Workshop Introduction
Multi-modal Spatial-Omics: From AI Models to Translational Applications

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The workshop "Multi-modal Spatial-Omics: From AI Models to Translational Applications" at the Pacific Symposium on Biocomputing 2027 brings together researchers developing and applying computational methods for spatial molecular data. Two keynote presentations and eleven selected talks connect advances in multimodal integration, tissue reconstruction, and mechanistic modeling with applications in cancer, brain aging, and kidney biology. The program spans histology-guided analysis, cross-assay representation learning, spatial genomics, and patient-level prediction. Through presentations and discussion, the workshop will examine how AI and statistical methods can support interpretable biological discovery and rigorously evaluated translational applications.

Keywords: Spatial omics; multimodal integration; artificial intelligence; histopathology; translational bioinformatics.

1. Background

Spatial omics technologies measure molecular variation within its tissue context, connecting cellular states to local organization and interactions. Integrating spatial transcriptomics, proteomics, metabolomics, and epigenomics with histological imaging provides complementary views of tissue biology. These data create opportunities to investigate how molecular programs are organized across cells and tissue regions, how this organization changes in disease, and which spatial features may inform clinical research.

Realizing these opportunities requires addressing substantial computational challenges. Modalities differ in resolution, coverage, noise, and sampling, and measurements may come from different tissue sections or patients. Integrative methods must align these observations while

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preserving biologically meaningful variation. Analyses also need to distinguish technical effects from tissue structure and connect two-dimensional measurements to three-dimensional organization. For predictive applications, evaluation across independent patients and cohorts is essential to assess whether a model generalizes beyond its training data.

AI and machine learning offer approaches to these problems through graph-based representations, deep learning, generative modeling, and transfer across modalities. Statistical modeling provides complementary tools for uncertainty assessment and interpretable inference. The central challenge is to connect computational advances to biological questions and establish when their predictions are reliable enough to support further experimental or translational investigation.

2. Workshop goals

This workshop brings together computational scientists, statisticians, experimental biologists, and translational researchers to examine the progression from multimodal data integration to biological interpretation and patient-level prediction. Building on the PSB 2026 workshop "Advances of AI Methods in Single Cell Spatial Omics," the 2027 program places particular emphasis on relationships among molecular assays, histopathology, and tissue architecture.

The workshop will address methods for cross-modal and cross-sample integration; representations that preserve spatial context; reconstruction of molecular and tissue organization; and models that connect spatial measurements to disease mechanisms or clinical outcomes. Across these themes, discussion will consider interpretability, uncertainty, reproducibility, and evaluation. A shared aim is to identify the evidence needed to move from descriptive spatial patterns toward testable biological hypotheses and robust predictive models.

3. Workshop program

The program combines two keynote presentations with eleven selected talks. Together, the contributions connect general computational methods with specific biological questions, from subcellular genome organization to tissue microenvironments and patient outcomes.

3.1. *Keynote presentations*

Mingyao Li, Professor of Biostatistics at the University of Pennsylvania, develops statistical and computational methods for single-cell, spatial, and multimodal genomics. Her research on cellular heterogeneity and integrative analysis provides a perspective on connecting spatial molecular measurements to disease biology.

Smita Krishnaswamy, Professor of Genetics and of Computer Science at Yale University, develops AI and machine learning methods for biological data. Her work in manifold learning, deep learning, and generative modeling provides a complementary perspective on representing cellular states, tissue organization, and biological dynamics.

3.2. *Selected presentations*

Multimodal integration and representation learning. Ben Raphael's contribution addresses spatial alignment and morphology mapping. Chao Chen presents LUDEN, which incorporates uncertainty into morphology-aware denoising of spatial transcriptomics. Yue Li and Dylan Mann-Krzisnik present SpatialJEPA, using graph-context distillation to transfer tissue and metabolic context across molecular assays. These contributions motivate discussion of how spatial and morphological information can guide integration without obscuring assay-specific biological signals.

Mechanistic interpretation and three-dimensional organization. Paveethran Swaminathan and colleagues present MetaKnogic, a framework for biochemically grounded AI reasoning about metabolic variation using multimodal spatial omics. Weixiu Dong and colleagues address reconstruction of extrachromosomal DNA (ecDNA) organization and its relationship to function in cancer. Caleb Hallinan and colleagues examine kidney nephron pseudostructure reconstruction for pseudo-three-dimensional comparison of gene expression gradients. Together, these talks connect computational representations to biochemical mechanisms and spatial structure.

Disease biology and translational prediction. Rachel Fox and colleagues investigate shared cortical axes of genomic variation and spatial transcriptomics in human brain aging. Spencer Watson, Raphael Gottardo, and the Mosaic Consortium present a multimodal glioblastoma atlas focused on extracellular matrix differences in perivascular border zones associated with immune infiltration. Lana Garmire and colleagues present HisToSpatialCNV, an interpretable deep learning approach for predicting spatial copy number variation from histopathology. Lihe Liu and colleagues present NICER, integrating spatial transcriptomics and histopathology for niche detection and patient-level prediction. Lulu Shang and colleagues address prototype-driven fusion of pathology and spatial transcriptomics for interpretable survival prediction. These studies raise questions about biological validation, patient-level evaluation, and the interpretation of spatial predictors.

Discussion across the program will focus on evaluating integration across assays and cohorts, distinguishing predictive associations from mechanistic explanations, and identifying useful benchmarks for translational research. If additional program time is approved, a panel will provide a dedicated forum for these questions.

4. Conclusions

Multimodal spatial omics creates opportunities to connect molecular measurements, tissue organization, and disease phenotypes. By bringing methodological contributions into dialogue with biological and translational applications, this workshop aims to clarify current capabilities, identify limitations that require further validation, and encourage collaboration on interpretable and generalizable computational approaches. The program provides a focused forum within PSB for defining the next questions at the interface of AI, spatial biology, and medicine.