

Artificial intelligence derived virtual oncology

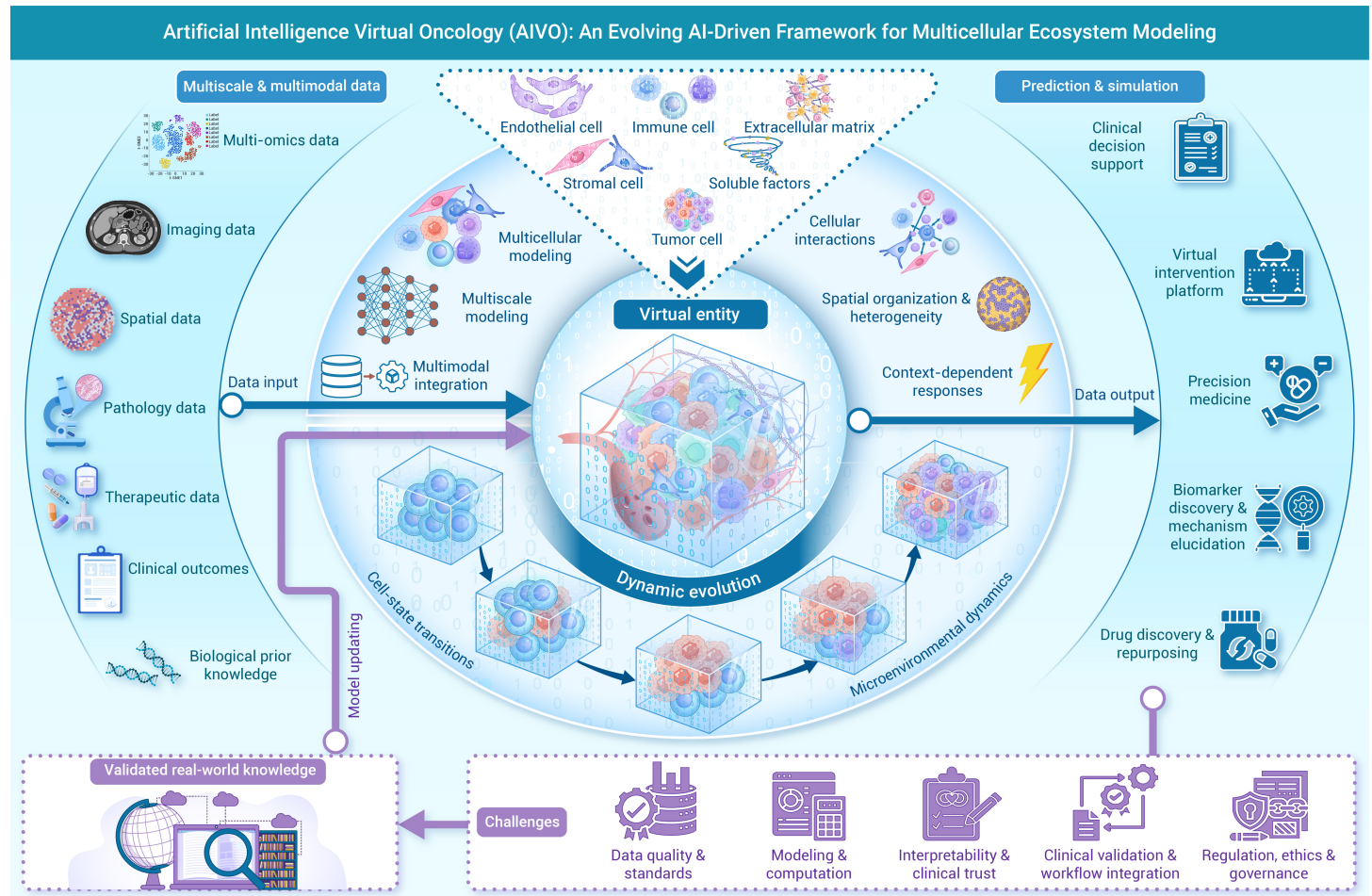
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Artificial intelligence virtual oncology (AIVO) extends individual-cell modeling to tumor ecosystems.
- AIVO as a virtual entity uses dynamic simulation to improve diagnosis and treatment for precision oncology.
- AIVO remains conceptual, facing challenges in standards, reproducibility, validation, regulation, and equity.
- Further interdisciplinary research and real-world validation are needed before AIVO becomes a reliable tool.

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Tumors are dynamic multicellular ecosystems in which heterogeneity, evolution, and cross-scale interactions remain major barriers to precision oncology. Although multiple technological advances have improved tumor characterization, they remain largely static and descriptive, limiting their ability to capture state transitions, treatment-induced remodeling, and evolving intercellular communication. Artificial intelligence virtual cell (AIVC) provides a foundation for modeling cellular states, perturbation responses, and functional outputs from multimodal data. We extend this concept to artificial intelligence virtual oncology (AIVO), a framework designed to reconstruct multicellular communication, coordinated evolution, and system-level remodeling among tumor, immune, and stromal compartments. This review summarizes the conceptual basis, construction strategies, and emerging applications of this progression from AIVC to AIVO in tumor diagnosis, dynamic monitoring, treatment response prediction, and drug screening. We further discuss key challenges in data integration, interpretability, patient-specific calibration, and clinical validation. Grounded in AIVC-based modeling, we propose AIVO as an emerging framework for multimodal integration, dynamic modeling, and decision support in future oncology.

INTRODUCTION

Cancer is not merely a disorder of uncontrolled cell proliferation, but a dynamic and heterogeneous disease process shaped by malignant transformation, clonal evolution, and continuous interactions with the surrounding tissue ecosystem.¹ These biological complexities limit the accuracy of precision diagnosis and effective treatment, drive therapeutic resistance, and thereby contribute to the persistent global burden of cancer-related mortality. Therefore, investigating tumor complexity and heterogeneity is essential to improve cancer classification, predict treatment response, and develop more precise and adaptive therapeutic strategies.

As the fundamental unit of life, the cell exhibits highly coordinated molecular, structural, and functional behaviors. Since the 1990s, scientists have envisioned the construction of comprehensive virtual cell models as research platforms capable of integrating biological knowledge, simulating cellular processes, and predicting cellular behavior.² For many years, however, this vision was constrained by a fundamental limitation: insufficient knowledge about individual molecules and their interactions. Traditional mechanistic modeling requires a pre-defined list of molecular components and precise kinetic parameters, which are largely unknown for complex systems like human cells.³ The slow pace of technological development has hampered this vision. With the emergence of high-throughput sequencing and its rapid progress in recent decades, the field of tumor research has been revolutionized, and this technology has also laid the essential data foundation for virtual cell modeling.⁴ Researchers have been enabled to access multilayer information from the genome, epigenome, transcriptome, proteome, metabolome, and more, which allows the comprehensive characterization of cancer biology and the dissection of tumor complexities and heterogeneity.⁵ However, the multi-omics technologies are typically static and endpoint measurements, and do not provide continuous, non-invasive monitoring of cellular states or capture dynamic evolution.⁶

The rapid development of artificial intelligence (AI) offers innovative pathways to address these limitations. Recent advances in AI have made it increasingly feasible to learn cellular patterns, regulatory relationships, and perturbation responses from large-scale biological datasets. The artificial intelligence virtual cell (AIVC) has emerged as a data-driven framework for predicting cellular states and behavior.⁷ Unlike conventional endpoint measurements, AIVC aims to predict perturbation responses, and explore hypothetical biological scenarios. By learning cellular behavior directly from massive data without predefined rules, AIVC has the potential to complement existing experimental systems and partially address limitations related to batch effects, incomplete spatial resolution, and correlation-based interpretation.

AI-driven virtual cell modeling has opened a new route for representing cellular states and predicting perturbation responses from multimodal data. However, the core problem in oncology lies beyond individual cells, in the evolving ecosystem formed by tumor, immune, and stromal compartments. This necessitates moving from cell-centered virtual modeling to ecosystem-level reconstruction. In this context, artificial intelligence virtual oncology (AIVO) can be viewed as an extension of AIVC toward modeling multicellular communication, coordinated evolution, and treatment-induced remodeling in cancer. By integrating these dimensions into a unified virtual representation, AIVO could connect molecular mechanisms with lesion-level phenotypes and clinical trajectories. This extension may enable a transition from fragmented observations of cancer toward a more holistic and predictive understanding of tumor behavior in patients. This review focuses on the conceptual and translational progression from AIVC to AIVO. The conceptual basis, historical evolution, construction strategies, and functional applications of AIVC are summarized. An overview of the current research on the application of AI-based virtual technology in various aspects of oncology is then provided. Finally, we outline future research directions and challenges. By providing a structured and integrated view of AIVO, this review aims to establish a foundation for further work at the interface of computational science, oncology, and precision medicine.

ARTIFICIAL INTELLIGENCE VIRTUAL CELL (AIVC) What is AIVC

AIVC refers to a computational model that integrates multi-scale and multimodal biological data using AI methods, capable of representing, simulating, predicting, and explaining cellular states and their dynamic changes.⁷ The goal is to leverage AI and extensive biological data to construct virtual entities capable of predicting cellular behavior, which thereby generate dynamic, predictive, and interpretable representations of cellular processes.

AIVC aims to learn the “intrinsic state representations” of cells under different conditions and to enable virtual simulations of *in vitro* experiments based on this understanding, such as predicting the effects of gene perturbations, drug interventions, cellular fate transitions, and changes in the microenvironment on cellular phenotypes.⁸ The construction of AIVC relies on a series of advanced AI model architectures and computational frameworks, which together form the “brain” and “skeleton” of AIVC. Its fundamental structure depends on three essential components: descriptors for multi-scale representation, encoders for adaptive representation, and a predictor for dynamic

function.⁸ Descriptors corresponding to different modalities of data inputs, such as multi-omics and microscopic imaging, point to the same cellular state. These descriptors can be used to compare cellular data measured in different experiments and serve as a reference frame for identifying new cellular states. The core of this architecture is the encoder. This module utilizes deep neural networks to extract high-level features from data obtained through multimodal omics and imaging. Subsequently, the aligned features are combined using concatenation and weighting to create a cohesive representation of the cell. The predictor can forecast cellular functions and dynamic behaviors.

History and milestones in AIVC

The emergence of AIVC is not an isolated event; rather, it builds on the continuous evolution of cell biology, whole-cell modeling, single-cell omics, and AI methodologies (Figure 1). In 1997, Schaff et al. proposed a universal computational framework called “virtual cell,” designed to combine biochemical and electrophysiological data describing individual responses with experimental microscopy image data describing their subcellular localization to serve the modeling and simulation of cell biological mechanisms.^{9,10} This can be regarded as an important starting point for modern platform-based modeling of the “virtual cell.” The E-Cell system, released in 1999, was one of the earliest computer software environments for whole-cell simulation,¹¹ providing a computational environment for simulating the interactions among cellular processes such as gene expression, signaling, and metabolism. This laid the methodological foundation for subsequent research on “virtual cells.” Although these early systems regarded cells as real objects amenable to comprehensive computational modeling, they heavily relied on manually specified mechanisms, had limited transferability, and were constrained in scalability.

In 2012, the first complete cell model of *Mycoplasma genitalium* was created by integrating multiple molecular processes into a unified predictive framework, encompassing all 482 genes and their associated molecular functions.³ This achievement is regarded as a significant breakthrough in whole-cell modeling. Following this groundbreaking research, this strategy was extended to other bacterial species, such as *Escherichia coli*.¹² These studies demonstrated that, in relatively simple prokaryotes, whole-cell modeling based on mechanistic principles and parameterized differential equations has strong interpretability and integrative capacity. However, it still cannot be readily applied to complex cellular systems such as higher eukaryotic cells, tumor cells, and complex microenvironments.

The next transformation was driven not by simulation techniques themselves, but by the rapid development of single-cell transcriptomics, proteomics, spatial transcriptomics, high-content imaging, and CRISPR perturbation screening technologies, which greatly expanded the observable dimensions of cellular states.^{13–15} Among these advances, perturb-seq and related methods are particularly important, as the combination of CRISPR perturbations with single-cell RNA sequencing directly links specific interventions to single-cell responses, shifting data from static descriptions toward more causal inference.¹⁶ In 2017, the Human Cell Atlas project was initiated, which systematically defines all human cell types and their molecular characteristics and provides a large-scale reference map for constructing a universal cell characterization across tissues and states.¹⁷ Although these advances did not directly produce integrated AIVC models, they provided a rich foundation of high-dimensional, multimodal perturbation data.

The rapid development of AI has enabled us to build algorithms that automatically learn patterns from vast amounts of data. In 2018, single-cell variational inference (scVI) was proposed, utilizing deep generative models to learn the latent representations of single-cell transcriptomes.¹⁸ This advancement laid the groundwork for the development of transferable cell-state characterization models. In 2021, AlphaFold2 achieved near-experimental accuracy in protein structure prediction.¹⁹ Although it does not constitute a complete cellular model, it significantly enhances the molecular-level prior knowledge required for AIVC and improves the feasibility of applying AI to biological modeling. In the direction of single-cell foundation models, representative studies such as scGPT and SCimilarity, proposed in 2024, further promoted the development of cell-state representation learning.^{20,21} The main value of such models lies in their ability to form reusable, generalizable latent

representations. In addition, a perturbation-prediction-oriented model such as xTrimoscFoundation further expanded the application potential of AI in modeling cell-state transitions and intervention responses.²² These AI-based methods offer advantages in scalability, cross-dataset adaptability, and the handling of high-dimensional, heterogeneous data, and are therefore closer to the needs of clinical translational research for inter-patient variability, multimodal data integration, and generalized prediction of unknown states. Although these models still have limitations, including insufficient direct interpretability, limited transparency of causal mechanisms, and the need for systematic experimental validation of predictive results, they provide a technical foundation for the development of AIVC.

Based on the above trends, Bunne et al. proposed the vision of the AIVC in 2024.⁷ The goal of AIVC is to create a universally applicable digital model of cells. Given any cell type and its environment, it can simulate the state of various molecular components within the cell and predict the cell's functional response. This marks the transition of AIVC research from a fragmented exploratory phase to a new stage characterized by a clear conceptual framework. In 2025, the Arc Institute launched the Virtual Cell Challenge, aimed at establishing a rigorous evaluation framework that points the way forward for the field.²³ This indicates that differences among current models are reflected not only in their technical architectures but also in their biological objectives, depth of validation, and how their predictions are connected to experimental results. The data pillar and closed-loop learning framework,²⁴ and the “Predict-Explain-Discover (P-E-D)” strategy²⁵ echo from different perspectives and emphasize the modeling goals and reinforce the core objectives of AIVC: predictability, interpretability, and experimental verifiability. These studies highlight the relationships among predictive performance, model interpretability, prior biological knowledge, and iterative experimental validation. They can therefore be regarded as methodological complements within the broader AIVC-related research ecosystem.

After the proposal of AIVC, AIVC-related studies increased rapidly from 2025 to 2026. However, AIVC remains largely a research vision or conceptual framework, rather than a mature technical system with clear boundaries and unified standards. Existing virtual cell prototypes or systems relatively close to the AIVC vision include T-World and 4DWCM. T-World has been extensively validated against independent experimental data and has shown the predictive value of domain-specific virtual cell in cardiomyocyte electrophysiology and drug-response evaluation, making it more directly relevant to cardiac drug safety assessment, especially arrhythmia and cardiotoxicity risk prediction.²⁶ 4DWCM was constructed and evaluated using experimental data and advanced whole-cell dynamic modeling through high-resolution spatiotemporal simulation, mainly supporting disease mechanism interpretation and potential target discovery.²⁷ Other AIVC-related models are mostly foundation models or task-specific models. Transcriptomic perturbation/state prediction models, such as AetherCell,²⁸ AlphaCell,²⁹ Lingshu-Cell,³⁰ SCALE,³¹ and Squidiff,³² learn conditional generative cell-state spaces to simulate transcriptomic changes under drug, genetic, disease, or developmental conditions. Morphology generation models, such as CellFluxV2³³ and CellFluxRL³⁴ encode microscopy images into latent morphological states and predict future or perturbed cellular phenotypes. Regulatory dynamics models such as RegVelo³⁵ combine RNA velocity with gene regulatory networks to constrain cell-state dynamics and predict cell-fate direction. Cell-level virtual screening models, such as CellVS-Net,³⁶ jointly model cell states and candidate compounds for drug-effect prediction and candidate ranking. These models remain unvalidated experimentally, so their clinical relevance should be considered potential and indirect, mainly through disease cell-state modeling, virtual perturbation, target prioritization, drug-response prediction, and patient-specific virtual cell construction. In addition, AIVC evaluation frameworks, such as VCBench,³⁷ have emerged. These studies suggest that the AIVC ecosystem is rapidly expanding, but with substantial differences in research scope, technological maturity, and level of evidence.

How to construct AIVC

The construction of an AIVC involves integrating multiple data types, advanced AI modeling techniques, and continuous feedback from both experimental and computational systems. AIVC is designed to model cellular behavior by combining knowledge from molecular biology, systems biology,

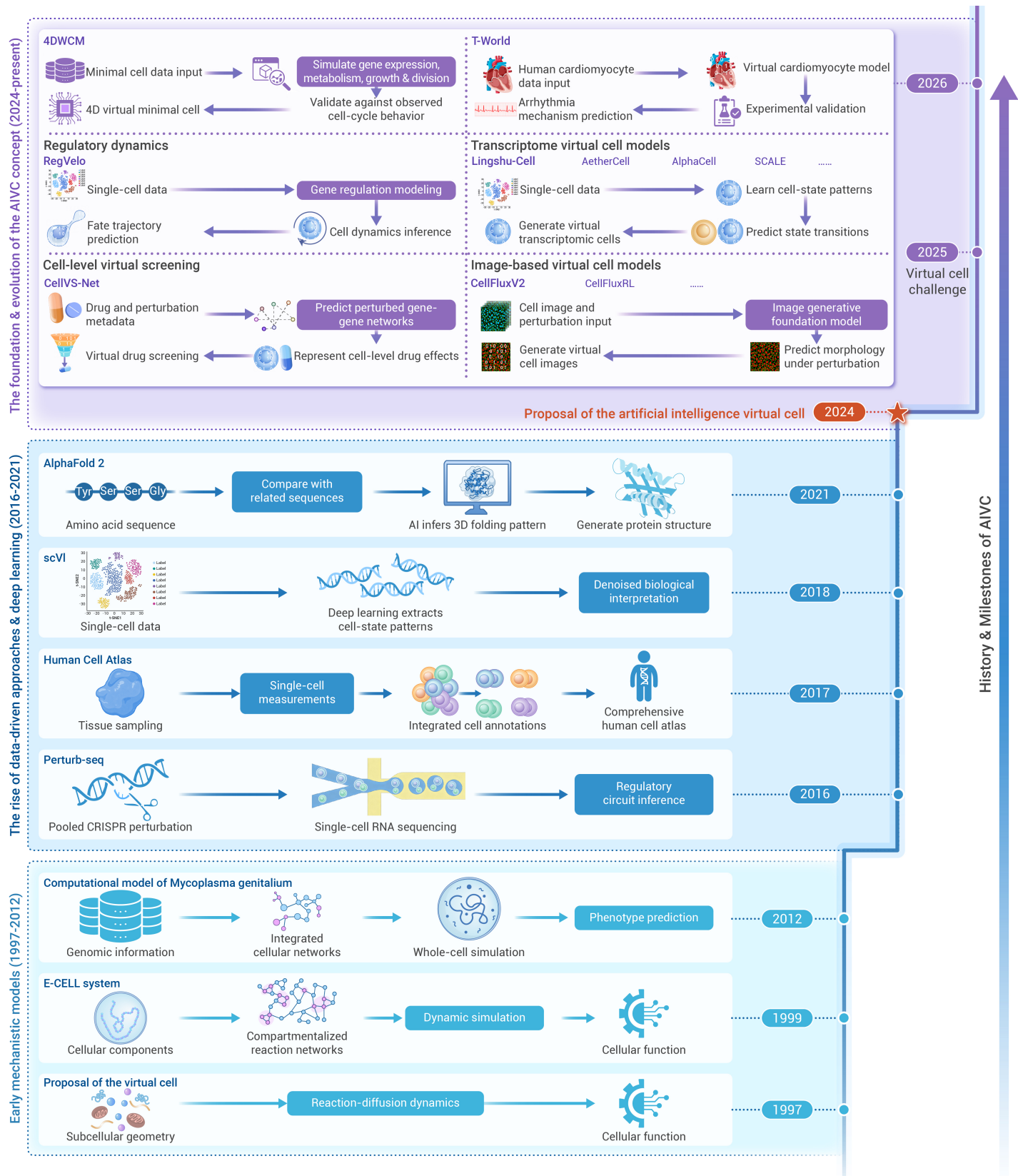


Figure 1. History and milestones of AIVC AIVC is built upon the continuous evolution of cell biology, whole-cell modeling, single-cell omics, and artificial intelligence methodologies. The field has progressed through three stages: an initial phase of early mechanistic models, followed by the rise of data-driven and deep learning approaches, and the foundation and evolution of AI-driven cell models.

and computational methods to create a dynamic, predictive, and interpretable model of cellular processes (Figure 2).

Data integration: building the foundation. The first step in constructing an AIVC is the collection and integration of high-quality, multi-modal biological

data.⁷ This means bringing together complementary sources of information, such as single-cell RNA sequencing, proteomics, metabolomics, and spatial transcriptomics, so that the model can describe the cell across different levels of organization. These data collectively link molecular features, including

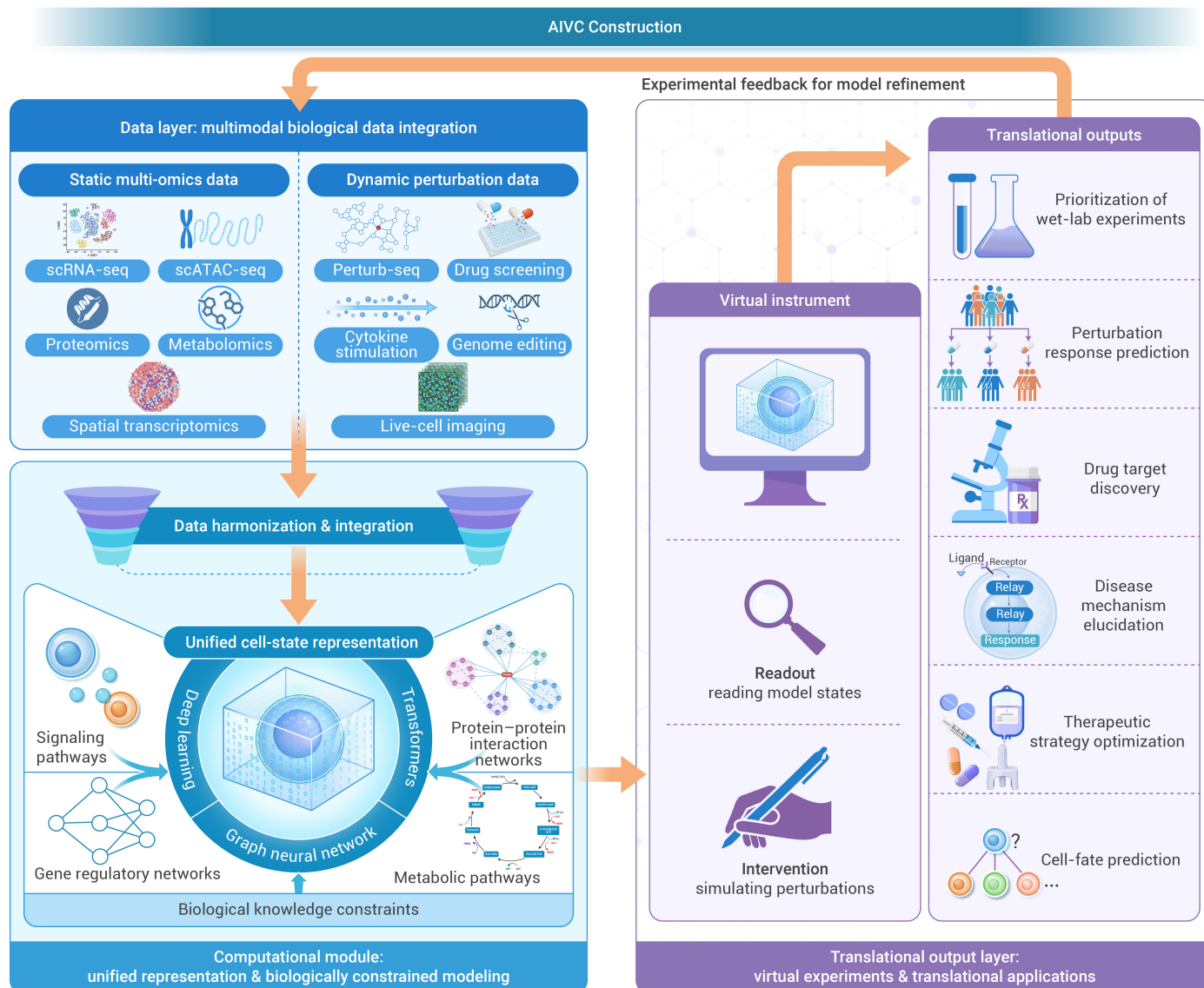


Figure 2. The construction of AIVC AIVC integrates static multi-omics and dynamic perturbation data to construct unified cell-state representations using computational models constrained by biological knowledge.

gene expression and protein interactions, to cellular responses and to tissue-level context, such as the spatial organization of cells. In this sense, integrated data provide the foundation on which the AIVC model can be built, and the scope of the resulting framework is likely to depend on the breadth, depth, and standardization of the available training data.

Observational data alone are unlikely to be sufficient. A model trained only on static snapshots may be useful for characterizing cell states, but it is less well suited to representing how those states change over time or in response to interventions. For that reason, perturbation-based and dynamic datasets are likely to be particularly important in AIVC development. Approaches such as Perturb-seq, drug screening, cytokine stimulation, lineage tracing, and live-cell imaging can provide information not only on what a cell looks like at a given moment but also on how it shifts under defined conditions.³⁸

Unified representation: encoding cellular states. Once these data have been gathered, the next critical step is to transform them into a unified representation of the cellular state. This is important because an AIVC-like framework depends on a coherent internal description of the cell rather than on separate datasets generated by different platforms. The aim is to encode molecular identity, ongoing biological activity, and aspects of environmental context into a shared format that can support downstream prediction and simulation.

This step can be approached using AI models that learn patterns across integrated datasets. Deep learning frameworks, graph neural networks (GNNs), and transformers are all relevant in this setting because they can capture relationships among genes, proteins, metabolites, and other cellular features. For instance, deep generative models, such as scVI, are employed to generate latent representations from single-cell transcriptomic data, which may then support the inference of cellular states under different conditions.^{8,18} These models help encode the cell's molecular identity, its biological processes, and its interactions with the microenvironment into a format that can be used for prediction and simulation.³⁹ In addition, integrating spatial omics data allows the incorporation of tissue architecture into the model, adding an extra layer of realism and biological relevance. The ability to model the three-dimensional spatial distribution of molecules and cells enhances the precision of the virtual cell, particularly for understanding how spatial organization influences cellular behavior.²⁴

Biological knowledge integration: constraining the model. Data-driven representations alone may not be sufficient. To improve interpretability and biological plausibility, the patterns learned by the model should be considered together with existing biological knowledge, including signaling pathways, gene regulatory networks, metabolic pathways, and cellular dynamics, which is crucial for enhancing model interpretability and biological relevance.⁴⁰

In practice, such knowledge can be incorporated into the model as priors or constraints, which may help align model outputs with established biology.⁴¹ For example, mechanistic descriptions of cell biology, such as intracellular signaling or metabolic networks, can provide structure that purely data-driven systems may otherwise lack. This is important because models trained only to fit data may identify statistical associations that do not necessarily reflect biologically meaningful relationships. Additionally, the integration of experimental feedback, including perturbation and knockout data, can then be used to iteratively refine the model and assess whether its predictions remain biologically plausible.⁴²

Virtual instrument (VI): enabling readout and in silico perturbation. A further step is to establish a way to interact with the model, which is where the virtual instrument (VI) becomes important. The VI can be understood as an interface operating on the unified representation. It reads the model state and translates it into outputs interpretable by researchers; it provides a way to simulate interventions within the modeled space and examine the resulting changes.⁷

Within the AIVC framework, such VI modules may allow researchers to explore predicted cellular responses to perturbations, predict the effects of genetic modifications, and explore how changes in the cellular environment might impact cellular behavior. For example, simulations of gene knockouts or drug treatments may be used to predict changes in gene expression, protein abundance, or cellular phenotypes. These simulations are essential for understanding complex biological systems and for conducting virtual experiments, thereby reducing reliance on expensive and time-consuming wet-lab experiments.³⁹

What's the function of AIVC

The fundamental function of AIVC is to compress complex multi-omics and spatial information into a unified cellular-state representation, thereby enabling a more accurate identification of cell types, cell subpopulations, functional states, and transitional states.⁴³ AIVC shows the potential to predict the effects of interventions (e.g., gene knockouts, transcription factor combinations, drug treatments, and cytokine stimulations) on cellular transcriptomes, proteomes, or phenotypes, under specific cohort or model conditions.²³ More importantly, compared to traditional analyses, AIVC is expected to better address issues related to batch differences, modality missingness, and cross-platform data integration.

A powerful virtual cell model, capable of learning and reasoning like a skilled biologist, can predict the responses of different cell types and states to unknown perturbations. This will support the development of new drugs, the study of disease mechanisms, and the practice of personalized medicine.

ARTIFICIAL INTELLIGENCE VIRTUAL ONCOLOGY (AIVO)

Tumors are not static lesions composed of a single population of malignant cells but dynamic ecosystems shaped by interactions among cancer cells, immune cells, stromal cells, and the extracellular matrix (ECM).⁴⁴ Therefore, the critical challenge in cancer research is not merely the identification of additional molecular abnormalities, but the understanding of how malignant cell states and multicellular systems interact, adapt, and co-evolve under therapeutic pressure.⁴⁵⁻⁴⁷ AIVC frameworks offer a new conceptual and computational strategy for modeling cell states as computable, updatable, and perturbation-responsive entities.^{7,48} Building on this foundation, AIVO extends the focus from individual cellular states to the tumor as an evolving system, integrating malignant cells, immune and stromal compartments, spatial architecture, and therapeutic perturbations into a unified virtual framework.^{41,49} The significance of this framework lies not merely in improving clustering or classification reliability but in moving cancer research beyond descriptive atlases toward predictive and clinically relevant modeling of tumor evolution, multicellular interaction, and treatment response. On this basis, the following sections discuss how AI applications in oncology, together with AIVC- and AIVO-related frameworks, can be used to reconstruct tumor cell states, model antitumor immunity, capture stromal and spatial constraints, and ultimately build integrated virtual tumors.

Artificial intelligence virtual tumor cell

Although conventional experimental models have substantially advanced

tumor biology, most remain better suited to describing tumor states at selected scales or time points than to capturing state transitions, therapy-driven adaptation, and the longitudinal evolution of tumor cells. In this context, the concept of the virtual tumor cells can be regarded as a cell-level module within future AIVO frameworks, enabling the digital reconstruction of the molecular characteristics, functional states, and dynamic trajectories of tumor cells through the integration of AI, multi-omics data, and computational modeling.⁵⁰ Although many existing AI-based oncology studies do not constitute AIVC systems in the strict sense, they provide important methodological foundations for tumor-state representation, spatial molecular reconstruction, dynamic evolution modeling, and therapeutic response prediction (Table 1). They can therefore be considered key building blocks for the future development of AI virtual tumor cell frameworks.

For cancer diagnosis and tumor-state characterization, more specifically, AIVC will integrate diverse data modalities, including single-cell transcriptomics, spatial omics, epigenomic profiles, histopathological images, and clinical imaging, to reconstruct a higher-dimensional state map of an individual patient's tumor. Xu et al. developed Prov-GigaPath, a whole-slide foundation model that was benchmarked for cancer subtyping and broader digital pathology tasks, highlighting the value of whole-slide modeling in digital pathology.⁵¹ Ding et al. developed TITAN, a multimodal whole-slide foundation model that showed promising performance in cancer classification, rare cancer retrieval, prognosis prediction, and pathology report generation.⁵² AI-based prediction of spatial transcriptomics also bridges digital pathology images and molecular states. Path2Space demonstrated the feasibility of predicting spatial gene expression profiles from routine histopathological sections using deep learning, thereby inferring spatial molecular features in breast cancer tissues.⁵³ For AI virtual tumor cells, the significance of such methods lies in their potential to serve as spatial molecular-state reconstruction modules, enabling virtual tumor cells to move beyond averaged molecular representations and progressively incorporate tissue spatial architecture and microenvironmental context.

The dynamic evolution of tumor cells represents another important aspect that should be incorporated into AI virtual tumor cell frameworks. Existing AI-based and mathematical modeling studies have begun to use longitudinal multimodal data, including imaging, serum biomarkers, pathological information, and treatment records, to characterize tumor progression and provide a foundation for dynamic tumor modeling. In prostate cancer, patient-specific models based on magnetic resonance imaging (MRI) and finite-element methods have been explored to simulate tumor growth and dynamic changes in prostate-specific antigen (PSA) levels.⁵⁴ Studies have suggested that even when PSA levels do not rise significantly, these models can still reconstruct tumor progression after diagnosis and help address the limitations of conventional serum-based monitoring.⁵⁵ In glioma, reaction-diffusion models have been used to characterize the spatiotemporal infiltration of tumor cells along white matter fiber tracts, and model the invasive behavior of diffuse brain tumors.⁵⁶ Such models have been further used to predict glioblastoma growth, the progression of postoperative residual disease, and the extent of tumor infiltration.⁵⁷ Studies have also used Brownian motion-based mathematical methods to model glioblastoma infiltration into surrounding brain tissue, with the aim of supporting the assessment of tumor invasion extent.⁵⁸ In breast cancer, growth models based on parameters such as tumor volume doubling time have shown consistency with clinical observations and have been explored for assessment of tumor progression rate and aggressiveness, with the potential to inform screening intervals and intervention timing.⁵⁹ These disease-specific models provide useful modeling strategies for the dynamic evolution module in the AI virtual tumor cell.

For treatment response prediction, existing models have been used to simulate or predict the efficacy of both surgical and nonsurgical interventions. A nephroblastoma oncosimulator integrating MRI data, chemotherapy regimens, and postoperative pathological information has demonstrated the potential to predict tumor volume changes and therapeutic response.⁶⁰ A spatiotemporal model of glioblastoma integrating imaging, pathological, and genetic information, along with pharmacokinetic and pharmacodynamic processes, has been used to simulate potential responses to temozolomide therapy.⁶¹ In breast cancer, the combination of quantitative MRI and mathematical modeling has demonstrated reasonable accuracy in predicting the

Table 1. Summary of artificial intelligence virtual cell (AIVC)-related models and foundational modules in tumor cells.

Type category	Model/ method	Tumor type/ application scenario	Evidence level	Brief introduction	Data modality	limitations/ challenges	Reference
Tumor cell	AetherCell	Pan-cancer	Benchmarked model	A generative foundation model for predicting drug responses, evaluating combination therapies, and stratifying patients, with applications to pancreatic, ovarian, and gastric cancer organoids and clinical cohorts across 17 cancer types.	scRNA-seq	Overlooks intra-tissue heterogeneity and multi-omics integration.	Ref 28
Tumor cell	Squidiff	Glioblastoma	Benchmarked model	Learns dynamic cellular state changes under external stimuli, and has been applied in glioblastoma research to predict the transcriptomic responses of tumor cells and oligodendrocytes to drugs, thereby supporting drug screening and precision therapy.	scRNA-seq	Demands long training time and heavy computation.	Ref 32
Tumor cell	SCALE	Pan-cancer	Benchmarked model	Uses conditional transport and a set-aware flow architecture with a LLaMA-based cellular encoder for virtual cell perturbation prediction, including chemical perturbation modeling in 50 diverse cancer cell lines.	scRNA-seq	Misaligns evaluation metrics with biological relevance and cannot capture intermediate cellular response dynamics.	Ref 31
Tissue-level digital pathology	Prov-GigaPath	Pan-cancer histopathology	Benchmarked model	Pretrains a whole-slide foundation model on 1.3 billion tiles from 171,000 slides using DINOv2 and LongNet to predict gene mutations, classify cancer subtypes, and perform zero-shot vision-language tasks.	Whole-slide images and pathology reports	Requires substantial computational resources and may retain institution-specific biases despite external benchmarking.	Ref 51
Tissue-level digital pathology	TITAN	Pan-cancer histopathology	Benchmarked model	Enables multimodal whole-slide representation learning through vision-language alignment using 336,000 whole-slide images, synthetic captions, and pathology reports, supporting zero-shot diagnosis, rare-cancer retrieval, and report generation.	Whole-slide images, synthetic captions, and pathology reports	Relies partly on region-crop pretraining and synthetic captions and still requires prospective clinical validation.	Ref 52
Tissue-level spatial transcriptomics	Path2Space	Breast cancer spatial profiling	Benchmarked model	A deep learning model that predicts spatial gene-expression patterns from H&E histology images, enabling scalable reconstruction of tumor microenvironment features.	H&E whole-slide images and paired spatial transcriptomics data	Limited by cancer-specific validation, reliance on paired histology-spatial transcriptomics data, and unproven clinical utility.	Ref 53
Tumor cell	Personalized prostatic carcinoma model	Prostate cancer	Proof-of- concept study	Integrates patient-specific MRI-derived ADC into a biomechanical model to simulate tumor growth and PSA dynamics under active surveillance.	MRI data	Validated on only four patients, limiting generalizability.	Ref 54

Table 1. (Continued)

Type category	Model/ method	Tumor type/ application scenario	Evidence level	Brief introduction	Data modality	limitations/ challenges	Reference
Tumor cell	Physics-informed machine learning digital twin	Prostate cancer	Proof-of-concept study	Integrates physics-based modeling, machine learning, MRI-derived tissue features, and longitudinal PSA measurements to reconstruct patient-specific prostate tumor growth.	MRI data and longitudinal PSA measurements	Misses non-PSA secreting tumor phenotypes and requires validation in larger independent cohorts.	Ref 55
Tumor cell	Reaction-diffusion model	Glioblastoma	Proof-of-concept study	Couples a reaction-diffusion equation for tumor cell density with a parametric deformation model based on directly manipulated free form deformation to approximate brain tumor mass effect by tracking landmarks on the gross tumor volume boundary.	MRI data	Uses a simplified deformation model and requires further validation with longitudinal patient imaging data.	Ref 56
Tumor cell	Triscale reaction-diffusion numerical model	Glioblastoma	Proof-of-concept study	Presents a finite-difference numerical model incorporating skull-imposed Neumann boundary conditions to simulate glioma invasion through inhomogeneous brain tissue and estimates tumor doubling time.	MRI data	Lacks statistical validation due to limited clinical data access.	Ref 57
Tumor cell	Brownian motion-based mathematical methods	Glioblastoma	Proof-of-concept study	Simulates anisotropic infiltration of glioma cells into brain tissue by exploiting diffusion tensor imaging data and modeling cell movement as a stochastic process.	MRI data	Excludes cell proliferation modeling and remains clinically unvalidated.	Ref 58
Tumor cell	Growth model	Breast cancer	Proof-of-concept study	Simulates tumor growth for virtual clinical trials of breast cancer screening and has been validated against clinical tumor volume-doubling times.	Clinical data on tumor volume doubling time	Simplifies interpatient and biological heterogeneity and does not model individual tumor trajectories.	Ref 59
Tumor cell	Oncosimulator/multiscale mechanistic model	Nephroblastoma	Proof-of-concept study	Adapts a mechanistic <i>in silico</i> model to predict tumor volume reduction after preoperative chemotherapy in nephroblastoma patients from different risk groups.	MRI data	Evaluated in a limited patient cohort and requires prospective external validation.	Ref 60
Tumor cell	MRI-based digital response model	Breast cancer	Experimentally validated system	Uses imaging-driven digital models to forecast patient-specific response to neoadjuvant chemotherapy.	MRI data	Presents no complete ground truth, risking accuracy overestimation.	Ref 62
Tumor cell	Multiscale mechanistic model	Non-small cell lung cancer	Proof-of-concept study	Quantifies the <i>in vivo</i> cell-killing efficacy of cisplatin-based doublet chemotherapy in patients with non-small cell lung cancer using retrospective computed tomography data and a multiscale simulation model.	CT imaging data	Lacks patient-specific proliferation parameters and suffers from uncertainties in tumor kinetics.	Ref 63

Table 1. (Continued)

Type category	Model/method	Tumor type/application scenario	Evidence level	Brief introduction	Data modality	limitations/challenges	Reference
Tumor cell	Mechanistic digital twin/therapy simulation	Pediatric liver tumors	Experimentally validated system	Uses mechanistic models and virtual patient simulations to identify ceritinib as a nuclear integrity-disrupting therapy, validated <i>in vitro</i> and <i>in vivo</i> .	Genetic and transcriptomic data	Has been validated preclinically but not yet evaluated in clinical trials.	Ref 64
Tumor cell	Theoretical pharmacodynamic model	Solid tumors	Proof-of-concept study	Develops a pharmacodynamic model to compare doxorubicin dosing strategies, suggesting that a high initial dose followed by lower doses may minimize P-glycoprotein induction and improve tumor cell-killing efficiency.	Literature-based pharmacokinetic parameters	Receives no experimental or clinical validation.	Ref 66
Tumor cell	QSP model	B-cell lymphoma	Proof-of-concept study	Establishes a quantitative systems pharmacology-based method to calibrate virtual tumors using <i>in vitro</i> cell viability data, characterize intratumoral heterogeneity, and predict responses to BH3 mimetics alone or in combination.	<i>In vitro</i> drug sensitivity (cell viability) and <i>in vivo</i> tumor growth inhibition data	Suffers from identifiability issues in protein expression distributions.	Ref 68

Abbreviations: scRNA-seq, single-cell RNA sequencing; H&E, hematoxylin and eosin; MRI, magnetic resonance imaging; ADC, apparent diffusion coefficient; PSA, prostate-specific antigen; CT, computed tomography; QSP, quantitative systems pharmacology.

response of triple-negative breast cancer to neoadjuvant therapy.⁶² Secondly, beyond conventional chemotherapy modeling, related computational approaches have supported individualized regimen selection and precision drug screening, providing useful precedents for AIVC-related therapeutic modeling. In non-small cell lung cancer, multiscale models have been applied to estimate differences in the cytotoxic efficacy of cisplatin-based regimens combined with gemcitabine, vinorelbine, or docetaxel, thereby helping inform the exploration of individualized treatment selection.⁶³ In the context of precision drug screening, studies of high-risk pediatric liver tumors have integrated clinical, genetic, and transcriptomic information to generate patient-specific digital twins, supporting the prediction and validation of the potential efficacy of ceritinib and underscoring the utility of this approach for candidate drug prioritization.⁶⁴ These studies suggest that integrating multimodal data with mechanistic models can, when coupled with experimental validation, support the preclinical prioritization of candidate drugs, thereby providing a valuable foundation for AI virtual tumor cell-related therapeutic modeling.

In drug research, multiscale models have moved beyond simple pharmacokinetic metrics to reveal the complex interplay among drug distribution, resistance evolution, and combination therapy. For drug delivery and anti-angiogenic therapy, several studies have suggested that delivery metrics alone, such as intratumoral drug concentration, are insufficient to capture the overall response of solid tumors, underscoring the need to integrate patient-specific tumor growth models for improved exploratory prediction of tissue-level therapeutic outcomes.⁶⁵ To address resistance and combination treatment, theoretical frameworks have described the dynamic interplay among intracellular doxorubicin exposure, P-glycoprotein induction, and tumor cell killing, thereby capturing a potential coupling between pharmacological activity and resistance evolution.⁶⁶ Acquired resistance mechanisms have also been incorporated into tissue-scale simulations, revealing that cellular resistance can give rise to more complex emergent response patterns at the tissue level.⁶⁷ Moreover, virtual tumor platforms have been used to model intratumoral heterogeneity together with intrinsic and acquired resistance in the context of multidrug therapy, supporting the exploration of how combination strategies may be linked to *in vitro* and *in vivo* response patterns.⁶⁸ These studies provide important insights for establishing the “perturbation-

response” module in AI virtual tumor cell frameworks. However, their predictive performance remains highly dependent on model assumptions, parameter settings, and the extent of experimental validation.

Artificial intelligence virtual immune cell

Unlike tumor-cell-centered models that mainly address malignant evolution, the immune compartment is defined more by functional plasticity and dynamic intercellular interactions.⁶⁹ Immune-cell states are continuously shaped by antigen stimulation, cytokine signaling, stromal cues, metabolic constraints, and therapeutic pressure.⁷⁰ Their effects on tumor control or immune escape, therefore, cannot be inferred from abundance alone. They must be understood through state transitions, spatial organization, and evolving communication networks within the tumor microenvironment (TME). This distinction is especially important in immunotherapy, where outcome depends less on the presence of immune subsets than on how they change, interact, and adapt over time.

Although single-cell and spatial profiling technologies have greatly improved the resolution of immune-cell characterization, most remain essentially descriptive.^{71,72} They can define cellular composition and signaling states with increasing precision, but they are less able to predict how immune states will evolve after treatment or which microenvironmental interactions will ultimately determine response or resistance. This limitation is particularly important in immunotherapy, where the outcome usually reflects the combined behavior of multiple cell populations rather than a single molecular feature. In particular, when baseline or limited time-point multi-omics data are used to infer post-treatment immune responses, a gap remains between the static immune profiles captured by these data and the continuously evolving response to immunotherapy. Against this background, AI virtual immune cell offers more than multimodal data integration. It provides a dynamic computational framework in which immune cells can be represented as computable and updatable units, and their interactions can be modeled explicitly.⁷³

Existing tumor-immune simulation studies have provided a foundation for AI virtual immune cell to describe dynamic biological processes. For instance, an agent-based model of anti-PD-1 therapy has suggested that spatial

structure and phenotypic heterogeneity may influence tumor-immune dynamics beyond what non-spatial models can capture.⁷⁴ In such systems, activation, exhaustion, suppression, and reprogramming can be treated as state transitions, while antigen presentation, cytokine diffusion, checkpoint signaling, infiltration, and exclusion can be formalized as interaction rules. This makes the AI virtual immune cell particularly suited to reconstructing immune-cell behavior in ways that static profiling alone cannot achieve.

From a clinical oncology perspective, predicting immunotherapy efficacy should not rely solely on immune-cell composition measured at a single time point. The role of an AI virtual immune cell in tumor immunology is not simply to describe immune ecosystems more precisely, but to predict how they will change under therapeutic intervention. Although many existing studies on tumor-immune digital twins, virtual patients, and therapeutic simulations are not directly equivalent to AI virtual immune cell, they provide important task scenarios and modular foundations for their development. Gong et al. developed a multiscale agent-based model to represent spatiotemporal interactions between tumor cells and cytotoxic T cells along the PD-1/PD-L1 axis, using effector, cytotoxic, and suppressed T-cell states to approximate functional changes in T cells.⁷⁵ However, this model remains a simplified state-transition framework and has not yet fully characterized the continuous differentiation trajectory of T cells from activation and effector states to progenitor exhausted and terminally exhausted states. Kather et al. developed a patient tissue data-based multi-agent spatial model of colorectal cancer, suggesting that stromal density and lymphocyte infiltration jointly influence tumor control.⁷⁶ In lymphocyte-rich tumors, the model indicated that high stromal density may contribute to immune escape, whereas combined simulation of immune activation and stromal permeabilization predicted a potential improvement in therapeutic response.⁷⁶ This provides a computational basis for understanding the involvement of the physical matrix of the TME in immune exclusion. These computational models and predictive frameworks provide methodological inspiration and modular foundations for future AI virtual immune cell to integrate the T-cell state transitions, exhaustion trajectories, and TME physical matrix-mediated immune exclusion. In addition, NeoAgDT illustrates how a digital twin of a patient's tumor cell population may be used to support the prioritization of personalized neoantigen vaccine composition, highlighting the emerging potential to support rational immunotherapy design in oncology.⁷⁷ These advances suggest a potential direction in tumor immunology, moving beyond static profiling of immune states toward predictive modeling of how antitumor immunity evolves, adapts, and fails in patient-specific contexts.

Tumor-immune modeling studies further suggest that the construction of AI virtual immune cell should not be limited to simulating immune-cell abundance or composition but should also incorporate immune-cell functional states, spatial distribution, and treatment-response dynamics. In glioma, digital twin models have integrated tumor cells, tumor-associated macrophage (TAM), and simulated the effects of radiotherapy and immunotherapy within a single framework, supporting computational exploration of therapeutic scenarios and hypothesis generation for TAM-targeted strategies.⁷⁸ Agent-based virtual tumor-immune models have further demonstrated that tumor antigenicity, immune evasion potential, and spatial heterogeneity substantially affect responses to immune checkpoint blockade, including PD-1/PD-L1-targeted therapies.^{49,74} In non-Hodgkin lymphoma, virtual patient populations constructed using digital twin approaches have been used to analyze the exposure-response relationship of mosunetuzumab.⁷⁹ The results suggest that drug sensitivity differs across pathological subtypes, while tumor proliferation rate, baseline T-cell infiltration, and T-cell activation capacity are the major determinants of therapeutic efficacy. In the context of cell therapy, models such as ABMACT have shown that enhancing effector-cell proliferative capacity, cytotoxicity, and sustained killing ability can improve the efficacy of adoptive cell therapy.⁸⁰ These studies indicate that immunotherapy outcomes are not determined by any single immune parameter, but rather by interactions among tumor antigenicity, immune-cell infiltration, functional activation, local suppression, and spatial organization.

However, existing models still largely operate at the level of tumor-immune system or treatment-regimen simulations, yet have not achieved unified modeling of the multi-omic states, T-cell receptor (TCR) clonal lineages, spatial migration, cellular communication, and long-term fate of individual

immune cells. Consequently, current models remain limited in their ability to reproduce adaptive immune memory, T-cell clonal evolution, stochastic events, and long-term therapeutic adaptation. Memory formation is influenced by antigen exposure history, tissue residency, and recall responses; clonal evolution is associated with TCR specificity, antigen loss, clonal competition, and therapy-imposed selective pressure; and immune-cell migration, target-cell contact, cytokine release, and the emergence of resistant clones are inherently stochastic processes that may become coupled with tumor-immune co-adaptation during long-term treatment. Future AI virtual immune cell models should further integrate longitudinal multi-omics, spatial omics, TCR clonal tracking, immune-cell state transitions, and clinical response data, thereby evolving into dynamic computational frameworks capable of predicting immune activation, exhaustion, memory formation, clonal evolution, and therapy-adaptive changes.

Artificial intelligence virtual stromal cell

Compared with tumor cells and immune cells, stromal cells have long been regarded as relatively passive structural components within tumor tissues. However, as research advances, this perception is gradually being transformed. Increasing evidence now indicates that tumor-associated stromal cells (TASCs), including cancer-associated fibroblast (CAF), endothelial cell, pericyte, adipocyte, and mesenchymal stem cell, can participate in tumor progression rather than merely support it structurally. Their importance lies not only in maintaining tissue architecture, but also in contributing to immunosuppressive niches, regulating stromal-tumor signaling, and creating conditions that may favor tumor growth and therapeutic resistance.⁸¹

Due to the complex diversity of stromal cell types, their remarkable dynamic plasticity, and highly heterogeneous spatial distribution,⁸² traditional two-dimensional cultures or animal models still exhibit limitations in systematically characterizing their overall features. In this context, AI virtual stromal cell can be regarded not simply as a data-integration strategy, but as a computational representation framework for stromal-cell states, spatial organization, and interaction rules. Such models may provide useful tools for exploring the potential roles of stromal components in tumor progression and treatment response.

The construction of AI virtual stromal cell relies on the integrated use of diverse data types. In addition to conventional single-cell transcriptomics, spatial transcriptomics, proteomics, metabolomics data, and high-resolution imaging data, emerging label-free detection techniques have also been applied in related research. Cho et al. utilized Raman spectroscopy combined with machine-learning methods to distinguish inflammatory CAF (iCAF) and myofibroblastic CAF derived from human pancreatic stellate cells. Through partial least squares discriminant analysis (PLS-DA), the study reported approximately 95% subtype recognition accuracy and identified lipid-associated Raman peaks as candidate markers for distinguishing iCAF. These findings may provide more specific, quantifiable input for the construction of AI virtual stromal cell models.⁸³

In the modeling approaches for AI virtual stromal cell, two representative technical routes currently prevail. The first is data-driven deep learning methods, which focus on learning implicit patterns from large-scale multi-source data. Examples include utilizing GNNs to effectively capture spatial dependencies between cells,⁸⁴ employing heterogeneous graph transformers for unified modeling of multimodal single-cell data, and applying attention mechanisms to learn relationships between cells and genes.⁸⁵ The second approach is mechanism-driven agent-based modeling (ABM), which emphasizes the explicit representation of cellular behaviors and interactions grounded in biological hypotheses. Johnson et al. proposed a "cellular behavior hypothesis grammar," allowing researchers to define cellular behaviors through natural language-like rule descriptions, which the system then converts into computable mathematical expressions. Taking pancreatic CAF as an example, they established a rule framework for CAF-tumor cell interactions based on existing biological knowledge and fitted key model parameters using *in vitro* experimental data, ultimately constructing an interpretable CAF-tumor cell interaction ABM model.⁸⁶

Stromal-cell-related computational models may provide important tools for exploring the mechanisms of tumor immune evasion, and serve as the basis for the immune-regulatory module of AI virtual stromal cell models.

Studies have suggested that TASCs can contribute to tumor immune evasion through immune checkpoint modulation, such as PD-L1 and B7-H3, as well as through the formation of physical and chemical barriers.⁸⁷ Computational models can be used to analyze potential interactions between stromal and immune cells and to generate hypotheses on how these interactions may regulate immune responses via the ECM and chemical signaling. In refined CAF phenotypic modeling, Lee and Kim constructed an ordinary differential equation model that classified CAF into four functional phenotypes: anti-immune, pro-immune, anti-cancer, and pro-oncogenic.⁸⁸ Through systematic simulation of tumor responses to PI3K inhibitors, PD-L1 inhibitors, and Treg inhibitors across different CAF phenotypic compositions, the model suggested that CAF heterogeneity could affect treatment-related model outputs.⁸⁸ For AI virtual stromal cell models, the significance of this study lies not in revealing the relationship between CAF heterogeneity and therapeutic response, but in providing a computational strategy for representing stromal functional heterogeneity as model states that can be further tested experimentally. At the spatial scale, Zhang et al. coupled quantitative systems pharmacology (QSP) with ABM to construct a spatial QSP platform.⁸⁹ Utilizing spatial molecular data from untreated hepatocellular carcinoma patients, they identified functional cellular neighborhood (FunCN) scores associated with overall survival, with higher FunCN scores correlating with poor prognosis and higher CD8+ T cells and tumor cells correlating with more favorable prognosis.⁸⁹ By simulating patients receiving combined therapy with immune checkpoint inhibitors and tyrosine kinase inhibitors, the platform further suggested that fibroblast spatial aggregation may limit contact between T cells and tumor cells, thereby generating a mechanistic hypothesis for immune therapy resistance.⁸⁹

Virtual stromal cell models are expected to become auxiliary tools for studying tumor metabolic reprogramming. The functions of stromal cells extend beyond traditional structural support; they may influence tumor cell survival and expansion by regulating energy supply and signaling pathways.⁹⁰ Under adverse conditions, such as hypoxia and nutrient deprivation in the TME, stromal cells not only support tumor cell survival but also sustain proliferation by modulating flexible metabolic pathways.⁹¹ Virtual stromal cell models enable in-depth exploration of how these stromal cells support tumor cell growth via metabolic reprogramming under unfavorable conditions, and to evaluate potential associations between stromal cell metabolic alterations and tumor responses to therapy.

Virtual stromal cell models can also be used to study tumor metastasis. During local invasion and distant metastasis, stromal cells have been implicated in tumor-cell migration through ECM remodeling and cytokine secretion.^{90,92} To capture this bidirectional feedback process in computational models, Metzcar et al. developed an ABM framework based on the PhysiCell platform that represents the local microstructure of the ECM using three variables: anisotropy, density, and fiber orientation.⁹³ Within this framework, cells such as cancer-associated fibroblasts are modeled as being able to remodel the local ECM density and fiber orientation.⁹³ Specifically, cell migration direction is represented as promoting ECM fiber realignment along the same axis, whereas ECM properties are modeled as influencing cell migration direction and velocity through contact guidance. In this model, highly anisotropic ECM provides directional migration cues to cells, whereas excessively high or low ECM density inhibits cell migration.⁹³ This bidirectional coupling framework provides a useful computational tool for exploring CAF-mediated ECM remodeling and its potential feedback effects on tumor cell invasion behavior. By simulating changes across different microenvironments, virtual models may help generate hypotheses regarding the potential roles of stromal cells in different metastatic pathways, thereby informing future experimental studies on metastatic progression.

Overall, AI virtual stromal cell models may become increasingly valuable for understanding how stromal compartments influence tumor progression and treatment response. Their potential lies in complementing experimental systems by integrating stromal states, spatial architecture, and multicellular interactions within a single computational framework.

AIVO for multicellular communication

In oncology, many clinically consequential phenotypes arise not from isolated cellular programs, but from coordinated interactions among malig-

nant, immune, stromal, and vascular compartments within the TME. Immune escape, therapeutic resistance, metastatic dissemination, and treatment failure are shaped by how these cell populations exchange signals, compete for space and resources, and reorganize their interactions under therapeutic pressure. This level of complexity is difficult to capture with approaches that profile individual compartments separately, because the biological and clinical behavior of a tumor is often determined by communication across compartments rather than by the state of any single cell type alone.

Given that AIVO remains a concept in development, it is not treated here as a model with a fixed technical roadmap or standardized implementation. We operationally define AIVO as an evolving, AI-driven framework for modeling multicellular ecosystems. This framework aims to reconstruct, simulate, and predict the interactions among multicellular components within the TME and their responses to therapy by integrating diverse data modalities, including but not limited to single-cell omics, spatial omics, digital pathology, radiomics, clinical treatment data, and biological prior knowledge. Based on this definition, AIVO can be viewed as a conceptual extension of AIVC, moving from single-cell state modeling to multicellular and tissue-level ecosystem modeling. It aims to provide a framework for representing the TME as a communication-centered ecosystem, in which multicellular interactions can be represented as dynamic, spatially constrained, and therapy-responsive processes relevant to oncologic decision-making.

AIVO is distinguished by its focus on dynamically modeling multicellular tumor ecosystems, bridging but remaining distinct from conventional predictive model, multimodal AI, AIVC, and tumor digital twin (Table 2). Unlike conventional predictive models, which primarily focus on predicting static endpoints, and unlike multimodal AI in oncology, which mainly emphasize multi-source data fusion and pattern recognition, the AIVO framework places greater emphasis on multicellular communication, spatial organization, temporal evolution, and responses to therapeutic perturbations. Compared with AIVC, which mainly focuses on single-cell states and perturbation responses, AIVO can be viewed as their conceptual extension toward the level of multicellular tumor ecosystems. In contrast, compared with digital twins, AIVO places greater emphasis on ecosystem modeling, whereas tumor digital twins more strongly emphasize patient specificity, longitudinal updating, and individualized clinical simulation.

AIVO extends AIVC from single-cell state representation to multicellular spatial ecosystem modeling. This transition should not be viewed as a simple aggregation of single-cell sequencing profiles, nor can it be accomplished by a single algorithm. Instead, it relies on cross-scale integration of single-cell states, spatial coordinates, tissue architecture, and intercellular communication, supported by multimodal AI and spatial-omics methods. Existing computational approaches provide important building blocks for this framework, including spatial mapping and deconvolution methods that project single-cell reference atlases onto spatial transcriptomic data, such as Tangram,⁹⁴ cell2location,⁹⁵ and RCTD;⁹⁶ spatial-domain and tissue-neighborhood modeling tools, such as SpaGCN,⁹⁷ STAGATE,⁹⁸ and cell-cell communication inference methods, such as CellChat,⁹⁹ NicheNet,¹⁰⁰ and COMMOT.¹⁰¹ In addition, GNNs can represent cells, spatial spots, or tissue regions as nodes, while encoding spatial proximity, morphological similarity, or inferred communication links as edges, thereby providing a flexible framework for modeling local immune infiltration, tumor-stromal interactions, and immune-exclusion structures. Collectively, these approaches shift the representation of the TME from a static inventory of cell types toward a spatially organized tissue network shaped by cellular neighborhoods, communication links, and ecological constraints.

Communication in oncology is not determined by molecular signaling; it is shaped by the physical and spatial architecture of the TME. Building on the data-driven spatial reconstruction described above, AIVO must further incorporate physical constraints, such as oxygen diffusion, vascular distribution, ECM remodeling, and tissue mechanics, to more faithfully simulate real tumor ecosystems. Oxygen gradients, vascular heterogeneity, ECM remodeling, and tissue mechanics collectively influence which cell populations can interact, how signals are transmitted, and whether these interactions are sustained or disrupted over time.¹⁰²⁻¹⁰⁵ In this context, hypoxia should not be viewed merely as a metabolic stressor, but as a regulator of multicellular communication that affects immune dysfunction, adaptive behavior, and treatment sensitivity

Table 2. Comparison of artificial intelligence virtual oncology (AIVO) with related artificial intelligence (AI)-based modeling approaches.

Concept	Operational focus	Modeling scale	Perturbation modeling capability	Key differences from AIVO
Conventional predictive model	Predicting clinical outcomes	Patient or cohort level	Typically static, with limited or indirect perturbation modeling	Focuses primarily on endpoint prediction and statistical associations rather than reconstructing the tumor ecosystem
Multimodal AI	Integrating multisource data for diagnosis, subtyping, and outcome prediction	Molecular, imaging, pathology, or patient level	Mostly static in many cases; does not necessarily constitute a virtual entity or simulate temporal evolution	Emphasizes data integration and pattern recognition but does not necessarily model tumor ecosystem dynamics
Digital twin	Constructing patient-specific virtual representations for individualized simulation	Individual patient or system level	Supports dynamic updating and simulation of patient-specific intervention scenarios	Emphasizes patient-specific implementation and continuous updating; AIVO may provide an ecosystem-modeling framework for oncology digital twins
AIVC	Modeling cellular states and perturbation responses	Single-cell or cellular-state level	Simulates cell-level perturbations and state transitions	Focuses mainly on individual cells or cell populations rather than spatially organized multicellular tumor ecosystems
AIVO	Reconstructing and simulating the multicellular tumor ecosystem	Multicellular, spatial, and tissue levels	Emphasizes virtual entities, tumor evolution, and cell-cell communication	-

Abbreviations: AI, artificial intelligence; AIVC, artificial intelligence virtual cell; AIVO, artificial intelligence virtual oncology.

across diseased tissue.^{106,107} The virtual TME model constructed by Schiavo et al. integrates oxygen diffusion equations with tumor cell metabolic models to quantitatively describe hypoxic regions under different vascular distributions and classify them into three types: chronic hypoxia, acute hypoxia, and anemic hypoxia. This framework may provide a quantitative tool for exploring how vascular architecture and oxygen availability influence radiotherapy response. Models incorporating heterogeneous tissue vasculature and oxygenation, therefore, provide a useful framework for understanding how spatially uneven oxygen supply alters the communicative landscape of oncology and modulates therapeutic response.¹⁰⁸ Likewise, ECM remodeling and mechanical regulation are not simply structural changes in the microenvironment. By altering matrix stiffness, fibrous orientation, and local tissue architecture, they reshape contact-dependent signaling, cellular migration, and exclusion, thereby influencing how communication networks are organized within tumors.¹⁰⁹ In a multicellular virtual tissue model based on the CompuCell3D platform, Swat et al. showed that oxygen and nutrient gradients, together with cell adhesion and survival constraints, may reshape tumor architecture and select for more aggressive phenotypes.¹¹⁰ These observations suggest that the physical microenvironment matters in oncology not only because it surrounds tumor cells, but because it determines how multicellular communication is spatially organized.

Beyond explaining multicellular interactions, multiscale virtual TME models related to the AIVO concept have also provided useful frameworks for intervention-oriented oncology research. In drug delivery, drug screening, and virtual intervention, these models can simulate the dynamic interplay among tumor cells, immune cells, stromal components, vascular structures, and therapeutic agents, thereby supporting preclinical hypothesis generation and the prioritization of candidate therapeutic strategies. These efforts offer important references for the future construction and clinical translation of AIVO. As for drug delivery, Hendriks et al. developed a multiscale kinetic model system to compare the delivery efficiency of liposomal doxorubicin versus conventional doxorubicin in different tumor environments.¹¹¹ This model, based on mechanistic descriptions of drug plasma pharmacokinetics, tumor physiology (e.g., microvascular density and blood flow), and subcellular drug distribution, quantified the critical roles of liposomal long-circulation characteristics and tumor vascular permeability in determining intratumoral drug exposure. It also highlighted that single delivery metrics, such as intratumoral drug concentration, are insufficient to reflect overall response in solid tumors.¹¹¹

Personalized treatment decision-making and patient-specific computational models represent critical directions in clinical translation of virtual TME. In drug delivery simulation, studies have established comprehensive nanoparticle transport models spanning from blood flow to tumor cell internalization, innovatively incorporating ligand-receptor affinity into multi-stage modeling.¹¹² The model has predicted that surface functionalization could

increase nanoparticle retention rates in tumor stroma from 33% to over 64%, providing a conceptual and methodological reference for precise simulation of targeted drug delivery in the virtual TME.¹¹² Regarding immunotherapy applications, a systematic review of CAR-T cell therapy summarizes the potential of digital twin technology to simulate tumor microenvironmental immunosuppression and predict acute toxic events, such as cytokine release syndrome.¹¹³ These studies collectively indicate that patient-specific multiscale immune microenvironment models lay an important foundation for future AIVO platforms that are verifiable, updatable, and applicable to personalized treatment decision-making. Table 3 summarizes representative foundational modules and computational frameworks related to virtual stromal cells, virtual immune cells, and AIVO-enabled multicellular communication.

FUTURE RESEARCH DIRECTIONS AND CHALLENGES

Previous sections have discussed the conceptual components and methodological foundations of AIVO from four levels: virtual tumor cells, virtual immune cells, virtual stromal cells, and multicellular communication. These studies indicate that the value of AIVO lies in integrating dispersed imaging, pathological, multi-omics, spatial, therapeutic, and clinical outcome data into computable, updatable, and interpretable virtual entities, while conceptualizing tumors as dynamic systems that evolve over time. These features provide an essential foundation for future AIVO research and for advancing its clinical translation.

Clinical applications of AIVO in diagnosis

An important future direction of AIVO in tumor diagnosis is to construct cross-scale and multiscale virtual representations of lesions and to capture the dynamic mechanisms underlying tumor initiation, progression, and growth, thereby providing temporally resolved data for more precise diagnosis, prognostic assessment, and risk warning.¹¹⁴ Within such a framework, lesion boundaries, internal composition, spatial distribution, and microenvironmental relationships can all be described in an integrated manner. This would not only help define lesion characteristics and reduce the bias introduced by inferring the overall disease state from limited local samples, thereby providing a clearer basis for subsequent diagnostic decision-making, but also assist in identifying tumor heterogeneity, aggressiveness, immune infiltration status, stromal barrier features, and recurrence risk, ultimately improving the recognition of complex lesions, tumors that are difficult to sample, and rare tumors. Radiomics represents an important technical foundation in this direction and can serve as the imaging-level input for AIVO, providing non-invasive information on tumor macrostructure, boundaries, heterogeneity, and treatment-related changes. Building on these techniques, AIVO can further integrate pathological, omics, and spatial microenvironmental information to construct a more comprehensive tumor representation model, thereby improving the recognition of tumor heterogeneity, aggressiveness, and recurrence risk.

Table 3. Summary of representative artificial intelligence virtual cell (AIVC)-related models and foundational modules in immune cells, stromal cells and multicellular communication.

Type category	Model/method	Tumor/ application scenario	Evidence level	Brief introduction	Data modality	Limitations/ challenges	Reference
Immune cell	Three-dimensional, on-lattice ABM	Bladder cancer	Proof-of-concept study	Captures spatial and phenotypic heterogeneity in tumor-immune dynamics, revealing that similar immune parameters can still lead to divergent outcomes in anti-PD-1 therapy.	Literature-derived biological parameters	Misses full tumor diversity and has no clinical validation.	Ref 74
Immune cell	NeoAgDT	Neoantigen vaccine design	Proof-of-concept study	Simulates individual cancer cells to model tumor heterogeneity and optimizes personalized neoantigen vaccine composition to maximize immune response coverage.	Whole-exome sequencing and RNA-seq data	Depends heavily on the quality of input predictions.	Ref 77
Immune cell	Tumor-macrophage model	Glioma	Proof-of-concept study	Models tumor-associated macrophage dynamics under radiotherapy and immunotherapy to compare myeloid-targeted strategies.	Longitudinal tumor volume and biomarker time-course data	Ignores spatial heterogeneity.	Ref 78
Immune cell	Systems-based QSP digital twin	Non-Hodgkin lymphoma	Experimentally validated system	Generates a virtual population to simulate dose-exposure-response and discover biomarkers.	Clinical tumor size response data	Neglects resistance mechanisms and tumor rebound.	Ref 79
Immune cell	ABM for adoptive cell therapy	Adoptive cell therapy	Experimentally validated system	Simulates effector-cell proliferation, cytotoxicity, and serial killing to guide adoptive cell therapy product development and treatment design.	scRNA-seq and longitudinal tumor growth data	Lacks a host level immune system and multi compartment biology.	Ref 80
Stromal cell	Machine learning-based label-free Raman spectroscopy	Pancreatic stellate cell-derived CAF	Experimentally validated system	Distinguishes inflammatory CAF and myofibroblastic CAF at molecular-fingerprint level; useful as a stromal-state input layer for virtual stromal cell construction.	Label-free Raman spectra and spatial transcriptomics and lipidomics	Generalizes poorly and yields an upper-bound accuracy estimate due to potential data leakage.	Ref 83
Stromal cell	Human-interpretable cell behavior hypothesis grammar with multicellular ABM	Pancreatic CAF-tumor interaction	Benchmarked model	Uses human-readable, rule-based grammar to encode CAF-tumor interactions and translate them into executable multicellular agent-based models.	scRNA-seq, spatial transcriptomics	Requires system-specific rule definition, parameter calibration, and further prospective validation for clinical translation.	Ref 86
Stromal cell	Ordinary differential equation model of CAF heterogeneity	CAF phenotypes	Proof-of-concept study	Simulates cancer-immune-CAF interactions with four CAF phenotypes to predict treatment outcomes for PI3K inhibitor, Treg inhibitor, PD-L1 inhibitor and their combinations.	Literature-derived parameters and biologically reasonable assumptions	Depends on many assumed or estimated parameters and omits spatial heterogeneity.	Ref 88
Stromal cell	Spatial quantitative systems pharmacology model	Hepatocellular carcinoma	Benchmarked model	Integrates agent-based modeling and CODEX spatial proteomic data to predict tumor microenvironment spatial states and response to cabozantinib plus nivolumab.	Spatial proteomics, spatial transcriptomics and clinical tumor volume and response data	Relies largely on static spatial snapshots and requires prospective clinical validation.	Ref 89
Stromal cell	PhysiCell-based agent-based modeling framework for extracellular matrix	Cell-extracellular matrix interactions	Proof-of-concept study	Represents extracellular matrix with local density, anisotropy, and orientation to enable bidirectional cell-extracellular matrix interactions and rapid model development via PhysiCell grammar.	Theoretical framework with rule-based parameters	Uses a mesoscale representation that does not explicitly resolve individual extracellular matrix fibers and requires further experimental calibration.	Ref 93

Table 3. (Continued)

Type category	Model/method	Tumor/ application scenario	Evidence level	Brief introduction	Data modality	Limitations/ challenges	Reference
Multicellular communication	Virtual-tumor model of heterogeneous vasculature and oxygenation	Hypoxic solid tumors/radio therapy planning	Proof-of- concept study	Models heterogeneous vasculature and oxygenation, distinguishing chronic, acute, and anemic hypoxia for virtual- tumor radiotherapy optimization.	Literature-based parameters and synthetic vascular networks	Abstracts vascular networks and lacks patient-specific data integration.	Ref 108
Multicellular communication	CompuCell3D multicellular virtual tissue model	Solid tumors	Proof-of- concept study	Simulates glucose gradients, cell adhesion, survival thresholds, and heritable phenotypic variation to investigate emergent tumor stratification and the evolution of reduced cell cohesion.	Literature-based model parameters and synthetic initial conditions	Represents a small, simplified two- dimensional tumor environment and lacks patient- specific validation.	Ref 110
Multicellular communication	Multiscale kinetic model of liposomal drug delivery	Solid tumors	Experimentally validated system	Couples plasma PK, tumor physiology, and subcellular drug distribution to quantify intratumoral delivery efficiency across different tumor microenvironments.	Literature-based pharmacokinetic data, <i>in vitro</i> cellular uptake data and human tumor imaging data	Ignores spatial heterogeneity and relies on averaged literature data, limiting precision.	Ref 111
Multicellular communication	Multistage computational model	Nanoparticle transport	Proof-of- concept study	Simulates nanoparticle transport through non-Newtonian blood flow, transendothelial transport, and tumor stroma, incorporating affinity forces to represent ligand-receptor interactions during targeted delivery.	Literature-based parameters and synthetic geometry	Relies on idealized computational conditions and requires further experimental and patient-specific validation.	Ref 112

Abbreviations: ABM, agent-based modeling; RNA-seq, RNA sequencing; scRNA-seq, single-cell RNA sequencing; QSP, quantitative systems pharmacology; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; PK, pharmacokinetics; CAF, cancer-associated fibroblast.

Previous studies have indicated that AI can serve as an assistive tool to help surgeons, medical oncologists, radiation oncologists, radiologists, and pathologists improve the efficiency of information integration, reduce the omission of key evidence, and facilitate more transparent decision-making processes.¹¹⁵ Therefore, at the clinical translation level, multidisciplinary tumor board discussions may represent a key application scenario for AIVO. In this context, AIVO could function as an assistive integrated decision-making interface, synthesizing imaging, pathology, genomics, spatial omics, treatment history, comorbidities, and baseline patient status into interpretable risk maps. This would help specialists from different disciplines jointly understand the disease state, reach diagnostic consensus, and evaluate the potential benefits and risks of different treatment strategies.

Clinical applications of AIVO in treatment

One key feature of the AIVO framework is its ability to reconstruct tumor cellular composition and spatial organization *in vivo*. Based on this system-level representation, and following prospective biological or clinical validation, AIVO may enable the prediction of therapeutic response, the optimization of treatment strategies, and the identification of optimal treatment timing. In perioperative and surgical oncology settings, AI is emerging as a promising decision-support tool. For example, in gastric cancer surgery, AI can integrate automation and advanced analytics to support preoperative assessment, surgical planning, and perioperative decision-making.¹¹⁶ In hepatopancreatobiliary surgery, AI has shown early potential for improving risk-benefit assessment, particularly through predictive modeling.¹¹⁷ Building on these advances, AIVO could support preoperative risk stratification, margin-risk prediction, lymph node metastasis assessment, selection of organ-preserving strategies, postoperative recurrence modeling, and adjuvant treatment sequencing. Beyond surgery, AIVO may also be applied to radiotherapy, chemotherapy, combination therapy, and immunotherapy, providing a more comprehensive basis for efficacy prediction, toxicity assessment, and dynamic treatment adjustment. A key future direction is to develop AIVO into a virtual experimental platform for simulating, comparing, and validating

treatment strategies. Such a platform could help identify patients most likely to benefit, guide combination therapy design, and provide early warnings of resistance, thereby reducing reliance on empirical trial-and-error and enabling a model in which treatments are first tested in virtual cellular systems before clinical application.

AIVO may further convert the evolution of an individual tumor into a computable dynamic trajectory, supporting longitudinal management throughout diagnosis, treatment, follow-up, and recurrence monitoring. Ideally, AIVO would integrate not only baseline imaging, pathology, omics, and clinical data, but also multi-time-point data to dynamically update the patient's virtual representation and assist in response assessment, risk prediction, recurrence warning, and treatment adaptation. Because repeated spatially comprehensive tissue biopsies are often impractical, a feasible approach is to build an initial model from baseline tissue, imaging, pathology, and molecular data, then periodically update it using minimally invasive sources such as liquid biopsy, longitudinal imaging, laboratory tests, blood immune profiling, and electronic health records. This strategy could allow AIVO to evolve toward an adaptive, patient-specific computational model for real-world oncology care.

Challenges in the application of AIVO

AIVO remains far from being a mature system that can be directly used for clinical decision-making. Because AIVO aims to integrate further tumor cells, immune cells, stromal cells, spatial organization, intercellular communication, therapeutic interventions, and longitudinal patient data, the challenges already present in AIVC may be further amplified at the tissue and patient levels.

Data quality and standardization challenge. A key challenge for AIVO is the limited standardized acquisition of multimodal data. AIVC mainly relies on single-cell, multi-omics, and perturbation data, whereas AIVO further requires the integration of imaging, pathology, spatial omics, treatment history, and clinical outcomes. However, these data from the same patient are often not collected synchronously, continuously, or completely, resulting in missing

modalities and mismatched time points. Medical institutions differ in data acquisition parameters and recording practices. Variations may also exist in lesion delineation, pathological interpretation, treatment response assessment, and outcome definitions, leading to inconsistent annotations and increasing the difficulty of multimodal data integration. In addition, simulating tumor dynamics and treatment responses requires continuous, standardized, and comparable longitudinal data, yet real-world clinical data are often affected by irregular sampling intervals, discontinuous time series, missing modalities, and incomplete follow-up information, and destructive sampling. Therefore, missing longitudinal samples not only limit the model's ability to characterize tumor evolution, treatment response, and resistance development, but also make it difficult to distinguish true biological changes from sampling bias or measurement error. These standardization issues may compromise the stability and accuracy of AIVO models.

Another challenge for AIVO is the presence of cross-platform batch effects and technical noise. The multimodal data required for AIVO are susceptible to batch effects and technical noise during acquisition, processing, and analysis. Sequencing platforms differ in sensitivity, read length, coverage depth, and quality-control criteria, while institutions may vary in sample preservation, experimental protocols, data preprocessing, and annotation standards. These differences can introduce systematic biases even within the same tumor type. Some batch effects are subtle and difficult to detect through routine quality control, and may be misinterpreted by models as true tumor heterogeneity or disease-specific features. Meanwhile, sequencing errors, image noise, sample degradation, and low-quality annotations can also interfere with model inference on tumor states and evolutionary patterns. Current AI methods remain limited in distinguishing biological heterogeneity from technical noise.¹¹⁸ Therefore, mitigating batch effects and aligning the latent spaces of real-world multimodal data from different sources remain key bottlenecks for the generalizability of AIVO models.

Modeling and computational challenges. AIVO faces difficulties in individualized modeling and parameter calibration. AIVC can model individual cells or cell states, whereas AIVO must further map these cell-level parameters onto tissue architecture, spatial niches, and patient treatment trajectories. Multiscale mechanistic models for AIVO usually involve a large number of biological and clinical parameters. Many key parameters are difficult to measure directly in real-world clinical settings and therefore often rely on literature reports, empirical assumptions, or indirect fitting. As a result, model parameters may deviate from the actual state of an individual patient. Moreover, different parameter combinations may yield similar simulation results, meaning that a model can fit existing observations without necessarily capturing the true disease mechanisms of the patient. This issue may be more pronounced when reconstructing tumor dynamics, where inferred evolutionary trajectories may represent approximate paths derived from limited time points, cross-sectional samples, or statistical associations, rather than the directly observed temporal process *in vivo*. Such discrepancies may arise from parameter non-identifiability, insufficient sampling time points, incomplete modeling of spatial heterogeneity, or inaccurate representation of treatment-induced dynamics in the multicellular tumor ecosystem. These factors may reduce the reliability of AIVO in individualized prediction and treatment optimization.

The sparsity of single-cell data and challenges in multi-omics integration also affect AIVO. As the cellular-level foundation of AIVO, AIVC models heavily rely on single-cell sequencing and multi-omics data. However, single-cell data are commonly affected by sparsity, dropout events, uneven sequencing depth, and biases in cell capture.⁸ These issues may further compromise the ability of AIVO to model the multicellular tumor ecosystem as a whole. Meanwhile, the cross-scale integration required for AIVO faces several major challenges, including the mismatch in resolution between single-cell data and spatial omics data, noise and batch effects across different omics modalities, limited capture efficiency of spatial transcriptomics, uncertainties in cell segmentation and deconvolution, the fact that cell-cell communication inference is often based mainly on expression correlations and lacks functional validation, and the difficulty of using static spatial maps to reflect therapy-induced dynamic ecological remodeling directly. The algorithms described above remain limited in their ability to extract robust biological signals from sparse, heterogeneous, and incompletely matched multi-omics data and to

achieve reliable cross-modal integration; these issues therefore continue to represent major computational challenges at the level of foundational methods for AIVO model construction.

Model reproducibility, computational scalability, and resource costs remain limiting factors for AIVO. The reproducibility of simulation results is a cornerstone of research credibility. However, owing to the complexity of multiscale models, AIVC is currently facing a “reproducibility crisis.”¹¹⁹ Similarly, AIVO typically relies on more extensive multimodal data and involves relatively complex model architectures and computational workflows, thereby posing additional challenges to reproducibility. In the absence of unified standards for data processing and model development, as well as publicly available code, standardized datasets, and independent external validation, study results may be difficult to reproduce and compare across studies, thereby compromising the reliability and generalizability of AIVO models. Technical benchmarking using standardized datasets and unified evaluation metrics can assess model performance, robustness, and computational stability, providing a basis for fair model comparison and reproducible results. Computational scalability is another major challenge for AIVO, referring to whether models can maintain efficient data integration, feature learning, spatial ecological modeling, and dynamic prediction as the number of cells, omics modalities, spatial resolution, sample size, and longitudinal time points increase. In addition, compared with conventional unimodal AI models, AIVO requires greater computational resources and technical support across multiple stages, including data storage, preprocessing, model training, hyperparameter optimization, model inference, and result visualization. It often depends on substantial computing power and specialized technical maintenance,²⁷ which increases deployment and operational costs and may limit its broader application.

Interpretability and clinical trust challenges. Interpretability is crucial for oncology-oriented AI systems.⁷ The pattern-recognition capability of AI models does not necessarily equate to a causal biological understanding. AIVC models may identify associations between cellular states and treatment responses; however, such associations do not prove that the identified cellular states causally drive therapeutic outcomes. After incorporating additional data modalities, AIVO may further amplify the potential confusion between correlation and causation. Computational performance alone is insufficient to establish biological credibility; model-derived mechanisms should be validated through perturbation experiments, and clinically oriented AIVO models should undergo calibration and uncertainty assessment to determine whether predicted risks or response probabilities are reliable. Without such validation, AIVO models may show limited interpretability and generalizability, performing well in training or internal validation cohorts but failing to remain stable across hospitals, testing platforms, or patient populations. In clinical settings, AIVO is expected not only to provide accurate predictions or recommendations but also to explain the rationale underlying its outputs, define the scope of its applicability, and characterize potential uncertainties. Interpretability becomes particularly important when model-derived conclusions conflict with clinicians' experience, conventional diagnostic and therapeutic pathways, or existing clinical guidelines. Therefore, improving model interpretability is not merely a technical requirement at the algorithmic level, but also a critical prerequisite for facilitating clinical translation.

Clinical validation, patient deployment, and workflow integration challenges. AIVO is still constrained by limited clinical validation and insufficient real-world evidence. Most of the models discussed above remain proof-of-concept studies or benchmarked models. At present, most studies on AIVC are still at the preliminary model development or single-center exploratory settings. AIVO, as an integrative extension of AIVC, remains largely conceptual and represents a theoretical possibility and a long-term developmental prospect. In this context, one of the key limitations is AIVO facing the insufficiency of clinical validation and real-world evidence. Because AIVO is not a single-task model, its clinical translation requires a higher level of evidence than conventional predictive models. In addition to good performance in training or internal validation cohorts, AIVO should be externally validated across institutions to assess its generalizability across hospitals, testing platforms, and patient populations. Subgroup analyses are needed to identify potential biases and applicability boundaries across cancer types, stages, molecular subtypes, ethnicities, age groups, and comorbidity profiles.

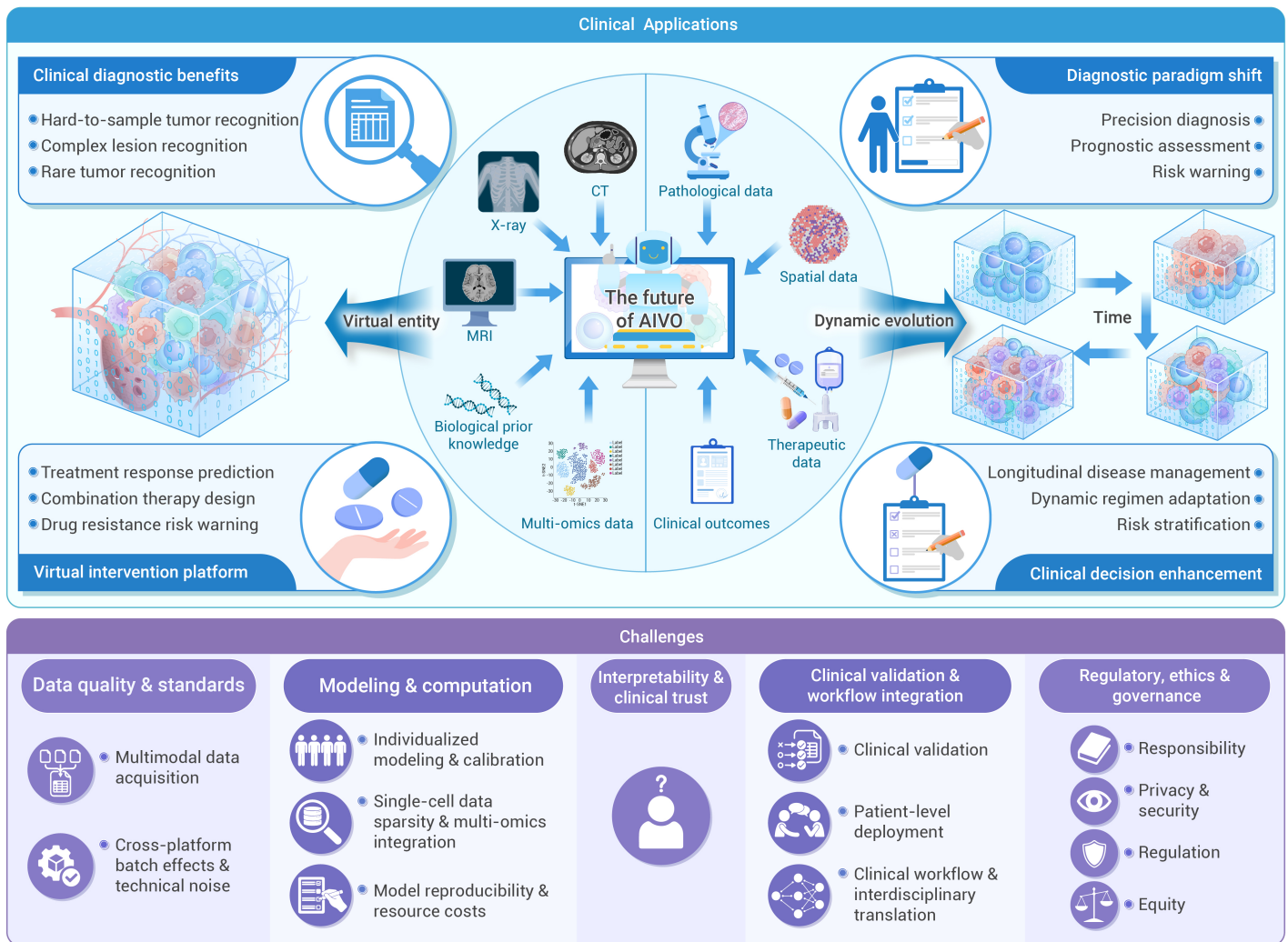


Figure 3. Future directions and challenges of AIVO AIVO integrates multimodal data to construct a virtual tumor entity capable of capturing tumor states and dynamic evolution, supporting virtual intervention for cancer diagnosis and treatment.

Prospective clinical utility studies are further required to determine whether AIVO can improve clinical decision-making, patient outcomes, or healthcare resource allocation. Without such evidence, AIVO may remain technically promising but clinically uncertain, thereby limiting its reliability, generalizability, and translational value.

Patient-level deployment and real-world application pose additional challenges for AIVO. The ultimate value of AIVO depends not only on model performance in research settings but also on whether it can be deployed at the patient level in a stable, safe, and sustainable manner. Real-world applications must address more complex patient heterogeneity, data incompleteness, and variability in diagnostic and therapeutic workflows, all of which may affect the quality of model inputs and the reliability of model outputs. During patient-level deployment, practical issues such as data acquisition, standardized processing, integrating the model into clinical workflows, and providing feedback on results must also be addressed. In addition, how model outputs should be presented to clinicians and patients, and how discrepancies between model recommendations and clinicians' judgments should be handled, require further clarification in real-world application scenarios. Therefore, AIVO must also place greater emphasis on patient-level usability, accessibility, safety, and workflow compatibility.

AIVO also faces challenges in its integration into clinical workflows and interdisciplinary translation. The clinical translation of AI in oncology requires its effective integration into routine clinical workflows.¹²⁰ For AIVO to exert genuine clinical value, it cannot remain merely an analytical tool used in

research settings; rather, it must be embedded into actual hospital workflows and become a usable component of the clinical decision-support chain. This requires AIVO-related systems to enable automated data import and standardized processing, rapid model execution, intuitive visualization of results, and effective interoperability with electronic medical record systems, pathology information systems, and multidisciplinary tumor board platforms. However, clinical practice is fast-paced and highly time-sensitive. If a model is computationally expensive, operationally complex, or dependent on extensive manual intervention, it will be difficult to integrate into routine clinical care. In addition, the development and application of AIVO typically require close collaboration among multiple disciplines, including computer science, clinical medicine, pathology, and biology.⁷ Differences among these fields in research objectives, evaluation criteria, professional terminology, and working practices can easily lead to a mismatch between model design and actual clinical needs.

Regulatory, ethical, and governance challenges. Attribution of responsibility is another challenge associated with AIVO. When AIVO models are applied to diagnostic decision-making, surgical planning, or therapeutic recommendations, any bias or error in their outputs that affects clinical outcomes may raise unresolved issues regarding attribution of responsibility, risk sharing, and legal liability. This is particularly relevant in multidisciplinary tumor board settings. If recommendations generated by AIVO conflict with clinicians' professional judgment, clear standards are needed to determine who should bear responsibility for the final decision, how the influence of

AIVO on the decision-making process should be audited, and whether patients should be informed that AI has participated in their diagnostic or therapeutic decision-making.

Regulatory issues remain an important challenge for AIVO. Compared with a single AIVC module, AIVO involves more complex multimodal patient data and dynamic updating mechanisms, thereby creating greater regulatory complexity. For AIVO systems that directly affect diagnostic or therapeutic decisions, the appropriate regulatory pathway should be clearly defined according to their intended clinical use and risk level, whether as AI-based medical devices, clinical decision support systems, or digital health tools. A key challenge to regulatory progress is the lack of up-to-date databases documenting AI-based medical devices and their key characteristics.¹²¹ Regulatory frameworks should not only focus on pre-market validation of technical performance and safety, but also cover post-market real-world surveillance, continuous performance evaluation, adverse event reporting, and model update approval procedures.

Privacy and security concerns also need to be addressed. AIVO technologies are highly dependent on multimodal patient data, placing higher demands on privacy protection, cross-institutional data sharing, informed consent, and data security. Although integration of multisource data can improve model performance, it also increases the risks of data re-identification, model inversion, cross-center data leakage, and unauthorized secondary use. Therefore, strict data governance measures should be implemented throughout data collection, storage, transmission, model training, and deployment, while promoting the adoption of privacy-preserving paradigms.¹²²

Equity and bias are also central issues in AIVO governance. If training data are predominantly derived from well-resourced medical centers, specific geographic regions, particular racial or ethnic groups, or certain cancer types, while underrepresenting older patients, patients with rare tumors, minority populations, patients from low-resource regions, or individuals with complex comorbidities, dataset bias may be introduced, particularly in the form of sample selection bias and inadequate population representativeness.¹²¹ As a result, models may perform well on training datasets but exhibit limited generalizability across other centers or different patient populations. This would not only constrain the reliability and clinical dissemination of AIVO modeling but could also exacerbate existing inequalities in diagnosis and treatment.

AIVO provides a promising conceptual framework for oncology research and clinical care. However, at the current stage, AIVO is in the early stages of methodological exploration and translational validation, and a mature clinical application system has not yet been established. Future development will require coordinated progress in technological optimization, clinically oriented model design, prospective validation, integration of longitudinal real-world data, interdisciplinary collaboration, standard-setting, and the construction of governance frameworks (Figure 3). If these challenges can be systematically addressed and clinical utility rigorously demonstrated, AIVO may ultimately mature into a trustworthy, interpretable, and clinically actionable decision-support paradigm capable of advancing precision oncology.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work the authors used ChatGPT in order to polish the manuscript. After using these tools, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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AUTHOR CONTRIBUTIONS

C.L., D.Y., F.Y., and Z.L. contributed equally to this work and share first authorship, including collecting and analyzing the data, and drafting and revising the manuscript. T.S., H.M., and B.L. conceived and designed the review, supervised the review and provided critical revisions for important intellectual content. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.