nature genetics

Perspective

https://doi.org/10.1038/s41588-026-02813-6

A unified framework for defining and analyzing spatial niches in spatial omics data analysis

Received: 23 March 2026

Accepted: 28 September 2026

Published online: 13 November 2026

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The term 'spatial niche' is widely used in spatial omics analyses but is inconsistently defined across studies. We survey the literature and find that it most commonly refers to the following three distinct concepts: (1) a proximity-based neighborhood around an anchor cell or spatial spot; (2) a computationally derived spatial domain comprising spatially proximal spots or cells with shared molecular features; and (3) a biologically grounded ecosystem comprising cellular and noncellular components that support resident cells. We organize existing studies under this taxonomy and distinguish two main analytical roles—niches as spot-level covariates for modeling local context, and niches as spot clusters for within-niche and between-niche compositional and molecular analyses. To reduce ambiguity, we recommend reserving 'niche' for biological ecosystems while using 'spatial neighborhood' and 'spatial domain' for the corresponding computational constructs. We also provide a practical decision framework to help researchers align niche definitions and analytical strategies with the biological questions at hand.

The word 'niche' originates from the Latin term 'nidus', meaning 'nest'. In science, the concept was first introduced in ecology to describe the specific set of environmental and biological conditions that enable a species to survive, reproduce and interact within a community[1–3]. It was later adapted to stem cell biology, as described in ref. 4, where the stem cell niche was defined as the localized microenvironment required to support stem cell self-renewal and function. The recent adoption of 'niche' in spatial omics analyses represents a third conceptual shift—here a niche is broadly understood as the critical surroundings that influence a biological entity of interest, such as a single cell or a group of spatially proximal cells[5–34].

However, despite its growing use, the term 'niche' has been defined diversely across studies, with no consensus on spatial scale, included components, or analytical role. It may refer to a small local region surrounding an anchor cell[5–9,30,31], a larger cluster of spatially proximal cells with similar omics profiles[10–16,24,25,32–34] or an anatomical compartment in which cells and molecules interact[17–23,26–29]. These differences are not merely semantic, because different niche definitions can lead researchers to analyze the same spatial data at different spatial units and, consequently, support different biological conclusions. For example, Niche-DE[5] and CellCharter[12] have been used to analyze overlapping data from the same CosMx nonsmall cell lung cancer dataset[35], but different operational definitions of 'niche' were used. Niche-DE defines each index cell's niche as its local spatial neighborhood, characterized by the neighborhood cell-type composition, and identifies niche-associated genes whose expression in the index cell type covaries with this local context[5]. CellCharter instead defines cellular niches as spatial clusters identified based on intrinsic and neighboring-cell features and examines the molecular programs that distinguish these clusters[12]. Accordingly, a 'niche-associated' molecular signal can represent an anchor-cell association with its local cellular context in one analysis but a molecular feature of a regional spatial state in another. Grouping such outputs

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under the common label of 'niche effects' therefore risks treating fundamentally different quantities as directly comparable and mistaking definition-driven differences for biological differences across studies. Adding further confusion, 'niche' is often used interchangeably with 'microenvironment', which itself is variably defined as either purely cellular contexts or broader cellular-plus-stromal ecosystems[8,29,36–39]. Together, this heterogeneous use of 'niche' has created substantial ambiguity in how spatial niches are interpreted and used, undermining the rigor of reported findings, complicating comparisons across studies and impeding the standardization of analytical pipelines[40].

In this Perspective, we aim to clarify the diverse use of the term 'spatial niche' by introducing a taxonomy that makes explicit the distinct definitions—whether stated or implicit—in the spatial omics literature and their downstream applications. Building on this taxonomy, we propose standardized terminology and a practical decision framework to align niche definitions with biological questions and analytical strategies, thereby reducing ambiguity and enhancing reproducibility across studies.

Definition of spatial niches in spatial omics data analyses

Across the spatial omics literature, the term 'spatial niche' is used to describe entities ranging from small local neighborhoods to broad anatomical regions, making it difficult to compare results across studies. To resolve this ambiguity, we partition the term into three nonoverlapping definitions—spatial neighborhood[5–9,30,31], spatial domain[10–16,24,25,32–34] and spatial ecosystem[17–23,26–29] (Fig. 1a and Supplementary Table 1), as elaborated below.

Defining a spatial neighborhood as a niche

The first definition of a spatial niche is a spatial neighborhood—a local region centered on an anchor spatial spot (or cell), whose boundary is determined solely by spatial proximity[5–9,30,31]. Each spot (or cell) therefore has a uniquely defined niche anchored at that location, capturing the local interactions it may be involved in. This definition can be used either to identify local extrinsic influences on the anchor's omics features[5,6,9] or to construct a richer spatially informed representation of the anchor for downstream clustering or trajectory inference[7,8,30,31].

Under this definition, spatial coordinates, rather than omics features, determine neighborhood membership through pairwise distances between spots (or cells), whereas omics or cell-type features may subsequently be used to profile or represent the resulting neighborhood. Quantitatively, neighborhoods are typically defined using Delaunay triangulation or kernel-based approaches, reflecting different types of cell–cell interactions. Delaunay triangulation identifies immediately adjacent spots (or cells) and is intended to capture contact-dependent interactions, whereas kernel-based approaches select spots (or cells) within a chosen spatial proximity and apply weighting to reflect the strength of influence, aiming to capture diffusion-dependent interactions[5,7–9,31].

Neighborhood size is a key question for this definition, but no universal consensus exists because the biologically relevant range varies with tissue architecture and signaling mechanisms. In published implementations, neighborhood scales range from immediate-contact graphs to *k*-nearest-neighbor neighborhoods containing approximately 5–50 cells or spots and distance-based kernels spanning tens to a few hundred micrometers, although these choices are heuristic and dataset-dependent rather than universal defaults[5,7,9]. Researchers should therefore evaluate multiple neighborhood sizes through biological validation while accounting for platform resolution, local sampling density and tissue geometry (Supplementary Note 1).

This neighborhood-based niche definition is most naturally suited to single-cell-resolution platforms, such as Xenium[41], CosMx[35] and MERFISH[42], in which measurements can be assigned to individual cells and the neighborhood therefore represents the local context of an anchor cell. However, this definition has also been adapted to multi-cell-resolution platforms, such as Visium[43], in which each capture spot contains molecular signals from multiple cells. In this setting, the neighborhood represents the local environment surrounding a mixed-cell capture unit rather than the immediate context of a single cell[5,9].

Defining a spatial domain as a niche

The second definition of a spatial niche is a spatial domain—a collection of spatial spots (or cells) identified by computational methods as sharing similar omics profiles and exhibiting spatial coherence[10–16,24,25,32–34]. An identified domain may correspond to either a single contiguous tissue region or multiple spatially separated subregions representing the same recurring spatial state. The primary goal is to uncover structured tissue organization that may correspond to functional or anatomical compartments, reducing complex spatial omics patterns to interpretable spatial units. Depending on whether niche memberships overlap, this definition can be divided into two subcategories.

In the nonoverlapping subcategory, niches are mutually exclusive and are identified using spatial domain detection methods. A common workflow represents each spot (or cell) using either its original measurements or a learned representation, followed by unsupervised clustering or other domain detection procedures. Different methods use different combinations of molecular, spatial, histological, neighborhood and contextual information, which determine the biological interpretation of the resulting domains (Supplementary Note 2). For broader methodological comparisons, we refer readers to a recent review[44] and benchmarking studies[45,46]. The applicability of individual methods depends on data resolution, with some restricted to single-cell-resolution data[13,25,32] and others applicable to both single-cell-resolution and multi-cell-resolution datasets[10–12,24,34]. In single-cell-resolution data, domains can reflect fine-grained spatial organization of cell types and states, whereas in multi-cell-resolution data, a domain more often represents a composite tissue state whose internal cellular heterogeneity and boundaries may be blurred by signal mixing across cells.

In the overlapping subcategory, niches are allowed to overlap and have so far mainly been inferred from multi-cell-resolution data using latent factor models[14–16]. Each niche corresponds to a latent factor representing characteristic cell-type composition, indicating which cell types tend to colocalize across multi-cell spots and in what proportions. Spots may score highly on multiple factors and thus belong to multiple niches. This strategy was originally introduced alongside the deconvolution method Cell2location[47] and has subsequently been adopted in several in-house analyses[14–16] (Supplementary Note 2).

In both subcategories, niches are identified computationally rather than derived solely from prior biological knowledge, underscoring that they are computational constructs rather than anatomical entities. Despite their methodological differences, both are treated as spot clusters in downstream analyses. A key determinant of niche scale in both subcategories is the number of domains or components ultimately retained, whether specified in advance or selected during model fitting. This choice affects the granularity of the resulting niche representation—fewer domains generally capture broader tissue organizations, whereas more domains resolve finer spatial structures. Biological knowledge, quantitative criteria and stability analyses can help guide this choice (Supplementary Note 2).

Defining an ecosystem as a niche

In the third definition, a spatial niche is conceptualized as an ecosystem in which a population of cells (termed resident cells hereafter) resides and interacts with surrounding biological elements[17–23,26–29]. These elements include not only neighboring supportive cells but also noncellular components such as anatomical structures (for example, blood vessels) and molecules, including extracellular matrix (ECM)

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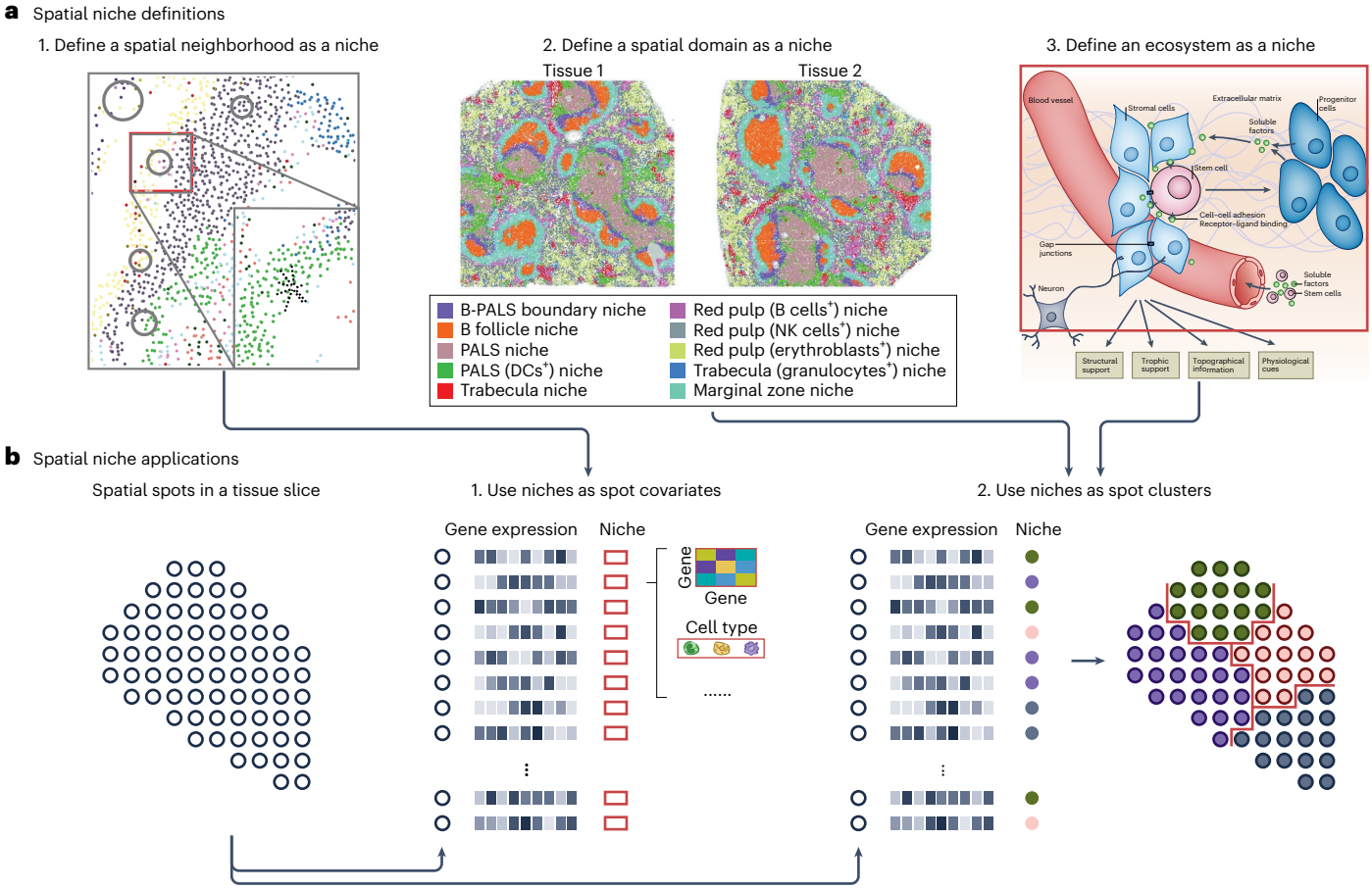


Fig. 1 | Conceptual overview of spatial niche definitions and their analytical uses. a, The three main spatial niche definitions in spatial omics data analyses—defining a spatial neighborhood, a spatial domain or an ecosystem as a spatial niche. **b**, The two main spatial niche applications in spatial omics analysis—using spatial niches as covariates of spots or as spot clusters. Images in **a** have been adapted from previously published material—the spatial neighborhood image (left) is adapted from ref. 7, under a Creative Commons license CC BY 4.0; the spatial domain image (middle) is adapted from ref. 12, Springer Nature Limited; and the ecosystem image (right) is adapted from ref. 65, Springer Nature Limited. DCs, dendritic cells; NK cells, natural killer cells; PALS, periarteriolar lymphoid sheath.

and soluble signaling factors. Among the three definitions, this ecosystem-type niche is most directly aligned with the original ecological notion of a niche and is the most biologically grounded, as it seeks to capture the full in situ environment that governs resident-cell behavior. This view traces back to the classical stem cell niche concept proposed in 1978 (ref. 4) and has since been extended to immune, fibrotic and tumor niches (Supplementary Note 3).

Spatial omics technologies have enabled systematic mapping of such ecosystems, allowing researchers to identify, from spatial omics data, interacting cell populations and candidate niche factors that may directly influence resident-cell fate and function[17–21,26–28]. However, because the exact boundaries of such ecosystems are rarely known, studies typically approximate them using regions of interest (ROIs) identified from microscopy, staining or other imaging modalities. The physical extent of an ROI is typically guided by anatomical or pathological landmarks and constrained by available tissue coverage, whereas the size of individual fields of view is often determined by the platform's capture area. Large ROIs may therefore require multiple fields of view to achieve adequate spatial coverage[48,49]. Because incomplete, truncated or overly broad regions may alter the inferred ecosystem composition and boundaries, alternative ROI definitions should be compared when ecosystem boundaries are uncertain.

Because this niche definition is grounded in anatomically or biologically defined structures and functions, its conceptual meaning does not depend on the resolution of the spatial omics data. However, spatial resolution determines the granularity at which ecosystem components and niche boundaries can be identified and the spatial precision with which localized ligand–receptor associations can be inferred. For example, single-cell or subcellular platforms can distinguish finer cellular compositions, sharper boundaries and shorter-range spatial associations, whereas multi-cell-resolution platforms average signals across cells, blur boundaries and often require deconvolution and orthogonal validation to support localized ligand–receptor inference.

Besides these three primary spatial niche definitions commonly encountered in spatial omics, a few studies adopt alternative usages. Some define the niche of a particular cell type as neighboring cells of other types located specifically at its boundary[50], whereas others introduce 'niche-specific genes' without explicitly defining the niche itself[37]. This heterogeneity further underscores the need for careful, explicit terminology. Further discussion of the conceptual distinctions and relationships among the three primary niche definitions, together with these alternative usages, is provided in Supplementary Note 4.

Applications of spatial niches in spatial omics data analyses

The concept of spatial niches has become an important tool in spatial omics data analysis, enabling the extraction of biologically meaningful insights from spatially resolved measurements. Depending on how niches are defined and on the goals of downstream analyses, spatial niches are typically used in one of two distinct analytical modes—either

as spot-level covariates that characterize the local environment influencing each spatial spot or as clusters of spatial spots that represent functional or anatomical regions where coordinated cellular interactions occur (Fig. 1b). The former is best suited to questions about how local context modulates individual cell or spot states, whereas the latter supports the discovery and comparison of larger-scale spatial domains and anatomically defined ecosystems.

Use of neighborhood-type niches as spot covariates

One common application of spatial niches is to use them as spot-level covariates. This use case is specific to the neighborhood-type definition, in which each spatial niche is defined as a neighborhood anchored at a spatial spot, creating a one-to-one correspondence between niches and spots. In this context, the niche provides an extended characterization of its anchor spot and can be viewed as a set of additional features that complement the spot's own omics profile.

Multiple computational strategies have been developed to construct quantitative representations of neighborhood-type niches, with the main goal of encoding the local cellular context and molecular interaction patterns surrounding each spot. Many studies focus on niche cell-type composition and accordingly represent each niche using cell-type proportions[5,8,30,31], binary indicators of cell-type presence[9] or fold enrichments of cell types (that is, observed cell-type frequencies within a niche relative to their global frequencies)[6]. A niche can also be represented by richer molecular summaries, such as shifted gene–gene covariance matrices capturing transcriptional dependencies across neighboring spots[7].

Using spatial niches as spot covariates is often aimed at two broad categories of questions. First, many studies seek to uncover associations between a spot's local spatial context and its omics features. This is typically formulated as a regression problem in which niche representations serve as regressors and an omics feature of the anchor spot is treated as the response variable, with statistical testing used to identify significant associations[5,6,9,30]. The predictor–response specification introduces statistical directionality (for example, testing whether the abundance of a particular neighboring cell type is associated with variation in the anchor spot's gene expression) but does not by itself establish the direction of biological influence, cell–cell communication or gene regulation. Such mechanistic interpretations require additional biological evidence and assumptions, including plausible ligand–receptor and downstream target relationships, an appropriate spatial scale, and adequate control for tissue region, cell-state and other spatial confounders. Unless spatially varying coefficients or interaction terms are explicitly modeled, these approaches generally assume a common anchor–neighbor association across the analyzed spatial spots.

Second, other studies leverage neighborhood-type niches to improve spot-level representations for downstream analyses, such as clustering or trajectory inference[7,8,31]. Here the central hypothesis is that spatial context carries information about a cell or spot's identity and function that is not fully captured by its own omics features. Niche-derived features have, for example, been used to improve spatial domain identification and data integration[7] or to construct neighborhood-level trajectories that are subsequently mapped back to individual spots[8]. Together, these studies illustrate how neighborhood-type niches can contextualize individual cellular states and support downstream spatial analysis.

Use of domain-type and ecosystem-type niches as spot clusters

Another common application of spatial niches is to use them as spot clusters in downstream analyses. In this setting, clusters of spatial spots correspond to either computationally derived regions (domain-type niches) or biologically informed regions (ecosystem-type niches) within tissues. For domain-type niches, computationally identified spatial domains directly serve as spot clusters for analysis. For ecosystem-type niches, spatial omics profiling is typically performed on ROIs that approximate the underlying ecosystem, and these profiled ROIs function as spot clusters in downstream analyses.

A major downstream focus is to characterize each niche individually, uncovering its cellular composition, transcriptional programs and niche-specific cell–cell communication mechanisms. A coarse but informative first step is to examine cell-type composition within each niche, which can reveal patterns of cell-type colocalization and provide preliminary clues about which cell types may interact[12,13,15,16,19,21,23,26,27]. Comparing such compositions across conditions (for example, healthy versus diseased) can further reveal pathological shifts in cellular organization and interaction[15,23,34]. At the transcriptional level, identifying differentially expressed genes or gene programs within a niche under different conditions highlights context-specific changes in gene regulation[19,34]. Another central within-niche analysis infers cell–cell interactions between colocalized cell types to uncover the signaling mechanisms that govern niche function. A common strategy is to quantify ligand–receptor activity, often incorporating spatial proximity between ligands and receptors, to identify signaling pathways and candidate niche factors[11,14,16–18,20]. Researchers deploy various computational methods for spatial ligand–receptor inference, including proximity-based approaches (for example, CellChat[51], LIANA+[52]) that score ligand–receptor activity from co-expression patterns weighted by spatial distance; optimal transport models (for example, COMMOT[53]) that simulate diffusion-like signaling; and spatially variable interaction frameworks (for example, SPIDER[54], spCorr[55]) that test whether ligand–receptor activity varies across space. Comparing ligand–receptor activity across conditions can further reveal changes in niche signaling under disease or perturbation[17,20].

Apart from these within-niche analyses, many studies compare niches to identify niche-specific transcriptional profiles and functional mechanisms[10,11,15,16,19,21,28]. Differential gene expression and gene ontology analysis across niches can uncover molecular signatures unique to each niche and link them to spatial and functional roles[10,11,15,16,19,21,28]. Analyses of gene expression changes across spatially ordered niches—for example, from pericentral to periportal regions in the liver—under different conditions can additionally reveal how transitions in niche identity and function respond to physiological or pathological changes[10].

Beyond treating niches as isolated units, another analytical direction examines spatial and functional relationships between niches. This is typically applied to domain-type niches rather than ecosystem-type niches, because the latter are conceptually assumed to encompass all interactions relevant to their resident cells. A key question studied here is whether different niches exhibit preferential spatial proximity in homeostatic or perturbed conditions, which may indicate potential inter-niche interactions and reveal how spatial arrangements shift in response to physiological or pathological changes[11,12,15]. Ligand–receptor activity can then be evaluated between cells drawn from different niches to further interpret inter-niche signaling[11].

Finally, recently emerging applications use defined spatial niches as reference labels for data integration and representation learning. Spatial foundation models, such as Nicheformer[32] and C2S-Scale[33], learn mappings between a cell's intrinsic gene expression and its surrounding tissue context to predict the niche label of unseen dissociated single-cell RNA-sequencing cells. This 'zero-shot' label transfer enables in silico spatial reconstruction of nonspatial datasets and the use of niche identity as a high-level representation for downstream tasks such as patient stratification or treatment response prediction.

Decision framework for spatial niche analysis

Selecting an appropriate spatial niche definition requires matching the underlying biological question to the analytical framework. To guide this process, we provide a practical decision framework (Fig. 2 and Supplementary Table 2) that maps biological questions to suitable

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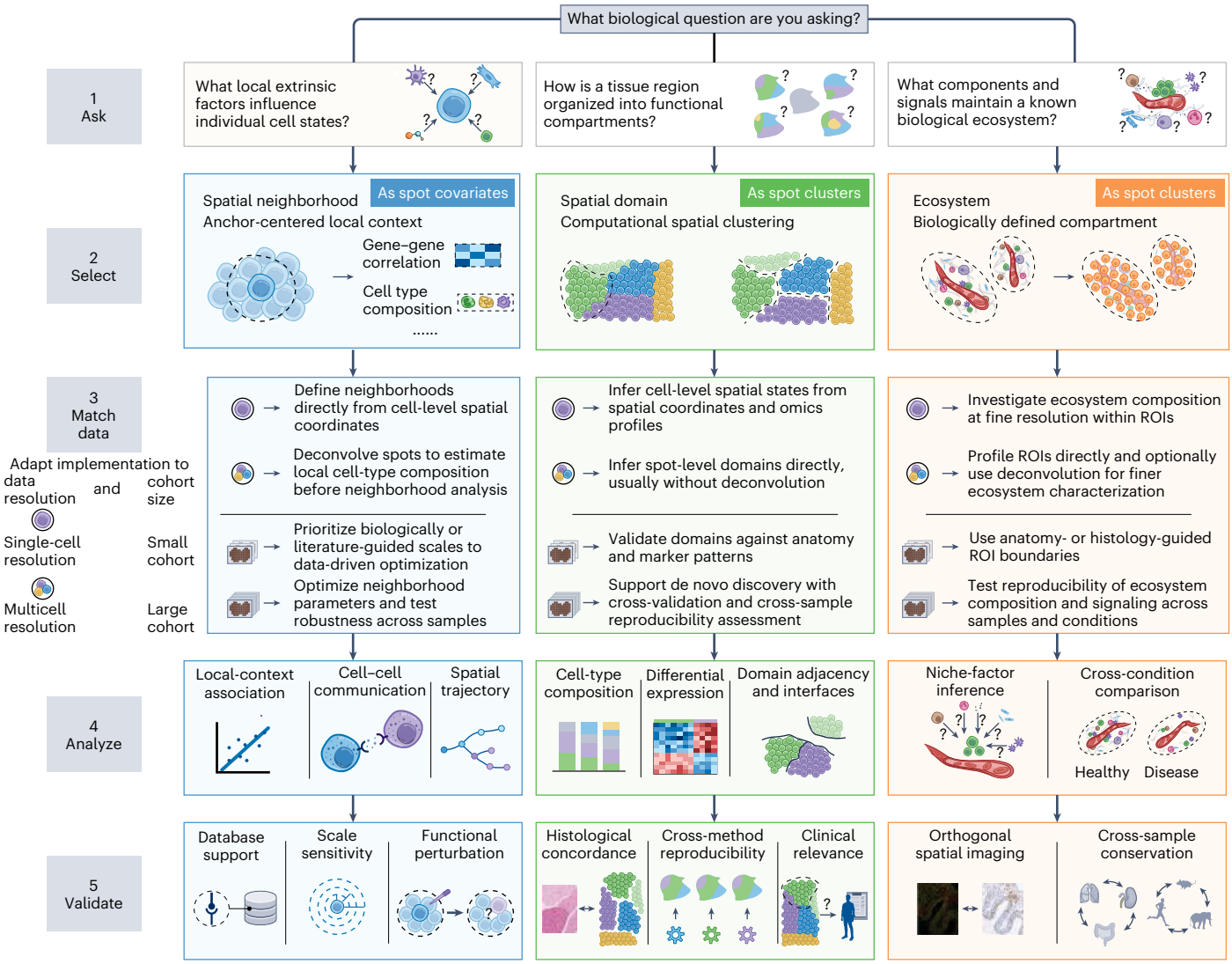


Fig. 2 | Overview of the decision framework for spatial niche analysis. The framework links the biological question to the appropriate niche definition and application mode, implementation choices tailored to data characteristics, downstream analyses and validation strategies. (1–2) Ask and select. Questions about local extrinsic influences on individual cells or spots motivate the spatial neighborhood definition, with neighborhood representations used as spot covariates. Questions about tissue organization into functional compartments prompt the spatial domain definition, whereas questions about the components and signals that maintain a known biological ecosystem trigger the spatial ecosystem definition; in both cases, the defined spatial objects can be used as spot clusters. (3) Match data. Single-cell-resolution data support direct cell-level neighborhood and domain analyses and finer characterization of ecosystems within ROIs. With multi-cell-resolution data, neighborhood analysis may require estimation of local cellular composition, domains can often be inferred directly at the spot level and ecosystems can be profiled at the ROI level, with deconvolution used as an optional refinement. With small-cohort data (<10 samples), neighborhood scales and ecosystem boundaries should generally be guided by biological or anatomical priors, whereas computationally discovered domains require validation against anatomical structures or marker patterns. Large-cohort data support more robust assessment of neighborhood parameters, cross-validated domain discovery and evaluation of ecosystem reproducibility across individuals and conditions. (4) Analyze. Neighborhood-based analyses address local-influence questions by relating neighborhood features to anchor-cell states, identifying candidate cell–cell communication signals and examining how changes in local context relate to spatial state progression. Domain-based analyses address tissue-organization questions by identifying the cellular composition and molecular programs that distinguish spatial states and examining how domains adjoin or transition. Ecosystem-based analyses address how known biological environments are maintained by identifying supporting cells, structural components and candidate niche factors and by comparing ecosystem composition and signaling across conditions. (5) Validate. Neighborhood findings can be evaluated using curated ligand–receptor databases, sensitivity analyses across neighborhood scales and functional perturbation. Domain interpretations can be assessed through histological concordance, cross-method reproducibility and associations with clinically relevant phenotypes. Ecosystem interpretations can be supported by orthogonal spatial imaging and conservation across samples, platforms or biological systems. Figure partially created in BioRender; Liu, P. https://biorender.com/gp0hdyf (2026).

niche definitions, application modes, implementation adapted to data characteristics, downstream analyses and validation strategies. Together, these steps provide a practical route from biological question to interpretable niche-based inference. A detailed discussion of the rationale, implementation considerations and representative methods is provided in Supplementary Note 5.

Emerging technologies and future directions

As spatial omics technologies continue to evolve, the concept and analysis of spatial niches are being reshaped by advances in spatial resolution, dimensionality, multimodal profiling, temporal mapping and artificial intelligence (AI). These developments are pushing the field beyond static, two-dimensional, single-modal descriptions of

https://doi.org/10.1038/s41588-026-02813-6

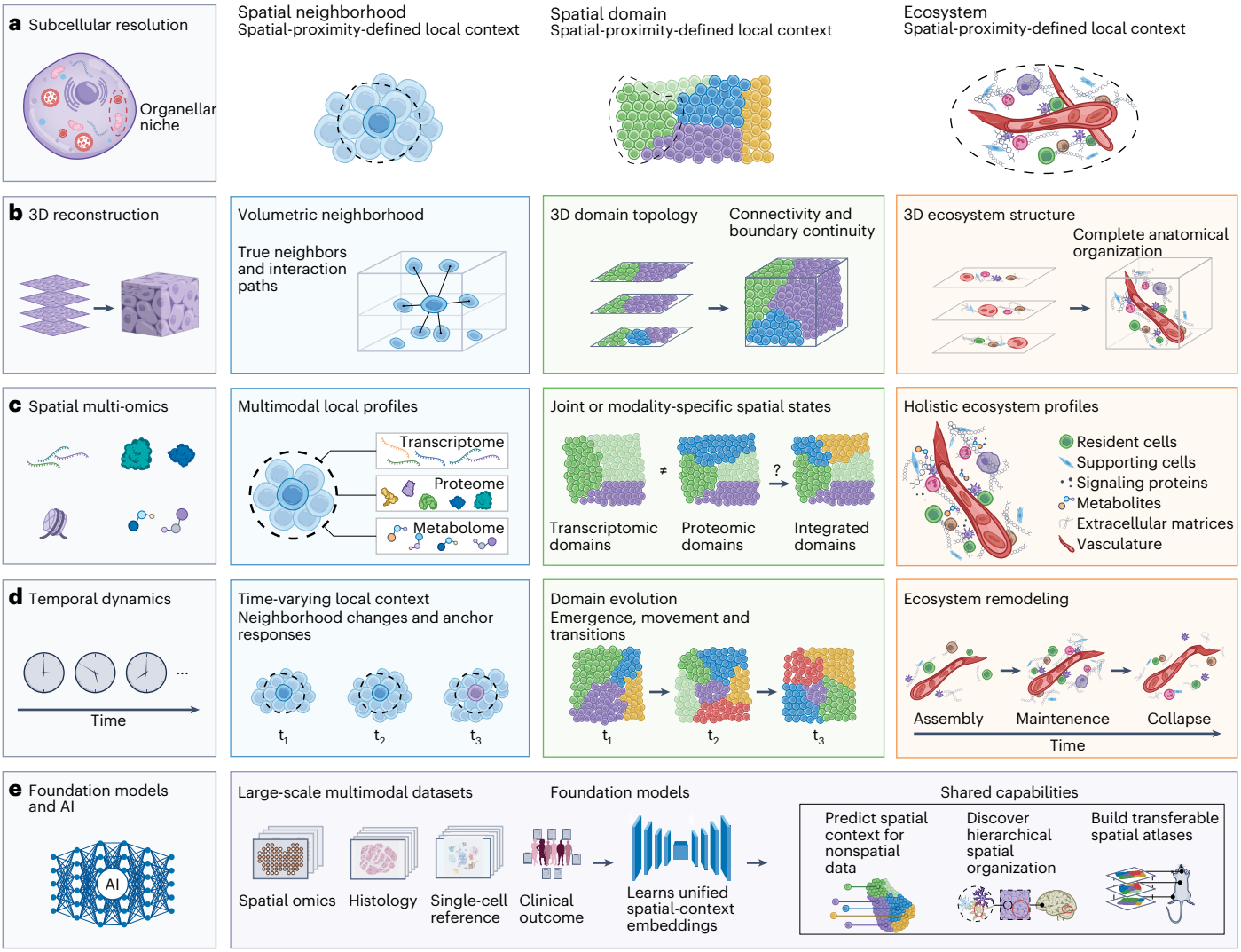


Fig. 3 | Emerging technologies and future directions for spatial niche analysis. **a**, Subcellular resolution. Evolving subcellular-resolution platforms may reveal localized molecular and organellar environments, raising the possibility of organellar niches as a finer-grained niche definition beyond the current cellular-to-tissue-scale taxonomy. **b**, 3D reconstruction. Transitioning from two-dimensional tissue sections to three-dimensional reconstructions can reveal true cellular neighbors and interaction paths for spatial neighborhoods, connectivity and boundary continuity for spatial domains and the complete anatomical organization of ecosystem compartments that may appear fragmented across individual sections. **c**, Spatial multi-omics. Spatially resolved measurements across multiple molecular modalities can provide multimodal local-context profiles for neighborhoods, reveal joint or modality-specific spatial states for domains and enable more comprehensive characterization of the cellular, molecular and structural components of ecosystems. **d**, Temporal dynamics. Temporal spatial profiling can relate changes in local neighborhoods to subsequent anchor-cell responses, track the emergence and transitions of spatial domains and characterize ecosystem assembly, maintenance, remodeling and collapse. **e**, Foundation models and AI. Foundation models can learn generalizable representations of spatial context from large-scale multimodal datasets, with potential applications including discovering hierarchical spatial organization, predicting spatial context for nonspatial data and building transferable spatial atlases. 3D, three-dimensional; AI, artificial intelligence. Figure partially created in BioRender; Liu, P. https://biorender.com/06asz3q (2026).

cell organization toward a dynamic, three-dimensional, multimodal understanding of tissue biology.

The emergence of platforms with subcellular resolution[35,41,56] raises the possibility of defining organellar niches at subcellular scales (Fig. 3a). At this scale, asymmetric positioning of intracellular structures, such as mitochondria or the endoplasmic reticulum, may create localized signaling environments, while distinct membrane domains, such as apical and basolateral surfaces in polarized epithelial cells, may represent functionally specialized spatial compartments. These subcellular organizations extend beyond the cellular-to-tissue scale of the three niche definitions summarized here and may constitute a fourth, finer-grained niche definition.

The field is also transitioning from two-dimensional tissue sections to three-dimensional reconstructions[57–60], which can reshape the spatial relationships represented by all three niche definitions (Fig. 3b). For neighborhoods, three-dimensional coordinates may reveal true cellular neighbors and interaction paths that are obscured in two-dimensional sections. For domains, regions that appear disconnected or sharply separated across individual sections may instead form connected or gradually transitioning structures in three dimensions. For ecosystems, volumetric reconstruction can reveal the complete anatomical organization of vascular, glandular or tumor-associated compartments whose boundaries and components extend beyond individual sections.

In parallel, the increasing availability of spatially resolved measurements across multiple omic modalities[30,39,61–63] will expand the information layers available to define and characterize each spatial object (Fig. 3c). For neighborhoods, transcriptomic, proteomic, epigenomic

https://doi.org/10.1038/s41588-026-02813-6

Table 1 | Key characteristics of the three main spatial niche definitions

Niche definition	Conceptual nature	Core focus	Defining information	Spatial organization	Components	Spatial scale	Primary analytical role	Primary application	Recommended terminology
Spatial neighborhood	Computational	Local interactions	Spatial coordinates	One neighborhood per spot or cell	Cells only	Local (~5 to 50 cells or spots)	Spot covariate	Modeling short-range cell–cell communication	Spatial neighborhood (avoid 'niche')
Spatial domain	Computational	Regional patterns	Omics features, spatial coordinates, and contextual features (optional)	A domain may be contiguous or recur in spatially separated regions	Cells only	Mesoscale (~50 to 20,000 cells or spots)	Spot cluster	Discovering de novo tissue architecture and compartments	Spatial domain (avoid 'niche')
Ecosystem	Biological	Biological functions	Biological prior knowledge	Biologically delineated region with potentially uncertain boundaries	Cells and noncellular factors (ECM, vasculature, signals)	Compartment-level (~200 to 50,000 cells or spots)	Spot cluster	Studying tissue homeostasis and disease pathology	Niche

and metabolic measurements may capture local cues with different biological meanings and effective interaction ranges. For domains, modality-specific spatial states may only partially overlap, requiring careful consideration of whether to define joint spatial states or retain modality-specific representations. For ecosystems, different omic modalities can provide complementary views of resident and supporting cells, signaling molecules, metabolites, ECM and other structural components.

Dynamic spatial profiling remains technically challenging but represents an important next step toward moving niche analysis from static descriptions to models of spatial change (Fig. 3d). For neighborhoods, temporal analyses can examine how changes in local context relate to subsequent anchor-cell responses. For domains, temporal analyses may track the emergence, movement and transitions of spatial states and relate these dynamics to phenotypic or clinical outcomes. For ecosystems, longitudinal and perturbational studies may reveal mechanisms underlying ecosystem assembly, maintenance, remodeling and collapse during development or disease.

From a computational perspective, foundation models and AI provide a cross-cutting framework for learning generalizable representations of spatial context across tissues, platforms and modalities[32,34,64]. Such models may predict spatial context for dissociated single-cell data, effectively 'spatializing' nonspatial datasets[32]. They also hold the potential to discover hierarchical spatial organization across scales, from local neighborhoods to tissue-level domains, and to build transferable spatial atlases by aligning spatial contexts across samples, tissues, platforms and modalities (Fig. 3e). However, AI-derived spatial representations remain computational constructs, and their interpretation as neighborhoods, domains or ecosystems requires definition-specific biological validation.

Conclusions

The concept of the spatial niche has become central to spatial omics, yet its utility is limited by inconsistent and context-dependent definitions. As we have outlined, 'niche' is currently used to describe three conceptually distinct spatial objects—proximity-based neighborhoods, computationally derived spatial domains and biologically grounded ecosystems. These concepts operate at different spatial scales, embody distinct assumptions and address different biological questions. Specifically, spatial neighborhoods capture local interactions and are optimally suited for modeling cell–cell communication; spatial domains reflect regional patterns and are best used for discovering de novo tissue architecture; and ecosystems represent complex functional environments, making them ideal for studying tissue homeostasis and disease pathology (Table 1). Collapsing these distinct objects into a single term 'niche' complicates interpretation, hinders cross-study comparison and undermines the reproducibility of analytical frameworks.

We therefore advocate for more precise terminology. The term 'niche' should ideally be reserved for the biologically defined ecosystem, which most closely reflects its traditional biological meaning, whereas 'spatial neighborhood' and 'spatial domain' should be used for the corresponding computational spatial objects (Table 1). While universal standardization may not always be feasible, studies invoking the concept of a spatial niche should clearly state their operational definition, including what information is used to define a niche, what it encompasses and its spatial scale. Doing so would provide a clearer basis for comparing methods and communicating biological findings across the field.

Beyond terminological clarity, progress in spatial niche research will depend on rigorous validation, cross-platform reproducibility and methodological transparency. As spatial analyses become increasingly multiscale, multimodal, dynamic and AI-enabled, a central challenge will be to ensure that increasingly complex spatial representations remain biologically interpretable. This will require transparent reporting of how niches are defined, methods benchmarked with clearly

documented trade-offs, robust and openly available software implementations and validation frameworks that connect computational evidence with orthogonal biological measurements and, where possible, functional perturbations.

Realizing this vision will require coordinated efforts among methods developers, experimental biologists, consortia and publishers to establish a shared conceptual language and reporting standards. We hope that the taxonomy and decision framework presented here provide a foundation for this effort. By grounding spatial niche analysis in explicit definitions and well-matched analytical strategies, the field can move beyond anecdotal uses of 'niche' toward a systematic framework for uncovering the organizational principles that govern complex tissues and, eventually, for translating those principles into diagnostic and therapeutic advances.

References

1. Grinnell, J. The niche-relationships of the California thrasher. *Auk* **34**, 427–433 (1917).
2. Grinnell, J. Geography and evolution. *Ecology* **5**, 225–229 (1924).
3. Whittaker, R. H., Levin, S. A. & Root, R. B. Niche, habitat, and ecotope. *Am. Nat.* **107**, 321–338 (1973).
4. Schofield, R. The relationship between the spleen colony-forming cell and the haemopoietic stem cell. *Blood Cells* **4**, 7–25 (1978).
5. Mason, K. et al. Niche-DE: niche-differential gene expression analysis in spatial transcriptomics data identifies context-dependent cell–cell interactions. *Genome Biol.* **25**, 14 (2024).
6. Agrawal, A., Thomann, S., Basu, S. & Grün, D. NiCo identifies extrinsic drivers of cell state modulation by niche covariation analysis. *Nat. Commun.* **15**, 10628 (2024).
7. Haviv, D. et al. The covariance environment defines cellular niches for spatial inference. *Nat. Biotechnol.* **43**, 269–280 (2025).
8. Wang, W., Zheng, S., Shin, S. C., Chávez-Fuentes, J. C. & Yuan, G.-C. ONTraC characterizes spatially continuous variations of tissue microenvironment through niche trajectory analysis. *Genome Biol.* **26**, 117 (2025).
9. Fischer, D. S., Schaar, A. C. & Theis, F. J. Modeling intercellular communication in tissues using spatial graphs of cells. *Nat. Biotechnol.* **41**, 332–336 (2023).
10. Qian, J. et al. Identification and characterization of cell niches in tissue from spatial omics data at single-cell resolution. *Nat. Commun.* **16**, 1693 (2025).
11. Birk, S. et al. Quantitative characterization of cell niches in spatially resolved omics data. *Nat. Genet.* **57**, 897–909 (2025).
12. Varrone, M., Tavernari, D., Santamaria-Martínez, A., Walsh, L. A. & Ciriello, G. CellCharter reveals spatial cell niches associated with tissue remodeling and cell plasticity. *Nat. Genet.* **56**, 74–84 (2024).
13. Vannan, A. et al. Spatial transcriptomics identifies molecular niche dysregulation associated with distal lung remodeling in pulmonary fibrosis. *Nat. Genet.* **57**, 647–658 (2025).
14. Kanemaru, K. et al. Spatially resolved multiomics of human cardiac niches. *Nature* **619**, 801–810 (2023).
15. Mayr, C. H. et al. Spatial transcriptomic characterization of pathologic niches in IPF. *Sci. Adv.* **10**, eadl5473 (2024).
16. Madissoon, E. et al. A spatially resolved atlas of the human lung characterizes a gland-associated immune niche. *Nat. Genet.* **55**, 66–77 (2023).
17. Rajachandran, S. et al. Dissecting the spermatogonial stem cell niche using spatial transcriptomics. *Cell Rep.* **42**, 112737 (2023).
18. Niec, R. E. et al. Lymphatics act as a signaling hub to regulate intestinal stem cell activity. *Cell Stem Cell* **29**, 1067–1082 (2022).
19. Lu, Y. et al. Spatial transcriptome profiling by MERFISH reveals fetal liver hematopoietic stem cell niche architecture. *Cell Discov.* **7**, 47 (2021).
20. Eyres, M. et al. Spatially resolved deconvolution of the fibrotic niche in lung fibrosis. *Cell Rep.* **40**, 111230 (2022).
21. Baccin, C. et al. Combined single-cell and spatial transcriptomics reveal the molecular, cellular and spatial bone marrow niche organization. *Nat. Cell Biol.* **22**, 38–48 (2020).
22. Rompolas, P., Mesa, K. R. & Greco, V. Spatial organization within a niche as a determinant of stem-cell fate. *Nature* **502**, 513–518 (2013).
23. Medaglia, C. et al. Spatial reconstruction of immune niches by combining photoactivatable reporters and scRNA-seq. *Science* **358**, 1622–1626 (2017).
24. Zuo, C. et al. stClinic dissects clinically relevant niches by integrating spatial multi-slice multi-omics data in dynamic graphs. *Nat. Commun.* **16**, 5317 (2025).
25. Guo, P. et al. Multiplexed spatial mapping of chromatin features, transcriptome and proteins in tissues. *Nat. Methods* **22**, 520–529 (2025).
26. Bandyopadhyay, S. et al. Mapping the cellular biogeography of human bone marrow niches using single-cell transcriptomics and proteomic imaging. *Cell* **187**, 3120–3140 (2024).
27. Mrdjen, D. et al. Spatial proteomics of Alzheimer's disease-specific human microglial states. *Nat. Immunol.* **26**, 1397–1410 (2025).
28. Guilliams, M. et al. Spatial proteogenomics reveals distinct and evolutionarily conserved hepatic macrophage niches. *Cell* **185**, 379–396 (2022).
29. Hulahan, T. S. et al. Extracellular microenvironment alterations in ductal carcinoma in situ and invasive breast cancer pathologies by multiplexed spatial proteomics. *Int. J. Mol. Sci.* **25**, 6748 (2024).
30. Goltsev, Y. et al. Deep profiling of mouse splenic architecture with CODEX multiplexed imaging. *Cell* **174**, 968–981 (2018).
31. Rius Rigau, A. et al. Characterization of vascular niche in systemic sclerosis by spatial proteomics. *Circ. Res.* **134**, 875–891 (2024).
32. Tejada-Lapuerta, A. et al. Nicheformer: a foundation model for single-cell and spatial omics. *Nat. Methods* **22**, 2525–2538 (2025).
33. Rizvi, S. A. et al. Scaling large language models for next-generation single-cell analysis. Preprint at *bioRxiv* https://doi.org/10.1101/2025.04.14.648850 (2026).
34. Paniagua, K. et al. Dissection of tumoral niches using spatial transcriptomics and deep learning. *iScience* **28**, 112214 (2025).
35. He, S. et al. High-plex imaging of RNA and proteins at subcellular resolution in fixed tissue by spatial molecular imaging. *Nat. Biotechnol.* **40**, 1794–1806 (2022).
36. McCaffrey, E. F. et al. The immunoregulatory landscape of human tuberculosis granulomas. *Nat. Immunol.* **23**, 318–329 (2022).
37. Saqib, J. et al. Identification of niche-specific gene signatures between malignant tumor microenvironments by integrating single cell and spatial transcriptomics data. *Genes (Basel)* **14**, 2033 (2023).
38. Fane, M. & Weeraratna, A. T. How the ageing microenvironment influences tumour progression. *Nat. Rev. Cancer* **20**, 89–106 (2020).
39. Keren, L. et al. A structured tumor-immune microenvironment in triple negative breast cancer revealed by multiplexed ion beam imaging. *Cell* **174**, 1373–1387 (2018).
40. Lee, C. Y. C., McCaffrey, J., McGovern, D. & Clatworthy, M. R. Profiling immune cell tissue niches in the spatial -omics era. *J. Allergy Clin. Immunol.* **155**, 663–677 (2025).
41. Janesick, A. et al. High resolution mapping of the tumor microenvironment using integrated single-cell, spatial and in situ analysis. *Nat. Commun.* **14**, 8353 (2023).
42. Chen, K. H., Boettiger, A. N., Moffitt, J. R., Wang, S. & Zhuang, X. RNA imaging. Spatially resolved, highly multiplexed RNA profiling in single cells. *Science* **348**, aaa6090 (2015).

43. Maynard, K. R. et al. Transcriptome-scale spatial gene expression in the human dorsolateral prefrontal cortex. *Nat. Neurosci.* **24**, 425–436 (2021).
44. Wang, Z. et al. A comprehensive review of approaches for spatial domain recognition of spatial transcriptomes. *Brief. Funct. Genomics* **23**, 702–712 (2024).
45. Yuan, Z. et al. Benchmarking spatial clustering methods with spatially resolved transcriptomics data. *Nat. Methods* **21**, 712–722 (2024).
46. Kang, L., Zhang, Q., Qian, F., Liang, J. & Wu, X. Benchmarking computational methods for detecting spatial domains and domain-specific spatially variable genes from spatial transcriptomics data. *Nucleic Acids Res.* **53**, gkaf303 (2025).
47. Kleshchevnikov, V. et al. Cell2location maps fine-grained cell types in spatial transcriptomics. *Nat. Biotechnol.* **40**, 661–671 (2022).
48. Dries, R. et al. Advances in spatial transcriptomic data analysis. *Genome Res.* **31**, 1706–1718 (2021).
49. Yeo, S., Schrader, A. W., Lee, J., Asadian, M. & Han, H.-S. Spot-based global registration for subpixel stitching of single-molecule resolution images for tissue-scale spatial transcriptomics. *Anal. Chem.* **96**, 6517–6522 (2024).
50. Fang, S. et al. Stereopy: modeling comparative and spatiotemporal cellular heterogeneity via multi-sample spatial transcriptomics. *Nat. Commun.* **16**, 3741 (2025).
51. Jin, S., Plikus, M. V. & Nie, Q. CellChat for systematic analysis of cell–cell communication from single-cell transcriptomics. *Nat. Protoc.* **20**, 180–219 (2025).
52. Dimitrov, D. et al. LIANA+ provides an all-in-one framework for cell–cell communication inference. *Nat. Cell Biol.* **26**, 1613–1622 (2024).
53. Cang, Z. et al. Screening cell–cell communication in spatial transcriptomics via collective optimal transport. *Nat. Methods* **20**, 218–228 (2023).
54. Li, S., Wang, R., Liu, S. & Li, S. C. Finding spatially variable ligand–receptor interactions with functional support from downstream genes. *Nat. Commun.* **16**, 7784 (2025).
55. Jiang, C. et al. spCorr: flexible and scalable inference of spatially varying correlation in spatial transcriptomics with spCorr. *Genome Res.* **36**, 1440–1454 (2026).
56. Chen, A. et al. Spatiotemporal transcriptomic atlas of mouse organogenesis using DNA nanoball-patterned arrays. *Cell* **185**, 1777–1792 (2022).
57. Zhao, H. et al. So3D: a comprehensive three-dimensional spatial omics resource for decoding tissue architecture in physiology and disease. *Nucleic Acids Res.* **54**, D1281–D1290 (2026).
58. Yu, Y. & Xie, Z. Spatial transcriptomic alignment, integration, and 3D reconstruction by STAIR. *Genome Biol.* **26**, 427 (2025).
59. Schott, M. et al. Open-ST: high-resolution spatial transcriptomics in 3D. *Cell* **187**, 3953–3972 (2024).
60. Wang, G. et al. Construction of a 3D whole organism spatial atlas by joint modelling of multiple slices with deep neural networks. *Nat. Mach. Intell.* **5**, 1200–1213 (2023).
61. Spraggins, J. M. et al. Matrix-assisted laser desorption/ionization imaging mass spectrometry. *Nat. Rev. Methods Primers* **6**, 44 (2026).
62. Deng, Y. et al. Spatial profiling of chromatin accessibility in mouse and human tissues. *Nature* **609**, 375–383 (2022).
63. Deng, Y. et al. Spatial-CUT&Tag: spatially resolved chromatin modification profiling at the cellular level. *Science* **375**, 681–686 (2022).
64. Liu, L., Pan, X., Yuan, Y. & Shang, L. Prototype-driven fusion of pathology and spatial transcriptomics for interpretable survival prediction. Preprint at https://doi.org/10.48550/arXiv.2602.12441 (2026).
65. Jones, D. L. & Wagers, A. J. No place like home: anatomy and function of the stem cell niche. *Nat. Rev. Mol. Cell Biol.* **9**, 11–21 (2008).

Acknowledgements

This work was supported by the National Institute of General Medical Sciences (NIGMS) of the National Institutes of Health (NIH) under award R35GM140888 and the National Human Genome Research Institute (NHGRI) under award R01HG014687 (to J.J.L.). Additional support was provided by NHGRI through an Opportunity Fund subaward from the Technology Development Coordinating Center (TDCC; U24HG011735).

Author contributions

P.L. and J.J.L. wrote and revised the manuscript. P.L. prepared the figures and tables.

Competing interests

All authors declare no competing interests.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41588-026-02813-6.

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Peer review information *Nature Genetics* thanks the anonymous reviewer(s) for their contribution to the peer review of this work.

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