A170 · EMMA: A Generative Energy-based Model for Multiscale Architecture of Spatial Transcriptomics

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Objective: Standard spatial transcriptomics (ST) pipelines use fragmented analytical steps, each requiring distinct assumptions and manual tuning. We introduce the Energy Model for Multiscale Architecture (EMMA), a unified theoretical framework for ST that naturally derives multiscale tissue architecture directly from molecular interactions. This approach overcomes biases in modularly organized pipelines and can function independently of images. Methods: In EMMA, spatial correlations between transcripts define an energy landscape governing gene expression probability. Biological entities across scales (genes, transcripts, cells) are embedded in a single space. Using this model, consecutive ST analysis tasks are unified into internally consistent components. EMMA was applied across 4 platforms (Xenium, CosMx, MERSCOPE, and Visium HD). Results: Across 4 platforms, EMMA assigned >97% of transcripts to cells without morphological images, achieving high structural agreement with reference segmentations (NMI > 0.9). Leveraging its unified embedding space, EMMA identifies cell types and marker genes, revealing organizational motifs consistent with immune exclusion and coordinated niche formation near tumors, and quantifying spatial variability of genes in terms of local and global interactions. Dataset integration via gene-vector alignment using a simple orthogonal transformation validates the embedding space. Conclusions: Our results show ST analysis can be performed within a coherent theoretical framework. By linking molecular correlations to tissue architecture within a unified framework, EMMA offers a principled approach with intrinsic interpretation for understanding the physical and biological rules governing tissue organization.