

REVIEW ARTICLE

Integrated artificial intelligence frameworks in single-cell multiomics: From intelligent automation to generative modeling

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Abstract

Single-cell multiomics has transformed biomedical research by enabling the study of gene expression, epigenetic modifications, and protein profiles within individual cells at an unprecedented level of detail. This approach has opened new opportunities for understanding complex biological systems, although significant challenges remain. As datasets increase in size and incorporate multiple modalities, issues such as data sparsity, integration complexity, and the need for scalable experimental methods have become prominent. In this review, recent progress combining computational tools, microfluidic technologies, and clinical applications is examined. The first section focuses on how advanced algorithms have been applied to interpret multimodal data, improve cell type identification, map developmental trajectories, and integrate diverse datasets. New techniques incorporating deep learning architectures, such as variational autoencoders, graph neural networks, and emerging foundation models, are highlighted for their role in enabling robust multimodal integration and predictive analysis. Subsequent sections address innovations in experimental workflows. Microfluidic devices integrated with smart automation and real-time monitoring have improved the reliability and efficiency of single-cell studies. These technical advances have had a tangible impact on translational research. In oncology, immunology, and infectious disease, multiomics-driven insights are informing diagnostic strategies and guiding therapeutic development. Finally, remaining challenges are considered, including regulatory requirements and the incorporation of emerging technologies such as spatial omics. Collectively, these advances point toward a future in which single-cell analysis becomes a cornerstone of precision medicine.

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1. Introduction

Single-cell multiomics provides the granularity needed to resolve biological systems, allowing for the simultaneous capture of transcriptomic, epigenomic, proteomic, spatial, and functional states within individual cells. Once niche experimental approaches, these

technologies are now foundational tools driving discovery across immunology, oncology, developmental biology, neuroscience, and precision medicine.

However, these capabilities create a significant computational bottleneck. Single-cell datasets are notoriously sparse, suffering from high dropout rates due to low mRNA capture efficiency, stochastic gene expression, and the inherent limitations of microfluidic chemistry.¹⁻³ Such sparsity amplifies noise and complicates analysis, requiring models that can robustly handle missing data. Moreover, the sheer dimensionality of multiomics datasets—often involving tens of thousands of features across millions of cells—strains traditional statistical methods. To address this, modern artificial intelligence (AI)-driven approaches, such as variational autoencoders (VAEs), graph neural networks (GNNs), and transformer-based models, provide necessary solutions for nonlinear embedding, denoising, batch correction, and scalable integration across species and tissues.^{4,5}

Beyond computation, the field faces a critical hardware and medical device hurdle. Even with advanced sequencing chemistry, experimental variability stemming from cell capture devices and microfluidic cartridges remains a barrier to clinical translation. Microwell and droplet-based systems are prone to physical inconsistencies such as irregular well geometry, cell loss, debris, and manufacturing defects, which directly degrade data reproducibility.⁶ Recent studies indicate that integrating AI for defect detection and computer vision-assisted quality control can significantly improve the reliability of these devices.⁷⁻⁹ By ensuring consistent capture efficiency, these automated pipelines reduce assay-to-assay variability and streamline regulatory compliance for clinical environments. More broadly, recent reviews highlight how the integration of microfluidic platforms with AI-based data analysis and modeling is reshaping experimental workflows across biological systems, reinforcing the role of intelligent microsystems in quantitative single-cell studies.¹⁰

Artificial intelligence is also reshaping analytical workflows beyond the device level. Machine learning (ML) models are now central to multiomics integration, cell type annotation, trajectory inference, and regulatory network prediction. As the field expands to encompass spatial, temporal, and imaging modalities, AI is becoming indispensable for harmonizing data across modalities at scale to generate mechanistic insights.

Merging single-cell biology with AI-driven modeling and medical device automation is fundamental to the next phase of biomedical discovery. Given the rapid proliferation of methods, there is a distinct need for a structured overview that connects computational innovation with

device-level engineering. This review synthesizes current advances in AI-driven single-cell multiomics, covering analytical methods, medical device development, and their translational applications.

Beyond its established role in downstream data analysis, AI is increasingly influencing upstream experimental decision-making in single-cell workflows. Recent work has begun to incorporate real-time sensing and adaptive control into microfluidic platforms, enabling experimental conditions to be adjusted during cell capture and library preparation. Rather than relying on fixed, pre-defined protocols, these approaches support more responsive and quality-aware workflows that can reduce technical variability and improve assay robustness. Together, these developments suggest a shift toward experimental pipelines in which AI contributes not only to data interpretation, but also to the design, optimization, and execution of single-cell experiments.^{11,12}

2. Single-cell multiomics technologies

The core of single-cell multiomics is the ability to profile multiple molecular layers from the same cells or parallel samples using integrated experimental and computational workflows. These approaches combine cell isolation and microfluidic capture with multiomics measurements and downstream AI-driven analysis to support biological interpretation and translational clinical applications. An overview of representative single-cell multiomics technologies and workflows is shown in [Figure 1](#).

2.1. Single-cell isolation and capture

In the early days of single-cell analysis, researchers relied on manual micropipetting, a method that was notoriously labor-intensive and restricted to low throughput.¹³ While fluorescence-activated cell sorting eventually improved scalability by depositing cells into microwell plates,¹⁴ the landscape changed dramatically with the introduction of microfluidic droplet technologies. Platforms such as the 10× Genomics Chromium now encapsulate individual cells in nanoliter droplets containing unique barcoded beads, enabling the parallel processing of thousands of cells.¹⁵ Droplet microfluidics effectively balances throughput with cost, though it is not without limitations, particularly regarding cell loss and doublet rates.^{16,17}

Alternative approaches, such as microwell devices, offer physical compartmentalization. These systems physically isolate cells prior to lysis, which facilitates specific multiomics barcoding strategies that are difficult to achieve in droplet-based systems.^{6-8,18} More recently, integrated microfluidic chips have consolidated the entire workflow, from capture to library preparation, onto a single platform.

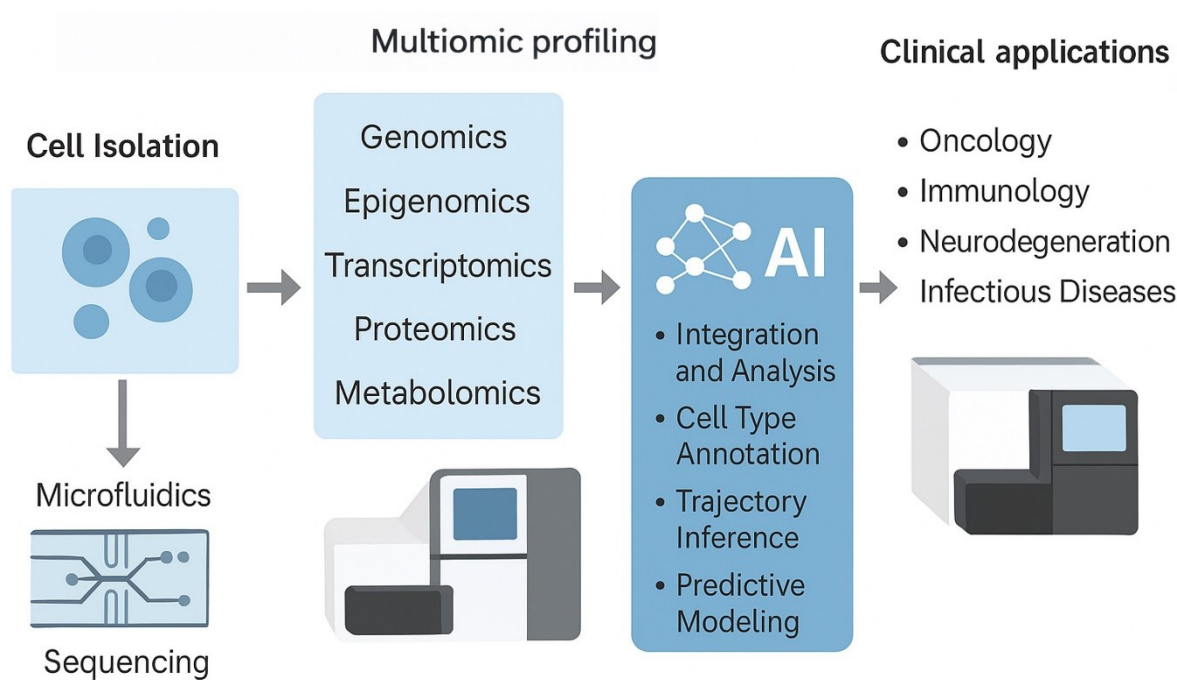


Figure 1. Overview of single-cell multiomics technologies and workflows. Major experimental and computational components are illustrated, including cell isolation and microfluidic capture, multiomics profiling modalities, artificial intelligence (AI)-assisted analysis, and downstream clinical applications. Icons in this figure were generated using Microsoft 365 Copilot, and illustrations were assembled and edited in Microsoft Powerpoint.

This design significantly reduces reagent consumption and contamination risks.¹⁹

Table 1 outlines commonly used single-cell platforms, comparing their supported modalities, throughput capabilities, and operational trade-offs.

2.2. Genomics and epigenomics

Single-cell whole-genome sequencing and whole-exome sequencing allow researchers to map somatic mutations, copy number alterations, and clonal evolution with high precision.^{20,21} Since the starting material is limited, amplification techniques like multiple displacement

Table 1. Comparison of major single-cell multiomics platforms

Technology	Modality	Cell throughput	Sensitivity	Strengths and limitations
10× Genomics Chromium	RNA, ATAC, and protein	~0.5–20,000 per library; multiplexing increases	High; droplet-based	High throughput; requires an instrument; moderate cost
BD Rhapsody	RNA, ATAC, and protein,	100–40,000 per cartridge	High; microwell-based	Flexible panels; low multiplet rate
Singleron SCOPE-chip	RNA	>10,000 per chip	Moderate	Portable; low cost; suitable for field or low-resource settings
Takara Bio ICELL8 cx	RNA	Up to 1,800 cells per chip	High; imaging-based QC	Automated dispensing; imaging QC; lower throughput
Parse Biosciences	RNA	Millions (combinatorial indexing)	Moderate	No instrument required; scalable; kit-based workflow
Fluent Biosciences	RNA	Thousands per run	Moderate	Instrument-free; emulsion-based; simple workflow
Mission Bio Tapestri	DNA, protein	Thousands per run	High for DNA genotyping	Single-cell DNA and multiomics; oncology focus

Abbreviations: ATAC: Assay for transposase-accessible chromatin; QC: Quality control.

amplification and primary template-directed amplification are necessary to maximize genome coverage while minimizing bias.^{22,23}

Beyond the genome, recent methods have begun multiplexing methylation and chromatin accessibility assays to capture epigenomic regulation. Single-cell assay for transposase-accessible chromatin (ATAC) using high-throughput sequencing, for instance, measures chromatin accessibility to pinpoint active regulatory elements.²⁴ By combining this with bisulfite sequencing or similar chemistries, it is now possible to simultaneously profile DNA methylation and chromatin modifications, shedding light on the epigenetic heterogeneity driving gene expression.²⁵⁻²⁷

2.3. Transcriptomics and proteomics

Single-cell RNA sequencing continues to serve as the gold standard for analyzing gene expression heterogeneity.²⁸ To bridge the gap between genotype and phenotype, multiomics methods often integrate protein measurements via oligonucleotide-barcoded antibodies (cellular indexing of transcriptomes and epitopes by sequencing), mass cytometry (cytometry by time-of-flight), or proximity extension assays.²⁹ Spatial transcriptomics adds another layer of resolution by preserving the positional context of gene expression in intact tissues, directly linking cellular state to tissue architecture.^{30,31} Furthermore, emerging advances in single-cell metabolomics are enabling the profiling of metabolic pathways and fluxes, providing a functional snapshot of the cell state that is closer to the actual phenotype.^{32,33}

2.4. Integrative multiomics platforms

The field is currently moving toward simultaneous multimodal profiling. Techniques such as simultaneous high-throughput ATAC and RNA expression sequencing and single-cell nucleosome, methylation, and transcription sequencing can measure chromatin accessibility, DNA methylation, and transcriptomic profiles within individual cells at the same time.^{34,35} As protocols evolve, they are expanding to cover additional modalities, offering deep integrative insights into gene regulation, signaling, and metabolism. The success of these assays relies heavily on efficient barcoding and reaction chemistry, often achieved through microfluidics or combinatorial indexing, to ensure that high-dimensional profiling remains scalable and cost-effective.^{36,37}

Recent advances in droplet-based single-cell multiomics have improved assay reliability, barcoding fidelity, and throughput, contributing to higher-quality multimodal datasets for downstream computational analysis.³⁸ In

parallel, AI has begun to be incorporated into experimental platforms to support more robust and automated operation of microfluidic workflows. Robotics, computer vision, and ML approaches have been applied to monitor and optimize key steps such as droplet formation, reagent handling, and cell capture, reducing technical variability and improving reproducibility across batches. Increasingly, these systems incorporate real-time monitoring and feedback to detect device defects, assess well occupancy, or identify droplet instability during assay execution. While still emerging, such AI-assisted platform-level controls represent an important step toward more reliable and scalable single-cell multiomics technologies, complementing downstream analytical advances.

3. Computational and artificial intelligence approaches for single-cell multiomics

The rapid growth of single-cell multiomics has generated complex, high-dimensional datasets that require sophisticated computational methods. AI and ML have become integral to extracting biological insights, enabling robust integration, interpretation, and predictive modeling across diverse modalities.

The analytical challenges of single-cell multiomics—such as high dimensionality, pervasive sparsity, batch effects, and heterogeneous data distributions—have driven the widespread adoption of AI as a core analytical framework. Classical linear methods often struggle to capture the nonlinear relationships and latent structure that characterize multimodal cellular states. In contrast, modern deep learning approaches, particularly generative and contrastive models, learn compact latent representations that preserve biological variation while mitigating technical noise.

Generative models aim to capture the underlying structure of the data, supporting tasks such as denoising, batch correction, and cross-modal imputation, while discriminative and contrastive approaches emphasize alignment and separation across modalities to improve integration and annotation. Together, these paradigms offer complementary strengths and form the foundation of many contemporary AI frameworks for single-cell multiomics analysis.

In parallel with advances in analytical modeling, learning-based strategies such as adaptive sampling and robust experimental design have begun to influence how biological data are generated, enabling models to prioritize informative experimental conditions and improve the efficiency of downstream multiomics analyses.³⁹

As shown in [Figure 2](#), recent advances in AI have

shifted single-cell multiomics analysis from isolated computational steps toward an integrated, conceptually structured analytical framework. Raw multimodal datasets, characterized by high dimensionality, sparsity, and batch effects, are increasingly processed through complementary AI modeling approaches, including generative and discriminative or contrastive models. Generative approaches learn latent representations that support denoising, batch correction, and cross-modal imputation, whereas discriminative and contrastive methods emphasize representation alignment and separation to facilitate integration, annotation, and phenotype discrimination.

Building on these core modeling approaches, a range of analytical tasks can be performed, including multimodal integration, cell type annotation, trajectory inference, and regulatory or predictive modeling. Representative frameworks such as single-cell multiomics autoencoder-based integration,⁴⁰ scPairing,⁴¹ and single-cell multiomics graph contrastive learning⁴² exemplify recent progress in generative and contrastive integration, while classical methods such as diffusion maps and RNA velocity continue to inform trajectory analysis alongside increasingly probabilistic and dynamic models.

Foundation models introduce an additional layer of abstraction by leveraging large-scale pre-training and transfer learning to support cross-modal and cross-context inference. Models such as single-cell generative pre-trained transformer (scGPT) illustrate how pre-

trained representations can be adapted for tasks including annotation and knowledge transfer across tissues or species, while also raising important considerations related to bias, generalizability, and interpretability. Earlier statistical frameworks, such as Multi-omics Factor Analysis v2,⁴³ provide interpretable factor-based integration across multiple modalities, offering a complementary alternative to deep learning approaches when model transparency and biological interpretability are prioritized. Together, these methods form a flexible ecosystem in which different AI paradigms can be selected or combined to translate complex single-cell multiomics measurements into actionable biological insights.

3.1. Data integration and dimensionality reduction

Integrating diverse molecular modalities measured at single-cell resolution requires aligning data types with distinct distributions, scales, and levels of sparsity. Early approaches such as canonical correlation analysis and matrix factorization established foundational strategies for multimodal alignment, but recent advances have been driven by AI-based integration methods. In addition to deep learning models, statistical frameworks such as Multi-omics Factor Analysis v2 support factor-based integration across multiple modalities and remain widely used in practice, particularly in settings where interpretability is important.⁴³

Contemporary multimodal integration methods can be broadly grouped into generative and contrastive or discriminative modeling approaches. Generative models,

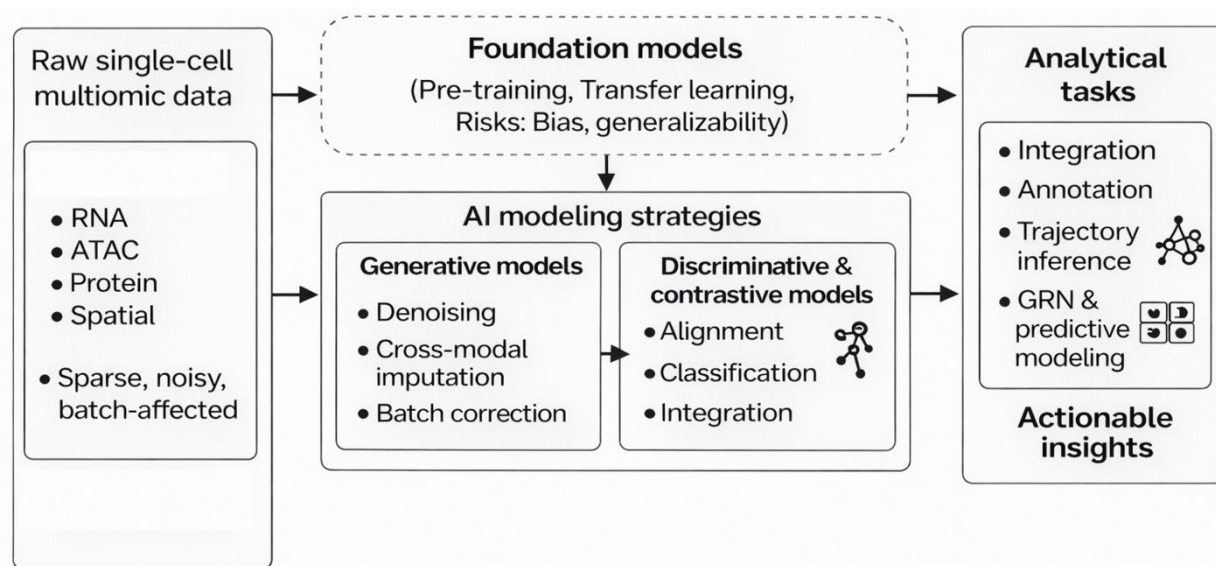


Figure 2. Landscape of AI approaches in single-cell multiomics. Icons of this figure were generated using Microsoft 365 Copilot, and illustrations were assembled and edited in Microsoft Powerpoint.

Abbreviations: AI: Artificial intelligence; ATAC: Assay for transposase-accessible chromatin; GRN: Gene regulatory network.

including VAEs, learn shared latent representations by modeling the joint distribution of observed modalities, enabling principled handling of missing data, probabilistic batch correction, and cross-modal imputation. In contrast, contrastive learning approaches align representations across modalities by maximizing agreement between paired observations while separating unrelated samples, often offering improved scalability and performance in label transfer tasks.

The choice between these approaches depends on analytical objectives. Generative models are particularly well-suited for cross-modal imputation and perturbation modeling, whereas contrastive and graph-based methods are often preferred for efficient integration, clustering, and annotation when paired data are limited.

Early applications of VAEs demonstrated the value of nonlinear probabilistic embeddings for denoising and modeling transcriptional heterogeneity in single-cell data.⁴⁴ Extensions of these models to hyperspherical and hyperbolic manifolds further improved the representation of hierarchical and tree-like biological processes, reinforcing the strengths of generative modeling for trajectory and lineage inference.⁴⁵

Building on these foundations, recent multimodal integration frameworks have moved beyond classical canonical correlation analysis toward deep generative and contrastive learning approaches tailored to single-cell multiomics, as illustrated in Figure 3. For example, single-cell multiomics autoencoder-based integration introduces a product-of-experts VAE that jointly models RNA, ATAC, and protein modalities, enabling batch correction and robust handling of missing data to produce harmonized low-dimensional embeddings that preserve biological structure across studies. scPairing extends this framework by combining generative and contrastive objectives to embed paired modalities into a shared space while also generating synthetic multiomics profiles when paired datasets are limited, supporting cross-modal imputation and data augmentation. Complementing these approaches, single-cell multiomics graph contrastive learning applies graph-based contrastive learning over cell–cell similarity graphs derived from RNA and ATAC data, improving clustering and label transfer while reducing computational cost.

Recent large-scale benchmarking studies provide practical guidance for selecting among these methods

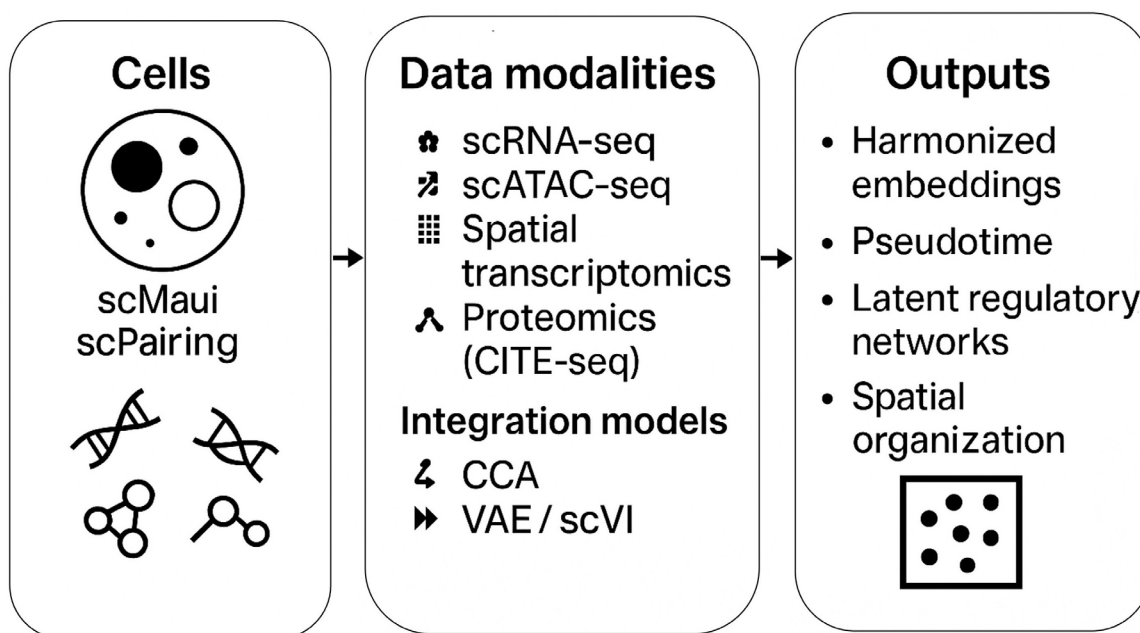


Figure 3. Single-cell multiomics integration framework, illustrating how artificial intelligence models harmonize diverse molecular layers (e.g., RNA, ATAC, spatial) into unified embeddings to enable downstream trajectory, regulatory, and predictive analyses. Icons of this figure were generated using Microsoft 365 Copilot, and illustrations were assembled and edited in Microsoft Powerpoint.

Abbreviations: CCA: Canonical correlation analysis; CITE-seq: Cellular indexing of transcriptomes and epitopes by sequencing; scATAC: Single-cell assay for transposase-accessible chromatin; scMaui: Single-cell multiomics autoencoder integration; scRNA: Single-cell RNA sequencing; scVI: Single-cell variational inference; VAE: Variational autoencoder.

by systematically comparing integration fidelity, batch correction performance, scalability, and computational requirements across diverse datasets. These analyses consistently demonstrate that no single framework performs optimally across all settings; rather, performance depends on modality composition, data pairing, dataset scale, and downstream analytical goals. Such benchmarks are essential for translating methodological advances into reproducible biological insights.

Although generative models have received substantial attention for their ability to handle missing data and quantify uncertainty, contrastive and discriminative strategies have become equally important in multiomics integration. By encouraging representations of similar cells or matched modalities to cluster closely while separating unrelated samples, these approaches can capture subtle phenotypic differences even in the presence of technical noise or incomplete pairing. Studies in phenotypic contrastive learning demonstrate the effectiveness of this strategy for distinguishing treatment-associated responses, highlighting its utility for integration, annotation transfer, and large-scale atlas alignment.⁴⁶

Given that integration frameworks differ substantially in how they handle batch effects, incomplete modality

coverage, and computational scalability, informed method selection is critical. Some models explicitly model technical variation, whereas others rely on post hoc alignment in latent space; similarly, certain frameworks naturally accommodate partially observed data, while others require fully paired measurements. Computational considerations further differentiate approaches, as graph-based and discriminative models often scale efficiently to atlas-sized datasets, whereas large generative and foundation models may require substantial computational resources. To support practical decision-making, [Table 2](#) summarizes representative integration models using criteria that reflect real-world data characteristics and resource constraints, rather than algorithmic novelty alone.

Generative models, particularly VAE-based frameworks, explicitly model latent sources of technical variation and therefore provide robust batch correction and principled handling of missing modalities through probabilistic inference. Beyond single-cell analysis, generative models in biology have also been successfully applied to the design and synthesis of biological sequences, illustrating their ability to learn meaningful latent structures that support interpolation and *in silico* perturbation modeling.⁴⁷

In contrast, discriminative and contrastive approaches

Table 2. Representative artificial intelligence models for single-cell multiomics

Model	Paradigm	Batch correction	Handles Missing Modalities	Scalability/compute	Key strengths
scMaui	Generative (VAE, product-of-experts)	Explicit latent modeling	Yes (probabilistic inference)	High GPU/high memory	Robust multimodal integration; handles noise and batch effects effectively
scPairing	Generative (contrastive VAE)	Implicit	Yes (cross-modal generation and imputation)	High GPU	Strong for paired/unpaired data, synthetic modality generation
scMGCL	Discriminative (graph contrastive learning)	Limited	Partial	Moderate CPU/GPU	Efficient alignment, fast clustering, low compute burden
MultiVI	Generative (probabilistic multimodal)	Explicit	Yes	High GPU	Joint RNA–ATAC modeling; uncertainty-aware inference
Seurat WNN	Discriminative (weighted multimodal nearest-neighbors)	Implicit	No	Moderate CPU	Widely used; flexible, intuitive integration
Harmony	Discriminative (batch-alignment)	Explicit	N/A	Low CPU	Very fast batch integration; works well across datasets
scGPT	Foundation model (transformer)	Implicit	Yes, with transfer learning	Very high GPU	Strong generalization; pre-training enables zero-shot and cross-atlas tasks

Abbreviations: ATAC: Assay for transposase-accessible chromatin; CPU: Central processing unit; GPU: Graphics processing unit; scGPT: Single-cell generative pre-trained transformer; scMaui: Single-cell multiomic autoencoder integration; scMGCL: Single-cell multiomics graph contrastive learning; WNN: Weighted nearest neighbor; VAE: Variational autoencoder.

prioritize efficient alignment and clustering but may rely more heavily on paired or well-aligned datasets. Foundation models extend these modeling approaches through large-scale pre-training and transfer learning, enabling strong generalization across datasets at the cost of increased computational demand and potential bias amplification. Multimodal weighted nearest neighbor approaches, implemented in tools such as Seurat v4, offer scalable and flexible integration that complements deep generative and contrastive models.⁴⁸

3.2. Cell type annotation and transfer learning

Automated annotation is increasingly driven by foundation models and deep transfer learning that can generalize across tissues and species. Li *et al.*⁴⁹ reviewed modern methods spanning marker-based classifiers to supervised and semi-supervised deep learners, emphasizing open-world recognition of rare cell types and strategies to mitigate long-tail class imbalance in single-cell RNA sequencing annotation. Within this trend, transformer-based foundation models like scGPT show promise for reference mapping and multimodal annotation.⁵⁰ By pre-training on tens of millions of cells and then adapting via transfer learning, these models improve robustness in heterogeneous clinical datasets. Together, these advances push annotation beyond static label transfer toward context-aware and cross-species generalization.

3.3. Trajectory inference

Trajectory analysis is evolving from static pseudotime ordering to probabilistic, dynamic modeling that captures transient states and branching lineages with improved rigor. A recent overview identifies best practices for trajectory inference in single-cell omics, detailing assumptions, validation protocols, and the integration of lineage tracing. The studies highlight methods that predict future cell fates and incorporate time-series designs to better resolve differentiation and state transitions.⁵¹ These developments provide clearer guidance for selecting algorithms and interpreting trajectories in complex developmental and disease contexts, complementing generative models that simulate downstream perturbations.

3.4. Regulatory network and causal modeling

Gene regulatory network (GRN) inference is shifting toward methods that jointly leverage multiomics and spatial context to improve regulator identification and target assignment. SCRIPro offers a streamlined pipeline for GRN reconstruction from single-cell and spatial multiomics. It combines density clustering across modalities and *in silico* deletion analyses to scan

regulator importance across more than 2,000 transcription regulators. This approach consistently outperforms motif-based baselines in recovering cell type, stage, and region-specific networks.⁵² In parallel, a review of foundation models for single-cell emphasizes their potential to unify transcriptomic and epigenomic signals for downstream regulatory inference. This suggests a path toward scalable, data-driven GRN discovery that preserves interpretability through knowledge integration. These advances help bridge descriptive regulons and causal, context-specific regulatory programs. Network-based, multi-layer modeling frameworks provide structured ways to unify phenotypic and molecular features, supporting the transition toward integrated experimental–computational systems.⁵³

3.5. Predictive modeling

Predictive modeling is moving toward generative, cross-modal frameworks that perform *in silico* experiments while maintaining integration performance. scCross, introduced in 2024, unifies multiomics integration with cross-modal generation (e.g., RNA to ATAC) and *in silico* cellular perturbations.⁵⁴ It enables hypothesis testing and mechanistic exploration within a single deep generative pipeline. More broadly, foundation-model reviews document growing evidence that pre-trained transformers can be adapted to tasks spanning drug response prediction, perturbation outcome forecasting, and biomarker discovery to provide flexible backbones for precision medicine applications. This trajectory signals a future in which predictive pipelines are both integrative and generative, supporting virtual screening and mechanistic validation.

3.6. Spatial methods

Spatial single-cell analysis is embracing multimodal reasoning by fusing histology, spatial coordinates, and expression with graph and language models. Spatial large language models (LLMs)⁵⁵ integrate a pre-trained single-cell language model (e.g., scGPT) with GNNs and multi-view attention to enhance spatial domain discovery across RNA, chromatin, and protein layers. It improves sensitivity and resolution versus the prior state-of-the-art across multiple platforms, illustrating the benefits of LLM-augmented spatial embeddings. These methods move spatial analysis toward context-aware, multimodal integration that aligns molecular signals with tissue architecture. Table 3 summarizes representative AI and ML methods across major analytical tasks in single-cell multiomics, highlighting how different modeling approaches map to integration, annotation, trajectory inference, regulatory analysis, predictive modeling, and

Table 3. Representative artificial intelligence or machine learning approaches and applications in single-cell multiomics

Task/domain	AI/ML approach	Representative works
Multiomics integration and dimensionality reduction	VAEs, deep learning	40-42
Cell type annotation and transfer learning	Neural networks, semi-supervised VAEs, transformers, LLM-based annotation	49
Trajectory inference and dynamic modeling	Graph-based pseudotime	51
GRN reconstruction and causal inference	GRN inference, SCRIPPro, causal graph models	52
Drug response prediction and clinical modeling	Deep generative models	54
LLMs, transformers, and generative models	scGPT, spaLLM, and generative AI for multiomics	50,55

Abbreviations: AI: Artificial intelligence; GRN: Gene regulatory network; LLM: Large language model; ML: Machine learning; spaLLM: Spatial large language model; scGPT: Single-cell generative pre-trained transformer; VAE: Variational autoencoder.

spatial reasoning.

4. Medical device integration and advances in single-cell multiomics

The maturation of single-cell multiomics has driven major innovations in medical device platforms, microfluidics, automation, and AI-driven workflows, accelerating the translation from basic research to clinical practice. These advances are shifting single-cell analysis from a labor-intensive research tool into a scalable, standardized solution for precision medicine.

The role of microfluidics in single-cell analysis is shifting rapidly as devices evolve from static, rule-based systems into adaptive platforms capable of interacting with AI-driven algorithms. Traditional automated workflows improve reproducibility and reduce hands-on time, but they do not fundamentally change how experimental conditions are chosen. More recent developments combine robotics, digital microfluidics, and real-time imaging with predictive modeling, forming a closed-loop experimental architecture that can iteratively optimize sample processing. In this framework, the microfluidic device is no longer merely an instrument but becomes part of a feedback system that tests model-generated hypotheses and uses observed outcomes to refine those hypotheses.

For example, a generative model may predict how changes in droplet size distribution, reagent mixing, or encapsulation efficiency will influence downstream RNA capture or protein quantification. The robotic system can then implement these proposed conditions, gather data, and return outcomes to the model to improve future predictions. This integration mirrors adaptive sampling frameworks in other areas of ML, where models gradually identify informative parts of the design space and reduce

the need for exhaustive experimentation.

At the same time, innovations in microfluidic engineering enable richer measurements to support this intelligence. New device designs allow simultaneous capture of molecular, morphological, and temporal phenotypes, supplying higher-dimensional supervisory signals for AI models. Advances in droplet-based multiomics further improve barcoding reliability and reduce assay variability, increasing the quality and breadth of datasets available for training. Together, these developments point toward a future in which experimental design, data acquisition, and analytical modeling operate as a fully integrated system that iteratively learns from and adapts to biological complexity.

4.1. Intelligent microfluidics and assay integration

Microfluidic systems remain central to high-throughput single-cell isolation and multiomic profiling. Droplet-based microfluidics, pioneered by platforms such as the 10× Genomics Chromium and MGI DNBelab, enable the parallel processing of thousands of cells using compartmentalization and barcode tagging.⁵⁶⁻⁵⁸ Automation of sample preparation, ranging from cell capture to library construction, has significantly reduced variability and hands-on time. Fully integrated workstations now offer end-to-end workflows that combine single-cell library preparation with sequencing to support clinical scalability.⁵⁹ In parallel, next-generation microfluidic platforms are expanding beyond molecular profiling to incorporate phenomic measurements that link genomic, epigenomic, morphological, and temporal features, enabling more holistic single-cell characterization within controlled microenvironments.⁶⁰

The integration of computational methods into biological workflows has evolved significantly. Prior to the advent

of deep learning for single-cell genomics, mathematical modeling was the primary instrument for designing and interpreting quantitative biological experiments.⁶¹ These mechanistic models established the necessary groundwork for understanding complex microenvironments. However, the field is now shifting from static modeling toward dynamic, AI-driven interactions that increasingly couple computation with experimental workflows.

Recent developments introduce AI-driven enhancements to these platforms. Robotic systems coupled with ML algorithms optimize droplet formation and reagent handling to improve precision and throughput.⁶² Generative models are increasingly applied to correct batch effects and impute missing data to ensure robust downstream analysis. Flexible microwell arrays provide an alternative format for capturing diverse cellular phenotypes, particularly in immunoprofiling and drug response assays. Notably, these arrays now incorporate AI-assisted machine vision for defect detection and well utilization, which enhances yield and data quality.

Technological progress now allows for the simultaneous measurement of multiple molecular layers within the same cell. Foundational approaches such as cellular indexing of transcriptomes and epitopes by sequencing (transcriptomics and surface protein quantification) and simultaneous high-throughput ATAC and RNA expression with sequencing (chromatin accessibility and transcriptomics) have expanded toward tri-omic and spatially resolved assays.⁶³ AI-powered multimodal integration frameworks—including total variational inference and multimodal variational inference—unify transcriptomic, epigenomic, and proteomic data to improve clustering, trajectory inference, and disease modeling. Furthermore, standardized metadata frameworks, like matrix and analysis metadata standards, facilitate the harmonization and reproducibility of single-cell multiomics data across platforms and laboratories, a step that is essential for regulatory approval and clinical deployment.⁶⁴

Beyond static automation, emerging robotic microfluidic platforms are increasingly coupled with generative and predictive modeling frameworks, enabling adaptive, closed-loop experimentation. In these systems, generative models learn mappings between experimental parameters such as droplet size, reagent ratios, or capture efficiency and downstream multiomics data quality, allowing assay conditions to be iteratively refined.

This shift moves robotic microfluidics from industrial process optimization toward intelligent experimental design, in which model-informed decisions guide both data acquisition and assay configuration. Such closed-

loop workflows reflect a broader shift in which generative AI moves beyond downstream data analysis to inform experimental control.

When integrated with single-cell generative models, robotic microfluidic systems can support hypothesis-driven experimentation at scale. For example, generative models trained on multimodal data may predict experimental conditions that maximize sensitivity for rare cell states or regulatory signals, guiding adaptive sampling strategies in real time. This convergence of generative modeling and device-level automation reflects a broader transition from high-throughput execution toward model-guided discovery, aligning with trends toward intelligent, AI-driven experimental ecosystems.

4.2. Clinical device integration

Coupling single-cell multiomics devices with AI analytics is redefining diagnostics and therapeutic decision-making. High-resolution molecular phenotyping of tumors uncovers intratumoral heterogeneity, informs prognosis, and identifies actionable targets to support adaptive treatment strategies in oncology. In clinical trials, single-cell assays track clonal evolution and resistance mechanisms to guide precision therapies. Noninvasive liquid biopsy platforms now combine microfluidics and AI to isolate circulating tumor cells and cell-free nucleic acids at extremely low abundance. This capability enables multiomics characterization for minimal residual disease monitoring.

Spatial multiomics adds anatomical context to dissociated cell data by integrating imaging with molecular profiling. AI-enhanced spatial omics workflows leverage GNNs and LLMs to decode tissue architecture and microenvironmental interactions, creating comprehensive cellular atlases for cancer and immune disorders. To support clinical scalability, federated learning and cloud-based architectures are emerging as secure solutions for multi-institutional data integration.⁶⁵ These systems preserve patient privacy while enabling collaborative diagnostics.

Despite these advances, challenges persist regarding assay sensitivity, data harmonization, and regulatory compliance. Addressing these issues will require explainable AI for clinical transparency, standardized automation protocols, and reproducibility frameworks to ensure cross-laboratory consistency. Continued innovation in AI-enabled automation and integrated device platforms promises to expand the translational impact of single-cell multiomics in diagnostics, drug discovery, and precision medicine. Together, these advances position robotic microfluidics not merely as an automation tool, but as a

critical interface through which generative AI can actively shape both data generation and biological discovery.

5. Challenges and limitations in single-cell multiomics

Despite breathtaking advances, single-cell multiomics faces several technical, computational, and practical challenges that must be addressed for broad application and clinical translation.

5.1. Technical and computational barriers

Single-cell RNA sequencing and other single-cell omics suffer from pervasive “dropout” and sparsity, where transcripts or molecules go undetected due to low abundance or measurement inefficiencies. This sparsity increases noise and complicates downstream analysis. While multiomics can partially mitigate missing information through cross-modal complementarity, each assay carries modality-specific biases and alignment challenges that complicate joint analysis.

Biological artifacts also pose a significant hurdle. Cells can be lost or transcriptionally altered during dissociation and processing, which may skew the representation of rare populations.

On the computational side, the sheer scale and heterogeneity of single-cell multiomics demand robust pipelines. Benchmarking and reproducibility remain major concerns, as preprocessing, normalization, and integration strategies differ widely across tools. Recent systematic benchmarks are helping to establish best practices, but true joint co-inference across more than two modalities is still maturing.⁶⁶

5.2. Interpretability, ethics, and regulation

Deep learning models deliver strong performance but often act as “black boxes.” To address this, recent work on interpretable architectures and explainable AI methods seeks to link predictions back to molecular mechanisms, thereby improving biological insight and clinician trust.^{67,68}

Clinical deployment also requires compliance with evolving regulatory and ethical frameworks that safeguard safety, privacy, and consent. Global guidance for large multimodal models (e.g., LMMs) in health highlights the risks of bias and opaque consent pathways, emphasizing the need for practical guardrails before these tools enter routine diagnostic use.

5.3. Trust, transparency, and governance

As AI becomes more tightly coupled to experimental design and clinical inference, concerns around transparency

and governance become increasingly important. Deep generative and foundation model architectures can achieve impressive predictive accuracy, but their decision-making processes may be opaque, making it difficult for clinicians or regulators to verify that outputs are consistent with known biology. Recent efforts in interpretable modeling emphasize linking latent features to biological pathways, providing rationales for predictions, and designing evaluation protocols that identify failure modes such as domain shift or demographic bias. Developing standards for documenting training data, model assumptions, and evaluation pipelines will be critical for translating advanced AI systems into clinical or regulatory environments.

5.4. Future outlook

Analysts’ projections foresee robust growth for the field, reflecting rapid adoption across oncology, neurobiology, and immunology. Technological advances will continue to expand both depth and breadth: long-read single-cell transcriptomics is improving isoform resolution, while targeted capture with long reads enhances throughput for actionable genes.⁶⁹

Simultaneously, the combination of multiomics with live-cell imaging is emerging. This enables the dynamic monitoring of signaling and protein–chromatin interactions in real-time, offering a richer mechanistic context than static snapshots.⁷⁰ AI, particularly transformer-based foundation models, will play a central role in this multimodal integration and hypothesis generation.

6. Conclusion

Single-cell multiomics has evolved from a high-resolution research tool into a foundational pillar of precision medicine. By integrating microfluidic automation, advanced sequencing chemistries, and AI-driven analytics, these technologies now offer an unparalleled view of cellular heterogeneity in health and disease.

The true power of this field lies in its convergence: hardware innovations are solving the scalability bottlenecks, while AI is overcoming the barriers of data sparsity and complexity. Importantly, this convergence is no longer limited to downstream analysis. Increasingly, AI is being embedded directly into experimental workflows, enabling adaptive quality control, model-informed assay optimization, and enhanced data generation efficiency. As the field moves toward spatial and temporal integration, we are approaching a holistic understanding of biological systems where “cause and effect” can be traced from the genome to the tissue phenotype.

While challenges in data standardization, interpretability, and ethical governance persist, the trajectory is clear.

Addressing these challenges will require not only technical advances but also shared standards, transparent evaluation frameworks, and close collaboration between academia, industry, and regulatory stakeholders. With continued collaborative efforts across engineering, computation, and biology, single-cell multiomics will define the next era of healthcare innovation.

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Conflict of interest

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