

Charting Cellular Networks in the Tumor Microenvironment: Graph Visualizations in Highly-Multiplexed Breast Cancer Tissue

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001 Abstract

002 The tumor microenvironment, composed of diverse
003 interacting cells, plays a pivotal role in cancer pro-
004 gression by influencing tumor growth, immune eva-
005 sion, and therapeutic outcomes. In this ongoing
006 work, we propose the use of interactive graph vi-
007 sualizations as a versatile tool for exploring and
008 analyzing biological data to unravel cell communi-
009 cation patterns in the tumor microenvironment and
010 identify graph representations of the multiplex data,
011 which can subsequently be leveraged by graph neu-
012 ral networks to contextualize cell interactions with
013 patient outcomes.

complex data, as well as visualization tools for data exploration and result interpretations are required.

In this ongoing work, we propose to use interactive graph visualization tools such as Gephi to qualitatively assess cell classification approaches which lack annotated ground truth labels and visualize cell communities in the TME to identify patterns of cell-cell interaction. Which can then be leveraged not only for visualization, but also for training Graph Neural Network (GNN), enabling the model to learn relationships in the graph. This integration bridges visualization with graph-based learning for more interpretable downstream analysis.

014 1 Introduction

015 Developments in immunotherapy have transformed
016 cancer treatment by activating a patient's immune
017 system to recognize and target cancer cells [1–3].
018 However, the variability in patient responses has
019 driven interest in understanding the underlying
020 mechanism of these therapies more deeply. The tu-
021 mor microenvironment (TME) plays a critical role
022 in cancer progression, as it consists of a number of
023 different cells which influence the tumor growth and
024 immune response, by e.g. allowing cancer cells to
025 evade immune detection or regulating their prolif-
026 eration rate [4–6]. To improve therapeutic outcomes
027 and identify cancer biomarkers that can be used for
028 early cancer detection, a better understanding of
029 the TME and its how cells communicate with each
030 other is essential.

031 Developments in spatial omics and imaging tech-
032 nologies enable spatial profiling of gene and protein
033 expression in tissue which allows for an unprece-
034 dented resolution of cells in terms of functional-
035 ity [7]. With the ability to measure a large number
036 of expressed proteins or genes per cell in the TME,
037 the complexity of this data grows rapidly, making
038 manual data inspection very challenging. There-
039 fore, computational tools for analyzing this highly

2 Related Work

Recent studies targeted to study cell interactions in tissue have exploited graph visualization tools. Karimi et al. used graph visualization tools for protein-protein interaction analysis in pancreatic Ductal adenocarcinoma [8]. So-called topological tumor graphs were derived from H&E stained whole slide images and combined with omic data to analyze melanoma histology in [9]. Cellular graphs were also proposed by Wang et al. to model the TME, alongside population graphs, capturing inter-patient similarities given their respective cellular graphs were proposed to study patterns in breast tumor microenvironments [10]. Protein interactions and networks were studied using graphs within the tumor in prostate cancer [11] and Rohail et al. proposed graph theoretical concepts to understand the TME of hematolymphoid cancer in H&E stained histological images [12].

3 Data

We analyze imaging mass cytometry (IMC) data, which detects up to 50 protein markers at subcellular resolution using metal-tagged antibodies and time-of-flight mass spectrometry. This dataset, derived from stained breast cancer tissue sections, provides spatially resolved, high-dimensional single-cell data to capture the phenotypic diversity of the TME.

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080 4 Methodology

081 Spatial analysis of IMC data typically involves cell
082 segmentation, using tools like Mesmer [13] for nu-
083 cleus and cell segmentation, followed by cell classi-
084 fication to identify recurring spatial patterns. Cell
085 classification remains challenging due to staining
086 variability, imaging differences, and limited anno-
087 tated ground truth data. Examples of such methods
088 are MAPS [14] and ASTIR [15], however different
089 marker panels targeted to study particular cell (sub-
090)types are not necessarily captured well or at all by
091 existing methods.

92 We apply a weighted Gaussian mixture model and
93 logical rules based on expected biomarker combina-
94 tions to achieve hierarchical cell type annotations
95 across four levels of granularity in breast cancer tis-
96 sue microarray images, with a focus on immune cells
97 and fibroblasts.

098 4.1 Graph Construction

99 We argue that interactive graph visualizations can
100 be useful in various ways.

101 I.) Classification Assessment

102 A bipartite graph can evaluate classification quality
103 by linking cell labels to expressed biomarkers, with
104 edges indicating biomarker expression in specific
105 cell types (figure 2). This visualization intuitively
106 reveals which biomarkers are associated with each
107 cell type, enabling an easily interpretable quality
108 check to ensure alignment with biological patterns
109 and highlighting potential classification issues.

110 II.) Cell Niche Detection

111 Cell niches can be visualized as a graph where nodes
112 represent cell types and edges indicate neighboring
113 cell types, capturing cell communities and their in-
114 teractions. This approach helps identify significant
115 communities in specific subpopulations or patient
116 groups for further statistical analysis.

III.) Protein Expression in Cell Niche Environments

119 By combining these approaches, we link cell-
120 biomarker bipartite graphs with cell neighborhood
121 data to map biomarkers to entire cell communities
122 This reveals unique biomarker expression patterns
123 within communities and their biological significance

IV.) Cell Subtype Discovery A graph of biomarkers, with edges indicating co-expression and thickness reflecting frequency, can reveal patterns that define cell subtypes (figure 1). Analyzing strongly connected clusters in this graph helps identify distinct cell subtypes.

130 5 Implementation

¹³¹ The graphs were made using the Python library
¹³² networkx [16] and the open-source software gephi

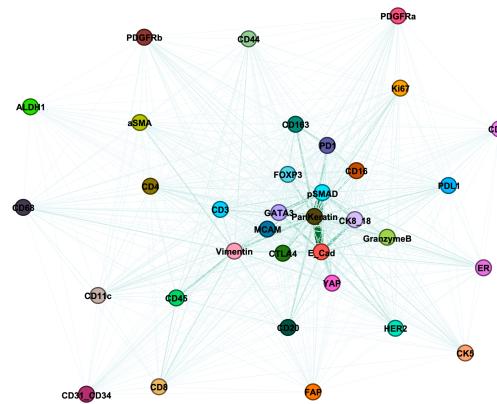


Figure 1. Co-occurrence graph of biomarkers. Edge thickness is proportional to co-occurrence frequency.

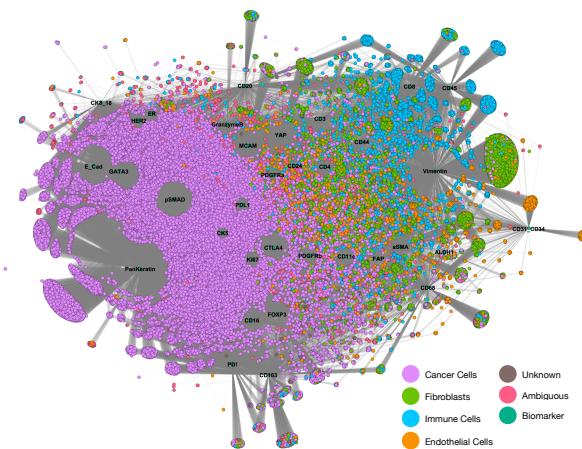


Figure 2. Bipartite graph of nodes; which represent either cells or biomarkers, with edges indicating the presence of a given biomarker within a cell.

[17]. The graphs are displayed following a *force atlas* layout, keeping the connected nodes closer and pushing away unconnected ones, highlighting existing clusters and communities in the graph. Defining the graphs with networkx enable the direct use of GNN implementations (such as Pytorch-Geometric), streamlining further analysis.

Gephi makes it easy to share visualizations through web pages or Gephi files, requires no Python expertise, and supports interactive exploration, making it ideal for interdisciplinary groups.

6 Conclusions

Interactive graph visualizations simplify complex biological data, revealing cell interactions and biomarker patterns in the tumor microenvironment. Combined with tools like Gephi and graph neural networks, they enable deeper insights and connections to patient outcomes.

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