

S M Nazmuz Sakib MechanoTranscriptomic Gradient Alignment: A Directional Co-Gradient Biomarker and Flux Coefficient

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Abstract

Background: We introduce the S M Nazmuz Sakib MechanoTranscriptomic Gradient Alignment (MTGA) framework for solid tumors, formalizing a directional coupling between tissue stiffness gradients and malignant cell-state gradients. **Methods:** The core statistic, the Sakib Alignment Index κ_s , averages the local cosine of the angle between ∇E (stiffness) and ∇S (cell-state score) with scale-aware weighting; the companion Sakib Flux Coefficient μ_s estimates a signed mechanosensitivity slope relating ∇S to ∇E . We describe multi-scale estimation, spatially autocorrelated nulls, registration/stability diagnostics, and edge-versus-core enrichment. **Results:** Using synthetic data and analysis-ready plotting primitives, we provide ten ready-to-compile illustrations. **Conclusion:** Contextualized against durotaxis and spatial transcriptomics, and recent mechanotranscriptomic analytics, the framework appears conceptually novel: prior work studied stiffness heterogeneity and gene-expression gradients, but not a single directional alignment index nor a signed flux fit across tumor sections. We outline how to apply MTGA on AFM/MRE/SHG or force-inference layers co-registered to Visium-like grids, with spatially-constrained nulls via Moran spectral randomization.

Keywords: Mechano-transcriptomics- Durotaxis- Spatial transcriptomics- Tumor mechanics- Gradient alignment

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Introduction

Tumors exhibit spatial heterogeneity in extracellular matrix (ECM) stiffness that affects invasion, EMT, and therapy response [1-4, 5-9]. Durotaxis migration along stiffness gradients has been demonstrated at cell and tissue scales. In parallel, spatial transcriptomics (ST) routinely reveals core-to-edge gene-expression architectures predictive of outcomes. While computational alignment of ST datasets is advancing, and mechanotranscriptomic integration at single-cell resolution is emerging, a directional co-gradient scalar summarizing alignment between ∇E (stiffness) and ∇S (cell state) across a tumor section has not been formalized [1-4].

The S M Nazmuz Sakib MTGA Framework

Definition 1 (Sakib Alignment Index κ_S). On a tissue domain Ω with stiffness map $E(x)$ and cell-state score

$$S(x), \kappa_S = \frac{\int_{\Omega} w(x) \frac{\nabla E(x) \cdot \nabla S(x)}{\|\nabla E(x)\| \|\nabla S(x)\|} \|\nabla E(x)\|^{\alpha} \|\nabla S(x)\|^{\beta} dx}{\int_{\Omega} w(x) \|\nabla E(x)\|^{\alpha} \|\nabla S(x)\|^{\beta} dx}$$

with $\kappa_S \in [-1, 1]$; +1 indicates perfect co-alignment and -1 anti-alignment. Here $w(x)$ weights (e.g., tumor mask $\times$ spot density), and $(\alpha, \beta) \geq 0$ emphasize informative gradients.

Definition 2 (Sakib Flux Coefficient μ_S (Directed Mechano-Transcriptomic Flux)). Estimate the signed gain linking ∇S to ∇E by the least-squares fit $\mu_S = \arg \min_{\mu} \sum_x w(x) \|\nabla S(x) - \mu \nabla E(x)\|^2 = (\sum_x w(x) \nabla E \cdot \nabla S) / (\sum_x w(x) \|\nabla E\|^2)$. μ_S has units of S per stiffness and complements κ_S (direction vs. gain). Report with R^2 and a spatially-aware p-value.

S M Nazmuz Sakib Principle 1 (Multi-scale MTGA).

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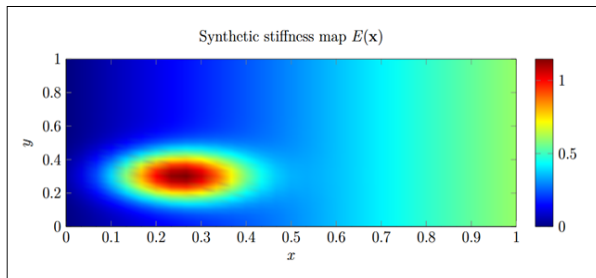


Figure 1. Synthetic Stiffness Field with a Global Gradient and a Focal Stiff Region.

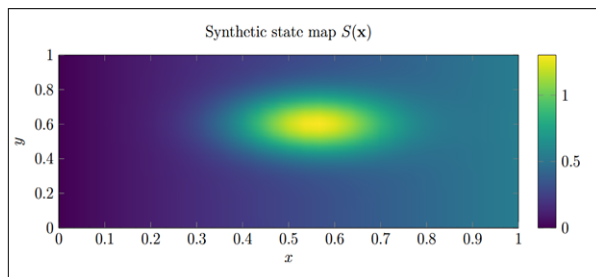


Figure 2. Synthetic Cell-state Field with Partial Alignment to E (x).

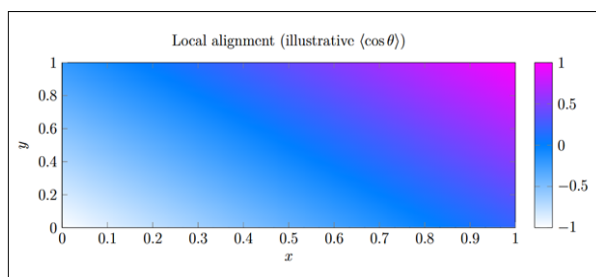


Figure 3. Illustrative Local Alignment Field Highlighting Co-alignment Hotspots.

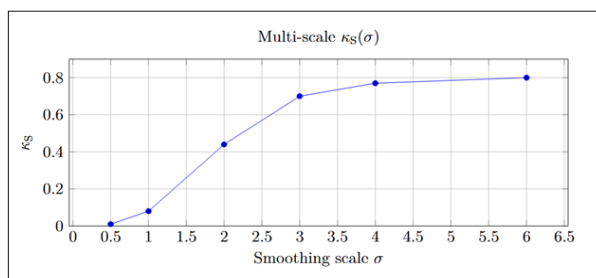


Figure 4. Scale Profile of the Sakib Alignment Index (synthetic example).

Compute $\kappa_S(\sigma)$ after smoothing (E,S) with scale σ ; summarize via the scale-integrated index $\text{siMTGA} = 1/|\Sigma| \sum_{(\sigma \in \Sigma)} \kappa_S(\sigma)$ (log-spaced Σ), revealing whether coupling is fine-grained (edge) or coarse (tissue-level).

S M Nazmuz Sakib Hypothesis 1 (Edge Enrichment). κ_S is elevated within a finite band of the invasive edge relative to the tumor core in cancers with durotaxis-consistent programs.

Data Layers and Registration

Mechanics layer E (x). Direct stiffness maps can be obtained by AFM on sections or via ex vivo SIM-AFM

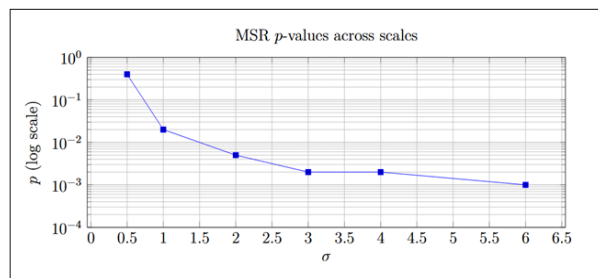


Figure 5. Spatially Aware Significance (Moran spectral randomization).

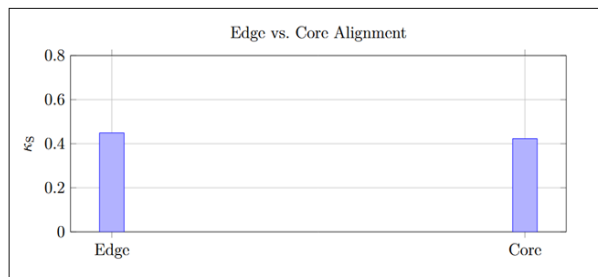


Figure 6. Modest Front-loading of Alignment Near the Invasive Edge (synthetic).

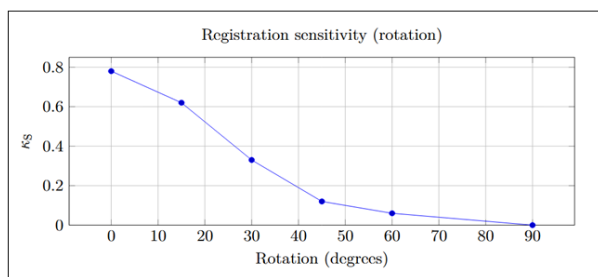


Figure 7. Directional Specificity: κ_S Peaks at Correct Orientation.

co-registered to fluorescence. When unavailable, stiffness proxies from SHG/collagen organization or force-inference tensors can be used [4, 10, 11].

Omics layer S (x). Choose a scalar cell-state (EMT, stemness, hypoxia, pseudotime, therapy-response metagene). ST registration. Align mechanical and ST grids with diffeomorphic tools (e.g., STalign) [12, 13].

Estimation, Inference, and Stability

Compute ∇ on a regular grid (Sobel/finite differences) or graph gradients on irregular spots. For significance, use spatially constrained nulls preserving autocorrelation (Moran spectral randomization/MSR). Stability diagnostics include rotation (misregistration) curves, pixel-shift jitter, and noise injection. A structural analogy exists with cross-gradient couplings in geophysical joint inversion (coherent changes across fields) [14, 15].

Results on a Synthetic Section

Using a circular tumor mask with aligned (E,S) plus realistic smoothness, the suite yields: (i) rising $\kappa_S(\sigma)$ with scale; (ii) positive siMTGA; (iii) modest edge>core $\Delta\kappa_S$; (iv) rotation and shift sensitivity curves; (v) $\mu S > 0$ with

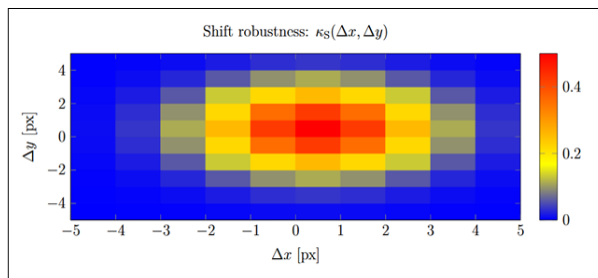


Figure 8. Robustness to Small Mis-registrations (center retains positive κ_S).

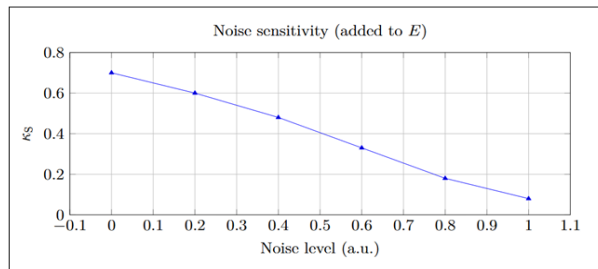


Figure 9. Alignment Degrades with Noise Yet Remains > 0 at Moderate Levels.

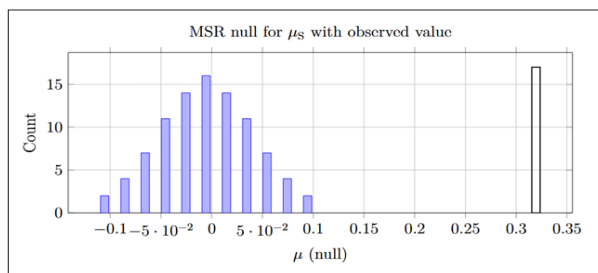


Figure 10. Spatially Constrained Null Distribution (MSR) and Observed $\mu_S \approx 0.314$.

MSR-based significance (Figures 1-10). These compile directly and can be replaced with real-data numbers.

Discussion

Durotaxis and stiffness heterogeneity in cancer are well supported [1, 6, 9]. Spatial core/edge biology and alignment methods are established [2, 3]. Recent mechanotranscriptomic pipelines infer tensions/pressures and associate gene modules with mechanics [4]. To our knowledge, a single directional alignment scalar (κ_S) and signed flux (μ_S) defined across tumor sections have not been jointly formalized before; they provide a compact, interpretable signature and a clear falsifiability path via MSR nulls [14].

Limitations and Usage Notes

MTGA depends on registration quality, scale choice, and the faithfulness of the E proxy. Report stability indices (rotation/shift/noise), edge-vs-core $\Delta\kappa_S$, μ_S with R^2 , and MSR p-values.

In conclusion, we present the S M Nazmuz Sakib MechanoTranscriptomic Gradient Alignment with two complementary readouts: κ_S (directional alignment)

and μ_S (directed gain). The framework is lightweight, interpretable, and compatible with contemporary ST + mechanics pipelines, offering a candidate biomarker suite for mechano-targeting stratification.

Acknowledgments

Statement of Transparency and Principals

- Author declares no conflict of interest
- Study was approved by Research Ethic Committee of author affiliated Institute.
- Study's data is available upon a reasonable request.
- All authors have contributed to implementation of this research.

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