

Toward next-generation machine learning and deep learning for spatial omics

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Abstract

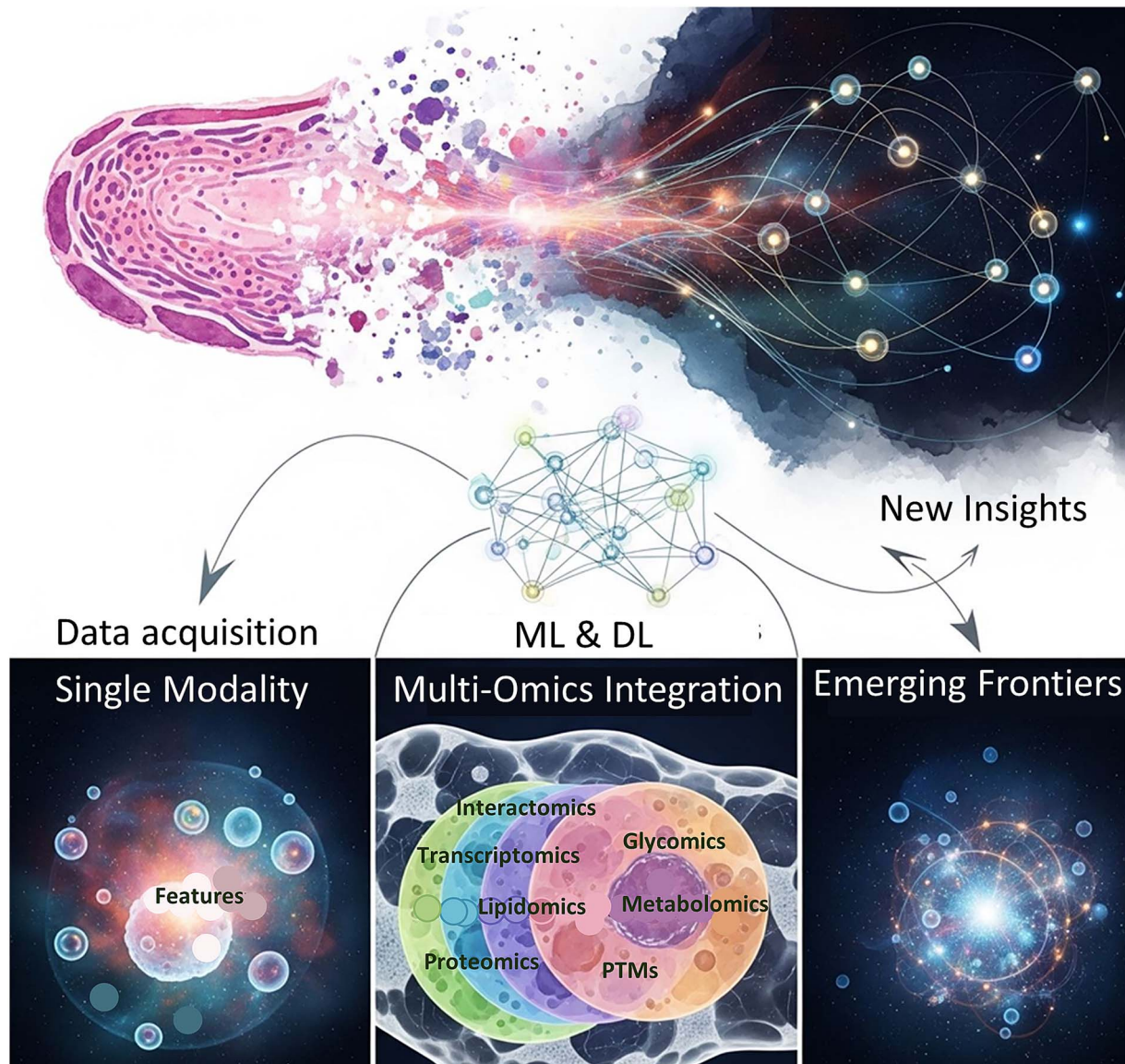
Spatial omics technologies generate high-dimensional, spatially resolved molecular data across transcripts, proteins, metabolites and lipids, requiring computational models that account for tissue topology, multi-scale organization, and experimental noise. Although machine-learning (ML) and deep-learning (DL) methods have rapidly proliferated to meet these demands, the field still lacks clear methodological guidance for selecting models adapted to specific spatial constraints and biological questions. Here, we provide a critical and comparative synthesis of ML/DL approaches across core spatial omics tasks, including batch-effect correction, resolution enhancement, tissue and cell segmentation, spatial domain discovery, cell-type deconvolution, and model interpretability. Classical ML methods such as clustering, random forests, and other ensemble classifiers, offer interpretable baselines but are limited in their capacity to model non-linear spatial dependencies. Modern DL architectures, including convolutional and graph neural networks, transformers and generative models, capture complex spatial patterns and support multi-omics integration, yet face persistent challenges related to data scarcity, annotation burden, computational cost, and uncertainty estimation. Emerging strategies such as optimal transport, cross-modal attention, graph-linked embeddings, and foundation models enhance cross-modality alignment but require rigorous evaluation of their assumptions and operational constraints. We further discuss practical solutions, including self-supervised pretraining, federated learning and the adoption of standardized spatial data formats, to enhance scalability, reproducibility, and clinical readiness. Finally, we propose a decision framework that highlights when specific ML/DL families are most suitable according to data modality, spatial resolution, tissue architecture, and intended clinical application. By integrating methodological critique with actionable recommendations, this review offers a roadmap for the reproducible, interpretable, and clinically translatable deployment of ML and DL models in spatial omics.

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Graphical Abstract



Keywords spatial omics, machine learning, deep learning, segmentation, multi-omics integration, foundation models, precision oncology, clinical translation

Introduction

Spatial omics technologies generate molecular measurements directly within intact tissues, enabling high-resolution characterization of cellular organization, microenvironmental cues, and tissue architecture. Early spatial transcriptomics approaches, including the original Spatial transcriptomics assay [1] and slide-seq [2], demonstrated that gene expression could be captured in situ across entire tissue sections. Imaging-based platforms such as MERFISH [3], seqFISH [4], CODEX [5], imaging mass cytometry, and MALDI-based imaging [6, 7] expanded this concept to proteins, lipids, and metabolites, enabling multi-layered molecular profiling at single-cell or subcellular resolution. Even earlier approaches, such as Tag-mass, achieved simultaneous imaging of transcripts and proteins using photocleavable mass

spectrometry tags [8]. These technologies produce complex, high-dimensional datasets analogous to multispectral satellite imagery, where each molecular layer offers a different view of tissue structure (Fig. 1). The analogy to remote sensing is particularly instructive. As in geospatial analysis, spatial omics requires segmentation of heterogeneous landscapes, extraction of spatial features, noise correction, and multiscale integration [9–11]. However, the dimensionality and density of spatial omics surpass classical geospatial problems: a single slide can contain hundreds of thousands of spatial locations and tens of thousands of molecular variables, generating gigabyte-scale observations per sample. These datasets strain conventional computational pipelines and motivate the use of high-performance computing and emerging paradigms such as quantum-inspired optimization for clustering, graph modeling, and high-dimensional inference [12, 13].

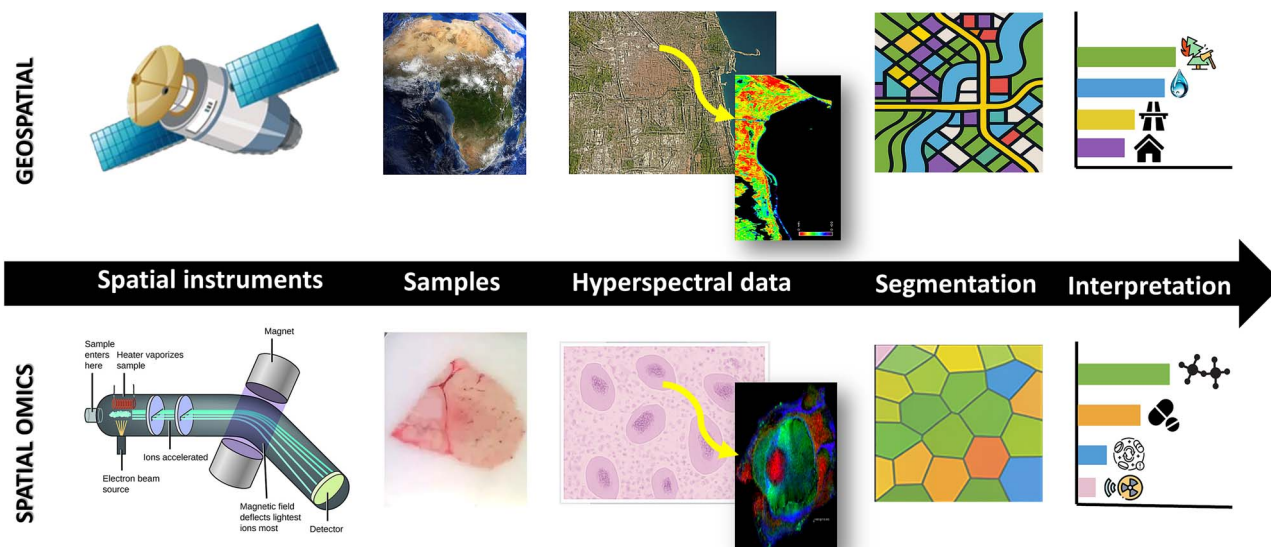


Figure 1 Conceptual parallel between geospatial remote sensing and spatial omics workflows. Both domains share a common analytical pipeline, beginning with specialized spatial instruments (satellites for geospatial imaging and mass spectrometry for spatial omics), followed by acquisition of samples (earth surface regions versus biological tissues). Each generates hyperspectral or high-dimensional molecular data, which must be processed through segmentation to identify meaningful regions (land-use zones versus tissue domains). Finally, segmented features are integrated for interpretation, enabling ecological, urban, or environmental insights in geospatial studies, and cellular, molecular, or pathological insights in spatial omics.

Beyond computational scale, spatial omics require conceptual tools to model tissue as an interactive system. Frameworks inspired by materials science (e.g. de-sintering analogies for separating densely packed cells) and by economics or game theory [14] offer new ways to characterize cellular cooperation, competition, and resource allocation within constrained niches. These perspectives highlight the emergent complexity of tissue architecture, patterns that are not readily captured by conventional statistical approaches.

Extracting actionable biological insights from spatial omics therefore depends on robust machine-learning (ML) and deep-learning (DL) approaches. Classical ML remains essential for exploratory analysis, including clustering, classification, spatial statistics, artifact detection, and interpretable modeling. Yet these approaches often struggle with nonlinear spatial dependencies, sparsity, and multimodal data integration.

Modern DL architectures, convolutional neural networks (CNNs), graph neural networks (GNNs), transformers and generative models, enable learning of complex spatial patterns, support resolution enhancement, and facilitate cross-modal alignment. These methods have advanced tasks such as cell segmentation, spatial domain discovery, and synthetic data generation, while addressing practical challenges including batch effects and heterogeneous noise. However, DL introduces new constraints: annotation requirements, computational cost and difficulties in interpretability and uncertainty quantification.

The integration of multiple molecular layers, including transcriptomics, proteomics, metabolomics, and epigenomics, into a unified spatial reference frame represents a major frontier. Early multimodal strategies relied on simple overlays or correlations [5, 15], whereas contemporary methods use graph-linked embeddings [16], optimal transport alignment [17], and cross-modal attention mechanisms to preserve spatial topology while harmonizing distinct modalities [18]. These techniques offer a more holistic representation of tissue

biology but still face challenges in scalability, interpretability, and reproducibility.

Despite rapid progress, spatial omics workflows remain limited by scarce high-quality annotations [19, 20], computational scaling bottlenecks [21], variability across platforms, and limited interpretability of complex models. Data standardization remains incomplete, although advances in open microscopy environment (OME) - tagged image file format (TIFF) formats [22] and AnnData extensions [23] support emerging 'geo-omics' paradigms. Clinical translation introduces further constraints related to privacy, regulatory frameworks, and sample processing [24, 25]. Promising solutions include federated learning for privacy-preserving integration [26], synthetic data generation [27], and quantum-inspired computational frameworks [12].

This review synthesizes ML and DL approaches across the spatial omics workflow, from data acquisition and preprocessing to conventional ML, advanced DL and multi-omics integration (Fig. 2). We provide a comparative, task-oriented analysis of strengths, limitations, and recommended use cases, with particular attention to interpretability, scalability, and reliability. By combining methodological critique with emerging computational paradigms, we outline a roadmap for constructing reproducible, clinically translatable, and spatially aware bioinformatics pipelines.

Machine learning and deep learning foundations

ML provides the computational backbone for spatial omics analysis, supporting tasks such as clustering, classification, segmentation, noise reduction, batch correction, and early exploratory analysis. Figure 3 synthesizes the major classical and emerging approaches, emphasizing their principles, typical applications, advantages, and limitations.

Across all ML/DL these techniques, robust preprocessing remains essential. Batch effects, heterogeneous noise, and platform-specific

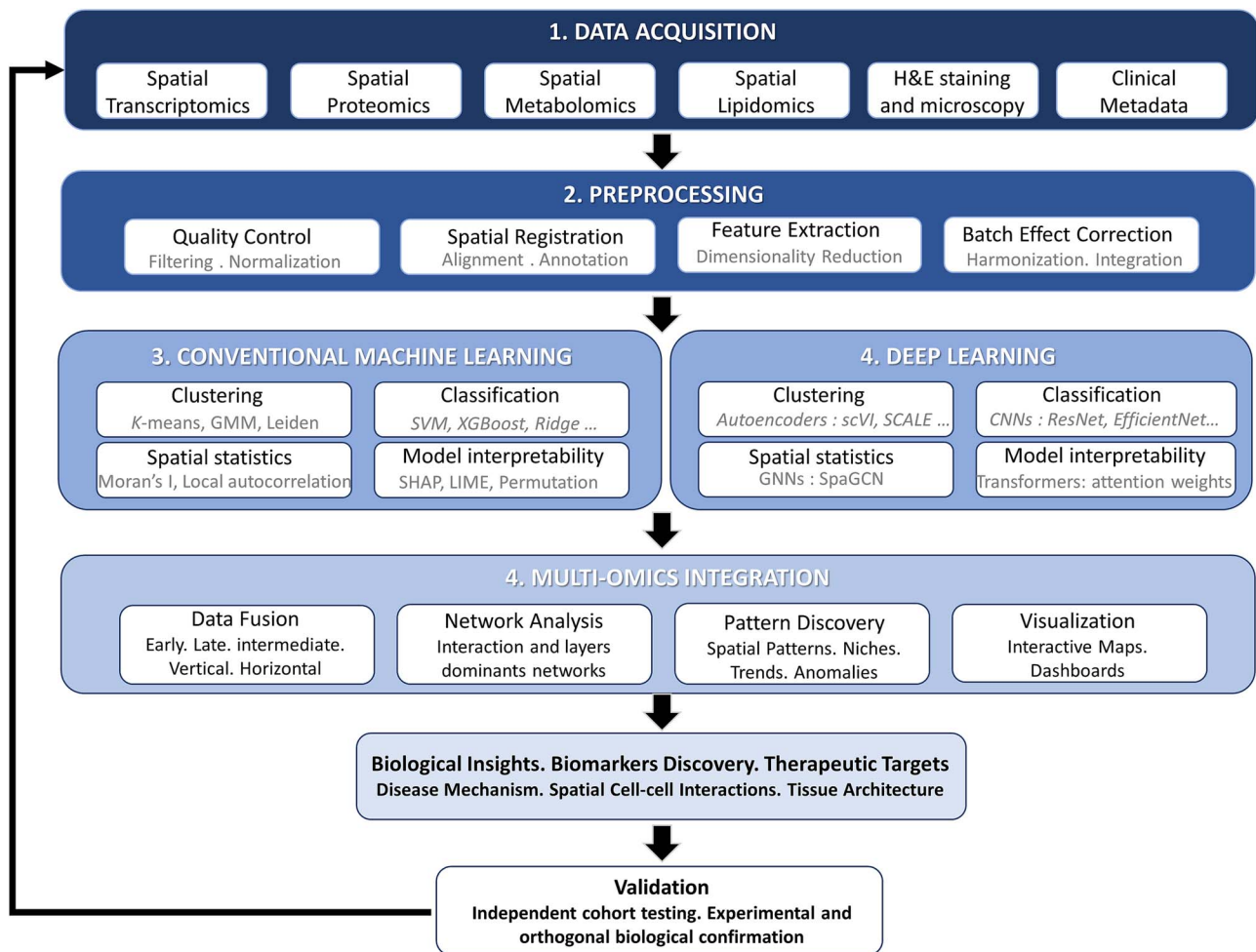


Figure 2 End-to-end workflow for spatial omics analysis. From multi-modal data acquisition to biological insight and validation, this pipeline integrates preprocessing, machine learning, deep learning, and multi-omics fusion to uncover spatial patterns and mechanisms.

biases must be corrected before any ML/DL analysis. Methods such as mutual nearest neighbors for alignment [28] and recommended normalization strategies [29] are indispensable to prevent algorithms from clustering by technical variation rather than biology. Practical implementation is increasingly facilitated by open-source ecosystems such as Scanpy and Squidpy [21], which standardize neighbor graph construction, clustering, visualization, and spatial statistics while improving reproducibility. These foundational steps establish the quality-controlled data substrate upon which all subsequent methods operate.

With preprocessed data in hand, unsupervised clustering often constitutes the first step in tissue-level spatial omics exploration, grouping spatial spots or coarse cellular aggregates into putative tissue domains based on their molecular profiles. Methods such as *k*-means [30] and *k*-means++ [31] offer fast, interpretable baselines, and scale efficiently to hundreds of thousands of cells. However, their assumption of spherical clusters limits their ability to capture nonlinear biological manifolds. Probabilistic approaches, including Gaussian mixture models, represent cluster membership as continuous probabilities and can be augmented with spatial priors, inspired by Markov random fields widely used in remote sensing segmentation. These spatially aware likelihood models mitigate the ‘salt-and-pepper’ effect (characterized by spatially fragmented, isolated assignments driven by local noise rather than biological continuity) and improve delineation of tissue

domains, as demonstrated in BayesSpace [27], which refines low-resolution Visium spot data toward subspot resolution.

When partial annotations are available, e.g. pathologist-defined regions or known clinical labels, supervised learning offers powerful discriminative models. Random forests [32] and gradient boosting [33] remain widely used due to their robustness to noise and built-in feature importance, providing biologically interpretable markers of cell identity or disease states. These models have been applied to spatial proteomics to identify prognostic signatures [34, 35]. However, many classical classifiers do not natively encode spatial relationships and instead rely on explicit feature engineering or neighborhood-based strategies. While methods such as *k*-nearest neighbors can incorporate local spatial context, classical approaches generally struggle to capture complex, high-dimensional nonlinear spatial dependencies compared to modern deep learning models. While the approaches described above primarily operate at the tissue or spatial-domain level, many spatial omics technologies, particularly imaging-based platforms, require analysis at single-cell resolution. This shift from tissue-level pattern discovery to cell-level segmentation and feature extraction introduces additional challenges related to cell density, overlapping boundaries, and morphological heterogeneity.

Before the emergence of DL, segmentation of multiplexed tissue images relied on thresholding, edge-based methods, and watershed algorithms [36]. While effective in low-density images, these

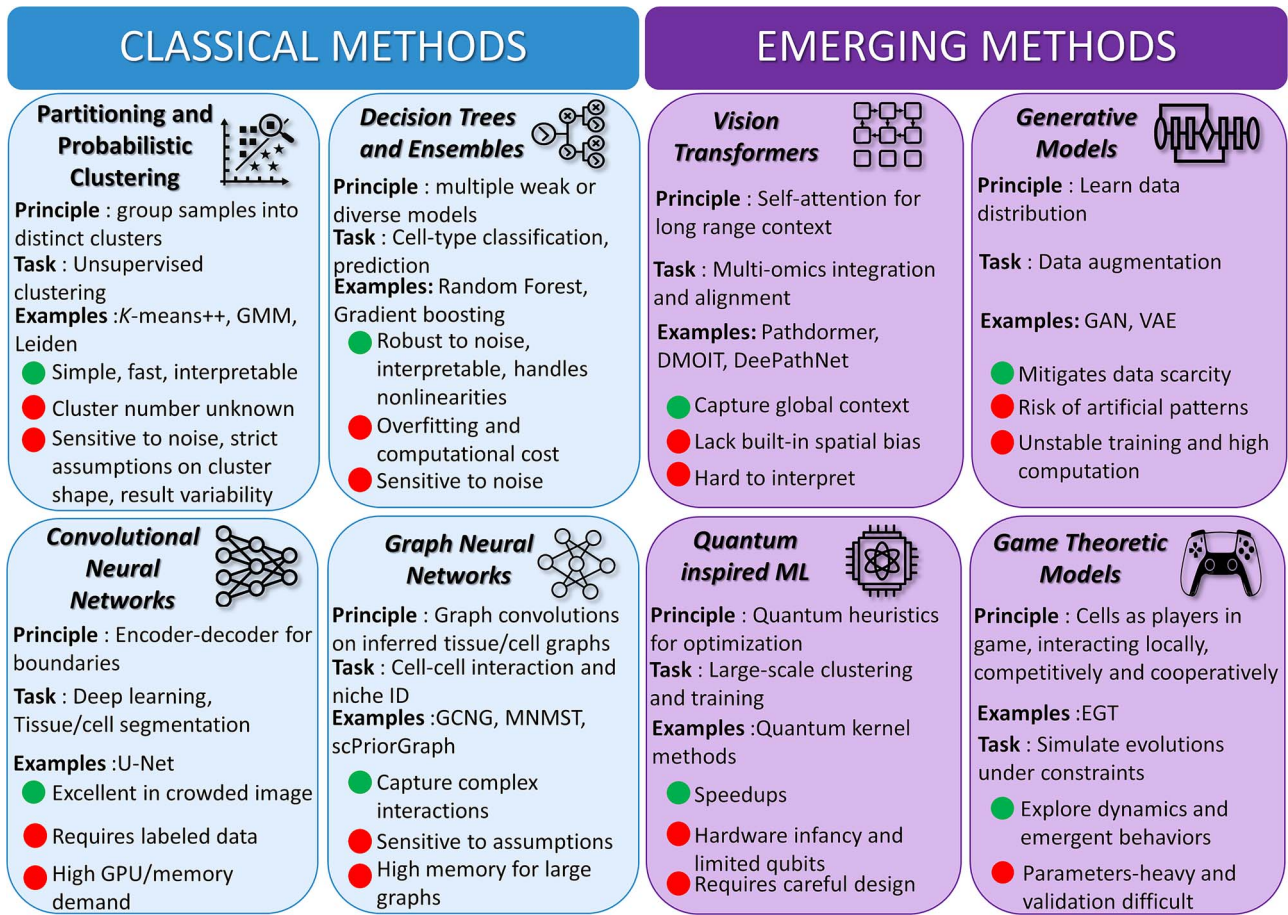


Figure 3 Overview of spatial omics algorithms. From classical to emerging approaches, highlighting their principles, typical tasks, advantages (green), and limitations (red). Classical methods comprise established machine learning techniques and foundational deep learning architectures and emerging methods include recently developed paradigms such generative models or quantum-inspired machine learning.

approaches fail when cells overlap, boundaries blur or multiplexed markers produce complex morphologies. Tools such as Ilastik [37] introduced pixel-level classifiers to handle noisy signals, but annotation requirements and limited generalizability remain constraints.

Deep learning transformed spatial omics by enabling robust, high-resolution cell segmentation, and feature extraction from multiplexed tissue images. U-Net [38] and its derivatives capture fine boundaries and global context simultaneously, enabling segmentation even in densely packed tissues. Pretrained generalist models such as Cellpose [20] and StarDist [19] now provide strong out-of-the-box performance across tissue types, drastically reducing annotation burden. These architectures, however, remain computationally intensive and require careful patch-based training for gigapixel images.

While CNNs excel at local pattern extraction, spatial omics inherently involves relational information, as cells interact with neighboring cells to form organized niches and microenvironments. Graph neural networks model these dependencies by representing each cell or spatial spot as a node (operating at single-cell or tissue-spot resolution depending on the experimental platform), and using message passing to encode local microenvironments [39, 40]. In spatial omics, the underlying graph is not directly observed and must be inferred, typically from spatial proximity or molecular similarity. GNNs have been used to characterize tumor microenvironments, identify cellular ecosystems and link spatial proteomic features to clinical outcomes

[41]. Their limitations include computational cost for large graphs, memory bottlenecks, limited interpretability of learned interactions and sensitive to graph construction assumptions.

Generative models introduce a different paradigm by learning the underlying data distribution. Generative adversarial networks (GANs) [42] and variational autoencoders (VAEs) [43] generate realistic synthetic images or molecular profiles, addressing annotation scarcity and enabling batch correction by learning latent representations invariant to slide-specific artifacts. Applications include generating multiplexed immunofluorescence images, simulating cellular distributions and harmonizing spatial transcriptomics across platforms [27]. Nonetheless, generative models may introduce artificial or biologically implausible patterns, as reported in biomedical imaging studies highlighting hallucinated structures and mode collapse in GAN-based synthesis, thereby requiring rigorous biological validation [44].

Self-supervised learning (SSL) has emerged as a key strategy, alongside generative modeling, to exploit large unlabeled datasets. Masked image modeling [45] and contrastive learning [46] enable models to learn representations of tissue structure, morphology, and spatial continuity without manual labels. These techniques show strong transferability across tissues and modalities, echoing trends in remote sensing and high-resolution microscopy. SSL provides a stepping stone toward spatial omics foundation models [47], trained on diverse datasets and

later fine-tuned for segmentation, phenotype prediction, or domain identification.

Autoencoders constitute a foundational class of deep neural networks for unsupervised representation learning in spatial omics. By compressing high-dimensional molecular or imaging data into low-dimensional latent spaces, they enable denoising, dimensionality reduction and batch effect correction, and are commonly used as a preprocessing step prior to clustering or predictive modeling [43, 48]. Variants such as denoising autoencoders and variational autoencoders further support robust feature extraction and probabilistic modeling, and have been applied to infer latent cellular states and spatial patterns from single-cell and spatial transcriptomics data [49]. However, autoencoder-based approaches exhibit several limitations: they are sensitive to architectural and distributional assumptions, and the biological interpretability of latent representations may be limited when complex nonlinear or multimodal variability is insufficiently captured [50]. These limitations underscore the need for careful model design and, in some cases, integration of prior biological knowledge to improve the relevance of latent embeddings [51].

Transformers originally developed for natural language processing (NLP) [52], extend these capabilities by capturing long-range dependencies beyond the receptive field of CNNs. Vision transformers and cross-modal transformers (e.g. CrossAttOmics, SpatialGlue) enable integration of transcriptomic, proteomic, metabolomic and histological features by learning attention-based relationships between distant cells or across modalities [16, 18]. Transformers present different limitations, including data requirements, computational burden, and interpretability, reinforce the need for careful model selection and pretraining.

Parallel to these developments, more speculative paradigms are emerging. Quantum-inspired machine learning [12, 13] offers new strategies for large-scale clustering, optimization, and graph inference, though current hardware limitations restrict practical deployment. Game-theoretic models conceptualize cells as interacting agents competing or cooperating within local microenvironments, providing frameworks for niche emergence and ecological stability [53, 54]. These approaches remain However, classical classifiers do not naturally promise but require careful validation and parameterization.

Together, these advances, spanning classical clustering, supervised learning, CNNs, GNNs, generative models, SSL, transformers, and emerging paradigms, form a continuum rather than separate silos, as illustrated in Fig. 3. Their integration provides a flexible toolbox tailored to the complexity of spatial omics, while their respective limitations underscore the need for careful method selection and harmonized preprocessing. This interplay sets the stage for developing the decision framework proposed in the next section, which maps these algorithmic families to specific data modalities, spatial resolutions, tissue architectures, and clinical objectives.

Persistent limitations and possible resolutions

Despite substantial progress in spatial omics technologies and computational analysis, several limitations continue to restrict scalability, reproducibility, and clinical applicability. These challenges appear repeatedly across studies and persist even as methodological sophistication increases. Central among them is the continuing scarcity of high-quality annotations: expert-defined labels such as precise cell identities, boundaries, or pathological regions remain costly and

difficult to obtain in complex or clinical tissues [19, 20]. Approaches such as synthetic data augmentation, generative modeling, or self-supervised learning have helped to alleviate this dependence [42, 43, 46], but they introduce their own risks: models may generate synthetic data with unrealistic patterns or artifacts when their architecture, priors, or training fail to adequately capture the underlying biological complexity of real tissues [27]. Incorporating human-in-the-loop workflows, iterative expert corrections or uncertainty-aware training can partially mitigate these issues, yet these strategies still lack standardized validation procedures. This methodological trade-off is illustrated in Fig. 4, which contrasts learning strategies based on annotation availability, robustness to modeling assumptions, interpretability, and downstream analytical objectives.

As the field increasingly moves toward large-scale datasets, ranging from whole organs to multi-modal reconstructions spanning millions of pixels or cells, computational scalability becomes a second major barrier. Small datasets are often tractable on local workstations, but tissue- or organ-scale analyses typically require distributed computing, graphics processing units (GPUs) or cloud resources; graph methods, transformers, and high-resolution segmentation pipelines do not yet scale uniformly across platforms [21]. Emerging paradigms such as quantum-inspired optimization may offer algorithmic speedups for high-dimensional clustering or graph inference [12, 13] but practical deployment remains limited by hardware maturity and software adaptation and restricted access to multi-GPU/TPU infrastructures required for large-scale analyses. To overcome these scalability barriers and promote reproducible, community-wide adoption, the field should adopt FAIR (Findable, Accessible, Interoperable, Reusable) computational practices [22], including: (1) transparent runtime and memory benchmarking (enabling researchers to select methods compatible with their resources), (2) tiling-based training strategies (allowing large-scale analyses on standard hardware by processing data in manageable chunks), (3) explicit GPU/TPU support in open implementations (maximizing efficiency when resources are available), and (4) standardized container-based deployment (ensuring reproducibility across platforms).

Even when computational demands are met, the increasing opacity of modern models raises another critical issue. As workflows integrate CNNs for morphology, GNNs for neighborhood modeling or transformers for cross-modal alignment, interpretability becomes essential, especially for clinical use. Local explanation methods such as local interpretable model-agnostic explanations / shapley additive explanations (LIME/SHAP) and saliency maps offer useful insights for classifiers and CNNs [55, 56]. Graph explainers can help decompose GNN outputs into influential subnetworks. However, interpreting attention patterns or multimodal embeddings (as in cross-attention transformers) remains difficult in practice. Practical strategies include model distillation (approximating complex predictors with simpler, interpretable surrogates) and multimodal attribution frameworks, but these require harmonized evaluation metrics and reporting standards before they can reliably support regulatory or clinical decision-making.

These methodological challenges are compounded by persistent problems in data format heterogeneity and reproducibility. Spatial omics lacks a single, widely adopted data model that integrates coordinates, intensities, modalities, and rich metadata; while community formats and software (e.g. AnnData/Scanpy, Squidpy) provide a growing foundation for interoperability and analyses [21, 29], cross-platform harmonization remains incomplete. Reproducibility

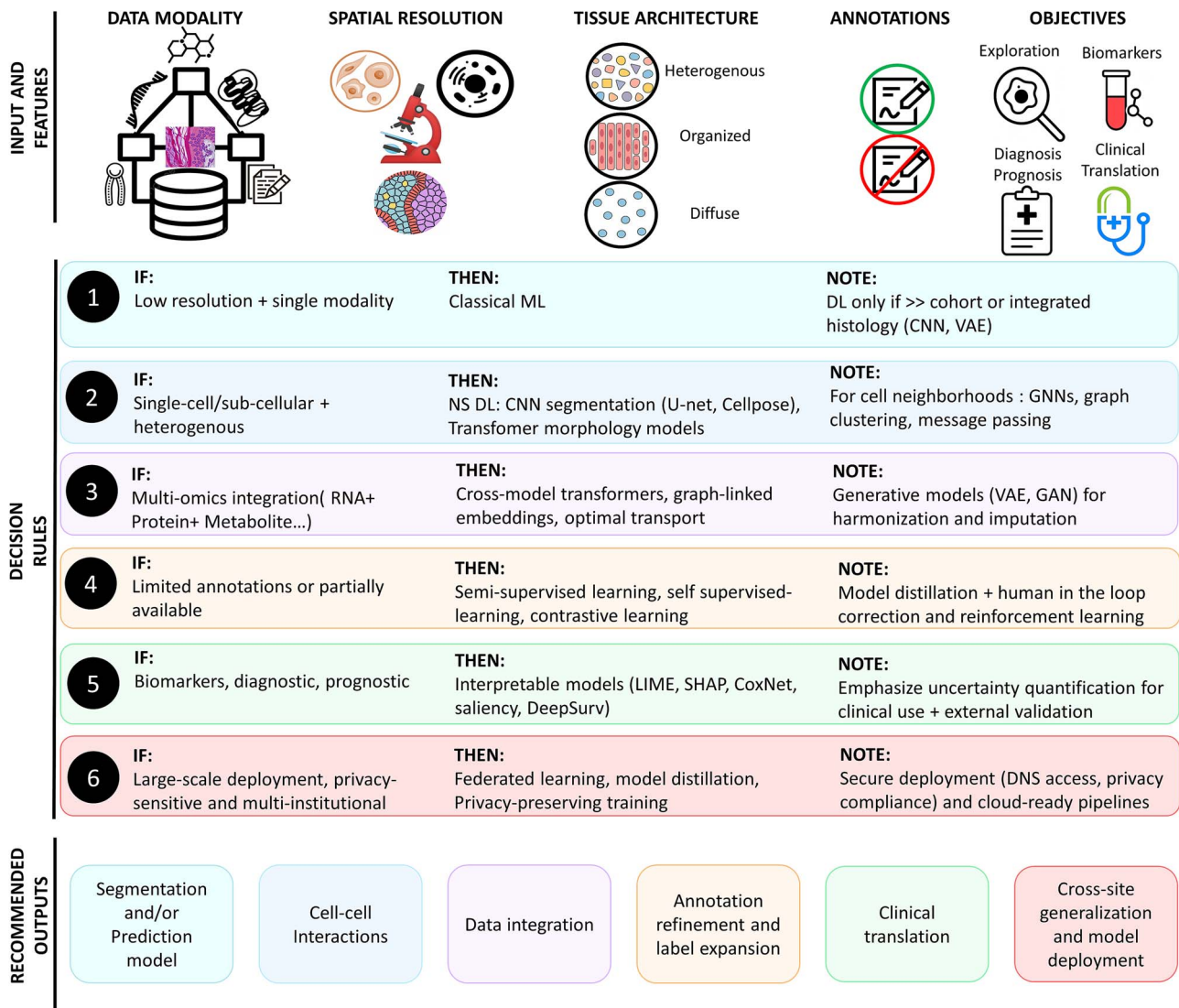


Figure 4 Decision framework for selecting ML/DL strategies in spatial omics. The framework integrates five keys: Data modality, spatial resolution, tissue architecture, annotation availability, and analytical objectives, to guide algorithm selection. Six decision rules map specific input conditions to recommend computational approaches (e.g. classical ML, CNN segmentation, cross-modal transformers, semi-supervised learning, interpretable models, federated learning). Notes highlight critical considerations such as generative harmonization, neighborhood modeling, uncertainty quantification, and privacy-preserving infrastructures. Recommended outputs include segmentation, cell-cell interaction modeling, data integration, annotation refinement, clinical prediction, and cross-site deployment.

depends on transparent preprocessing, pipeline sharing, and community benchmarks; initiatives that curate standardized testbeds and leaderboards will be critical to evaluate integration tools fairly.

Clinical translation amplifies these constraints through variable sample quality, privacy restrictions, and regulatory requirements. Federated learning and privacy-preserving training paradigms are promising approaches for multi-institutional development of robust models without raw data sharing, an idea we recommend pursuing alongside standardized validation datasets and audit trails.

Decision framework for spatial omics analysis

Selecting an appropriate computational strategy for spatial omics remains a central challenge due to the diversity of data modalities, spatial resolutions, tissue architectures, and analytical objectives. While Fig. 3 outlines the major ML/DL families used in the field,

translating these options into practical choices requires a structured, context-aware approach. Figure 4 presents such a framework, mapping dataset characteristics, and user goals to principled recommendations for model selection, preprocessing strategies, and deployment considerations. Rather than prescribing a single optimal method, the framework highlights decision pathways shaped by five factors: modality, resolution, tissue organization, annotation availability, and intended application (exploration, biomarker discovery, prognosis, or clinical translation).

The first and second axis concerns data modality and spatial resolution. Low-resolution or single-modality datasets, such as Visium, early multiplexed assays and MALDI-MSI [1, 2], which are well served by classical ML (e.g. clustering, dimensionality reduction) due to their interpretability and efficiency. In contrast, subcellular-resolution and morphologically heterogeneous tissues benefit from deep segmentation architectures such as U-Net [38], Cellpose [20],

StarDist [19], or transformer-based morphology models, while neighborhood-dependent patterns justify the use of graph neural networks for microenvironmental inference [39–41].

A third decision point involves multi-omics integration, which increasingly requires cross-modal embeddings and alignment strategies. Approaches leveraging optimal transport [17, 28], graph-linked embeddings [16], and cross-modal attention [18] provide scalable solutions for harmonizing transcriptomic, proteomic, metabolic, and histological information. Generative models such as VAEs and GANs [42, 43] further aid batch correction, imputation, and simulation across modalities.

A fourth axis addresses annotation availability, a major bottleneck in spatial omics [19, 20]. When labels are scarce or partially available, semi-supervised learning, contrastive learning [46], and masked modeling [45] enable robust representation learning. Human-in-the-loop workflows, reinforcement learning, and model distillation provide additional pathways for iterative annotation refinement and label expansion, especially in complex tissues or clinical cohorts.

A fifth-dimension concerns interpretability and clinical readiness. Applications centered on biomarker discovery, diagnosis, or prognosis often require transparent predictors, including random forests [32], gradient boosting [33], interpretable deep survival models [57], and explainability tools such as SHAP, LIME, or saliency maps [55, 56]. The need for uncertainty quantification and external validation becomes critical in these settings [24, 25].

Finally, the framework incorporates computational and infrastructural constraints. Large-scale, multi-institutional or privacy-sensitive analyses motivate the use of federated learning and secure, privacy-preserving training [26], along with model distillation and cloud-ready, domain named system-secured deployment pipelines. These considerations are essential for real-time or clinical environments and for enabling cross-site generalization.

Together, these decision rules form a practical, reproducible roadmap for selecting ML/DL strategies tailored to distinct spatial omics scenarios, from low-resolution transcriptomics to subcellular multiplexed imaging, from well-annotated datasets to unlabeled tissues, and from exploratory analyses to regulated clinical workflows. By making model selection explicit and data-driven, the framework in Fig. 4 supports methodological rigor, scalability, and clinical translation in spatial omics.

Future directions in computational spatial omics

Looking forward, the next generation of computational methods for spatial omics will likely emerge at the intersection of ML, physics, remote sensing, advanced manufacturing, and systems biology. As datasets grow in scale, complexity, and heterogeneity, traditional ML/DL pipelines will become insufficient for capturing deeply multiscale structure, modeling emergent tissue behavior, and supporting clinical-grade robustness. Table 1 summarizes several promising directions, each offering new capabilities while also presenting substantial technical and conceptual challenges. A first promising frontier concerns quantum-inspired and quantum-accelerated algorithms. Quantum support vector machines [58, 59], variational circuits [60], and annealing-based clustering [61] have the potential to reduce computational bottlenecks associated with large-scale graphs, multimodal embeddings, or latent space optimization [12, 13]. If hybrid quantum-classical workflows can overcome hardware instability [62], they may enable the analysis of organ-level

datasets at resolutions previously impractical, for instance by accelerating nearest-neighbor graph construction or large-kernel attention operations. Table 1 highlights such scenarios, including quantum-assisted clustering of million-cell atlases and quantum-enhanced classifiers for large multi-omics cohorts.

A second direction draws inspiration from satellite imaging, geospatial statistics, and Earth observation. The analogy between terrain mapping and tissue mapping, both involving multichannel signals, spatial autocorrelation, and hierarchical structures, has already begun to influence spatial smoothing, domain segmentation, and object detection. Methods routinely used in remote sensing, such as Markov random field smoothing, multi-scale segmentation, land-cover classification, or geodesic distance modeling, may provide new tools for denoising molecular maps, detecting tissue compartments, or handling multiscale heterogeneity [69]. Table 1 illustrates this parallel through examples where tissues are treated as ‘biological landscapes,’ enabling algorithms developed for satellite segmentation to refine noisy or low-resolution biological data. Similar spatial modeling concepts have been applied in spatial transcriptomics to capture local dependencies and tissue architecture, demonstrating a direct analogy with geospatial techniques [70, 71].

A third emerging perspective comes from morphological operations [36] and de-sintering analogies rooted in materials science and additive manufacturing. Concepts such as iterative dilation/erosion, particle separation, and unsintering dynamics can be translated into novel segmentation strategies for densely packed tissues, where classical watershed or even CNN-based models struggle with overlapping nuclei, intertwined fibers or irregular morphologies [72]. Although speculative, early studies suggest that morphological analogies may improve instance segmentation in tumor organoids or complex stromal environments.

Another highly interdisciplinary direction involves economic and game-theoretic models, which conceptualize tissues not as static aggregates but as dynamic ecosystems. Under this perspective, cells act as agents competing or cooperating for resources, adjusting strategies in response to microenvironmental pressures or therapeutic interventions [53]. Game-theoretic frameworks may reveal equilibrium behaviors, niche emergence or therapy-driven evolutionary dynamics not captured by standard statistical models. Examples include modeling nutrient allocation, immune-tumor interactions or evolutionary shifts under drug pressure. More immediately actionable advances are expected in self-supervised learning, contrastive pretraining, and the rise of spatial omics foundation models. As large unlabeled datasets accumulate across institutions, SSL will become the default first step, enabling models to learn universal morphological, topological, and molecular patterns without manual annotations [45, 46]. Foundation models trained jointly on histology, spatial transcriptomics, proteomics and molecular imaging could provide task-agnostic representations that generalize across tissues and species, reducing the need for repeated model development. Table 1 outlines examples where such models could perform segmentation, classification, integration, and spatial querying within a unified architecture.

Finally, federated learning and privacy-preserving computation represent essential innovations for clinical deployment. Since multi-center spatial omics studies are critical for robust biomarker discovery but constrained by data-sharing restrictions, federated learning provides a mechanism to train shared models without exchanging raw patient data. This strategy has proven effective in radiology and

Table 1 Emerging computational and theoretical directions in spatial omics and their potential impact. Each direction is summarized by its core innovation, expected benefits for spatial omics, major obstacles, concrete examples of how it may intersect with spatial analyses and its representative references.

Direction	Key innovation	Potential benefit for spatial omics	Major obstacles	Example intersection	Representative references
Quantum computing algorithms	Quantum kernels, quantum SVMs, quantum annealing for clustering and optimization	Acceleration of analyses on massive, high-dimensional datasets (e.g. whole-organ maps)	Immature hardware, noise, low qubit counts; need for hybrid quantum-classical workflows	Hybrid quantum–classical clustering of million-cell atlases; quantum-enhanced multi-omics classification	[12, 59]
Satellite-mapping analogies	Multi-channel segmentation, geospatial statistics at cellular scale	More robust segmentation and domain detection by leveraging remote-sensing algorithms	Scaling concepts from macro (terrain) to micro (cells) is non-trivial; morphological differences between tissues and landscapes	Applying MRF-based smoothing to noisy single-cell expression maps; treating cell types as ‘land cover’ classes	[38, 63]
‘De-sintering’ and morphological operations	Iterative morphological transformations inspired by advanced manufacturing	Improved separation of densely packed or overlapping cells; computational ‘unsintering’ of fused nuclei	Biological plausibility uncertain; requires high-resolution imaging to validate transformations	Refining segmentation in packed tumor organoids by separating nuclei analogous to unsintering fused particles	[36, 64]
Economic / game-theoretic modeling	Cost optimization, multi-agent games, equilibrium dynamics	New insights into cellular cooperation/-competition (e.g. tumor–immune interactions)	Economic assumptions (rational agents, utilities) may not translate to biology; requires quantifying ‘costs’ in microenvironments	Modeling tumor–immune interactions as evolutionary games; cost functions identifying nutrient-usage equilibrium states	[65, 66]
Self-supervised & contrastive learning	Unlabeled-data training via masked reconstruction or contrastive objectives	Strongly reduces manual annotation; improves model transferability across tissues/platforms	Requires large, diverse datasets; latent features may be difficult to interpret	Foundation model pre-trained on pathology + spatial transcriptomics; contrastive alignment of histology and omics	[45, 46]
Federated learning	Distributed training without raw data sharing	Enables multi-center clinical studies while preserving patient privacy	Sample prep heterogeneity; communication overhead; model security	Training a predictive model across 10 hospitals without pooling patient data	[67, 68]
Spatial omics foundation models & cross-modal transformers	Large-scale multimodal transformer architectures	Unified models for segmentation, integration, prediction; long-range and cross-modal reasoning	Extremely data- and compute-intensive; risk of spurious correlations and low interpretability	Transformer pre-trained on multi-omics images + sequences capable of querying T-cell-rich cytokine-high regions	[52]

pathology and may become foundational for spatial omics, particularly when combined with audit trails, harmonized preprocessing and standardized evaluation datasets.

Taken together, these future directions suggest that computational spatial omics is continuing a long-standing pattern of cross-disciplinary innovation that has historically driven machine learning breakthroughs, from neural networks inspired by biological neurons, to convolutional architectures informed by the mammalian visual system, to GANs drawing from game theory. As summarized in Table 1, the integration of ideas from physics, geospatial science, economics, and large-scale representation learning has already begun to shape methods for processing spatial omics datasets, and this

cross-disciplinary tendency is likely to accelerate, addressing the unique challenges of spatially resolved, high-dimensional molecular profiling. These developments will not only expand analytical capabilities but also form the methodological substrate for the decision-making strategies described in the preceding section.

Conclusion

Spatial omics is rapidly transitioning from an exploratory technology to a mature analytical paradigm capable of resolving tissue biology with unprecedented spatial and molecular precision. This shift has been enabled largely by the parallel evolution of machine learning

and deep learning, which now underpin every step of the computational workflow, from preprocessing and batch-effect correction to segmentation, spatial domain discovery, multimodal alignment and biological interpretation. As synthesized in this review, classical ML approaches remain essential for interpretable modeling, quality control, and initial exploration, while modern deep architectures, including CNNs, GNNs, transformers, and generative models, provide the expressive power required for high-resolution, multimodal, and non-linear spatial inference.

Despite these advances, several fundamental challenges persist. Annotation scarcity, computational scaling, heterogeneity across platforms and the opacity of increasingly complex models continue to constrain reproducibility and clinical uptake. Addressing these obstacles will require community-wide adoption of standardized data formats, uncertainty-aware inference, transparent benchmarking, and rigorous validation on diverse biological contexts. Equally important is the development of scalable infrastructures, GPU/TPU computation, distributed training, federated learning, to ensure that next-generation algorithms are accessible beyond specialized centers.

Looking ahead, the future of spatial omics analysis will likely be shaped by interdisciplinary convergence. As outlined in Table 1, quantum-inspired optimization, geospatial and satellite-imaging analogies, morphological ‘de-sintering’ operations, game-theoretic modeling, and large-scale self-supervised and foundation models collectively offer new conceptual and computational lenses. These approaches promise not only increased performance but also new forms of biological insight, reframing tissues as dynamic ecosystems, landscapes, or energy-driven systems rather than static anatomical units. Such perspectives may be essential for capturing emergent behaviors such as niche formation, immune–tumor coevolution or spatially constrained metabolic competition.

Another critical step toward maturity involves rational model selection. With a growing diversity of algorithmic families, users need principled guidance to identify which models are appropriate for a given modality, resolution, tissue architecture, and clinical objective. The decision framework proposed in Fig. 4 directly addresses this need by mapping data characteristics and analytic goals to recommended model classes, interpretability tools, and computational strategies. By making method selection explicit and reproducible, this framework supports rigorous, transparent, and clinically relevant spatial omics analysis. In addition to these future directions, it will be increasingly important to develop user-friendly computational platforms, such as Profiler [73] for omics data analysis, that democratize spatial-omics workflows by guiding non-specialists through appropriate preprocessing, normalization, integration, and learning strategies. By replacing ad-hoc heuristics with transparent, rule-based recommendations, such tools make advanced ML/DL pipelines accessible to researchers and clinicians without requiring extensive computational expertise.

In summary, ML and DL have become indispensable to spatial omics, enabling the field to move from descriptive mapping toward mechanistic insight and translational impact. Continued progress will depend on unifying methodological innovation with biological grounding, integrating algorithms across scales and modalities and maintaining a strong emphasis on reproducibility and interpretability. As spatial omics datasets continue to grow in richness and complexity, and as interdisciplinary methods mature, the field is poised to unlock new principles of tissue organization, disease progression, and therapeutic intervention. The convergence of scalable computation, advanced ML/DL and spatially resolved molecular profiling promises

a transformative decade ahead for precision biology and precision medicine.

Key Points

- Machine learning and deep learning methods span the entire spatial omics analytical workflow, from preprocessing and batch-effect correction to segmentation, spatial domain discovery, and cell-type deconvolution.
- Graph neural networks and vision transformers outperform classical ML for capturing nonlinear spatial dependencies and cell-cell microenvironmental interactions across heterogeneous tissue architectures.
- Optimal transport, graph-linked embeddings, and cross-attention mechanisms represent the current methodological frontier for harmonizing transcriptomic, proteomic, metabolomic, and histological layers within a unified spatial reference frame.
- Annotation scarcity, computational scaling, model opacity, and data format heterogeneity remains the four central bottlenecks limiting reproducibility and clinical translation of spatial omics pipelines.
- A five-axis decision framework integrating data modality, spatial resolution, tissue architecture, annotation availability, and clinical objective provide actionable guidance for principled ML/DL model selection across spatial omics applications.

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Author contributions

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Conflict of interest

The authors declare to have no conflict of Interest. No data availability statement.

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