

SAMCNet: Towards a Spatially Explainable AI Approach for Classifying MxIF Oncology Data

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ABSTRACT

The goal of spatially explainable artificial intelligence (AI) classification approach is to build a classifier to distinguish two classes (e.g., responder, non-responder) based on their spatial arrangements (e.g., spatial interactions between different point categories) given multi-category point data from two classes. This problem is important for generating hypotheses towards discovering new immunotherapies for cancer treatment as well as for other applications in biomedical research and microbial ecology. This problem is challenging due to an exponential number of category subsets which may vary in the strength of their spatial interactions. Most prior efforts on using human selected spatial association measures may not be sufficient for capturing the relevant spatial interactions (e.g., surrounded by) which may be of biological significance. In addition, the related deep neural networks are limited to category pairs and do not explore larger subsets of point categories. To overcome these limitations, we propose a Spatial-Interaction Aware Multi-Category deep neural Network (SAMCNet) architecture and contribute novel local reference frame characterization and point pair prioritization layers for spatially explainable classification. Experimental results on multiple cancer datasets (e.g., MxIF) show that the proposed architecture provides higher prediction accuracy over baseline methods. A real-world case study demonstrates that the proposed work discovers patterns that are missed by the existing methods and has the potential to inspire new scientific discovery.

CCS CONCEPTS

• **Computing methodologies** → **Spatial and physical reasoning**.

KEYWORDS

spatially explainable classifier, MxIF, oncology, spatial interactions

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1 INTRODUCTION

Our spatially explainable AI classification approach aims to build a classifier that can learn spatial patterns in multi-category point patterns to distinguish between two classes. When each data point belongs to a distinct category feature, it logically follows that the value of different spatial interactions between various points is additionally significant for the classification task. For example, the impact of one type of immune cell (e.g., cytotoxic T lymphocytes (CTLs)) on nearby cancer cells may be affected by other immune cells (e.g., T regulatory cells) [28].

This problem is important because spatial configurations, a proxy for physical interactions, help generate new hypotheses towards discovering disease therapeutics (e.g., immunotherapies for cancer treatment). These hypotheses could be used in applications such as medical pathology, biomedical research, and microbial ecology, where multi-category point patterns frequently appear. In many diseases, such as cancer, spatial arrangements and associations between distinct phenotypic markers are crucial to understand normal tissue function and disease biology. For example, the development of effective intervention strategies relies on knowledge of the spatial arrangement and cellular mechanisms of coronavirus infections [27]. Researchers in immunology also seek to understand the spatial configurations of immune and tumor cells to help evaluate the effectiveness of the immune checkpoint inhibitors (e.g., anti-PD-1) in cancer treatment [12]. Table 1 presents use case of the proposed model in different application domains.

This problem is challenging due to the following reasons. First, the number of potential spatial patterns is exponentially related to the number of different category subsets. The second challenge is that multi-category point patterns are heterogeneous and form complicated structural and higher-order spatial interactions. In addition, the spatial association between various point pair instances is not always equal, requiring the model to learn these distinctions. CTL-tumor cell interactions, for example, are more biologically relevant in the context of effector function (e.g., a CTL must engage

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Table 1: Use cases of proposed model

Application Domain	Use Case (Objective)
Oncology	Understanding the spatial configuration between immune and tumor cells to evaluate the effectiveness of ICI [12]
Pharmacology	Identifying protein interactions and bindings towards discovering structure-based drugs [8]
Ecology	Inferring predator-prey spatial interactions in food webs [20]
Paleontology	Studying fossils to classify organisms and examine their interactions with each other and the environment [11]
Epidemiology	Investigating the relationship between human mobility and spread of Covid-19 [24]

a tumor cell to kill it); in contrast, B cell-tumor cell interactions are more indirect. Lastly, point patterns possess different properties (e.g., invariance to permutation), which means the classifier needs to meet the same requirements to achieve a robust surrogate representation.

Most of the prior works to identify spatial relationships in multi-category point patterns can be classified into hand-constructed features using spatial association measures (e.g., Pearson correlation, G-cross, Ripley’s cross-k, Participation index) [3, 16, 18, 23]. For example, [18] uses the classical statistics measures (e.g., Pearson Correlation), which are sensitive to the choice of spatial partitioning. In addition, neighbor-graph-based approaches (e.g., [3, 25]) are primarily a function of distance, which may not accurately model the true spatial relationships among categorical points on a three-dimensional surface (e.g., organ). In more recent work, a spatial-relationship aware neural network (SRNet) [15] aims to confound these limitations by leveraging machine-constructed features to model spatial relationships between points of different categories. However, SRNet is limited to only binary spatial relationships, and the importance between distinct binary category pairs is assumed to be equal.

To overcome these limitations, we propose a **Spatial-interaction Aware Multi-Category deep neural Network (SAMCNet)** architecture for spatially explainable AI classification and contribute novel local reference frame characterization and point pair prioritization layers. SAMCNet provides a promising way to identify the importance between different point pair instances and the most discriminative N-way spatial relationships. As shown in Fig. 1a, we first aim to provide a better way to represent spatial information using a multi-scale local reference frame characterization (LRFC) and spatial feature decomposition (described in Section 5.1) before applying an EdgeConv operation [29]. As indicated in Fig. 1b, a point pair prioritization sub-network is designed to specify a weight on point pair instances that are more important in an N-way spatial relationship (described in Section 5.3). A point pair instance describes the spatial relationship between a point belonging to one category and its neighbor belonging to the same or a different category. Two- and three-way spatial relationships are indicated by hyperedges connecting vertices belonging to different categories (Fig. 1b). Lastly, we use an asymmetric function (e.g., average pooling) to aggregate information across all points neighboring the center point $\hat{v}_i$. The thickness of different edges shows the contribution of distinct category pairs in the overall representation of $\hat{v}_i$. Fig. 1 shows the overall framework of the proposed SAMCNet.

This paper makes the following contributions:

- It proposes a dynamic point pair prioritization sub-network to learn the most discriminative features in N-way spatial relationships (e.g., tertiary, ternary, etc.) and uses it in a

Spatial-interaction Aware Multi-Category deep neural Network (SAMCNet).

- It experimentally shows that the proposed model outperforms existing baseline methods, and is also computationally more efficient than the competing DNN architecture (e.g., SRNet).
- It presents case studies on two cancer datasets which show the proposed model is able to identify high-order spatial patterns that are ignored by the related work and has the potential to advance scientific discovery.

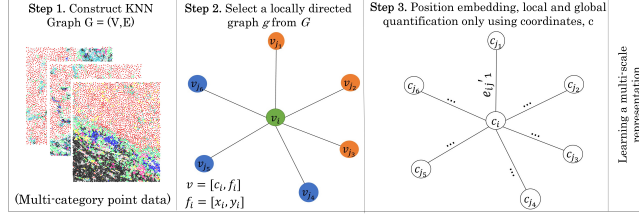
Scope: We aim to identify N-way spatial relationships to help distinguish between point patterns belonging to two different classes. Analyzing the presence of noisy points in the building of a neighborhood graph and the evaluation of standard data augmentation techniques (e.g., rotation) are not considered. Field trials to assess the clinical value of the proposed method also fall outside the scope of this study. Patient privacy and the propriety nature of the data prevent us from publishing the dataset.

Organization: The rest of the paper is organized as follows: Section 2 briefly describes an important application domain of this problem. Related work is reviewed in Section 3. Section 4 formally defines the problem. Section 5 describes the details of our proposed work. In Section 6, we present the experimental results and case study. Finally, Section 7 concludes the paper and outlines some future research.

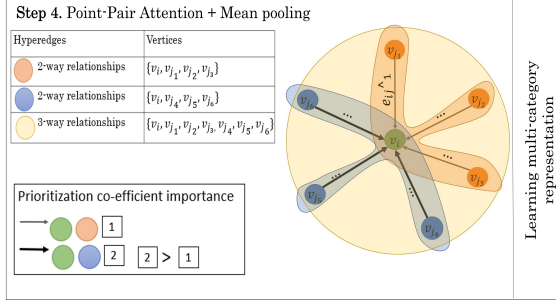
2 AN ILLUSTRATIVE APPLICATION DOMAIN

The recent development of multiplex immunofluorescence (MxIF, Fig. 3a) technology has enabled exploration into the complexity of tumor-immune microenvironments (TME) within spatially-preserved metastatic tissue and in the therapeutic context of immune checkpoint inhibitors (ICI). ICI therapy works by augmenting the antitumor properties of pre-existing tumor-specific CTL, which become more efficient in infiltrating tumor masses and destroying cancer cells. Through cyclic rounds of antibody staining, imaging and dye inactivation, MxIF technology provides a state-of-the-art method to visualize and identify many cell subtypes (e.g., immune and malignant) and their corresponding spatial coordinates using single-cell analysis of formalin-fixed paraffin-embedded (FFPE) tissue sections including metastatic melanoma lymph nodes. With the continuous refinement of these techniques, it is currently possible to identify over 50 cellular phenotypic markers (e.g., CD3, FoxP3, CD14) and their corresponding cellular phenotypic and functional characteristics within a single tissue section.

Emerging research in this area has begun to highlight the need for an automated process to analyze the complex spatial relationships among different cellular subsets and functional states in the context of ICI therapy, in order to identify critical intercellular interactions relevant to clinical outcomes. Furthermore, it is clinically crucial to examine the importance of cell species along with their activation status in a spatially informed manner due to the clinical implications of interactions in close spatial proximity (See Fig. 2). For example, a CTL will likely be unable to kill a cancer cell if it is nearby a tumor-associated macrophage that expresses PDL1 on its surface. In contrast, a CTL is more likely to kill a cancer cell if it is expressing Granzyme B and is not in close proximity to FoxP3-expressing regulatory T cells (Treg).



(a) A multi-scale spatial representation learning using local reference characterization and EdgeConv operation. For simplicity, we are only showing one edge feature.



(b) Learning a point pair importance a based on categorical attributes (node colors) in N-way spatial relationships.

Figure 1: The overall framework of SAMCNet.

Many metastatic diseases (e.g., lung, breast, prostate cancers) beyond current case studies (e.g., metastasis melanoma) in the therapeutic context of ICI treatment could benefit from a spatially informed analysis to reveal new insights. We highlight that direct contact between immune and malignant cells is needed for CTLs to kill cancer cells. Therefore, a neighborhood distance should be chosen to allow direct bio-chemical interactions among tumor and immune cells. Finally, unlike the cell-count-based methods of the traditional clinical research, spatial association measures allow identifying critical spatial relationships relevant to clinical outcomes in a complex TME landscape. For example, both responder and non-responder patients undergoing ICI therapy have tissue with both killer cells (e.g., CTLs) and tumor cells. Therefore, baseline techniques (i.e., data-driven spatial quantification methods) can potentially identify the missing mediators between these groups to improve clinical diagnosis. Our proposed method aims to provide an algorithmic description of the importance of different relationships to characterize spatial patterns better in a tumor-microenvironment, potentially revealing insights to enhance the manual visual assessments provided by pathologists.

3 RELATED WORK

The related work can be classified into two major categories: (1) Data-driven spatial quantification and (2) Machine-constructed features using deep neural networks (DNN).

Data-driven spatial quantification: A spatial association (i.e., spatial co-location) is an intuitive representation to help understand the spatial interactions of a multi-category point pattern by identifying a subset of points frequently located in close spatial proximity to one another [25]. Spatial association interest measures (e.g., Pearson correlation, Cross-k, G-cross, Participation index) are commonly used in spatial data mining to quantify multi-category

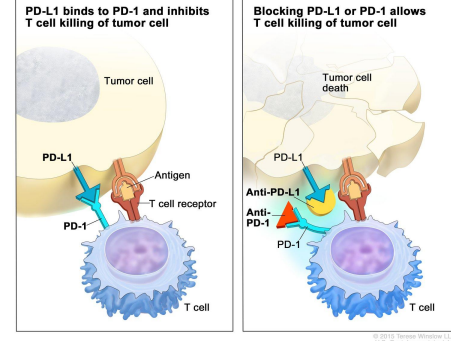


Figure 2: Importance of spatial analysis in evaluating the effectiveness of ICI therapy in killing tumor cells [19].

point patterns. Previously, a spatial association between tumor and immune cells in breast cancer digitized images of hematoxylin/eosin (H&E) stained tissues was studied using classical statistical methods (e.g., Pearson correlation coefficient) after imposing a spatial grid partitioning on a two-dimensional map of the cell center points [18]. However, the classical statistics measures are sensitive to the choice of spatial partitioning. More recent work used neighborhood-based spatial statistical measures such as G-cross to quantify the spatial association between cancer and immune cells in lung cancer [3]. The limitation with this approach is that it is used in isotropic space, with the same intensity regardless of measurement direction, which may not be enough to capture relevant spatial interactions (e.g., surrounded by) that might be biologically significant. Finally, quantifying spatial associations between different communities (e.g., at the sub-graph-level) [16] does not reveal critical information regarding the spatial relationship between distinct categorical points within each community.

Machine-Constructed features using DNN: A new approach that begins to address these limitations leverages machine-constructed features using a spatial-relationship aware neural network (SRNet) [15] to model the spatial relationships between points of different categories. However, SRNet is limited to only binary spatial relationships, and the importance between distinct binary category pairs is assumed to be equal. Also, SRNet uses a fixed-neighborhood distance to construct the input graph to the network, and no operator is defined to work with different sized neighborhoods. All the feature-based DNNs reviewed in a recent computational pathology survey [7] use images, i.e., a regular grid, as the input. Hence, they cannot handle a simple but significantly important geometric structure, the point pattern¹.

4 PROBLEM FORMULATION

4.1 Basic Concepts

Definition 4.1. A **spatial object** is the representation of an entity or phenomenon in a 2/3-dimensional geographical space, e.g., a point representing a hospital or a tumor cell.

Definition 4.2. A **categorical feature** refers to the conceptual abstraction of a set of spatial objects with the same feature type, such as cell types, plant species, or a business category.

¹We provide a detailed description of DNN architectures for point cloud data [21, 22, 29] in appendix Section C.

Definition 4.3. A **multi-category** point pattern is a collection of spatial objects with their corresponding categorical features (e.g., immune and tumor cells). Fig. 3a illustrates the point patterns between two classes responder and non-responder, indicating two clinical responses to immunotherapy treatment. Each data point shows the centroid coordinates of a cell in a pixel and the color of its corresponding cell type.

Before to understand **spatially explainable AI**, we need to define **explainable AI (XAI)**. XAI is creating a suite of machine learning techniques that produces more explainable models (e.g., understood by humans) while maintaining a high level of learning performance (e.g., prediction accuracy). Interested readers can refer to [2], which provides a more detailed taxonomy on XAI and related concepts.

Definition 4.4. **Spatially explainable AI** classification is the process of classifying data into a given number of classes and determining the most discriminative features according to their spatial arrangement. For example, Fig. 3b shows a simple decision tree separating responder class from non-responder class at the tumor-margin region according to the spatial the arrangements between pairs of cells (e.g., B cells and Regulatory T cells) based on the participation index values [25].

4.2 Problem Statement

The problem of spatially explainable AI classification can be expressed as follows:

Input: multi-category point data from two classes

Output:

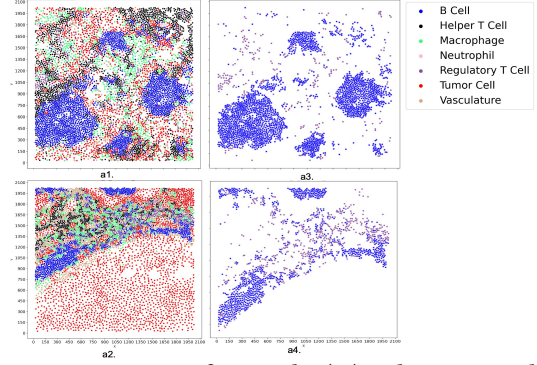
- A classifier algorithm separating two classes
- Most discriminative explanatory features

Objective: High classification performance on selected metrics (e.g., accuracy)

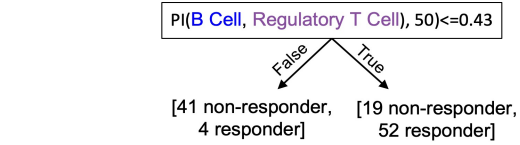
Constraints: Points are in a planer Euclidean space

Given multi-category point data from two classes (Fig. 3a (a1, a2)), an example of spatially explainable AI classification is indicated in Fig. 3b separating two classes (e.g., responder and non-responder). We used hand-constructed spatial association measures (e.g., participation index) as explanatory features (e.g., B cell and Regulatory T cell, Fig. 3a (a3, a4)). The decision-tree root-node uses a threshold of 0.43 on the participation index ((B cells, Regulatory T cells), distance = 50 pixels), which is the minimum of the probability of the presence of B cells within 50 pixels (17 micrometers) of Regulatory T cells or vice-versa. We argue that traditional spatial association measures (e.g., cross-k, participation index) are primarily suited to describe spatial arrangements between pairs and cannot capture clinically relevant features (e.g., surrounded by).

Our model has three key building blocks. The first is a multi-scale local reference frame characterization (LRFC), which takes as input a neighborhood graph that models the spatial distribution of one point and its neighbors. The second block uses an EdgeConv [29] operation to learn local and global information and a semantic representation by dynamically updating the neighborhood graph at each layer (Section 5.2). The third is a prioritization sub-network to distinguish between point pair instances that belong to different categories by learning the importance of each distinctive pair



(a) MxIF point patterns of responder (a1) and non-responder (a2) detailing all cell classes. MxIF point patterns detailing spatial arrangements between B cells and Regulatory T cells (a3, a4).



(b) A simple decision tree to distinguish between responder and non-responder at the tumor-margin.

Figure 3: Spatially explainable AI classification via a spatial association measure, participation index (PI).

(Section 5.3). We use an asymmetric function (e.g., average pool) to aggregate the information of one point and all its neighbors.

5 THE PROPOSED WORK (SAMCNET)

The primary objective of the proposed neural network architecture is to learn N-way spatial relationships in a multi-category point pattern. The main difference between SAMCNet and traditional data-driven association interest measures is LRFC, which allows categorical points belonging to different distributions (e.g., clustering versus even distribution) to be represented through a multi-scale representation, overcoming the inefficiency of intrinsically single-scale methods like radial basis function kernels or discretization. Furthermore, SAMCNet differs from the competing state-of-the-art DNN architecture SRNet in two distinct ways. First, it incorporates a point pair prioritization sub-network, which learns the importance of point pairs in N-way spatial relationships based on their categorical attributes. Second, the connectivity of nodes in a locally connected graph allows SAMCNet to learn relevant high-order spatial patterns based on the input k nearest neighbors and aggregation choice.

5.1 Local Reference Frame Characterization

Given a point set $P = \{p_i = (c_i, f_i) | p_1, \dots, p_n\}$, where $c_i = (x_i, y_i)$ are the spatial coordinates and f_i is the categorical attribute², we compute directed graph $G = (V, E)$, where V and E are the vertices and edges. We construct G as the k -nearest neighbor graph of each c_i point $\in \mathbb{R}^F$, where $E = V \times K$. Note that the neighborhood graph of each consecutive layer in SAMCNet relies on the output of the preceding layer, which is dynamically updated based on dimension F , which represents the feature dimensionality of the

²The categorical feature f_i associated with each p_i is preserved throughout the network using a skip connection for point pair prioritization sub-network computations (See Fig. 4).

given layer. For example, in the beginning, neighborhood graph G is constructed as the k -nearest neighbor points of each c_i point $\in \mathbb{R}^2$, which represent the spatial coordinates. This approach allows the network to learn how to build the graph G utilized in each layer, rather than using a fixed constant graph established before the network is evaluated. Reconstructing the neighborhood graph in the embedding space produced by the hidden layer is empirically beneficial in related classification tasks (e.g., [29]).

The next step is to use local reference frame characterization (LRFC) to model the distribution of one point and its neighbor using only spatial coordinates. This technique allows us to model the relative distance between a given point c_i with respect to its nearest points c_j , where $1 \leq j \leq k$, into a corresponding edge e'_{ij} . The intuition behind LRFC is that spatial coordinates are illustrative location indicators; using discretization or feed-forward neural network techniques is insufficient to capture the spatial distribution due to the lack of feature decomposition between spatial and categorical attributes. Inspired by a multi-scale periodic representation of grid cells in mammals [1] and a vector representation of self-position [10], Mai et al. [17] proposed a multi-scale embedding method namely, positional encoding PE , which uses sine and cosine functions of different frequencies to represent positions in space. We adopt this idea in our network as follows.

Given a point c_i in a studied 2D space, $e[c_i] = \text{EdgeConv}(PE_s(c_i))$, where $PE(c_i)$ is a multi-scale representation s_j , $1 \leq j \leq s$, to capture the distribution of mixture multi-category point patterns. The overall formulation of local reference frame characterization (LRFC) is as follows:

$$PE_s(c_i) = [PE_{s,1}(c_i); \dots; PE_{s,s}(c_i)], \quad (1)$$

$$PE_{s,j}(c_i) = [\cos(\frac{\langle c_i, a_j \rangle}{\lambda_{\min} \cdot g^{s/(S-1)}}); \sin(\frac{\langle c_i, a_j \rangle}{\lambda_{\min} \cdot g^{s/(S-1)}})], \quad (2)$$

$\forall j = 1, 2, 3,$

where $a_1 = [1, 0]^T$, $a_2 = [-1/2, \sqrt{3}/2]^T$, and $a_3 = [-1/2, -\sqrt{3}/2]^T$ are unit vectors, the angles between every pair of vectors is $2\pi/3$; $\lambda_{\min}$ and $\lambda_{\max}$ are the minimum and maximum grid scales; and $g = \frac{\lambda_{\max}}{\lambda_{\min}}$. We define the embedding along each edge as the distance between the center point c_i and its k -nearest neighbors c_j , $|PE(c_i) - PE(c_j)|$, where $1 \leq j \leq k$.

5.2 Local and Global Quantification

The EdgeConv operation is defined as edge feature $e_{ij} = h_{\Theta}(c_i, c_j)$, where $h_{\Theta} : \mathbb{R}^F \times \mathbb{R}^F \rightarrow \mathbb{R}^{F'}$ is a nonlinear function with a set of learnable parameters Θ . Lastly, an asymmetric operation (e.g., Σ or Max) is applied to aggregate information along all the edge features neighboring center node c_i . The choice of h_{Θ} is critical in defining EdgeConv, such as using the dot product between a set of filters $\Theta = \{\theta_1, \dots, \theta_M\}$ and image pixels x_j in a regular grid and aggregating the information using Σ results in a standard convolution. A detailed discussion of different forms of h_{Θ} can be found in [29].

We have adapted the EdgeConv operation from DGCNN [29] in our network to learn both global shape structure, captured by the center coordinates c_i , and local neighborhood information, captured by $|c_i - c_j|$. The overall formulation is as follows:

$$e''_{ij} = \text{leakyrelu}(\theta_m \cdot |PE(c_i) - PE(c_j)| + \phi_m \cdot c_i), \quad (3)$$

where θ_m and ϕ_m are learnable parameters for local and global information, respectively, and PE is the positional embedding to represent the relative distances along each edge starting at c_i .

5.3 Point Pair Prioritization Sub-Network

Thus far, we have built the graph and defined the edge embeddings in terms of strictly spatial features. If we follow existing point pattern graph-based DNN architectures (e.g., Pointnet++ [22], DGCNN [29]), we would simply concatenate the categorical features into the embedded feature space. However, the importance of interactions between vertices of categorical features f_i and $f_j \in \mathcal{N}_i$ would not be learned in this way. As a result, the model would be confined to learning individual category features. Instead, the classifier should learn how to correctly weight diverse point pair associations as a stronger inductive bias. To this end, we propose a point pair prioritization layer to learn the importance (i.e., strength) of the spatial relationship between different category pairs, followed by an average pooling layer to weigh different subsets accordingly. As a whole, this layer is analogous to a weighted average pooling function, where the weights correspond to the importance of the categorical interaction.

The input to this layer is an edge embedding e''_{ij} , which is the output from the EdgeConv layer. In the prioritization layer, we first derive $\hat{e}_{ij}$, an edge embedding augmented by the strength of categorical pairwise association:

$$\hat{e}_{ij} = \bar{a}_{f_i f_j}^T W e''_{ij}, \quad (4)$$

where W is a learnable linear transformation on the original embedding to aid prioritization expressivity, and $\bar{a}_{f_i f_j}$ is our learned pairwise association weight vector for categorical point pair features (f_i, f_j) .

In this formulation, we have included $f_j \in \mathcal{N}_i$, where $\bar{a}_{f_i f_j}$ is a learned self-weighting based only on the categorical feature of v_i . We also note that interactions are assumed invariant with respect to the ordering of the categories; for example, $\alpha_{C_1 C_2} \equiv \alpha_{C_2 C_1}$. Similar to other prioritization (i.e., attention) layers, we then apply a LeakyReLU (LR) activation function, followed by a softmax function, resulting in the normalized pairwise association:

$$\alpha_{f_i f_j} = \frac{\exp(\text{LR}(\hat{e}_{ij}))}{\sum_{k \in \mathcal{N}_i} \exp(\text{LR}(\hat{e}_{ik}))}, \quad (5)$$

where $\alpha_{f_i f_j}$ is the learned categorical pairwise association for each neighbor, such that $f_j \in \mathbb{R}^k$. With this normalized attention coefficient, $\alpha_{f_i f_j}$, we can calculate the weighted average pooling and produce the final vertex embedding:

$$\hat{v}_i = \sigma \left(\frac{1}{|\mathcal{N}_i|} \sum_{j \in \mathcal{N}_i} \alpha_{f_i f_j} W e''_{ij} \right). \quad (6)$$

This formulation can be extended to K heads, following other prioritization networks such as GAT [26], where each head learns a separate categorical pairwise association $\alpha_{f_i f_j}^k$ and linear transformation weight W^k followed by an aggregation operation (AGG) over the different head outputs:

$$\hat{v}_i = \text{AGG}_{k=1}^K \sigma \left(\frac{1}{|\mathcal{N}_i|} \sum_{j \in \mathcal{N}_i} \alpha_{f_i f_j}^k W^k e''_{ij} \right), \quad (7)$$

where σ is a non-linear activation function such as LeakyRelu and the aggregation operation can take the form of an average or a

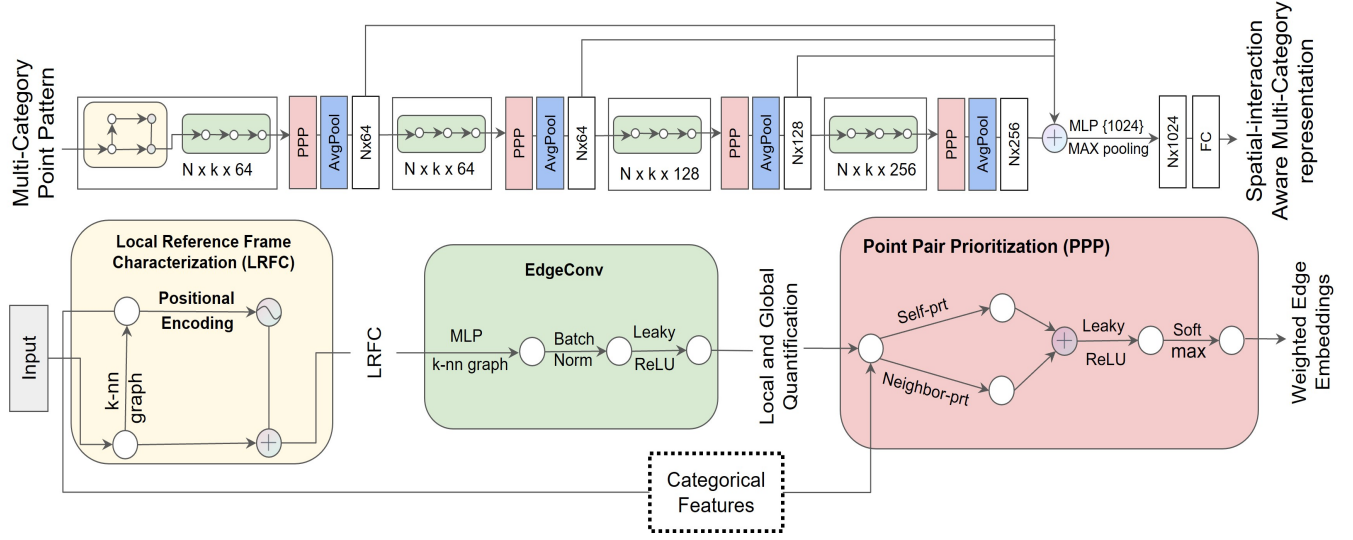


Figure 4: SAMCNet Architecture. The network architecture takes as input a multi-category point set containing n points, where a local reference frame characterization (LRFC) layer calculates an embedding for each point using its spatial coordinates and neighborhood spatial distribution. The embeddings are then passed into an EdgeConv layer to specify an edge feature set of size k for each point. The categorical features are passed using a skip connection, where a point pair prioritization sub-network calculates the importance between a point and its k nearest neighbors belonging to different category pairs. Lastly, an average pooling function aggregates the information from all k points to the center point. Notice that since a K-nn graph is built in the LRFC layer, the reconstructing of the K-nn graph in the first EdgeConv layer is skipped.

concatenation. Since this layer preserves the identity of the center vertex, it can also be extended to multiple layers of the network by maintaining the categorical features of vertices between layers with a skip connection. We do this by adding point pair prioritization after each layer’s EdgeConv operation. In the context of hierarchical feature learning, our network is therefore effectively capable of learning the importance of categorical N-way interactions in a hierarchical feature space.

Finally, we note that the choice of aggregation is not limited to average pooling; for example, one may choose to select a large number of k -nearest neighbors when building the graph, while taking only a top- k' subset of highest features to pool, in order to filter out an overpowering number of weak interactions. Max pooling can be demonstrated as a special case of this concept, where only the top-1 of a neighbor’s features is selected.

6 VALIDATION

6.1 Experimental Settings

Evaluation Tasks: We validated our proposed approach with (1) a *comparative analysis* to evaluate the proposed SAMCNet against classical spatial association interest measures and state-of-the-art DNN architectures on this problem, (2) a *sensitivity analysis* to evaluate the impact of key building blocks (e.g., self-prioritization) along with key parameters on selected performance metrics (Section B in appendix), and (3) a feature selection analysis to evaluate the **impact of the prioritization sub-network** in learning the importance of different point pair instances and identify **the most relevant N-way spatial relationships**.

Model Architecture: Fig. 4 shows the proposed SAMCNet architecture. The proposed SAMCNet was implemented in Pytorch. For

local reference frame characterization, the grid-scale, minimal grid cell size and maximal grid cell size were set to 5, 1, and 100, respectively. The number of k nearest neighbors was set to 6. We followed the same settings for the 4 EdgeConv layers, residual block connection, batch normalization, activation functions, and dropout as described in [29]. We used the Adam optimization algorithm with a learning rate of 10^{-3} and cross-entropy loss for 200 epochs to train the SAMCNet. The batch size, momentum, and prioritization heads were set to 7, 1, 0.9, respectively. All hyper-parameters were set through tuning on the validation set. DNN candidate methods were tested with the same setting described above.

Baseline Methods: We compared our proposed framework on selected classification metrics with the following baseline methods. First, point patterns were composed of hand-constructed features using participation index (PI) [25], then PI values were fed into a (1) decision tree with a max depth of 2 (**PI+DT**), (2) Random Forest with similar depth (**PI+RF**), and (3) fully connected neural network (**PI+NN**) with four Relu hidden layers and 2048 neurons. Under similar settings, we used point patterns composed of cross- k [13] values fed into similar classifiers previously described, giving us three more candidate methods: (4) **cross- k + DT**, (5) **cross- k + RF**, and (6) **cross- k + NN**. We used a fixed-neighborhood distance of 50 pixels to construct participation index and cross- k values. Traditional classifiers and fully connected neural network were implemented with the Python scikit-learn package, with hyper-parameters set to default values unless otherwise stated. We also evaluated proposed model with three state-of-the-art DNN architectures: (7) **PointNet** [22], a neural network architectures that directly consume point sets for applications ranging from object classification to part segmentation; (8) **DGCNN** [29], a dynamic

Table 2: Model performance on all datasets.

Model	Tumor-Margin classification			
	Precision	Recall	F1-Score	Acc
PI + DT	0.93	0.93	0.93	0.93
Cross-K + DT	0.60	0.50	0.44	0.50
PI + RF	0.85	0.82	0.82	0.82
Cross-K + RF	0.61	0.61	0.61	0.60
PI + NN	0.32	0.57	0.41	0.57
Cross-K + NN	0.71	0.70	0.71	0.70
PointNet	0.82	0.68	0.66	0.68
DGCNN	0.76	0.46	0.33	0.46
SRNet	0.90	0.89	0.89	0.89
SAMCNet (ours)	0.97	0.96	0.96	0.96

Model	Tumor-Core classification			
	Precision	Recall	F1-Score	Acc
PI + DT	0.70	0.62	0.64	0.62
Cross-K + DT	0.52	0.72	0.60	0.72
PI + RF	0.73	0.75	0.70	0.75
Cross-K + RF	0.52	0.72	0.60	0.72
PI + NN	0.75	0.75	0.75	0.75
Cross-K + NN	0.52	0.72	0.60	0.72
PointNet	0.68	0.67	0.67	0.67
DGCNN	0.49	0.33	0.29	0.33
SRNet	0.96	0.95	0.95	0.95
SAMCNet (ours)	0.96	0.95	0.95	0.95

Model	Disease classification			
	Precision	Recall	F1-Score	Acc
PI + DT	0.76	0.77	0.76	0.77
Cross-K + DT	0.85	0.85	0.85	0.85
PI + RF	0.82	0.80	0.78	0.80
Cross-K + RF	0.84	0.82	0.80	0.82
PI + NN	0.84	0.78	0.75	0.78
Cross-K + NN	0.40	0.63	0.49	0.63
PointNet	0.76	0.6	0.48	0.60
DGCNN	0.54	0.57	0.46	0.57
SRNet	0.78	0.77	0.76	0.77
SAMCNet (ours)	0.94	0.94	0.94	0.94

graph convolutional neural network architecture for CNN-based high-level point cloud tasks such as classification and segmentation; (9) **SRNet** [15], a DNN architecture for binary spatial relationships in multi-category point patterns.

Dataset: Experiments were conducted on two multi-category point pattern cancer datasets from MxIF images. The first dataset was used for two distinct classification tasks, (1) **tumor-margin** classification and (2) **tumor-core** classification. The second dataset was used for a (3) **disease** classification task. In the **tumor-margin** classification task, we used 145 FOV point sets indicating two different clinical outcomes of ICI therapy, 68 of which were labeled as responders, and 77 labeled as non-responders for individuals who progressed and experienced recurrence in less than a year. In the **tumor-core** classification task, we used 103 FOVs point sets, 30 of which were labeled as responders and 73 non-responders, extracted from tumor area of metastatic lymph nodes. In the **disease** classification task, we used 143 point sets of chronic pancreatitis and 53 pancreatic ductal adenocarcinomas (PDAC).

Evaluation Metrics: The model performance was measured by using the weighted average of precision, recall, F1-score, and accuracy (ACC).

Data Preparation: In each classification task, we divided the data into 80% training and 20% testing. Ten percent of the training set was selected to be the validation set. Due to the limited number of learning samples, we used data augmentation techniques, whereby each learning sample was rotated 12 degrees clockwise five times during the training procedure. We restricted rotation to only five times due to potential overfitting issues. We uniformly sampled 1,024 points from each point set for the underlying classification task.

Platform: We used a K40 GPU composed of 40 Haswell Xeon E5-2680 v3 nodes. Each had 128 GB of RAM and 2 NVidia Tesla K40m GPUs. Each K40m GPU has 11 GB of RAM and 2880 CUDA cores.

6.2 Experimental Results

Comparative Analysis: We tested the candidate methods on the three classification tasks described in Section 6.1. Results on selected classification metrics are presented in Table 2. Results show the superiority of the proposed SAMCNet over traditional data-driven spatial association interest measures and existing DNN competition (i.e., PointNet, DGCNN, SRNet). Most notably, we were able to improve accuracy over SRNet by a margin of 7.0%, and 17.0% on tumor-margin, and disease classifications, respectively. These results suggest that local reference frame characterization (LRFC) and specifying different weights to points of the same neighborhood with the distinct categorical attribute are beneficial.

Table 3: Model time complexity on all datasets.

Model	Time (second)		
	tumor-margin	tumor-core	disease
SRNet	30.51	25.34	19.18
SAMCNet	4.04	2.41	5.77

In addition, we used the model inference time on the three classification tasks as a measure of the model’s computational time complexity and examined the trade-off between time complexity and classification accuracy. In this experiment, we compared our proposed model only with SRNet since it is specifically designed to learn spatial associations in multi-category point patterns. Result showed SAMCNet is not only more accurate than SRNet, but it also runs from 3 to 10 times faster on the three classification tasks. Table 3 provides the details on each classification task. Pytorch Profiler³ was used to measure the inference time across different candidate methods.

Sensitivity Analysis: To evaluate the performance of the primary building blocks inside our suggested DNN architecture, we asked: How does the model perform in the presence and absence of important components? To answer this, we incrementally added key elements of the model (e.g., LRFC, self-prioritization (self-prt), neighbor-prioritization (neighbor-prt), etc.) and assessed performance using a variety of classification measures.

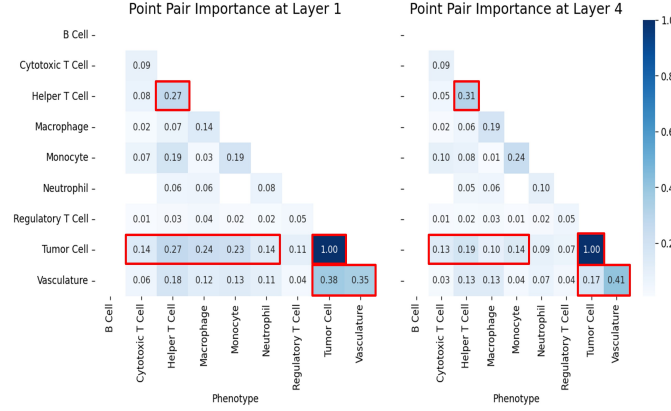
Results on selected classification metrics are presented in Table 4. The results show that using a prioritization sub-network is beneficial to filter out the exponential number of weak interactions caused by center points (e.g., center cells) and neighboring points (e.g., neighboring cells). In addition, it can be observed that the local reference frame characterization (LRFC) plays a critical role in representing relative distances and mixture distributions caused by neighboring points (e.g., cells), where LRFC combined with a prioritization sub-network (i.e., self or neighbor prioritization) provides better classification performance in most cases. This last result suggests that the proposed model performs best when local reference frame characterization layer is integrated with the point pair prioritization sub-network as a whole.

Impact of Prioritization Sub-network: The goal of this experiment was to demonstrate the interpretability of SAMCNet by measuring the impact of various point pair values (e.g., contribution between distinct cells) for distinguishing between point patterns of different classes (e.g., responder and non-responder). However, DNN architectures require non-linear activation functions for learning complex configurations, making ML models hard to interpret and this task challenging. To address this problem, we separated

³https://pytorch.org/tutorials/recipes/recipes/profiler_recipe.html

Table 4: Model performance based on different building blocks on all datasets.

Tumor-Margin classification					Tumor-Core classification					Disease classification				
Model	Precision	Recall	F1-Score	Acc	Model	Precision	Recall	F1-Score	Acc	Model	Precision	Recall	F1-Score	Acc
Only LRFC	0.64	0.61	0.6	0.61	Only LRFC	0.44	0.66	0.53	0.67	Only LRFC	0.66	0.66	0.66	0.66
Only self-prt	0.94	0.93	0.93	0.93	Only self-prt	0.83	0.81	0.81	0.81	Only self-prt	0.84	0.83	0.82	0.83
Neighbor-prt	0.86	0.86	0.85	0.86	Neighbor-prt	0.83	0.81	0.81	0.81	Neighbor-prt	0.83	0.83	0.83	0.83
LRFC+ self-prt	0.89	0.89	0.89	0.89	LRFC+ self-prt	0.87	0.86	0.86	0.86	LRFC+ self-prt	0.87	0.83	0.82	0.83
LRFC+ Neighbor-prt	0.93	0.93	0.93	0.93	LRFC+ Neighbor-prt	0.87	0.86	0.86	0.86	LRFC+ Neighbor-prt	0.9	0.89	0.88	0.89
self-prt + Neighbor-prt	0.86	0.82	0.81	0.82	self-prt + Neighbor-prt	0.85	0.81	0.78	0.81	self-prt + Neighbor-prt	0.87	0.86	0.86	0.86
Entire model	0.97	0.96	0.96	0.96	Entire model	0.96	0.95	0.95	0.95	Entire model	0.94	0.94	0.94	0.94

**Figure 5: The relative importance values between distinct cells that were learned through different layers of the point pair prioritization sub-network.**

the feature vector indicating the relevance of distinct point pairs from the pooling layer and non-linear activation functions. We transformed the feature vector from each distinct point pair to a scalar value $\widehat{pp}_i$ using a vector norm [14] to measure the magnitude (i.e., importance) of the learned associations. We divided each $\widehat{pp}_i$ by the maximum value found across all point pair scalars to further normalize them for a direct comparison.

The feature vectors were composed of distinct cell values extracted at layer-1 and layer-4 from the point pair prioritization sub-network, an indication of the ability of SAMCNet to learn hierarchical feature representations. These values represent a vector norm of $\vec{a}_{f_i f_j}^T$ in equation 5. Results are presented in Fig. 5, where it can be observed that the spatial interactions between points within the same category (e.g., {Tumor Cell, Tumor Cell}, {Vasculature, Vasculature}) remain critical across all layers. By contrast, the spatial interactions between distinct pairs (e.g., {Tumor Cell, Macrophage}) are adjusted through out the different prioritization layers, while still remaining relatively important in learning the N-way spatial relationships separating the two distinct classes (e.g., responder and non-responder) in the tumor-core. Note that we chose the tumor enriched areas of the lymph node (tumor-core) to interpret the proposed SAMCNet because tumor-core is primarily used in oncology analysis to determine the efficacy of ICI therapy by examining the various spatial interactions and variability between different cell species.

Most Relevant N-way Spatial Relationships: Thus far, we have demonstrated how the most distinctive point pairs are discovered;

Table 5: Most relevant spatial relationships

Rank	Center cell	Neighboring cells
1	[Macrophage]	[Macrophage, Neutrophil, Tumor Cell]
2	[Tumor Cell]	[Tumor Cell, Vasculature]
3	[Tumor Cell]	[Macrophage, Tumor Cell]
4	[Vasculature]	[Tumor Cell, Vasculature]
5	[Vasculature]	[Neutrophil, Tumor Cell, Vasculature]

but the main purpose of this work is to show SAMCNet’s ability to identify the most significant high-order spatial interactions. Hence, each sample point pattern was represented by extracting its corresponding feature vectors composed of all N-way spatial relationships (e.g., tertiary, ternary) with respect to its center and neighboring points (e.g., different cell categories). To be more precise, the trained SAMCNet was used to extract features after the point pair prioritization network at layer-4, where the model has learned both spatial and categorical associations. Thus, we have a feature vector $\vec{v} = \text{Mean}([k'' * f'])$ for each N-way spatial relationship, where each composed of an aggregation (e.g., mean) over k'' representing the distinct point categories located around the center point and f' representing the embedded feature space (e.g., 256). An example of a 3-way spatial association is having a tumor cell as a center cell (i.e., data point) and unique counts of macrophages and neutrophils as neighboring cells.

We evaluated the importance of the identified spatial relationships, namely, the SAMCNet representation for different category subsets, through permutation feature importance. This metric measures the importance of a given feature by the increase observed in the prediction error caused by randomly shuffling the feature space. The relevance of the discovered N-way spatial relationships was measured in this experiment by the classification accuracy after exchanging the corresponding elements in the representation vectors. The top five most relevant spatial associations found within the tumor-core are shown in Table 5.

6.3 Clinical Implications

While the pro-tumor (non-responder) relationship between tumor-associated macrophages and tumor-associated neutrophils has been studied in past works [6], its nature remains not entirely clear. Tumor-associated macrophages appear to play a protective role against antitumor immunotherapy, and the association of tumor-associated macrophages with tumor cells preferentially in patients who do not respond is consistent with established biology. However, added to this is the effect of tumor-associated neutrophils which also appear to promote tumor cell survival and lack of response to immunotherapy. The latter phenomenon is less well understood, with notable findings indicating that tumor-associated neutrophils are relevant to tumor progression but not necessarily to

immunotherapy resistance or a relationship with tumor-associated macrophages.

These findings suggest a previously unknown shared biology among these two populations of myeloid cells (macrophages and neutrophils) and provide new insight into the possibility of a relationship between tumor-associated macrophages and tumor-associated neutrophils as they engage tumor cells in the tumor core. This is an intriguing pattern that has not yet been studied. Future research is warranted to understand the relationships of macrophage, tumor cell, and neutrophil sub-populations in these interactions.

7 CONCLUSION AND FUTURE WORK.

In this paper, we propose SAMCNet, a neural network architecture with local reference frame characterization and a point pair prioritization sub-network. SAMCNet provides a promising way to help understand the spatial configuration of multi-category point patterns and most relevant N-way spatial relationships. Experimental evaluation shows that the proposed model outperforms existing DNN techniques.

In the future, we plan to investigate a dynamic local reference frame characterization layer to learn the spatial distribution of an embedded feature space between a given point and its neighbor. We also plan to identify a multi-category public benchmark dataset for a larger and broader evaluation of the proposed method. We plan to extend this work to consider spatial variability by learning point pair importance based on density and distribution of multi-category points in different sub-regions.

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A REPRODUCIBILITY

Code and Implementation Details: To promote open science and reproducibility, we made the code used in the experiments available through Github ⁴.

Patient privacy and the propriety nature of the data prevent us from publishing the dataset. A recent paper (AstroPath) highlighted a similar dataset used in the experiments on big data for cancer immunology and conducting spatially-preserved analysis [4]. This dataset may use to evaluate the capability of the proposed model. However, this dataset was not publicly available at the time of submission. A more detailed discussion on this can be found here: <https://ventures.jhu.edu/news/astronomy-pathology-biopath-biomarkers-cancer/>.

Table 6 presents the details of all parameters used to train SAMCNet.

Table 6: Details of the parameter settings in proposed model.

Parameters	Value
Epoch	200
Batch Size	7
Learning rate	0.001
momentum	0.9
num_points	1024
num_heads (prioritization head)	1
dropout	0.5
k (nearest neighbor)	6
emb_dims (shared fully-connected layer to aggregate multi-scale features)	1024
min_grid_scale	1
max_grid_scale	100
grid_scale_count	5

B ADDITIONAL EXPERIMENTS

We further evaluated our proposed model by varying key parameters, namely grid scale count, k-nearest neighborhood size, and prioritization head count.

As shown in Fig. 6a, the trends show that classification accuracy is sensitive to the choice of scale representation, where increasing grid-scale does not guarantee better performance. For example, the classification accuracy drastically dropped to lower than 0.75% in disease classification when the grid-scale count (i.e., s in equation 1) for a multi-scale representation was set to 10. While we did not thoroughly test all feasible grid-scale counts, our intuition is that representing the relative distance in an embedded space very close or even higher than the first multi-layer perceptron (i.e., first EdgeConv in layer-1); makes it challenging to approximate local information.

We tested our model with different sizes of k nearest neighborhoods. As shown in Fig. 6b, a large k neighbor size results decreases classification performance. Beyond a certain threshold density, the

locally connected neighborhood graph fails to approximate geodesic distance and destroys the geometry of each patch, as discussed in [29]. This confirms result the hypothesis that a large size of k allows an overpowering amount of weak point pair interactions contributing to the overall representation of the center node. Hence, as discussed in Section 5.3, one may investigate in a combination of different aggregation operations as the size of K increases.

Lastly, we also tested SAMCNet with a different number of heads, $H = \{1, 2, 4\}$, at each layer. As shown in Fig. 6c, our point pair convincingly learned point pair interactions between various categorical attributes. This implies that compared to a multi-head attention network, our one-head prioritization sub-network provides the best trade-off in model complexity, computational time complexity, and classification performance in terms of learning fewer parameters and taking less time.

C DNN ARCHITECTURES FOR POINT PATTERN CLASSIFICATION

The success of convolutional neural networks (CNNs) in many pattern recognition tasks (e.g., [5, 9]) has inspired researchers to generalize convolution-like operations to directly apply to 2D/3D point cloud data without any computationally expensive intermediate conversion layers. PointNet [21], the first neural network architecture that directly applies to point cloud data, learns point features independently through several fully connected neural network layers and aggregates them using an asymmetric function operation (e.g., Max pooling). PointNet++ [22], a variation of PointNet, accounts for the local structure by applying a graph coarsening operation and a shared PointNet recursively to a set of local points chosen by farthest point sampling and subsequently their k -nearest neighbors. However, these techniques are limited in learning fine-grained local structures since they largely treat points independently at a localized scale to preserve permutation invariance.

DGCNN [29] proposes a dynamic graph CNN that dynamically updates the graph network at each layer by learning both local and global information. This work is inspired by PointNet using a simple operation known as EdgeConv, where rather than independently applying to individual points, a locally connected neighborhood graph is constructed to exploit from both center nodes and edge features.

Many other efforts have been made to learn local structure. However, these approaches are not designed to learn spatial relationships in multi-categorical point sets. In addition, they do not fully exploit the spatial distribution of points beyond simply measuring relative distance or applying a discretization or feed-forward neural network to coordinates.

D BACKGROUND: SPATIAL CO-LOCATION MEASURES.

Cross-K Function: Spatial statistics [13] uses the cross-K function, a generalization of Ripley's K function, to detect spatial relationships between point patterns with more than one feature. The cross-K function $k(h)$ for binary spatial features is defined as $K_{ij}(h) = \lambda_j^{-1} E[\# \text{ type } j \text{ instances within distance } h \text{ of a randomly chosen type } i \text{ instance}]$, where i and j represents two category types, λ_j is the density of type j instances, h is the distance,

⁴https://github.com/majid-farhadloo/SAMCNet_2022

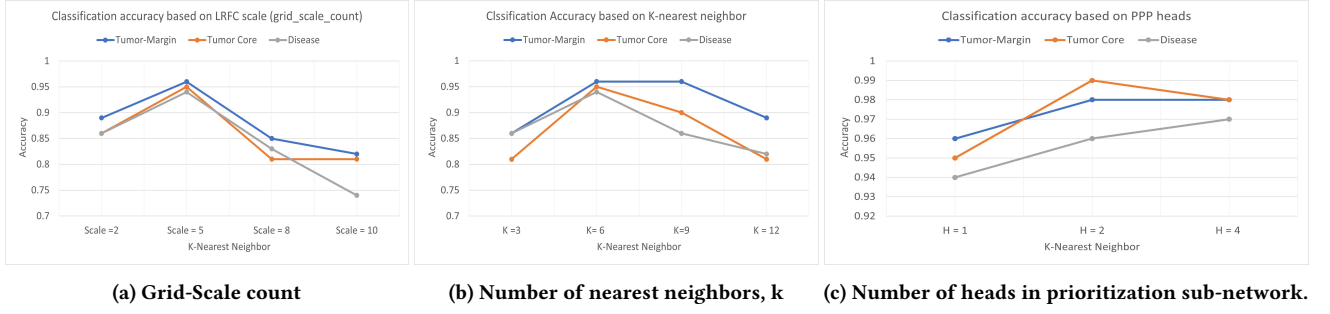


Figure 6: Key parameters evaluation.

and $E[\cdot]$ is the expectation. The cross-k function could be estimated in the form of $K_{ij}(h) = \frac{1}{\lambda_i \lambda_j W} \sum_k \sum_l I_h(d(i_k, j_l))$, where $d(i_k, j_l)$ is the distance between the i_k instance and the j_l instance, I_h is an indicator function, and W is the study area [25]. The value of cross-k is a function of neighborhood distance h , which implies the spatial relationship between categorical points at different scales.

Participation Index: The interest measure for co-location patterns most related to the cross-k function is the participation index. The participation index, an upper-bound approximation of the cross-K function, possesses an anti-monotone property that can be used for computational efficiency. The participation index is based on another interest measure, the participation ratio. The participation ratio $Pr(C, f_i)$ of feature f_i in a co-location pattern $C = \{f_1, \dots, f_K\}$, $1 \leq i \leq k$, is the fraction of spatial objects of feature f_i in the neighborhood of instances of co-location C . Thus, participation index $Pi(C)$ is defined as the minimum participation ratio of the features in a co-location pattern, that is $Pi(C) = \min_{f_i \in C} \{Pr(C, f_i)\}$.

The overall formulation of the participation ratio is as follows:

$$Pr(C, f_i) = \frac{\text{Number of distinct } f_i \text{ in instances of } C}{\text{Number of } f_i} \quad (8)$$

From this equation, it can be observed that the value of the participation index is between 0 and 1. A large $Pi(C)$ value shows that events of f_i tend to be located in close spatial proximity of

other events of features in C . We used the cross-k function and participation index to quantify the spatial relationship between categorical point sets. For example, given a point set containing points belonging to g categories and a set of neighborhood distance thresholds $H = \{h_1, \dots, h_s\}$ and $1 \leq i \leq s$, there will be $g(g-1) * s$ cross-k functions or participation index pairs.

E LRFC

Local reference frame characterization is proposed based on the following theorem whose proof is given in [10].

THEOREM E.1. Let $\Psi(x) = (e^{i\langle a_j, x \rangle}, j = 1, 2, 3)^T \in \mathbb{C}^3$ where $e^{i\theta} = \cos \theta + i \sin \theta$ and $\langle a_j, x \rangle$ is the inner product of a_j and x . $a_1, a_2, a_3 \in \mathbb{R}^2$ are 2D vectors such that the angle between each pair is $2\pi/3, \forall j, \|a_j\| = 2\sqrt{\alpha}$. Let $C \in \mathbb{C}^{3 \times 3}$ be a random complex matrix such as $C * C = I$. Then $\phi(x) = C\Psi(x)$, $M(\Delta x) = C \text{diag}(\Psi(\Delta x))C^*$ satisfies

$$\phi(x + \Delta x) = M(\Delta x)\phi(x) \quad (9)$$

and

$$\langle \phi(x + \Delta x), \phi(x) \rangle = d(1 - \alpha \|\Delta x\|^2) \quad (10)$$

where $\phi(x)$ is the representation of location x , $d = 3$ is the dimension of $\phi(x)$, and Δx is a small displacement from x .

$\Psi(x)$ is represented as a concatenation of the position embedding (PE) at S scales.