

STATISTICS REVEALS HOW GENE NETWORKS CHANGE WITHIN TUMORS

STATISTICAL

SIGNIFICANCE

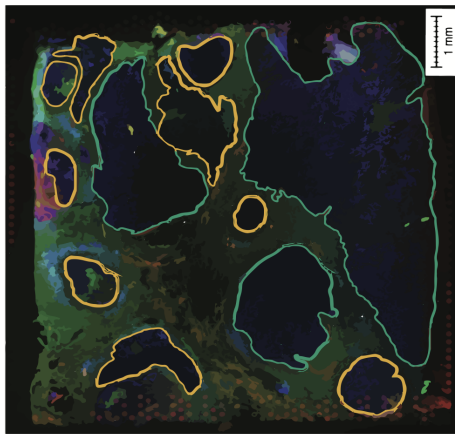
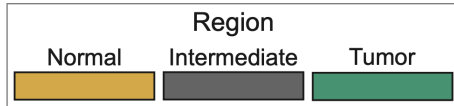
Advances in spatial transcriptomics, spatial statistics, and machine learning are transforming how researchers study cancer. Tumors are driven by the coordinated activity of genes within networks rather than by genes acting in isolation. These patterns of coordination can differ from one tissue region to another. Many existing methods either analyze genes individually or estimate a single network for the entire tissue, potentially overlooking important local patterns within the tumor microenvironment. **Spatial Covariance Regression** maps how gene relationships strengthen, weaken, or reverse across the tissue, helping researchers prioritize gene pairs for laboratory validation and potential therapeutic development.

Tumors Have a Geography. Statistics Can Map It.

THE AVERAGE CAN HIDE THE STORY

Spatial transcriptomics has transformed cancer research by measuring gene activity while preserving its location within tissue. This spatial information is especially important because cancer is driven not by isolated genes, but by gene networks that can vary across the tumor microenvironment. Gene relationships that are strong in one region may be weak, absent, or reversed in another. Yet few methods capture these spatially changing networks. Estimating a single network for the entire tissue assumes uniform gene relationships and may obscure important local cancer biology.

What the image shows. This breast cancer tissue contains distinct normal, intermediate, and tumor regions. Because gene relationships may differ across these regions, a single tissue-wide network may obscure important local patterns in cancer biology.

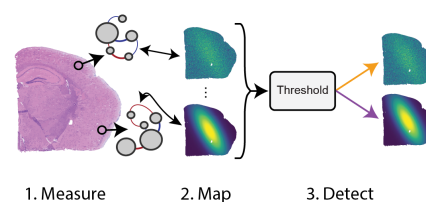


This motivates SCR. By mapping gene networks across the tissue, Spatial Covariance Regression reveals region-specific relationships that a single tissue-wide network may miss.

MAPPING GENE NETWORKS ACROSS TISSUE

We developed **Spatial Covariance Regression (SCR)** to estimate spot-specific gene co-expression networks across tissue. SCR produces these networks and identifies **spatially co-expressed genes (SCGs)**: gene pairs whose correlations vary meaningfully across the tissue. By preserving this spatial variation, SCR reveals local biological patterns that a single tissue-wide network may miss.

SCR Finds Gene Relationships That Vary Across Tissue



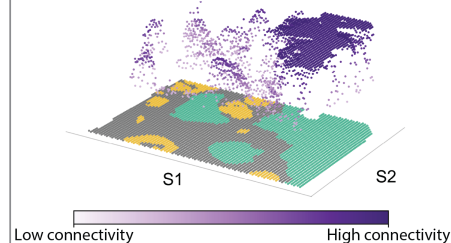
How SCR reveals spatial change

- 1. Measure.** Record gene activity at thousands of tissue locations.
- 2. Map.** Estimate a gene co-expression network at each measured tissue location, or spot, then map the strength and direction of each gene-pair correlation.
- 3. Detect.** Identify SCGs whose correlations vary meaningfully across the tissue while limiting false discoveries.

Pathway-level view: Metastasis

The invasion and metastasis pathway showed its highest connectivity in the tumor region.

Metastasis Pathway Connectivity Across the Tumor



How to read the map. Each spot shows pathway connectivity. **Higher connectivity → stronger local coordination.**

TWO LOCAL STORIES REVEALED INSIDE ONE TUMOR

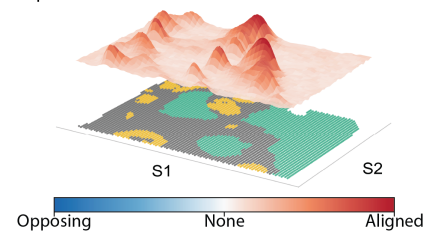
In a human HER2-amplified breast cancer sample, SCR revealed that gene-pair correlations varied across the tissue. Two pairs illustrate distinct immune and metabolic patterns within the same tumor.

How to read the maps. Each spot shows local gene-pair correlation. Color indicates direction, while height indicates absolute strength. Tall red peaks show strong positive correlation, tall blue peaks show strong negative correlation, and flat white areas indicate little or no correlation.

1. Immune coordination at the boundary

HLA-DRB1 and *HLA-A* showed a strong positive correlation along the tumor boundary but little or no correlation in the core. This pattern is consistent with antigen presentation near the boundary.

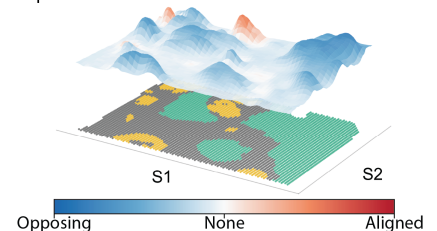
Tumor-Promoting Inflammation
Spatial correlation between *HLA-DRB1* and *HLA-A*



2. Altered energy use in the core

TPI1 and *COX6C* showed their strongest negative correlation in the tumor core, consistent with a pronounced trade-off between glycolysis and oxidative phosphorylation.

Reprogramming Energy Metabolism
Spatial correlation between *TPI1* and *COX6C*



WHY THIS MATTERS FOR CANCER RESEARCH

See what averages conceal

Researchers can detect local immune, metabolic, and signaling patterns that may be obscured in a single tissue-wide network.

Prioritize the next experiment

The maps help prioritize gene pairs, pathways, and tissue regions for laboratory validation and potential therapeutic development.

Extend beyond cancer

SCR also revealed broad network reorganization in an Alzheimer's disease mouse model and works with sequencing- and imaging-based platforms.

Responsible interpretation. These spatial patterns generate biologically informed hypotheses; they do not by themselves establish causation or clinical utility.