The spatial organization of cell states in NSCLC reveals a non-random, hierarchically encoded ecosystem architecture, wherein topological coherence among diverse cellular populations points to a conserved spatial grammar underpinning tumor ecology. To decode these mesoscale communities, we employed a sliding-window algorithm that delineates spatially resolved cellular neighborhoods (CNs) by aggregating all lineage-defined cells within a fixed 40-pixel radius (Fig. 3a; see Methods). This unsupervised framework resolved ten canonical CNs that recapitulate archetypal tissue ecologies with distinct immunologic or stromal imprints (Fig. 3b), spanning tumorigenic hubs, fibrotic scaffolds, and immunologically engaged or excluded compartments. The resulting CN taxonomy encompassed a tumorigenic core (CN01), macrophage-dominant enclave (CN02), B cell niche (CN03), stromal-fibrotic domain (CN04), plasma cell cluster (CN05), neutrophil-predominant zone (CN06), tumor–stroma interface (CN07), T cell compartment (CN08), pan-immune activation focus (CN09), and vascular interface (CN10) (Fig. 3d–f).

We profiled CN distributions across tumor cores and aligned spatial architectures with clinicopathologic variables. In SCC, CN06, characterized by neutrophilic dominance, was preferentially enriched in high-grade tumors, whereas CN08, CN09, and CN10, reflective of lymphoid and vascular activation, were more prominent in non-invasive and early-stage lesions (Fig. S3a-b). In ADC, CN06 was likewise elevated in poorly differentiated tumors with larger diameters; conversely, CN07 and CN08 were concentrated in smaller lesions, with CN08 and CN09 displaying enrichment in high-grade tumors of limited size (Fig. S3c-d; Table S7). Although prognostic associations were limited within individual subtypes and only ADC CN08 showed a positive correlation with overall survival (Fig. S3d), more consistent patterns emerged through integrative modeling of the full NSCLC cohort. Specifically, univariate Cox analysis delineated CN01, CN04, and CN06 as spatially entrenched tumor–myeloid consortia associated with unfavorable prognostic trajectories, whereas CN03, CN05, CN07, and CN08, enriched for B cells, plasma cells, and vascular–immune circuitry, consistently demarcated immuno-supportive niches predictive of improved clinical outcomes (Fig. 3c). These associations were consistently recapitulated in an independent TMA validation cohort (n=110), underscoring the generalizability of CN-based spatial signatures (Fig. S4a-b). Collectively, these findings position CN-defined ecosystems as biologically structured and prognostically informative spatial units that transcend histologic classification and refine risk stratification in lung cancer.

The discordant association of CNFoundry ecotypes with immunotherapeutic signatures across cohorts (Fig. 4j) underscores the limitations of fixed spatial clustering in decoding the complex immunoarchitecture of response, emphasizing the need for integrative, multiscale spatial IO biomarkers (39138341). To address this limitation, we devised a spatial recomposition framework—**CNFoundryX** (*e****X****plainable spatial habitat integration*)—designed to reassemble fragmented contextual tissue niches into integrative and functionally coherent spatial modules (see Methods). Diverging from conventional metrics such as habitat abundance or classification, this approach centers on modeling emergent spatial features encompassing ecological diversity, mesoscale spatial organization, intermodular connectivity, topographic distance metrics, and non-distance-based transition entropy (Fig. 5a; Table S).

To translate this spatial modeling approach into actionable analytic output, we deployed CNFoundryX across the Stanford neoadjuvant immunotherapy discovery cohort (*n* = 150; Fig. 5a), extracting a structured panel of 262 spatially grounded features (Table S15). These features were hierarchically classified into six functional domains, reflecting spatial principles that integrate higher-order inter-to-extracellular ecological structuring: (1) Composition, quantifying the relative abundance of each habitat across individual tumor sections (n = 10); (2) Diversity, reflecting the ecological complexity of habitat mixtures (n = 6); (3) Spatial metrics, delineating intra-habitat spatial organization using multiscale statistical descriptors (n = 90); (4) Interaction, inferring inter-habitat spatial coupling through pairwise proximity modeling (n = 100); (5) Distance, measuring absolute spatial segregation between habitat pairs (n = 55); (6) Transition, an entropy-based, non-distance metric reflecting spatial intermixing (n = 1) (see Methods).

Within the discovery cohort, five habitats (H01, H04, and H06-08) emerged as dominant spatial units that collectively constituted the architectural scaffold of the NSCLC TIME. Spatial co-localized mapping uncovered a recurrent juxtaposition of H03 with H08, and H02 with H10, signifying the formation of immune–vascular convergence zones. By contrast, H01 exhibited marked spatial segregation from both H04 and H08, establishing an exclusionary topology that reflects immune-privileged niches within hyperproliferative tumor territories. Clinically, tumors enriched for H01, H06, and H10 demonstrated inferior PFS, while the presence of H02, H07 and H08 delineated immunologically engaged ecosystems predictive of durable clinical benefit from ICB (Fig. 5b; Table S14). To further evaluate habitat-level spatial alignment associated with therapeutic response, we stratified tumors by ICB outcome and calculated the Scaled Jaccard Index across habitat pairs. Responders exhibited increased spatial contiguity between H08 or H02 and tumor-associated habitats such as H01, H04, and H06, suggesting preferential topologic coupling between immune-permissive and tumor-intrinsic niches that may facilitate immune infiltration and potentiate therapeutic efficacy (Fig. 5c).

In parallel, we assessed the prognostic relevance of spatial architecture using habitat-level spatial metrics. Elevated Ripley’s K and L values in H06 and H10 were strongly aggregated and associated with shorter PFS, implicating tightly clustered neutrophilic and vascular niches in the emergence of immunosuppressive configurations that impede effector cell infiltration and diminish therapeutic efficacy (XXXXXX) (Fig. S7a). Conversely, higher F function in H01 and increased kernel density in H03 and H08 correlated with prolonged PFS, indicating that spatially permissive or hypocellular tumor regions may facilitate immune cell trafficking and amplify antitumor immune engagement (XXXXXX) (Fig. 5d). We applied RAA strategy to rank predictive features and visualize representative feature constellations. One combination, defined by high abundance of H03 and H08, elevated Shannon diversity, and increased kernel density in H08, was observed in a responder sample (Image #1038061) characterized by dense TIL infiltration and well-formed TLSs. In contrast, a non-responder sample (Image #1039887) exhibited high frequencies of H01 and H04, increased Fisher’s alpha, and elevated F function in H01, reflecting an immune-desert and fibrotic phenotype. These two representative cases also occupied opposite ends of the STE distribution, each falling within the top quartile of either high or low STE values, thereby emphasizing the contribution of habitat transition complexity to ICB responsiveness (Fig. 5f). At the network level, graph-based spatial connectivity analysis further identified H01, H04, H06, H07, and H08 as central interaction hubs, anchoring the structural framework of the NSCLC TIME (Fig. 5g). Together, these multiscale spatial features delineate an immunologic landscape in which CNFoundryX captures salient architectural signatures predictive of immunotherapy outcomes.

A small subset of spatial features has been shown to underpin critical clinico-pathologic assessments (XXXXXX). Building on this rationale, we tested whether a compact panel of spatial descriptors derived from routine H&E images could reliably predict immunotherapy outcomes. Leveraging the internal cohort (randomly split into 75% training and 25% validation), we sequentially applied two independent feature selection strategies following redundancy reduction (see Methods). Thirteen features consistently overlapped across both methods, converging into a robust and parsimonious predictive signature (Fig. S7b). A multivariate Cox model trained on this signature demonstrated progressively increasing prognostic accuracy over extended time horizons, achieving mean AUROCs (100 iterations) of 0.78 at 180 days, 0.81 at 365 days, and 0.82 at 730 days (average C-index = 0.70; Fig. 5h), highlighting its capacity to anticipate durable therapeutic benefit.

The 13-feature immunotherapy model exhibits coherent biological interpretability, emphasizing the predictive prominence of immune-centric spatial patterns within the TIME over tumor-intrinsic compartments. Among these, protective features (β < 0) primarily reflect immune-activated features. The spatial juxtaposition of H08, enriched in T helper and cytotoxic lymphocytes, with H03, a B cell–dominant niche, indicates coordinated T–B cell interactions and suggests the presence of TLSs, a hallmark of adaptive immune engagement and indicator of IO responsiveness (Fig. 5e). Adjacent positioning of H01 and H03 may potentiate antigen presentation, fostering T cell priming essential for IO efficacy. Supporting this, low J-function values within H03 reflect a spatially regular B cell distribution, consistent with structurally organized immune zones linked to favorable outcomes (XXXXXX). Moreover, elevated habitat richness, reflecting diverse ecological architectures, may encode organized immunologic compartmentalization conducive to effective antitumor responses rather than reflecting disordered heterogeneity (Fig. 5i). In contrast, risk features (β > 0) trace spatial correlates of immune suppression. Elevated frequency of H06 corresponds to accumulation of neutrophils expressing HIF1A and ARG1, consistent with N2-like TANs implicated in immune evasion (XXXXXXX). Interactions between H04, a CAF-enriched region, and H09, comprising diverse immune cells, suggest that within fibrotic and Treg-rich immunosuppressive TMEs, NK cells frequently undergo functional exhaustion, which synergistically impairs antitumor immunity and undermines the efficacy of ICB therapy (XXXXXX). Frequent H05–H03 contact, involving plasma and B cells, may reflect inefficient or exhausted humoral activity, with expansion of non-neutralizing antibody responses (XXXXXX). Close proximity between H02, populated by macrophages and dendritic cells, and H09 may promote M2 polarization and anti-inflammatory cytokine signaling (e.g., IL-10, VEGF-A), suppressing antigen presentation (XXXXXX). The increased pair correlation in H02 indicates dense macrophage clustering, potentially marking immunosuppressive TAM hubs that inhibit effector cell access (Fig. 5i). Collectively, these spatial motifs encapsulate the immune-architectural logic through which the TME resists ICB therapy.

Crucially, the CNFoundryX-derived risk score exhibited robust discriminatory capacity in stratifying patients according to immunotherapeutic responsiveness (Fig. S7c), revealing markedly divergent PFS trajectories between responders and non-responders (*P* < 0.001; Fig. 5j), irrespective of PD-L1 expression levels (CPS = 0 or CPS > 1%; Fig. 5k, S7d). Surpassing the predictive utility of PD-L1 as a clinical biomarker, CNFoundryX further delineated immunologically responsive subsets within EGFR and KRAS mutant tumors, which represent molecular subtypes traditionally considered refractory to immune checkpoint blockade due to consistently poor historical response rates (Fig. S7d-e). Remarkably, its prognostic fidelity remained stable across therapeutic modalities, encompassing both monotherapy ICI and combination chemoimmunotherapy regimens (Fig. S7g). Multivariate Cox proportional hazards analysis identified CNFoundryX as the sole independent predictor of PFS (P < 0.001), aside from smoking history (Fig. S7h), underscoring its clinical relevance as a spatially encoded biomarker of treatment benefit.

01 Tumorogenic Core

02 Macophage Enriched

03 B-cell Enriched

04 Fibrotic Activity Hub

05 Plasma cell Enriched

06 Neutrophil Prominent

07 Tumor Interface

08 T-lymphonic Enriched

09 Pan-immune Active Zone

10 Vasculature Niche

| **特征类型** | **β > 0 含义** | **β < 0 含义** |
| --- | --- | --- |
| Ripley’s K / L | 越聚集，可能为免疫排斥屏障 | 趋向分散，利于免疫细胞渗透 |
| F function | 越稀疏（空点到细胞距离大），越好 | 紧密结构可能为抑制区 |
| G function / Kernel | 越稠密 → 若是免疫区则可能利好 | 若为肿瘤核心则可能预后差 |
| Clark-Evans | 越均匀分布越好 | 越聚集可能不利 |
| J function | 高值 = 聚集性主导 → 不良 | 低值 = 均匀稀疏 → 良好 |

我现在已经得到的结果，对于150例肺癌免疫治疗的H&E的 patch level 的CN预测，有些是已经出来的结果，有些还有问题：请帮我排下顺序理清思路，每一个（1-7）的专业英文名称句子是什么，给予解答。

（1）freq，每张image的CN占比，计算了co-occurace和每个CN的PFS unicox，这个我想纳入后面的机器学习模型。

（2）计算了diversity，目前是这几个参数Richness Shannon Simpson Inv\_Simpson Pielou Fisher\_alpha， 还不知道怎么做，纳入后面的机器学习模型？

（3）计算了每张image 每个CN的空间spat feature，（Ripley\_K\_mean Ripley\_L\_mean Pair\_corr\_g\_meanG\_mean F\_mean J\_mean Clark\_Evans Quadrat\_chisq Kernel\_density），这个我进行了和PFS的Partial R分析，目的是观察这些CN的空间分布和PFS的关系，引出后面的distance，和interaction。但这里要对应的展示几张CN label的HE,说明问题。

（4）计算了GNN（800pixel），edge和GCN score，目的是评估队列中那些CN的互作强度更大，作用更密切。

（5）承接（4）计算相同半径下，scimap输出的多个image的CN-CN互作网络zscore，计算unicox，这个我想纳入后面的机器学习模型。

（6）最后是计算CN之间的distance（不在半径范围内部），就是直接距离，然后和PFS的unicox，计算unicox，这个我想纳入后面的机器学习模型。

（7）最后是LASSO 和RF 进行特征筛选，构建机器学习模型，评估这些特征的意义，画出模式图，training组5-fold交叉验证，validation组验证。

1. Frequency/ Composition（CN level）

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CN\_term | lr.p | uni.cox.p | hr | hr.upper | hr.low |
| frequency\_CN01 | 0.00487 | 0.00578 | 1.99 | 3.24 | 1.22 |
| frequency\_CN02 | 0.033414 | 0.0355 | 0.608 | 0.967 | 0.383 |
| frequency\_CN03 | 0.097999 | 0.0997 | 0.71 | 1.07 | 0.473 |
| frequency\_CN04 | 0.41926 | 0.419 | 1.17 | 1.7 | 0.802 |
| frequency\_CN05 | 0.282127 | 0.284 | 1.31 | 2.16 | 0.798 |
| frequency\_CN06 | 0.037303 | 0.04 | 1.77 | 3.05 | 1.03 |
| frequency\_CN07 | 0.014595 | 0.0156 | 0.613 | 0.911 | 0.412 |
| frequency\_CN08 | 0.030782 | 0.0319 | 0.653 | 0.964 | 0.442 |
| frequency\_CN09 | 0.136368 | 0.141 | 0.598 | 1.19 | 0.302 |
| frequency\_CN10 | 0.082349 | 0.0848 | 1.58 | 2.65 | 0.939 |

2. Diversity； 这是每个image 水平的结果

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| CN\_term | lr.p | uni.cox.p | hr | hr.upper | hr.low |
| Richness | 0.129051 | 0.133 | 0.63 | 1.15 | 0.345 |
| Shannon | 0.04478 | 0.0462 | 0.675 | 0.993 | 0.459 |
| Simpson | 0.058974 | 0.0605 | 0.697 | 1.02 | 0.478 |
| Inv\_Simpson | 0.058974 | 0.0605 | 0.697 | 1.02 | 0.478 |
| Pielou | 0.175311 | 0.177 | 0.773 | 1.12 | 0.531 |
| Fisher\_alpha | 0.067814 | 0.0696 | 1.47 | 2.23 | 0.97 |

**🔍 各指标解读：**

**1. Shannon**

* p = 0.0462，统计显著
* HR = 0.675（< 1）→ 多样性越高，PFS 越好
* ✅ **是目前唯一显著的指标**，建议在图中高亮 + 写入 main text

**2. Simpson / Inv\_Simpson**

* p 接近显著（~0.06）
* HR ≈ 0.70，趋势与 Shannon 一致
* ✅ **次要支持证据**，可作为附图或用于模型特征

**3. Fisher\_alpha**

* p = 0.0696，接近显著
* HR = 1.47（>1）→ 趋势相反：Fisher 指数越高，预后越差
* ❗ 说明稀有 CN 占比高的样本 PFS 反而差 → 可能提示免疫扰乱或不均衡
* 🔍 值得深入分析：**它与 Shannon 的方向相反**

**4. Richness**

* p = 0.13，HR = 0.63，但不显著
* 🟡 有一定趋势，非决定性特征

**5. Pielou**

* 均匀度指标，p = 0.177，不显著

3. Spat\_feature 每个image 中每个CN level

Ripley’s K

Ripley’s L

Pair corr g(r)

G function

F function

J function

Clark-Evans

Quadrat test

Kernel density

Ripley’s K Ripley’s L CN05 06 10 越高，PFS越小

F function CN01 CN05越高，pfs越长

Clark-Evans CN06 越高 pfs越长

Kernel density CN03 CN07 CN08越高 pfs越长

### 🧬 生物学解读建议：

#### 1. **Ripley’s K & L（聚集性）**

* 在某些 CN（如右侧的紫色/黑色 CN，对应 CN06/07/08）显著负相关（蓝色，带黑圈）：
  + ➤ **解释**：在这些区域中，细胞越聚集，PFS 越差。
  + ➤ **可能机制**：高度聚集可能反映免疫抑制微环境、肿瘤密度升高，抑制免疫细胞渗透。

#### 2. **F Function（空点到最近细胞距离）**

* 多个 CN 显著正相关（红色 + 黑圈）：
  + ➤ **解释**：如果从空点到最近细胞的距离变大（F 函数变大），PFS 变好。
  + ➤ **可能机制**：表示该区域细胞“稀疏”或存在空隙，有利于免疫细胞流动与扩散。

#### 3. **Kernel Density（核密度估计）**

* 在多个 CN（如橘色、蓝绿、紫红）显著正相关（红色 + 黑圈）：
  + ➤ **解释**：这些区域密度越高，PFS 越好。
  + ➤ **可能机制**：可能是**T细胞富集区**或“免疫热点”，密度反而代表免疫活跃而非抑制。

#### 4. **Clark-Evans**

* 有一处显著正相关：
  + ➤ **解释**：更接近均匀分布（值高）与 PFS 增加相关。
  + ➤ **机制猜想**：免疫细胞在组织中**均匀分布**可能更有效控制肿瘤。

4. GNN-derived CN Connectivity Graph (radius = 800 pix)

总结

**🧠 CN-specific 空间行为与PFS关联总结（Frequency / Diversity / Spatial Feature）**

**🔴 CN01 – Tumorigenic Core**

* **Frequency高 → PFS差**（HR = 1.99，p = 0.00578）
* **F function高 → PFS好**：F函数代表点到最近邻的分布，提示 CN01 更靠近免疫结构，可能存在一定浸润趋势。
* **解释**：Tumor core 占比大为负面标志，但其空间邻近免疫细胞时，反而提示有反应性免疫浸润。

**🟡 CN02 – Macrophage Enriched**

* **Frequency高 → PFS好**（HR = 0.608，p = 0.0355）
* **解释**：提示MΦ富集可能与良好预后相关，可能呈M1偏向或抗肿瘤状态。

**🟢 CN03 – B-cell Enriched**

* **Kernel density高 → PFS好**
* **Quadrat Chisq较高 → 分布不均**
* **解释**：高密度、聚集的B细胞结构可能反映 tertiary lymphoid structure（TLS），与免疫应答增强相关。

**🟩 CN04 – Fibrotic Activity Hub**

* **Frequency 与 PFS无显著关联**
* **解释**：虽然为间质主导区，但其在本队列中对免疫治疗的影响可能较中性。

**🔶 CN05 – Plasma cell Enriched**

* **F function高 → PFS好**
* **Ripley’s K/L高 → PFS差**
* **解释**：当plasma cells过度聚集（Ripley高），可能提示免疫抑制性结构；但当其呈均匀分布、邻近肿瘤/免疫区时，反而提示良好响应。

**🟠 CN06 – Neutrophil Prominent**

* **Frequency高 → PFS差**（HR = 1.77，p = 0.04）
* **Ripley’s K/L高 → PFS差**
* **Clark-Evans高 → PFS好**
* **解释**：高度聚集的中性粒细胞通常与免疫抑制、NETs形成有关，但当其较分散（Clark-Evans高）时，可能免疫环境更良好。

**🔵 CN07 – Tumor Interface**

* **Kernel density高 → PFS好**
* **解释**：Tumor Interface 越丰富，提示免疫细胞越可能在边缘启动反应；高密度有望代表活跃的肿瘤边界免疫应答。

**🔷 CN08 – T-lymphocyte Enriched**

* **Kernel density高 → PFS好**
* **解释**：T细胞密度是良好预后的标志，可能反映更强的免疫浸润状态。

**🟣 CN09 – Pan-immune Active Zone**

* **Frequency 与PFS无显著关联**
* **解释**：尽管为免疫主导区，但多样化免疫构成可能掩盖其总体作用。

**🟤 CN10 – Vasculature Niche**

* **Ripley’s K/L高 → PFS差**
* **解释**：过度血管结构聚集提示新生血管活跃，或伴随免疫抑制结构（如VEGFA相关），与免疫逃逸相关。

**🧩 总结建议：**

1. **CN-specific空间特征可用于反映其微环境功能**，如：
   * 聚集（K/L）代表异质结构。
   * F/G函数反映最近邻或环境密度。
   * Kernel density 可解释细胞丰度与反应性。
   * Clark-Evans 与空间均匀性有关。
2. **Frequency + Spat feature + Diversity 三类特征组合分析**可提供更加全面的免疫景观理解。
3. 建议你：
   * 结合HE图像展示某些代表性CN（如CN01/03/05/06/08）的空间分布差异。
   * 最终特征筛选时，整合这三类信息进入机器学习模型（如LASSO）。

如果你需要我继续帮你做一个表格来总结这些点（按CN编号分行，按频率 / 空间特征 / 生物意义分列），可以告诉我！

4. Freq diversity spatfeature相关系数矩阵

Cluster1：frequency\_CN02 frequency\_CN10 Kernel density\_CN03 Kernel density\_CN08 frequency\_CN03 frequency\_CN08

Cluster2：frequency\_CN04 Fisher\_alpha 相关；frequency\_CN06 frequency\_CN09相关

Cluster3：F function\_CN05 Clark−Evans\_CN06 frequency\_CN01 F function\_CN01

Cluster4：frequency\_CN07 Kernel density\_CN07 Richness Inv\_Simpson Pielou Shannon Simpson

Cluster5：frequency\_CN05 Ripleys K\_CN10 Ripleys L\_CN10 Ripleys K\_CN05 Ripleys L\_CN05 Ripleys K\_CN06 Ripleys L\_CN06

### **📌 4. 聚类结果解读（整合 corr 分析）**

你聚类出了 5 个 cluster，综合了 Frequency / Diversity / Spatial Features：

#### ✅ Cluster 1：**免疫活跃型 CN**

* 变量：frequency\_CN02/03/08, kernel\_density\_CN03/08
* 特征：这些 CN 表现高密度/高频率分布，**PFS 较好**
* 结论：代表 **B-cell/NK/T cell 富集型亚群**，体现出抗肿瘤免疫的正反馈机制

#### ✅ Cluster 2：**Fisher异常群 & 非典型免疫样本**

* 变量：frequency\_CN04/06/09，Fisher\_alpha
* 特征：这几个 CN 没有显著 PFS 相关性，Fisher 指数高但结果不稳定
* 结论：可能为 **功能不明或异质性高但免疫抑制主导的区域**

#### ✅ Cluster 3：**空间非聚集免疫支持型**

* 变量：F\_function\_CN01/05，Clark\_Evans\_CN06，frequency\_CN01
* 特征：反映局部免疫结构不聚集，有利于 T cell 渗透
* 结论：**高免疫渗透力型 CN**，如 Tcyto/NK friendly 区域

#### ✅ Cluster 4：**免疫复杂度/多样性型**

* 变量：freq\_CN07, kernel\_density\_CN07, Richness, Shannon, Pielou...
* 特征：一致反映高异质性，**PFS 长**
* 结论：**抗原识别广泛、免疫响应高度复杂的区域**

#### ✅ Cluster 5：**肿瘤空间抑制型**

* 变量：Ripley’s K/L CN05/06/10, freq\_CN05
* 特征：空间聚集性强，频率高，**PFS 差**
* 结论：可能为 **肿瘤免疫排斥屏障/“免疫冷”区域**

6. Spatial Transition Entropy----non-distance-based spatial diversity metric

**Spatial Transition Entropy（空间转换熵）** 衡量的是不同空间单元（如 patch）之间的标签（如 CN label）**转换频率的复杂性**，而不是距离本身。上面1-5都是spatail distance based

请问Spatial Transition Entropy应该怎么做，代表什么意思，空间转换是多个CN好还是2个CN之间的，有没有什么代表文献

**解读：**

* 高 Spatial Transition Entropy = **区域之间高度交错/界限模糊**；
* 低值 = **功能区边界清晰**；
* 作为“结构混杂性”补充距离熵指标，非距离约束下的组织复杂性评估。

|  |  |  |  |
| --- | --- | --- | --- |
| **术语层级** | **描述** | **建议加入的 cellular 层次** | **说明** |
| **Cell** | 单细胞层面（e.g. H&E核分割，cell type annotation） | **intra-cellular** | 可描述细胞内特征：如 RBP/ESCRT 表达、核特征、transcriptional state 等 |
| **Intercellular interaction** | 两个细胞之间的直接邻近关系、空间交互、L-R分析等 | **inter-cellular** | 明确对应，描述细胞-细胞之间的空间关系、免疫抑制轴（如PVR–TIGIT）等 |
| **CN with cell-state** | 将细胞聚类为CN，整合cell lineage与activation/exhaustion状态 | **inter-cellular**（或transition zone） | 跨cell-state组合反映micro-niche构建 |
| **Habitat** | mesoscale生态单元（多个细胞组成的功能区域） | **inter-/extra-cellular** | 描述habitat内部细胞交互及其与周围组织的边界 |
| **Ecotype** | 样本级整合生态组合（跨habitat模式的组合） | **extra-cellular** | 类似于macro-environmental signature，可用来推测系统级免疫状态 |
| **Feature recomposition** | 基于空间组合的指标重构（composition/diversity/STE） | all layers | 可跨 intra/inter/extra，重构反映的是多层级融合特征 |
| **Model prediction** | 基于上述特征预测ICB反应、预后 | all layers | 模型输入特征可包含不同层级的空间表征指标 |