. They numerically solve the continuous-time dynamics defined by a neural network.

Unlike discrete models (that step one time unit at a time), a Neural ODE defines **continuous evolution**. The solver integrates/projects this differential equation from an initial time to any desired future time.

Training the system:

- Input: Longitudinal data (time-stamped tumor sizes, often from clinical trials).
- Loss: Matches predicted vs. observed sizes, plus regularization for stability and physical plausibility.
- Data augmentation on truncated sequences helps with early prediction and robustness.

Outputs:

- Continuous tumor growth curves (excellent extrapolation from early data with low bias).
- Patient-specific kinetic metrics (e.g. growth/proliferation rates).
- Downstream predictions, such as overall survival (OS) via integration with models like XGBoost.

XGBoost (eXtreme Gradient Boosting): XGBoost builds an ensemble of weak decision trees sequentially. Each new tree corrects the errors (residuals) of the previous ones by focusing on the hardest examples. This "boosting" approach, combined with strong regularization, leads to excellent predictive performance.

Advantages in Tumor Kinetics

- **Continuous & Flexible:** Handles irregular/sparse clinical measurements naturally.
- **Personalized:** Learns individual dynamics rather than population averages.

- **Explainable Elements:** Kinetic parameters have physical meaning; can incorporate pharmacology priors.
- **Multimodal Extensions:** Combined with graphs (e.g. genomics + drug targets) or physics-informed losses for hybrid models.
- **Applications:** Predicting response to therapy, early OS estimation, virtual trial simulation, and integration with imaging or PDX data. Variants exist for breast cancer (DN-ODE), glioblastoma, tumor-immune interactions, etc.

Neural ODEs for tumor dynamics bridge mechanistic modeling and deep learning, making them powerful for precision oncology. Implementations are available in PyTorch (e.g. TDNODE GitHub repo with torchdiffeq).

Patient-Specific Mechanistic Models Integrated with AI and Big Data

Hybrid approaches combine mechanistic models (e.g., reaction-diffusion for proliferation/invasion) with AI for personalization. They use multimodal data (imaging, genomics, pharmacodynamics) to predict tumor growth, treatment response, and optimize therapies ^{[231][232][233][234]}.

Examples include genomics-informed Bayesian hierarchical modeling of NSCLC tumor dynamics ^[235] (linking alterations like TP53 to growth rates, resistance fractions) and spatial QSP (quantitative systems pharmacology) models calibrated to tumor microenvironment (TME) data for immunotherapy in hepatocellular carcinoma, and other tumors ^{[236][237][238][239][240][241][242]}.

Agent-Based and Cellular Automata Models Enhanced by Deep Learning

Deep cellular automata or transformer/PINN surrogates model cell-level interactions, movement, and clonal dynamics in tumors, reducing computational costs for large-scale simulations while capturing force balances and morphology (e.g. mild vs. aggressive tumors over months).

These simulate heterogeneity, resource availability effects on ploidy/clonal interference, and long-term forecasting.

Metabolic and Cellular Kinetic Modeling

Generative ML frameworks (e.g. RENAISSANCE) parameterize large-scale kinetic models of metabolism using omics data, applicable to tumor microenvironment reprogramming ^{[243][244]}.

Semi-mechanistic CK/PD models for CAR T-cell therapy incorporate binding-driven expansion, phenotypes, and tumor killing, calibrated to clinical data.

AI augments high-throughput screens (e.g. virtual replicates in DRUG-seq) to detect pathway perturbations and weak signals in cell responses.

Additional Applications

Machine learning for growth rate prediction: Models trained on features predict in vivo breast and other cancer growth rates ^{[245][246]}.

Subclone detection: Physics-informed AI with chemical master equations identifies driver-gene subclones and risk from expression data ^[247].

Spatial and multi-omics integration: Tools predict immune features, cell communication (e.g. NicheCompass), or TME interactions for response biomarkers.

Overall benefits include scaling experiments virtually, personalizing predictions, extracting kinetics from static data (e.g. imaging/genomics), and handling uncertainty in heterogeneous tumors ^[248]. Challenges remain in data integration, validation against wet-lab results, and interpretability, but hybrids of mechanistic modeling and AI are particularly powerful. These tools accelerate research toward better therapies by simulating "what-if" scenarios in tumor kinetics.

Classical Machine Learning

Before the widespread adoption of deep learning, classical machine learning methods — support vector machines (SVM), random forests, k-nearest neighbors (kNN), and gradient-boosted trees such as XGBoost — were applied to hand-crafted features extracted from cell images or clinical data. These methods remain widely used, particularly when datasets are modest in size or when interpretability of individual features is important. For example, comparative studies of tumor cell proliferation dynamics have found that random forest and decision tree models can predict cell growth trajectories with accuracy comparable to, or exceeding, mechanism-based differential equation models, though the latter retain the advantage of providing biologically interpretable parameters.

Convolutional Neural Networks and Image Segmentation

The dominant AI paradigm for extracting cell kinetic information from microscopy images is the convolutional neural network (CNN). Encoder-decoder segmentation architectures, most notably the U-

Net design introduced for biomedical image segmentation, use skip connections between contracting and expanding pathways to achieve precise pixel-level delineation of cell and nuclear boundaries even with limited training data. Building on this foundation, subsequent architectures have combined instance segmentation frameworks (such as Mask R-CNN-style detectors) with tracking modules to jointly identify and follow individual cells across frames, an approach exemplified by end-to-end networks such as CellTrack R-CNN, which combines and integrates detection, segmentation, and inter-frame association within a single trainable model.

A representative example is DeepSea, a deep-learning model developed for efficient single-cell segmentation and tracking in time-lapse phase-contrast microscopy. DeepSea combines auxiliary edge-detection branches with residual network blocks and was shown to recover cell-cycle-linked size dynamics in embryonic mouse stem cells, including subtle regulation of cell size during a shortened G1 phase that would be difficult to detect through manual scoring. Follow-on work extending this line of research introduced generative approaches, including a CycleGAN-based synthetic data generator (cGAN-Seg) and GAN-based super-resolution video synthesis, specifically to address the scarcity of annotated time-lapse training data that limits segmentation accuracy across diverse cell types and imaging modalities.

Recurrent and Temporal Architectures

Cell kinetics is inherently a time-series problem: cell states evolve continuously, cells divide into daughter cells that must be linked into lineage trees, and migration trajectories unfold over many frames. Recurrent neural networks (RNNs), including long short-term memory (LSTM) networks, and more recently transformer-based sequence models, are used to model these temporal dependencies, associating detected cells across frames, predicting future positions or division events, and reconstructing full lineage trees from image sequences. A persistent challenge in this setting is that tracking errors can compound over long sequences, and that mitotic events introduce discontinuities that standard sequence models do not naturally represent, since a single trajectory branches into two.

Generative and Representation-Learning Models

Variational autoencoders (VAEs) have been used to learn low-dimensional latent representations of cell state directly from imaging data, without requiring explicit phase-specific fluorescent markers. For instance, a VAE-based model called CC-VAE was trained with auxiliary tasks predicting marker intensity

and enforcing temporal consistency in the latent space, allowing cell-cycle phase to be inferred from a generic DNA stain rather than a dedicated phase reporter, thereby freeing up fluorescent channels for other experimental readouts.

Related work, such as CellCycleNet, has shown that convolutional models trained on a single nuclear stain (DAPI) can classify cells into G1 versus S/G2 phases with high accuracy, benchmarked against ground truth from the FUCCI cell-cycle reporter system, and that three-dimensional models outperform simpler two-dimensional classifiers such as support vector machines in this task.

Generative adversarial networks (GANs) serve a complementary role: rather than predicting cell state, they are used to create realistic microscopy data to augment limited training sets, to translate between imaging modalities (for example, generating fluorescence-like images from label-free phase-contrast input), or to increase the effective temporal or spatial resolution of acquired data. This synthetic-data role has become increasingly important as a mitigation strategy for the annotation bottleneck that affects nearly all deep-learning applications in this domain.

Hybrid Mechanistic-Machine-Learning Models

A growing body of work combines classical mechanistic models of cell and tumor growth with machine-learning components, aiming to combine the interpretability and extrapolation ability of mechanistic models with the flexibility and predictive accuracy of data-driven methods.

Examples include a Bayesian framework that combines a low-dimensional mechanistic model of tumor time-to-recurrence with a machine-learning-based density estimator of otherwise unmodeled clinical variables, and a hybrid model for glioblastoma that joins a graph-based semi-supervised learning component with a mechanistic proliferation-invasion partial differential equation model to predict spatially resolved tumor cell density from multiparametric MRI.

Comparative studies of tumor proliferation dynamics under metabolic perturbation have similarly found that while purely data-driven models such as random forests can achieve the highest raw predictive accuracy, mechanism-based models remain valuable for their ability to generalize outside the training distribution and to yield biologically interpretable parameters. Table 6.

AI Approach	Typical Cell-Kinetics Task	Representative Input Data	Key Limitation
Convolutional Neural Networks (CNNs)	Cell/nucleus segmentation, morphology classification	Phase-contrast or fluorescence images	Requires large labeled image sets; sensitive to imaging modality shift
Recurrent/Temporal Networks (RNN, LSTM, Transformer)	Lineage tracking, trajectory and division-time prediction	Time-lapse image sequences, tracked feature vectors	Long sequences and mitotic events are hard to model; error accumulation over time
Variational Autoencoders (VAE)	Cell-cycle phase staging from unlabeled or weakly labeled images	Nuclear stain or reporter images	Latent space may not align with true biological phase boundaries
Generative Adversarial Networks (GAN)	Synthetic data generation, image-to-image translation, super-resolution	Paired or unpaired microscopy images	Risk of generating unrealistic artifacts that bias downstream analysis
Classical ML (Random Forest, SVM, XGBoost, kNN)	Tabular prediction of proliferation, differentiation lineage, treatment response	Extracted morphological or clinical features	Depends heavily on hand-crafted feature engineering
Hybrid Mechanistic-ML Models	Tumor growth forecasting integrating biological priors	Imaging biomarkers plus mechanistic model parameters	Increased model complexity and calibration burden

Table 6. Overview of AI approaches commonly applied to cell-kinetic tasks.

Applications of AI in Cell Kinetics

Cell-Cycle Phase Prediction and Proliferation Modeling

Accurately staging individual cells within the cell cycle is foundational to cell-kinetics analysis, since proliferation rate, drug sensitivity, and differentiation potential all vary systematically with cell-cycle position. AI models now allow cell-cycle phase to be inferred directly from label-free or minimally labeled images, reducing dependence on genetically encoded reporter systems such as FUCCI, which are not available in all cell types or experimental contexts. Beyond phase classification, AI-based proliferation models are being used clinically: because tumor cell-cycle dynamics carry prognostic value in cancers including breast, gastric, and prostate cancer. Because cell-cycle evaluation can predict sensitivity or resistance to specific chemotherapeutic regimens, AI-derived cell-cycle features are increasingly incorporated into treatment-planning pipelines alongside radiomic and genomic biomarkers.

Image-Based Cell Segmentation and Tracking

Segmentation and tracking form the technical backbone on which most downstream cell-kinetic analyses depend: without accurate delineation of individual cell boundaries and consistent identity assignment across frames, quantities such as division time, migration speed, and lineage structure cannot be measured.

Reviews of this literature note that despite substantial progress, cell tracking remains complicated by low signal-to-noise ratios in label-free imaging, dense and overlapping cells, and the non-rigid, shape-changing nature of migrating or dividing cells.

Deep-learning tracking pipelines such as DeepSea and CellTrack R-CNN address these challenges by jointly optimizing segmentation and association within unified network architectures, while dissertation-level work in this area has additionally explored generative data augmentation strategies to compensate for the chronic scarcity of manually annotated time-lapse ground truth, a limitation repeatedly identified as the primary bottleneck hampering further accuracy gains in this subfield.

Tumor Growth Kinetics and Treatment-Response Forecasting

At the tissue and organism scale, AI is being used to forecast tumor growth trajectories and treatment response, often in combination with mechanistic tumor-growth models. Personalized prediction of

time-to-recurrence in ovarian cancer patients undergoing neoadjuvant chemotherapy has been demonstrated using a Bayesian framework that combines a two-compartment mechanistic model, distinguishing chemotherapy-sensitive from chemotherapy-resistant cell subpopulations, with a machine-learning density estimator for clinical covariates such as patient age.

In glioblastoma, hybrid models that combine machine learning with a proliferation-invasion mechanistic model have been shown to predict spatially resolved tumor cell density from multiparametric MRI more accurately than either component alone, with direct implications for planning surgical and radiation-therapy.

At the cellular scale, comparative work modeling breast cancer cell proliferation under glucose-limiting conditions found that random forest models achieved the highest predictive accuracy among several machine-learning approaches, narrowly outperforming decision trees, kNN regression, and a mechanism-based ordinary differential equation model, illustrating both the promise and the current accuracy trade-offs between purely data-driven and mechanistic approaches to tumor kinetics modeling.

Stem Cell Fate Prediction and Differentiation

Predicting how stem and progenitor cells will differentiate is central to regenerative medicine and tissue engineering, and AI is allowing this prediction to move from fixed, endpoint assays toward real-time, live-cell forecasting.

Approaches such as DEEP-MAP combine multi-day, multi-color live imaging of pluripotent human stem cells with deep neural networks to map and predict, at single-cell resolution, which of the three germ-layer fates a cell will adopt, based purely on morphological and proliferative features and without requiring lineage-specific reporter constructs. Notably, such models have been shown to predict fate changes as early as, or earlier than, transcription-factor-based reporters can detect them.

Related work has applied deep learning to bright-field images to prospectively predict the differentiation of hematopoietic stem and progenitor cells into granulocytic/monocytic versus megakaryocytic/erythroid lineages, to identify neural stem cell differentiation from single-cell imaging, and to predict adipogenic versus osteogenic differentiation of human mesenchymal stem cells from morphology alone, with convolutional architectures such as ResNet reported to achieve high classification accuracy on these tasks.

More recent work has also begun to fuse imaging-based fate prediction with single-cell transcriptomic lineage tracing, for example using deep-learning models to infer early fate bias directly from gene-

expression profiles of clonally related cells, extending fate prediction beyond morphology into the molecular domain.

Data, Benchmarking, and Evaluation Practices

The performance and credibility of AI models in cell kinetics depend heavily on the quality, scale, and diversity of training data, as well as on the rigor of evaluation. Several practices have become common in the field.

First, benchmark datasets with curated ground truth — such as large-scale labeled nuclear image collections released alongside cell-cycle staging models — are increasingly shared publicly to allow standardized comparisons across methods.

Second, ground-truth labels are frequently derived from orthogonal experimental reporters (for example, FUCCI cell-cycle reporters or lineage-specific transcription factor reporters) rather than manual annotation alone, providing an objective standard against which image-based AI predictions can be validated.

Third, cross-validation strategies that include large cohorts of patients, experiments, or cell lines — rather than randomly splitting frames or cells — are important for realistically estimating how well a model will generalize to new biological contexts, since naive random splits can substantially overestimate performance due to correlation between frames from the same time-lapse movie/video or patient.

Evaluation metrics vary by task: segmentation is typically assessed with pixel-level or object-level overlap measures, tracking with lineage-reconstruction accuracy and identity-switch rates, and predictive kinetic models (such as tumor growth or fate prediction) with regression metrics such as the coefficient of determination (R-squared) or classification metrics such as accuracy and area under the receiver operating characteristic curve (AUC). Reported performance in the literature varies considerably by task and dataset. For example, models predicting mesenchymal stem cell lineage commitment from morphology have reported classification accuracies in the range of roughly 85 to 96 percent depending on the architecture and differentiation lineage considered, while tumor growth regression models have reported R-squared values ranging from roughly 0.7 for mechanism-based models to above 0.9 for the best-performing machine-learning alternatives on specific datasets. Such figures should be interpreted cautiously, since they are typically reported on relatively small, single-laboratory datasets and may not transfer directly to other experimental settings.

Challenges and Limitations

Data and annotation scarcity: Manual annotation of time-lapse microscopy for training data remains labor-intensive, and many models are trained on relatively small, single-laboratory datasets, motivating growing interest in synthetic data generation and self-supervised or weakly supervised learning strategies.

Generalization across imaging modalities and cell types: Models trained on one microscopy modality (for example, phase-contrast) or one cell line often transfer poorly to other modalities or cell types without additional fine-tuning, limiting out-of-the-box applicability.

Handling of discontinuous events: Cell division, death, and cells entering or leaving the field of view create discontinuities that standard sequence models do not naturally represent, complicating lineage-tree reconstruction over long time-lapse sequences.

Interpretability: Deep-learning models, particularly those operating on raw images, often function as black boxes, which can be a barrier to clinical adoption in oncology where mechanistic understanding of treatment response is valued; hybrid mechanistic-ML approaches are one response to this concern.

Validation against ground truth: Because true cell-cycle phase or fate commitment is often only indirectly observable, models are frequently validated against other imperfect proxies (such as fluorescent reporters), which limits how confidently absolute accuracy claims can be made.

Computational and data infrastructure demands: High-content, long-duration time-lapse imaging generates large data volumes, and training and deploying deep models at scale requires computational resources and data-management pipelines that are not uniformly available across laboratories.

Comparing traditional vs AI approaches for cell kinetics

Traditional approaches rely on experimental assays and mathematical/mechanistic models, while AI methods leverage data-driven models (neural networks, deep learning, generative models, etc.) trained on imaging, single-cell omics, or time-series data. Table 7.

Aspect	Non-AI / Traditional Approaches	AI-Based Approaches	Key Advantages of AI Relative to Traditional
Core Methods	Direct cell counting (hemocytometer, automated counters); metabolic assays (MTT/MTS/XTT); DNA synthesis labels (BrdU/EdU/[³ H]-thymidine); DNA content analysis (flow cytometry with propidium iodide); proliferation markers (Ki-67 IHC); dye dilution (CFSE); time-lapse microscopy; mathematical models (ODE/PDE, logistic growth, microdosimetric kinetic model, local effect model)	Deep neural networks, graph neural networks (GNNs), transformers, neural SDEs/ODEs, generative models (e.g., scDiffEq, RENAISSANCE, DeepKINET, CellRank, TrajectoryNet, ANAKIN), ensemble ML (random forest, decision trees), physics-informed or hybrid ML	Handles high-dimensional, noisy, heterogeneous single-cell data at scale; learns complex non-linear dynamics without explicit equations
Data Requirements	Endpoint or limited time-point measurements; population averages; often requires cell fixation, labeling, or dissociation; smaller datasets	Large-scale time-series imaging, scRNA-seq, multi-omics, lineage tracing; can use single time-point data via generative modeling	Excels with big data; reconstructs continuous trajectories from snapshots
Resolution	Often population-level or limited single-cell (via flow or manual tracking); phase distribution snapshots	Single-cell resolution; continuous trajectories; spatial and temporal dynamics; gene-level kinetics	Captures heterogeneity, stochasticity, and rare subpopulations better
Predictive Power	Good for mechanistic insight and simple growth curves; limited for complex multi-factorial or long-term predictions; e.g., mechanism-based models achieve moderate R^2 (~0.77 in glucose-access tumor growth examples)	Often higher accuracy (e.g., random forest $R^2=0.92$ vs. mechanistic 0.77 for tumor cell growth under glucose limitation; transformers >95% accuracy for mitotic outcomes hours ahead); predicts fates, drug responses, perturbations in silico	Superior for forecasting, in silico experiments, and generalization across conditions/cell types

Aspect	Non-AI / Traditional Approaches	AI-Based Approaches	Key Advantages of AI Relative to Traditional
Mechanistic Insight	High — explicit parameters for rates, checkpoints, feedback; biologically interpretable equations	Variable — pure data-driven models can be “black box”; hybrid/physics-guided or explainable AI (XAI) recover known biology (e.g., overkilling effect) and reveal hidden circuits	Hybrids combine best of both; pure AI can discover novel patterns but needs XAI for interpretability
Throughput & Speed	Labor-intensive manual counting/tracking; multi-hour assays; limited parallelization	Automated image analysis (Cellpose-style segmentation), high-throughput profiling, rapid inference once trained	Dramatically faster analysis of large image/omics datasets; non-destructive real-time monitoring possible
Strengths	Biological interpretability; well-validated classic techniques; works with small samples; direct measurement of specific processes (e.g., S-phase via EdU)	Scalability; handling of stochastic + deterministic dynamics; multi-scale (single-cell to tissue); prediction of unseen perturbations/drug effects; integration of multi-modal data	Better at complex systems (e.g., collective migration, metabolic states, hematopoietic trajectories)
Limitations	Laborious; destructive (fixation/labeling); averages out heterogeneity; hard to parameterize complex models; limited long-term or multi-variable prediction	Requires large high-quality training data; risk of overfitting or bias; computational cost for training; interpretability challenges without hybrid/XAI methods	Data-hungry; performance depends on training set diversity
Typical Applications	Basic proliferation rate estimation; cell-cycle phase distribution; radiobiology RBE; simple growth modeling in culture or tumors	Single-cell trajectory reconstruction; fate prediction; kinetic rate estimation (splicing/degradation); mitotic checkpoint modeling; tumor growth under constraints; CAR-T	Expanding into digital twins, virtual cells, and precision oncology

Aspect	Non-AI / Traditional Approaches	AI-Based Approaches	Key Advantages of AI Relative to Traditional
		kinetics; in silico drug/gene perturbation screening; collective cell dynamics	

Table 7. AI vs. traditional cell kinetic studies

Discussion and Conclusions

Tumor kinetics and chemotherapy-induced cell destruction kinetics are best understood as coupled, non-linear processes rather than as independent phenomena. Tumor growth is frequently approximated by Gompertzian or related saturating models, in which the relative growth rate declines as burden increases and microenvironmental constraints accumulate. Chemotherapy, in turn, is often governed by fractional kill dynamics, meaning that each cycle eliminates a proportion of susceptible cells rather than a fixed absolute number, which explains why repeated exposure is required to drive the tumor burden downward. The clinical consequence of this interaction is that treatment efficacy depends not only on drug potency but also on the tumor growth phase, heterogeneity, vascular support, the timing and density of dosing, the barriers imposed by the TME, and the cell's resistance mechanisms.

A major lesson from this literature is that classical maximum tolerated dose strategies are not universally optimal. While high-dose therapy can produce rapid initial cytoreduction, it also imposes strong selection pressure, often favoring resistant clones and allowing repopulation after treatment hiatuses. By contrast, adaptive therapy seeks to preserve a controllable population of sensitive cells so that competitive suppression of resistant subclones is maintained over time. This shifts the therapeutic objective from eradication at all costs to ecological control, and it is particularly compelling in tumors whose growth is sufficiently slow or heterogeneous that complete elimination is unlikely with acceptable toxicity. In this framework, tumor kinetics are not just a background biological property; they become a parameter that can be exploited therapeutically.

Metronomic chemotherapy further extends this logic by replacing intermittent high-dose exposure with continuous low-dose administration. Rather than maximizing single-cycle kill, metronomic schedules

aim to maintain pressure on tumor cells, endothelial cells, and the tumor microenvironment, thereby reducing angiogenesis, modulating immune suppression, and limiting the rebound growth that often follows pulsed regimens. Importantly, the response to metronomic therapy is often delayed but is more durable, and its modeled performance can outperform maximum tolerated dose approaches over repeated cycles because dose density becomes more important than peak concentration in controlling the cumulative tumor burden. This is especially relevant for tumors whose growth follows Gompertzian kinetics, since the decelerating growth phase may be more susceptible to sustained containment than to abrupt but transient cytoreduction.

Taken together, these concepts support a more unified view of cancer treatment as a problem in **population dynamics, evolutionary ecology, and control theory**. The fractional kill hypothesis explains why repeated dosing is necessary. Gompertzian growth explains why tumor expansion slows and why growth rate is size dependent. Adaptive therapy explains how preserving competition may delay resistance. And, metronomic chemotherapy explains how sustained low-intensity pressure can reshape the kinetics of both tumor and vasculature. The convergence of these concepts suggests that optimal therapy will increasingly depend on matching the schedule of drug delivery to the kinetic state of the tumor rather than relying on a universal dosing paradigm. In this sense, future progress will likely come from combining longitudinal imaging, biomarker kinetics, evolutionary modeling, and individualized treatment adaptation into a single quantitative framework.

Tumor doubling time is a highly informative but context-dependent metric that bridges tumor biology and clinical decision-making. Its value lies in its simplicity, but that same simplicity can obscure substantial biological and methodological complexity. Current evidence indicates that TDT varies markedly by histology, molecular subtype, imaging phenotype, and modeling framework, with particularly strong data supporting its utility in lung and breast cancer. A rigorous approach to TDT should therefore emphasize definitions, model assumptions, and the biological sources of heterogeneity rather than presenting doubling time as a universal constant. When interpreted carefully, TDT remains a useful tool for understanding cancer growth kinetics and for informing screening, prognosis, and translational modeling.

The integration of artificial intelligence into the study of tumor kinetics represents a transformative leap in oncology, offering unprecedented capabilities to model, predict, and personalize cancer treatment dynamics. By leveraging machine learning algorithms on multimodal data—including imaging, genomics, and longitudinal clinical records—AI systems can uncover subtle patterns in tumor growth

rates, heterogeneity, and therapeutic responses that elude traditional mathematical models. This not only enhances the accuracy of proliferation predictions and resistance forecasting but also accelerates the discovery of novel treatment strategies, ultimately improving patient outcomes and reducing the trial-and-error burden in clinical practice. As AI continues to evolve alongside advancing computational power and data availability, its role in tumor kinetics promises to shift cancer care from reactive to proactive paradigms, paving the way for more precise, timely interventions and a deeper understanding of the complex biological processes driving malignancy. Future efforts should focus on validating these models across diverse populations and seamlessly integrating them into clinical workflows to realize their full potential.

Traditional methods remain foundational for direct, interpretable measurements and remain essential for generating ground-truth data. AI approaches (especially neural differential equations, generative models, and hybrid physics-machine learning) are increasingly superior for analyzing large-scale single-cell dynamics, predicting complex behaviors, and enabling *in silico* experimentation. Recent comparative studies (e.g., mechanism-based vs. machine learning (ML) for glucose-limited tumor proliferation) show ML often achieves higher predictive accuracy while hybrids preserve mechanistic insight.

The field is rapidly moving toward hybrid AI–mechanistic models that combine the strengths of both paradigms.

Statements and Declarations

Funding

No specific funding was received for this work.

Potential Competing Interests

No potential competing interests to declare.

Use of Generative AI

AI was used to transform the APA style references to Vancouver format.

AI was used to eliminate duplicate references.

AI was used for syntax and style corrections.

2(Supplement 67).

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Declarations

Funding: No specific funding was received for this work.

Potential competing interests: No potential competing interests to declare.