Review

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Architectural Dynamics in Living Tissues: Integrating Structure, Physical Fields and Spatial Networks

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Abstract

Biological tissue analyses rely on morphological descriptors like shape, layering and cellular composition. We introduce *Architectural Dynamics*, a framework that employs more than one hundred quantifiable parameters to define architectural and dynamical properties of a cellular microenvironment, including structural, mechanical, geometrical, physical, network-theoretic, cellular and biochemical features. Biological tissues are portrayed as weighted networks whose nodes and edges carry measurable physical quantities like diffusion conductance, mechanical impedance, curvature and material anisotropy. Standard network metrics like global efficiency, modularity, diameter and centrality acquire physiological meaning as indicators of accessibility, compartmentalization and exposure to mechanical or biochemical cues. In parallel, physical fields such as diffusion, mechanics, curvature and topography generate patterns of transport, signaling, force propagation and communication that link microscale architecture to mesoscale dynamical behavior. Using combined descriptions, we show that behaviors like migration patterns, polarization, domain formation, compartmentalization, metabolic coupling, signal propagation and stability of functional domains emerge from agent dynamics shaped by weighted topology, structural heterogeneity, mechanical anisotropy and geometric confinement. Our perspective shifts the emphasis from cellular identity to quantitative analysis of local physical cues and global topological organization within a high-dimensional architectural space, enabling prediction of cellular behaviors directly from tissue architecture. Changes in development, health or disease correspond to movements along well-defined architectural directions rather than to simple morphological or biochemical alterations. Our framework applies to engineered scaffolds, organoids and regenerative medicine as well as extracellular matrices, cortical microcircuits and pathological architectures like tumors, where the modulation of architectural regimes becomes central to interpreting tissue organization.

Keywords: mesoscale modeling; anisotropic transport; microenvironment topology; field–structure coupling; spatial heterogeneity analysis

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Introduction

Current approaches to biological tissues emphasize descriptors such as morphology, layering and cellular composition, often complemented by molecular markers or lineage information (Aljakna, Fracasso, and Sabatasso 2018; Yoshimura et al. 2019; Beumer and Clevers 2021; Olguín-Martínez, Ruiz-Medina, and Licona-Limón 2021; Meliante et al. 2025; Wells et al. 2025). While these descriptors are indispensable, they provide only partial insight into how physical context shapes cellular behavior. Existing quantitative frameworks usually emphasize one dominant dimension of the microenvironment, whether tissue mechanics, diffusion dynamics, geometric curvature or network connectivity (Bidan et al. 2012; Callens et al. 2020; Trubuil, D'Angelo, and Solon 2021; Muntz et al. 2022; Gehrels et al. 2023; Gooshvar et al. 2023; Tam and Baar 2025). These single-domain representations capture foremost structural or functional aspects, but do not account for the way these features jointly constrain transport, communication, accessibility, dynamical stability, etc. Moreover, most analytical methods treat tissues as either collections of cells or as passive continua, limiting the ability to integrate mesoscale architecture with local physical fields. Therefore, understanding how spatial heterogeneity, anisotropy and topology jointly shape migration, polarization, signalling and compartmentalisation is challenging. A shift is required toward architectural representations capable of capturing the interplay between geometry, topology and field dynamics, setting the stage for a framework in which measurable architectural features collectively define the operative microenvironment.

We introduce Architectural Dynamics, a quantitative representation in which tissues are described as weighted spatial networks embedded in heterogeneous geometric and physical fields. Our framework employs a large set of measurable parameters encompassing structural, mechanical, geometric, physical, network-theoretic, cellular and biochemical features, allowing tissue organization to be expressed as a point or a trajectory in high-dimensional phase spaces. Weighted nodes and edges might encode diffusion conductance, mechanical impedance, curvature, anisotropy and related quantities, enabling standard network metrics to acquire explicit physiological interpretation. Coupling these weighted networks to endogenous fields such as diffusion, mechanics, curvature and topography might allow dynamical patterns to be interpreted as consequences of architecture rather than solely of cellular identity. Our integrated formulation might provide a unified route to analyze how structural heterogeneity, geometric confinement and anisotropic communication jointly shape agent-level behaviors. Within this setting, our theoretical approach aims to determine whether quantifiable architectural descriptors could predict observed spatial dynamics and whether movements along specific architectural directions could correspond to recognizable transitions in tissue organization.

We will proceed as follows: we first outline the methodological construction of Architectural Dynamics, then examine its hypothetical consequences and their interpretation, and finally discuss subsequent developments and broader implications.

Architectural Components of the Cellular Microenvironment

A cellular microenvironment consists of a complex ensemble of spatially organized features whose combined configuration shapes the conditions under which cells operate. We provide here an expanded conceptual description of the microenvironmental components that later sections quantify, detailing how each domain contributes to the overall organization without yet entering explicit analytical procedures. The purpose is to clarify the rationale for treating tissue architecture as a high-dimensional system composed of interdependent physical elements, ensuring that the subsequent quantitative formulations emerge from a clearly delineated conceptual framework.

Structural properties form the base layer of architectural organization, encompassing the arrangement of material elements such as extracellular fibers, pores, rigid segments and heterogeneous tissue units (Sekiguchi and Yamada 2018; Moussian 2019; Gomi and Imamura 2020; Gardeazabal and Izeta 2024). These features determine how matter is distributed across space and impose constraints on how other physical quantities can vary. Structural discontinuities, gradients or repeating motifs influence the connectivity of the microenvironment and define the spatial template through which forces, signals and diffusing agents propagate (Cortesi et al. 2020; He et al. 2023; Schimek et al. 2024; Sun et al. 202. Closely related to structure are the mechanical properties, which describe how the microenvironment responds to deformation, compression, shear or tension (Park et al. 2020; Petroll, Varner, and Schmidtke 2020; Bhargav et al. 2021; Massey et al. 2024). Local stiffness, viscoelastic behavior and mechanical anisotropy are essential descriptors because they govern how physical forces are transmitted, dissipated or concentrated (Chaudhuri et al. 2020; Atcha et al. 2021; Wu et al. 2022; Tao et al. 2023; Zhang et al. 2023). Whereas structure describes what occupies space, mechanics describes how that space reacts to stress, providing the background against which cells perceive rigidity, deformability and load-bearing capacity (Zhu et al. 2025). Together, structural and mechanical features define the material substrate of the microenvironment.

Geometrical properties capture shape-derived constraints imposed by curvatures, interfaces, boundaries and thickness variations (Campisi et al. 2018; He et al. 2018; Gorb et al. 2020; Wang et al. 2024; Chen et al. 2025). These shape features influence whether physical or chemical quantities tend to concentrate, disperse or follow preferred directions, modulating confinement at both micro- and mesoscales. Geometry adds a distinct layer of constraints because it does not merely reflect how matter is distributed, but how spatial form restricts the degrees of freedom available to physical and biological processes. Network-theoretic features complement this picture by recasting microenvironment as a weighted topology, where nodes represent spatial units and edges express adjacency or the availability of transport routes (Pan et al. 2022; Coy et al. 2022; Sun et al. 2024). While geometry defines the global configuration of spatial shapes, network structure elucidates the global organization of connectivity, enabling the microenvironment to be described not only as a continuous medium but also as a discrete set of pathways through which matter, forces and information can travel (Bjordahl et al. 2013; Dobaño-López et al. 2021). The interplay between geometrical form and connective topology forms a backbone for understanding accessibility, compartmentalization and the overall organization of interaction routes.

Cellular properties introduce local heterogeneity derived from the distribution, arrangement, morphology and orientation of the cells inhabiting the microenvironment. These features specify how active biological units occupy and modify space, impose local constraints through their packing and polarity, and contribute to the dynamic remodeling of surrounding structures (Boutilier and Elsawa 2021; Gao, Liang, and Wang 2022; Wang et al. 2022; de Freitas Nader and García-Arcos 2023). Unlike structural or mechanical descriptors which concern the passive substrate, cellular descriptors incorporate the influence of individual and collective cell behaviors on the architecture itself. Biochemical properties further enrich the environment by defining the spatial distribution of molecules, signaling gradients, metabolic substrates and diffusible mediators (Acharya et al. 2020; Giotti et al. 2024; Shi et al. 2025). These features determine the chemical context against which cells sense and respond, as well as the spatial domains where reactions can occur or where concentrations remain stable. Biochemical landscapes often show steep gradients or localized maxima, making them essential components of the architectural regime (Samarah et al. 2025).

Physical fields integrate and modulate all preceding components by representing continuously varying quantities such as diffusional fluxes, stress distributions, hydraulic pressures or electric potentials (DuFort, DelGiorno, and Hingorani 2016; Kumar et al. 2023; Liu et al. 2024). Unlike structural or biochemical features, which may be directly tied to material composition, physical fields evolve according to equilibrium, transport or propagation laws and therefore form the dynamic layer of architectural organization. They provide a bridge between static features and time-dependent phenomena, enabling architecture to be interpreted not only as a static arrangement of components but as a set of interacting fields whose configuration depends on and further shapes the underlying structural, mechanical, geometrical, network and chemical properties.

Together, these architectural components constitute the conceptual backbone for a unified representation of tissue organization. The appendix provides a summary of all features that characterize the architectural properties of the tissue microenvironment. Each family contributes a distinct yet interdependent dimension of the microenvironment and none is sufficient in isolation. In next section, conceptual categories will be transformed into explicit mathematical quantities and measurable parameters.

Quantitative Characterization of Architectural Features in Cellular Microenvironments

We examine here how structural, mechanical, geometrical, network-theoretic, cellular, biochemical and physical-field descriptors jointly characterize the architectural properties of a cellular microenvironment. To obtain an unified quantitative treatment, each category is developed through measurement procedures, explicit mathematical formulations and detectable features, allowing architectural organization to be represented as a coherent analytical space.

1. Structural features. Structural features provide the baseline material organization upon which all other architectural descriptors depend.

Structural characterization begins by defining the tissue domain $\Omega \subset \mathbb{R}^3$ and discretizing it into volumetric elements $\{V_1, \dots, V_N\}$. Each element possesses measurable descriptors including density ρ_i, porosity π_i and a fiber-orientation vector $\mathbf{f}_i$. Density can be extracted from imaging data through calibrated voxel intensities, while porosity is computed as

$$\pi_i = 1 - \frac{\mathrm{vol}(\mathrm{cellular})}{\mathrm{vol}(V_i)}.$$

Fiber orientation can be measured by the structure tensor. For an intensity field $I(\mathbf{x})$, the tensor at $\mathbf{x}$ is

$$T(\mathbf{x}) = \int_{\mathcal{N}(\mathbf{x})} \nabla I(\mathbf{y})\, \nabla I(\mathbf{y})^\top\, w(\mathbf{x} - \mathbf{y})\, d\mathbf{y},$$

with w a Gaussian kernel. The eigenvectors of T give principal orientations and the eigenvalues encode coherence. Spatial structure can be summarized via the autocorrelation

$$C_S(r) = \langle (\rho(\mathbf{x}) - \bar{\rho})(\rho(\mathbf{x} + r\hat{\mathbf{u}}) - \bar{\rho}) \rangle_{\mathbf{x},\hat{\mathbf{u}}},$$

integrated into a heterogeneity index

$$H_S = \int_0^R \mid C_S(r) \mid\, dr.$$

Structural adjacency can be encoded through

$$A_S(i,j) = \begin{cases} 1 & \text{if } V_i \text{ and } V_j \text{ share a face,} \\ 0 & \text{otherwise,} \end{cases}$$

with weighted connectivity

$$W_S(i,j) = \exp\left(-\alpha \mid \rho_i - \rho_j \mid\right) \exp\left(-\beta \mid \pi_i - \pi_j \mid\right).$$

Tools for structural detection include watershed segmentation, level-sets, convolutional filtering, Fourier analysis and supervised classifiers applied to confocal, multiphoton or micro-CT datasets (Li et al. 2019; Kornilov, Safonov, and Yakimchuk 2022; Son et al. 2022; Zhou and Yang 2022; Whybra et al. 2024). The resulting descriptors form the structural backbone of the architectural microenvironment.

2. Mechanical features. Mechanical features quantify resistance, deformation and force transmission across the microenvironment.

Mechanical architecture can be formulated through spatially varying stiffness, viscoelastic response and anisotropic impedance. The local linear constitutive relation is

$$\sigma(\mathbf{x}) = C(\mathbf{x}) : \varepsilon(\mathbf{x}),$$

where σ is the Cauchy stress, $\varepsilon = \frac{1}{2}(\nabla \mathbf{u} + \nabla \mathbf{u}^\top)$ is the infinitesimal strain, and $C(\mathbf{x})$ is a fourth-order elasticity tensor. For isotropic elasticity,

$$C_{ijkl} = \lambda\, \delta_{ij}\delta_{kl} + \mu\, (\delta_{ik}\delta_{jl} + \delta_{il}\delta_{jk}),$$

with Lamé parameters λ, μ. Spatially heterogeneous stiffness can be detected by techniques such as AFM indentation, Brillouin microscopy, traction force microscopy and micro-rheology.

Viscoelastic response can be represented through a standard linear solid model, with stress satisfying

$$\sigma + \tau_\sigma \dot{\sigma} = E_1 \varepsilon + (E_1 + E_2)\tau_\varepsilon \dot{\varepsilon}.$$

Local mechanical impedance $Z(\omega)$ can be computed from oscillatory indentation data using

$$Z(\omega) = \frac{\hat{\sigma}(\omega)}{\hat{\varepsilon}(\omega)}.$$

Mechanical anisotropy can be extracted by diagonalizing $C(\mathbf{x})$ in fiber coordinates, producing directional stiffness values $E_\parallel, E_\perp$. Spatial maps of mechanical heterogeneity can be quantified through

$$H_M = \int_\Omega \parallel \nabla E(\mathbf{x}) \parallel\, d\mathbf{x}.$$

Force transmission pathways can be identified by solving the equilibrium equation

$$\nabla \cdot \sigma(\mathbf{x}) + \mathbf{b}(\mathbf{x}) = \mathbf{0}$$

under boundary conditions, producing deformation fields $\mathbf{u}(\mathbf{x})$. From these, mechanical geodesics can be computed by minimizing

$$\mathcal{L}[\gamma] = \int_0^1 \sqrt{\gamma'(s)^\top C(\gamma(s))\,\gamma'(s)}\,ds,$$

which quantify low-resistance directions for force propagation.

Tools for mechanical probing include AFM arrays, calibrated micro-beads, high-resolution elastography, Brillouin scattering, micropipette aspiration and digital volume correlation (Brener 2015; Li et al. 2017; Palombo and Fioretto 2019; Bednář and Dvořák 2022; Helal and Kojima 2022; Kojima 2022; Ray et al. 2025; Ren et al. 2025). These measurements define the mechanical landscape able to influence local interactions.

3. Geometrical features. Geometrical features describe shape-derived constraints that modulate pattern formation, transport and spatial confinement.

Geometric structure is anchored in the shape operator and curvature tensors of the tissue domain. Let the microenvironment boundary be a smooth surface S with normal vector $\mathbf{n}$. The shape operator $S_p\colon T_pS \to T_pS$ satisfies

$$S_p(\mathbf{v}) = -D_{\mathbf{v}}\mathbf{n}.$$

The eigenvalues $\kappa_1, \kappa_2$of S_p are the principal curvatures; mean and Gaussian curvature are

$$H = \frac{\kappa_1 + \kappa_2}{2}, K = \kappa_1\kappa_2.$$

Curvature maps can be estimated from triangulated meshes reconstructed via confocal stacks or multiphoton surfaces. Discrete mean curvature can be obtained from the Laplace–Beltrami operator

$$H(\mathbf{x}_i) = \frac{1}{2A_i}\sum_j (\cot\,\alpha_{ij} + \cot\,\beta_{ij})(\mathbf{x}_j - \mathbf{x}_i)$$

with A_i an area element and α_{ij}, β_{ij} opposite angles.

Geometric confinement can be quantified by distance-to-boundary fields

$$d(\mathbf{x}) = \min_{\mathbf{y}\in\partial\Omega} \parallel \mathbf{x} - \mathbf{y} \parallel,$$

and by curvature-weighted confinement

$$C_G(\mathbf{x}) = d(\mathbf{x})^{-1}(1 + | H(\mathbf{x}) |).$$

Thickness variation can be measured by computing orthogonal trajectories to the boundary and solving

$$t(\mathbf{x}) = \mathrm{length}(\gamma_{\mathbf{x}}),$$

where $\gamma_{\mathbf{x}}$ is a geodesic perpendicular to $\partial\Omega$.

Geometrical detection tools include surface reconstruction algorithms, active-contour segmentation, differential geometry estimators, Laplace–Beltrami operators, finite-element meshing and confocal–derived isosurface extraction (Ma et al. 2020; Fan et al. 2022; Fallahdizcheh, Laroia, and Wang 2023; Bhansali et al. 2023; Ma et al. 2023). These features quantify how geometric shape can constrain diffusional, mechanical and topographical interactions.

4. Network-theoretic features. Network-theoretic features express architecture as weighted topologies that quantify accessibility, compartmentalization and communication pathways.

The tissue domain can be represented as a graph $G = (V, E)$, with $V = \{1, \dots, N\}$ the volumetric elements and E edges encoding adjacency. Weighted connectivity is defined by

$$W(i,j) = w_{ij},$$

where w_{ij} may encode structural similarity, mechanical coupling or diffusional conductance.

Shortest paths can be computed using weights w_{ij}^{-1}, producing the path-length matrix

$$L(i,j) = \min_{\gamma: i\to j} \sum_{(u,v)\in\gamma} w_{uv}^{-1}.$$

Global efficiency is

$$E_{\text{glob}} = \frac{1}{N(N-1)}\sum_{i\neq j} \frac{1}{L(i,j)}.$$

Modularity can be computed from

$$Q = \frac{1}{2m}\sum_{ij}(w_{ij} - \frac{k_i k_j}{2m})\,\delta(c_i, c_j)$$

with total weight $m = \frac{1}{2}\sum_{ij} w_{ij}$, strengths k_i, and community labels c_i. Betweenness centrality is

$$B(i) = \sum_{s \neq i \neq t} \frac{\sigma_{st}(i)}{\sigma_{st}}$$

with σ_{st} the number of shortest paths from s to t, and $\sigma_{st}(i)$ those passing through i. Diffusion-weighted edges can be computed from Fickian conductance

$$w_{ij} = \frac{D_{ij} A_{ij}}{\ell_{ij}},$$

where D_{ij} is diffusivity, A_{ij} shared area and ℓ_{ij} centroid distance.

Detection tools include graph reconstruction from voxel adjacency, anisotropic kernels, persistent connectivity filtering, spectral graph decomposition and diffusion-weighted metrics (Radua et al. 2014; Onal Ertugrul, Ozay, and Yarman Vural 2018; Petrovic et al. 2019; Cheng, Cloninger, and Coifman 2020; Zhao et al. 2020; Raj et al. 2024). Overall, network-theoretic features provide a global account of accessible communication pathways.

5. Cellular features. Cellular features describe local heterogeneity in cell size, shape, polarity, turnover and spatial arrangement.

Cells occupy subsets $\{\mathcal{C}_1, \dots, \mathcal{C}_M\} \subset \Omega$. Each cell has a centroid $\mathbf{x}_k$, shape tensor

$$S_k = \int_{\mathcal{C}_k} (\mathbf{y} - \mathbf{x}_k)(\mathbf{y} - \mathbf{x}_k)^\top d\mathbf{y},$$

and polarity vector $\mathbf{p}_k$ derived from asymmetric membrane markers or cytoskeletal orientation.

Packing density can be quantified through Voronoi tessellations, producing volumes V_k^{Vor}. Cellular anisotropy can be measured by eigenvalue ratios of S_k. Pair-correlation structure is summarized by

$$g(r) = \frac{1}{\rho_c} \langle \sum_{k \neq \ell} \delta(r - \| \mathbf{x}_k - \mathbf{x}_\ell \|) \rangle,$$

where ρ_c is mean cell density.

Turnover rates can be quantified from time-lapse imaging using lineage tracking. Spatial gradients in cellular properties can be computed via

$$\nabla \rho_c(\mathbf{x}), \nabla \mathbf{p}(\mathbf{x}).$$

Detection tools include segmentation (U-Net, watershed), 3D tracking, shape-tensor reconstruction, Voronoi geometry and fluorescence-based polarity extraction (Widengren 2010; Bozza et al. 2012; Novaes et al. 2016; Beeche et al. 2022; Yin et al. 2022; Yousef et al. 2023).

6. Biochemical features. Biochemical features quantify gradients, reaction capacities and diffusible mediator distributions affecting interaction ranges.

Let $c_i(\mathbf{x})$ be the concentration of biochemical species i. Steady-state distributions satisfy

$$D_i \nabla^2 c_i - k_i c_i + s_i(\mathbf{x}) = 0$$

for diffusivity D_i, decay k_i and source s_i. Gradients are quantified by $\| \nabla c_i \|$, and heterogeneity by

$$H_B = \sum_i \int_\Omega | c_i(\mathbf{x}) - \bar{c}_i | \, d\mathbf{x}.$$

Ligand–receptor binding potentials can be described by

$$R_{ij}(\mathbf{x}) = k_{on} c_i(\mathbf{x}) r_j(\mathbf{x}) - k_{off} b_{ij}(\mathbf{x}),$$

with r_j receptor density and b_{ij} ligand–receptor complexes.

Reaction–diffusion coupling can be captured by

$$\frac{\partial c_i}{\partial t} = D_i \nabla^2 c_i + F_i(c_1, \dots, c_n, \mathbf{x}),$$

with F_i nonlinear reaction terms. Steady-state maps are solved numerically using finite-element or finite-difference schemes.

Detection tools include immunofluorescence, FRET sensors, mass-spectrometry imaging, in-situ hybridization and ratiometric biosensors (Mohsin, Ahmad, and Iqbal 2015; Bajar et al. 2016; Cost, Khalaji, and Grashoff 2019; Huo et al. 2019; Wang et al. 2019; Spring, Goggins, and Frost 2021). These features describe chemical landscape variations across the microenvironment.

7. Physical fields. Physical fields integrate structural, mechanical, geometric and biochemical factors into continuously varying dynamical quantities.

Diffusion fields satisfy

$$\frac{\partial u}{\partial t} = \nabla \cdot (D(\mathbf{x}) \nabla u),$$

where spatially varying diffusivity $D(\mathbf{x})$ reflects structural and biochemical heterogeneity. Stress fields obey equilibrium

$$\nabla \cdot \sigma(\mathbf{x}) = \mathbf{0}$$

with constitutive laws depending on $C(\mathbf{x})$.

Electric potential ϕ satisfies Poisson's equation

$$-\nabla \cdot (\epsilon(\mathbf{x}) \nabla \phi) = \rho(\mathbf{x}),$$

with $\epsilon(\mathbf{x})$ permittivity and $\rho(\mathbf{x})$ charge density.

Hydraulic pressure $p(\mathbf{x})$ obeys Darcy's law

$$\mathbf{v} = -\kappa(\mathbf{x}) \nabla p,$$

with permeability κ. Coupling between fields can be expressed through composite operators; for example, diffusion–mechanics coupling yields

$$\frac{\partial u}{\partial t} = \nabla \cdot (D(\mathbf{x}, \sigma) \nabla u).$$

Detection tools include fluorescence recovery after photobleaching (for diffusion), traction force microscopy (for stress), microelectrode arrays (for potential) and microfluidic perfusion (for hydraulic fields) (Hur et al. 2020; Lekka et al. 2021; Moud 2022; Zancla et al. 2022; Saito, Matsunaga, and Deguchi 2023; Saito and Deguchi 2023).

Together, structural, mechanical, geometrical, network-theoretic, cellular, biochemical and physical-field descriptors provide a unified quantitative representation of the tissue microenvironment. By grounding each feature family in explicit measurement procedures, mathematical characterizations and detectable quantities, a consistent analytical basis can be defined for describing architectural organization and its underlying variability.

Hypothetical Domains of Architectural Dynamics

Architectural Dynamics examines how hypothetical cellular environments, whether inspired by known tissues or entirely conceptual, might generate biological function through their physical organization. Geometry, material composition and spatial connectivity are understood not as secondary descriptors but as primary determinants of transport, communication and mechanical interaction. The central premise is that any microenvironment, either real or hypothetical, can be represented as a physically informed spatial network in which nodes and edges carry weights derived from measurable or inferable fields, including diffusion conductance, local stiffness, curvature, hydraulic resistance, surface texture and matrix heterogeneity. This representation simultaneously preserves the locality of continuum physics and the global structure of graph topology, allowing the environment to be characterized through the combined lens of anisotropic transport, spatial modularity, weighted accessibility and geometry-dependent force propagation. The following hypothetical examples illustrate how the framework operates across diverse architectural regimes.

Intestinal villus-field microenvironment. A hypothetical intestinal villus-field microenvironment illustrates how Architectural Dynamics might interpret an intestinal surface composed of protruding, variably tapered villus structures. Each villus would form a vertically oriented geometric domain whose curvature profile could generate directionally biased transport pathways and mechanically distinct compartments. The bases of the villi would constitute a network of entry and exit portals whose adjacency might define the graph underlying lateral diffusion and paracellular routes, while nutrient absorption would be assumed to occur continuously along the entire epithelial surface. Each villus could be assigned structural weights reflecting epithelial thickness, stromal fiber density and basement membrane porosity, thereby producing a heterogeneous map of diffusion conductance, absorptive capability and hydraulic resistance along its axis. Mechanical fields might arise from rhythmic, peristaltic-like deformations propagating through the lamina propria, creating time-varying impedance patterns and conditionally shifting the effective topology of preferred flow and transport corridors. Biochemical cues, modeled as nutrient or signaling gradients, could propagate along curvature-aligned trajectories where structural impedance would be minimized and surface area maximized. Network-theoretic descriptors might identify modules composed of villi that share comparable geometric tapering or mechanical signatures, while nodes at villus–intervillous junctions could act as high-betweenness interfaces governing transitions between vertical absorptive pathways and lateral communication routes. The model would further incorporate a hypothetical stromal compartment whose mesenchymal elements might modulate stiffness and thereby reweight graph edges. Through this integration of curvature, conditional mechanical anisotropy, porosity gradients, oscillatory deformation and distributed absorption along the epithelial surface, this villus-field microenvironment would exemplify how an architectural regime might govern communication and nutrient handling within an intestinal-like system.

Cortical sheet with curvature-dependent conductivity. A hypothetical neuronal cortical sheet would demonstrate how Architectural Dynamics might conceptualize a layered surface populated by orientation fields and variable curvature. The sheet would contain abstract columnar units whose dendrite-like projections would follow locally varying preferred directions, producing an orientation field with spatial coherence lengths that could differ across regions. Structural density would vary as a function of depth, creating stratified impedance to diffusive and electrophysiological signals. Mechanical heterogeneity would be introduced through depth-dependent stiffness gradients, allowing the sheet to sustain curvature-driven tension patterns that might influence both transport and local deformation. Curvature would be treated not merely as a geometric descriptor but as a modulating factor for conductivity, where convex regions might amplify hypothetical field potentials and concave regions might attenuate them. The sheet's topology would be recast as a weighted graph in which nodes would correspond to microdomains defined by orientation clusters and edges would encode adjacency modulated by conductivity, fiber angle difference and extracellular porosity. Biochemical landscapes, represented by generic concentration gradients, would diffuse anisotropically according to local curvature and orientation coherence. Physical fields such as electric potential or stress waves would propagate through the sheet with anisotropic velocity determined by the combined influence of depth, curvature and structural stiffness. Network metrics would identify curvature extrema as functional hubs, reflecting their enhanced capacity to redistribute diffusive and mechanical signals. By blending laminar structure, curvature geometry, anisotropic conductivity, biochemical gradients and mechanical tension, our cortical sheet would become an illustrative case in which architecture shapes the organization of the microenvironment.

Fibroelastic meshwork with adaptive stress corridors. A hypothetical fibroelastic meshwork would exemplify how a conceptual connective-tissue analogue could be interpreted within Architectural Dynamics. This meshwork would be constructed from interwoven fibers whose alignment would vary stochastically across regions, generating local anisotropy and heterogeneous stiffness. Structural heterogeneity would be expressed through nodes representing fiber junctions and edges corresponding to fiber segments weighted by tensile strength, hydraulic permeability and local tortuosity. Mechanical fields would arise from embedded contractile units standing for fibroblast analogues that might impose localized tensile forces along specific orientations, producing adaptive stress corridors where stiffness and curvature could evolve dynamically. Geometric irregularities such as fold-like indentations would generate curvature-induced attractors that concentrate deformation energy. Biochemical gradients would diffuse along preferential paths determined by both mechanical softening and porosity modulation, while the meshwork's topology would evolve as stresses reweight edges to reflect altered deformation resistance. This would create a constantly shifting graph in which transport routes, mechanical pathways and diffusion basins might reconfigure in response to local perturbations. Network-theoretic analysis would reveal transient modules representing stress-stabilized compartments, while centrality measures would highlight junctions serving as transient relay points for both diffusive and mechanical signals. By integrating stochastic fiber orientation, dynamic stiffness gradients, evolving curvature, biochemical field propagation and topology reweighting, the hypothetical fibroelastic meshwork would conceptualize environments in which structure and physics co-determine spatial organization in real time.

Chromatin–loop manifold with multi-compartment regulatory gradients. A hypothetical chromatin–loop manifold would illustrate how Architectural Dynamics might conceptualize the three-dimensional genome as a branching, deformable and multi-compartment regulatory environment. Chromatin fibers would form looped and nested branches whose curvature, compaction and contact angle would evolve conditionally in response to mechanical constraints and biochemical modifications. Each loop interior would function as a quasi-isolated regulatory compartment with diffusion-limited accessibility, while the interloop matrix, composed of linker regions and scaffold proteins, would behave as a second compartment characterized by anisotropic polymer mobility and variable stiffness. Structural features would include locally heterogeneous compaction states, variable loop diameters and gradients of nucleosome density along fiber segments. Mechanical interactions would arise from molecular motors, torsional stresses and condensin- or cohesin-mediated tension, producing curvature changes that would feed back into contact topology and the effective movement of transcriptional machinery. Biochemical gradients, including hypothetical distributions of epigenetic marks or transcription factors, would diffuse with different efficiencies across loop interiors and the interloop matrix, shaped by local porosity and polymer viscoelasticity. Edges of the corresponding graph representation would encode both physical adjacency and probabilistic contact frequency, weighted by conductance metrics derived from compaction, curvature-dependent impedance and local polymer stiffness. Network metrics would detect regulatory bifurcation points such as loop anchors or extrusion stall sites, identifying them as organizational bottlenecks that concentrate mechanical stress or modulate access to distal regulatory elements. In touch with our proposed approach, Zhou et al. (2025) showed that the structure of individual chromatin molecules can determine physical properties of chromatin condensates and cellular chromatin organization. Through this mixture of dynamic geometry, compartmentalized diffusion, mechanical feedback and structural heterogeneity, this hypothetical chromatin–loop manifold would serve as a conceptual system in which Architectural Dynamics could align genome folding dynamics with weighted connectivity and field-like propagation across the nuclear landscape.

Cancer niche with heterogeneous resistance corridors. A hypothetical cancer niche would provide an example of how Architectural Dynamics might conceptualize a microenvironment in which structural irregularity, mechanical heterogeneity and biochemical compartmentalization would jointly define the conditions experienced by malignant cells. The niche would consist of densely packed cellular clusters embedded within a variably stiff extracellular scaffold whose fiber architecture would be distorted by anisotropic remodeling. Structural regions of high density would generate diffusion barriers, while mechanically softened corridors created by proteolytic degradation would form low-resistance channels for both fluid transport and cell migration. Geometric irregularities, including lobulated boundaries and micro-invaginations, would impose curvature fields that could bias mechanical stress distribution and modulate access to surrounding tissue compartments. Biochemical landscapes would be shaped by uneven metabolite consumption, generating pockets of hypoxia and acidosis that diffuse anisotropically according to local porosity and vascular proximity. Niche topology would be represented as a weighted graph in which nodes correspond to microdomains differing in stiffness, nutrient availability or curvature, while edges encode adjacency modulated by hydraulic conductivity, proteolytic permeability and diffusive resistance. Network metrics would reveal mechanically protected compartments acting as retention zones and highlight high-betweenness invasion fronts driving both outward expansion and therapeutic infiltration. Physical fields such as interstitial pressure or electric potential would propagate through the niche along tortuous, architecture-dependent pathways, influenced by the co-occurrence of heterogeneous stiffness and irregular geometry. Through this integration of distorted structure, dynamic compliance, biochemical gradients and topology reweighting, our cancer niche would illustrate how an architectural regime might shape malignant microenvironments.

Xylem-degradation niche in diseased olive tissue. Olive-tree decline in Puglia is driven by *Xylella fastidiosa*, a xylem-inhabiting bacterium that disrupts water transport by inducing vessel blockage, wall degradation and hydraulic dysfunction (Roper, Castro, and Ingel 2019; Landa et al. 2022; Scortichini et al. 2023). Infected trees progressively show leaf scorch, branch dieback and structural collapse of the canopy (Vergine et al. 2020; Burbank and Roper 2021; Castro, DiSalvo, and Roper 2021). The disease spreads through insect vectors and transforms the vascular microenvironment into a fragmented, low-conductance network. An hypothetical xylem-degradation niche would illustrate how Architectural Dynamics might conceptualize a plant-disease microenvironment in which vascular obstruction, wall degradation and anisotropic stress redistribution could jointly determine tissue behavior. In this representation, the affected olive xylem would be modeled as a branching network of conduits whose hydraulic conductance would vary conditionally due to localized occlusions formed by pathogen-induced gels or tyloses. Structural heterogeneity would arise from patchy cell-wall thinning, creating regions of decreased stiffness that might alter the propagation of tension forces driven by transpiration. Geometric irregularities, including vessel collapse or asymmetric swelling, would impose curvature-dependent mechanical fields that could bias fluid trajectories and modify lateral cross-flow between vessels. Biochemical gradients (modeled as hypothetical distributions of pathogen-derived enzymes, phenolic compounds and plant defense mediators) would diffuse anisotropically through altered wall porosity, generating chemical compartments that differ in reactivity, oxidative stress and metabolic burden. The niche’s topology would be represented as a weighted graph in which nodes correspond to vascular microdomains with differing obstruction levels or wall composition, while edges encode adjacency modulated by hydraulic permeability, diffusion resistance and mechanical compliance. Network metrics would identify high-betweenness choke points functioning as dominant regulators of residual sap flow and mechanically weakened junctions might emerge as structural bottlenecks where vessel failure or embolism would preferentially propagate. Physical fields such as pressure gradients, cavitation waves and osmotic potentials would traverse the niche along architecture-dependent paths shaped by the interplay between obstruction patterns, curvature and wall stiffness. Through the integration of variable conductance, pathological wall alteration, biochemical compartmentalization and dynamically reweighted topology, the hypothetical olive xylem niche would illustrate how a diseased plant environment could be governed by architectural regimes rather than by biological agents alone.

These hypothetical examples illustrate how Architectural Dynamics could interpret diverse physiological and pathological microenvironments by integrating geometry, material heterogeneity, spatial connectivity and field dynamics into cohesive architectural regimes. By treating structural features and physical fields as jointly weighted elements of a single spatial network, Architectural Dynamics accommodates a wide spectrum of organizational patterns.

Conclusions

Architectural Dynamics reframes tissue organization by treating physical architecture as a quantifiable, multidimensional regime in which structural, mechanical, geometrical, network-theoretic, cellular, biochemical and field-derived descriptors are integrated into a unified representation. The novelty lies in shifting the analytical focus from cellular identity or isolated physical processes to the ensemble of measurable architectural variables, jointly shaping communication, transport and mechanical signaling. This makes it possible to describe biological tissues as weighted spatial systems in which local constraints and global organization are treated consistently, allowing architecture to be tackled with the same rigor reserved for molecular or dynamical models.

Compared with existing techniques, Architectural Dynamics departs from frameworks analysing individual dimensions of the microenvironment in isolation. Traditional structural assessments describe morphology or fiber organization, but do not connect these features to the mechanical or diffusive regimes they shape. Mechanical studies quantify stiffness or viscoelasticity but lack a spatial interpretation linking local material properties to global pathways of stress transmission. Geometrical analyses highlight curvature or thickness but treat these parameters independently from biochemical gradients or field propagation. Network-based models capture connectivity but do not incorporate physically derived weights or heterogeneous material properties. Reaction–diffusion and continuum mechanics models provide strong mathematical formalisms, yet do not explicitly integrate discrete architectural heterogeneity. Machine-learning approaches infer high-dimensional patterns but do not preserve physical interpretability or enforce coupling among structural, mechanical and geometrical variables. Architectural Dynamics merges these perspectives into a unified, physically grounded representation in which weights derive from measurable features rather than abstractions. It also aligns local physical descriptors with graph-theoretic structure, preserves field continuity and maintains the interpretability associated with classical architectural analysis.

Architectural Dynamics can be classified as a mesoscale integrative framework standing between continuum-level physical models and discrete, cell-centric representations. It preserves the scale-appropriate resolution required to describe local microstructural heterogeneity, while also incorporating the global descriptors required to characterize long-range communication patterns. Situated alongside structural analysis, biomechanics, geometric morphometrics, network theory and field modelling, it stands for a bridging category in which spatially distributed physical cues and topological organization are understood as concurrent determinants of microenvironmental behaviour.

Our framework carries several limitations. Any high-dimensional architectural representation depends on the availability, consistency and accuracy of measurements. This means that variability in resolution, sampling density or noise can reduce the reliability of derived parameters. The complexity of architectural parameterization also introduces challenges in dimensionality reduction, interpretability and calibration, particularly when spatial domains change over time or undergo remodeling. In abstracting cellular identity and molecular specificity into architectural descriptors, our framework may overlook biologically relevant influences that are not easily expressible in structural or physical terms. Network-based representations further rely on discretization choices that shape the inferred topology and may obscure alternative long-range interaction patterns. Additional limitations arise from the need to harmonize multimodal datasets collected under different experimental conditions, the difficulty of validating architectural descriptors against ground-truth measurements at multiple scales and the risk of overfitting high-dimensional architectural spaces with limited or heterogeneous data.

The broader scope of Architectural Dynamics suggests several future directions. The integration of multimodal datasets (combining imaging, mechanical mapping, spatial transcriptomics and field measurements) could refine parameter definitions and allow more accurate reconstruction of architectural regimes. Agent-based or continuum simulations informed by weighted architectural parameters could generate testable hypotheses about how perturbations in stiffness, curvature, porosity or modularity influence emerging behaviors such as compartmentalization or signal spread. Experiments that systematically manipulate architectural features, such as engineered scaffolds with controlled anisotropy or organoids with altered curvature, could elucidate how distinct architectural dimensions influence functional outputs. Longitudinal observations of evolving tissues may clarify how movement along architectural axes corresponds to transitions in development, regeneration or pathology. Recommendations emerging from our synthesis include adopting standardized protocols for quantifying architectural parameters, integrating physical fields explicitly when analyzing microenvironments and designing experimental systems to probe architecture-function relationships across scales.

The central research question addressed in this work concerns whether the physical architecture of a microenvironment can be represented through a unified system of quantifiable variables collectively illuminating the pathways through which cells interpret and inhabit their surroundings. The take-away message is that architecture, when treated as a structured set of measurable features rather than a qualitative backdrop, becomes an analyzable determinant of microenvironmental behavior. Our descriptive standpoint does not replace molecular or dynamical frameworks, but rather provides the intermediate scale at which structure, geometry, mechanics, connectivity and fields converge into a coherent analytical space.

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Appendix A. Notation and Symbol Glossary

This appendix summarizes all the structural, mechanical, geometrical, network-theoretic, cellular, biochemical and physical features defining the architectural properties of a cellular microenvironment. All variables are defined generically and can be applied to any multicellular system or engineered scaffold.

1. **STRUCTURAL AND MATERIAL PARAMETERS**

E_{mat} : stiffness of the material ⇒ sets global mechanical environment
ξ : domain or pattern length scale ⇒ controls repeating architectural motifs
t_i : wall or barrier thickness ⇒ regulates confinement and barrier strength
δ_i : material degradation rate ⇒ governs remodeling and turnover
ϕ_i : solid fraction ⇒ determines porosity and load-bearing capability
σ_i^{hyd} : hydration stability ⇒ controls swelling and shape changes

γ_i : surface tension ⇒ affects curvature and compartment formation
$P_{i\leftrightarrow j}$: boundary permeability ⇒ mediates exchange between compartments
τ_i^{shear} : boundary shear stress ⇒ provides mechanical cues at interfaces

2. MECHANICAL PARAMETERS

E_i : local elastic modulus ⇒ defines stiffness gradients sensed by cells
τ_i : viscoelastic relaxation ⇒ sets adaptation timescale to deformation
$Z_{ij}(\omega)$: mechanical impedance ⇒ regulates force transmission at frequency ω
k_{ij} : connecting stiffness ⇒ determines mechanical coupling strength
α_i : anisotropy ⇒ channels forces along preferred axes
λ_i : stress relaxation ⇒ mechanical dissipation control
$\hbar_i^{\text{mech}}$: energy loss ⇒ damping in repetitive loading
Φ_{ij} : force propagation ⇒ mechanical communication across tissue
p_i : hydrostatic pressure ⇒ drives fluid/structural deformation
$\dot{\gamma}_i$: shear rate ⇒ generates shear-mediated cues
$\vec{v}_{\text{IF}}$: interstitial fluid velocity ⇒ advects signals and metabolites

3. GEOMETRICAL PARAMETERS

V_i : volume of region i ⇒ sets spatial capacity
S_i : surface area ⇒ regulates adhesion and exchange
d_i : pore diameter ⇒ controls accessibility and confinement
L_{ij} : path length ⇒ sets transport distances
A_{ij} : cross-section ⇒ controls transport and flow capacity
τ_{ij} : tortuosity ⇒ modulates effective diffusion or migration
$\vec{u}_{ij}$: orientation vector ⇒ defines structural anisotropy
H_i : mean curvature ⇒ affects stresses and gradients
K_i : Gaussian curvature ⇒ marks geometric hotspots
∇H_i : curvature gradient ⇒ imposes directional cues
R_i : roughness ⇒ modulates adhesion and protein adsorption
$\hbar$: spatial heterogeneity ⇒ captures disorder or patchiness
σ_{scale} : hierarchical scale ⇒ quantifies multiscale organization
$\mathbf{r}_i$: node coordinates ⇒ embed network in real space
κ_{ij} : edge curvature ⇒ influences transport and alignment

NETWORK-THEORETIC PARAMETERS

E_{glob} : global efficiency ⇒ overall accessibility of architecture
$E_{\text{loc}}(i)$: local efficiency ⇒ robustness of local neighborhoods
D : network diameter ⇒ maximal separation of compartments
ρ : network density ⇒ overall connectivity richness
Q : modularity ⇒ identifies architectural compartments
k_i : degree ⇒ interaction capacity of region i
B_i : betweenness ⇒ bottleneck importance
C_i^{eff} : efficiency centrality ⇒ exposure to global cues
C_i, C_{glob} : clustering ⇒ local cooperation potential
$\mathcal{C} = \{C_1, \dots, C_\ell\}$: communities ⇒ higher-order architecture
S_ϵ : entrance spacing ⇒ boundary accessibility

R_{ij}, R : redundancy ⇒ robustness of routes
$P(k)$: degree distribution ⇒ global architecture class
$\mathscr{L}$: graph Laplacian ⇒ governs propagation on the structure
λ_2 : spectral gap ⇒ cohesion and synchronizability
$\mathscr{H}_{\text{top}}$: topological entropy ⇒ complexity of network structure
$\mathcal{S}(f)$: smoothness functional ⇒ coherence of fields on the network

CELLULAR STATE AND BEHAVIORAL PARAMETERS

$\mathbf{x}_k$: cell position ⇒ defines spatial organization
$\mathbf{p}_k$: polarity vector ⇒ determines directionality
$P_{i \to j}^{(k)}$: migration probability ⇒ movement likelihood
τ^{mot} : motility persistence ⇒ directional memory
σ_k^{mot} : motility noise ⇒ stochastic variability
ρ_i : local cell density ⇒ crowding effects
x_k : internal state ⇒ activation/differentiation level
Ω_k : receptor occupancy ⇒ sensing capacity
σ_{ij} : contact signaling ⇒ cell–cell regulatory interactions
a_{kl} : adhesion coefficient ⇒ binding strength
p_i^{crowd} : crowding pressure ⇒ mechanical constraint
χ^{CI} : contact inhibition ⇒ space-regulation mechanism
γ_i : proliferation rate ⇒ growth dynamics
θ_i^{act} : activation threshold ⇒ cue sensitivity
Π_i^{prolif} : proliferative pressure ⇒ net growth tendency

SURFACE CHEMISTRY AND ECM PARAMETERS

λ_i : ligand density ⇒ controls adhesion and sensing
η_i : adhesion molecule density ⇒ anchoring strength
θ_i : contact angle ⇒ wettability and protein adsorption
Π_i : protein adsorption ⇒ surface conditioning
$\mathbf{e}_i$: ECM composition ⇒ biochemical identity
μ_i : enzymatic susceptibility ⇒ matrix remodeling rate
K_d : binding affinity ⇒ strength of molecular interactions

PHYSIOLOGICAL FIELD PARAMETERS

pH_i : local pH ⇒ chemical environment
G_{ij} : ionic/electrical conductance ⇒ rapid communication pathway
$\mathscr{M}_i$: metabolic activity ⇒ energetic state
χ_i : thermal dissipation ⇒ heat regulation
L_i : signal concentration ⇒ cue landscape
κ_i : signal decay ⇒ range of influence
$\hat{\mathbf{g}}$: gradient direction ⇒ orientation cue
θ_i^{sig} : saturation threshold ⇒ nonlinear response limit

4. TRANSPORT AND DIFFUSION PARAMETERS

D_{ij} : diffusion coefficient ⇒ molecular mobility
$C_{ij}^{\text{diff}} = \dfrac{D_{ij} A_{ij}}{L_{ij}}$: diffusion conductance ⇒ effective transport capacity
P_{ij} : permeability ⇒ ease of passage across barriers

R_{ij}^{hyd} : hydraulic resistance ⇒ impedance to fluid flow

c_i : molecule concentration ⇒ resource availability
∇c_i : concentration gradient ⇒ directional cue
Q_i : production/consumption rate ⇒ source/sink dynamics
ξ_i^{prod} : production noise ⇒ variability in generation

$\eta_{ij}^{\mathrm{edge}}$: edge transport noise ⇒ stochasticity along paths

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