1. Post-hoc explainers

In this section, we present the details of the considered graph explainability techniques (explainers) in this work: GRAPHLRP (Section 1.2), GRAPHGRAD-CAM (Section 1.3), GRAPHGRAD-CAM++ (Section 1.4), GNNEXPLAINER (Section 1.5), and RANDOM (Section 1.6).

1.1. Notation

We define an attributed undirected entity graph \( G := (V, E, H) \) as a set of nodes \( V \), edges \( E \), and node attributes \( H \in \mathbb{R}^{\mid V \times d} \). \( d \) denotes the number of attributes per node, and \( \mid \cdot \mid \) denotes set cardinality. We denote an edge between nodes \( u \) and \( v \) as \( e_{uv} \in E \). The graph topology is defined by a symmetric graph adjacency, \( A \in \mathbb{R}^{\mid V \times \mid V} \), where \( A_{uv} = 1 \) if \( e_{uv} \in E \). \( H_{n,k} \) expresses the k-th attribute of the n-th node. The forward prediction of a cell-graph \( G_{CG} \) is denoted as, \( y = \mathcal{M}(G_{CG}) \), where \( \mathcal{M} \) is a pre-trained GNN, and \( y \in \mathbb{R}^{\mid T} \) are the output logits. Notation \( y(t) \) if \( t \in T \) denotes the output logit of the t-th class. We refer to the logit of the predicted class as \( y_{\text{max}} = \max_{t \in T} y(t) \), and the predicted class as \( t_{\text{max}} = \text{argmax}_{t \in T} y(t) \).

1.2. Layerwise relevance propagation: GRAPHLRP

Layerwise Relevance Propagation (LRP) [1] is a feature attribution based post-hoc explainer. LRP explains an output logit by determining the individual contribution of each input element to the logit value. An output logit, defined as the output relevance for a given class, is layerwise back-propagated until the input to compute the positive or negative impact of the input elements on the output logit. LRP, initially proposed for fully connected layers (LRP-FC), works as follows. Given a pre-trained fully connected layer \( W \in \mathbb{R}^{z_1 \times z_2} \) between layer 1 and layer 2, where \( z_1 \) and \( z_2 \) are the number of neurons in layer 1 and layer 2, respectively, we compute the contributions of a neuron \( i, i \in \{1,...,z_1\} \) using the propagation rules in [6]. In this work, we are interested in identifying the input elements positively contributing to the prediction. To this end, we use the \( z^+ \) propagation rule that back-propagates the positive neuron contribution from layer 2 to layer 1 as:

\[
R_t = \sum_{j}^{z_2} \frac{f_l[w_{ij}]}{\sum_{k}^{z_1} f_k|w_{kj}|} R_j \quad \text{(LRP-FC)}
\]

where \( |w_{ij}| \) is the absolute value of the weight between i-th and j-th neuron in layer 1 and 2, respectively. \( f_i \) denotes the activation of the i-th neuron in layer l.

The extension from LRP-FC to LRP for graph isomorphism network (GIN) layers (GRAPHLRP) is achieved by following the observations in [8]. First, the aggregate step in GNN corresponds to projecting the graph’s adjacency matrix on the node attribute space. For simplicity, assuming a 1-layer MLP as an update function, the GIN layer with mean aggregator can be re-written in its global form as:

\[
H^{(l+1)} = \sigma \left( W^{(l)} (I + \tilde{A}) H^{(l)} \right) \quad (1)
\]

where \( \tilde{A} \) is the degree-normalized graph adjacency matrix, i.e. \( \tilde{A}_{ij} = \frac{1}{\mid N(i) \mid} A_{ij} \). \( \sigma \) is the ReLU activation function. Second, this representation allows us to treat the term \((I + \tilde{A})\) as a regular, fully connected layer. We can then apply the \( z^+ \) propagation rule with weights \( w_{ij} \) defined as:

\[
\begin{align*}
    w_{ij} &= 1 \quad \text{if } i = j \quad (2) \\
    w_{ij} &= \frac{1}{\mid N(i) \mid} \quad \text{if } e_{ij} \in E \quad (3) \\
    w_{ij} &= 0 \quad \text{otherwise} \quad (4)
\end{align*}
\]

LRP outputs an importance score for each node i in the input graph.
1.3. Saliency-based: GRAPHGRAD-CAM

Grad-CAM [9] is a feature attribution post-hoc explainer that identifies salient regions of the input driving the neural network prediction. It assigns importance to each element of the input to produce Class Activation Map [11]. While originally developed for explaining CNNs operating on images, GRAD-CAM can be extended to GNNs operating on graphs [7].

GRAPHGRAD-CAM processes in two steps. First, it assigns an importance score to each channel of a graph convolutional layer. The importance of channel $k$ in layer $l$ is computed by looking at the gradient of the predicted output $\logit y$ w.r.t. the node attributes at layer $l$ of the GNN. Formally it is expressed as:

$$w_k^{(l)} = \frac{1}{|V|} \sum_{n=1}^{|V|} \frac{\partial y_{\text{max}}}{\partial H_{n,k}^{(l)}}$$  \hspace{1cm} (5)

In the second step, a node-wise importance score is computed using the forward node feature activations $H^{(l)}$ as:

$$L(l, v) = \text{ReLU}\left(\sum_k d^{(l)} w_k^{(l)} H_{n,k}^{(l)}\right) \quad \text{(GRAPHGRAD-CAM)}$$

where $L(l, v)$ denotes the importance of node $v \in V$ in layer $l$, and $d^{(l)}$ denotes the number of node attributes at layer $l$. Since we are only interested in the positive node contributions, i.e. nodes that positively influence the class prediction, we apply a ReLU activation to the node importances. Following prior work [7], we take the average node importance scores obtained over all the GNN layers $l \in \{1, ..., L\}$ to obtain smoother node importance scores.

1.4. Saliency-based: GRAPHGRAD-CAM++

GRAPHGRAD-CAM++ extends GRAD-CAM++ [2] to graph structured data. It improves the node importance localization by introducing node-wise contributions to channel importance scoring in Equation 5. Specifically, the modification is presented as:

$$w_k^{(l)} = \frac{1}{|V|} \sum_{n=1}^{|V|} \alpha_{n,k}^{(l)} \frac{\partial y_{\text{max}}}{\partial H_{n,k}^{(l)}}$$  \hspace{1cm} (6)

where $\alpha_{n,k}^{(l)}$ are node-wise weights expressed for each attribute $k$ at layer $l$. The derivation of a closed-form solution for $\alpha_{n,k}^{(l)}$ is analogous to the derivation in [2], where the size of graph, i.e. number of nodes, replaces the spatial dimensions of a channel as:

$$\alpha_{n,k}^{(l)} = \frac{\frac{\partial^2 y_{\text{max}}}{\partial H_{n,k}^{(l)}}}{2 \frac{\partial^2 y_{\text{max}}}{\partial H_{n,k}^{(l)^2}}} + \sum_{n=1}^{|V|} H_{n,k}^{(l)} \left(\frac{\partial^3 y_{\text{max}}}{\partial H_{n,k}^{(l)^3}}\right)$$  \hspace{1cm} (7)

The subsequent node importance computation in GRAPHGRAD-CAM++ is same as GRAPHGRAD-CAM.

1.5. Graph pruning: GNNEXPLAINER

The GNNEXPLAINER [10, 5] is a graph pruning based post-hoc explainer for explaining GNNs. GNNEXPLAINER is model-agnostic, i.e. it can be used with any flavor of GNN. Intuitively, GNNEXPLAINER tries to find the minimum sub-graph $G_s \subset G$ such that the model prediction $y = \mathcal{M}(G)$ is retained. The inferred sub-graph $G_s$ is then regarded as the explanation for $G$. This approach can be seen as a feature attribution method with binarized node importance scores, i.e. a node $v \in V$ has importance one if $v \in V_s$, and zero otherwise. Exhaustively searching $G_s$ in the space created by nodes $V$ and edges $E$ is infeasible due to the combinatorial nature of the task. Instead, GNNEXPLAINER formulates the task as an optimization problem that learns a mask to activate or deactivate parts of the graph. The initial formulation by [10], developed for explaining node classification tasks, learns a mask over the edges, i.e. over the adjacency matrix. Instead, we follow the prior work in [5] to learn a mask over the nodes. Indeed, as we are concerned with classifying $G$, the optimal explanation $G_s$ can be a disconnected graph. Furthermore, in cell graphs, the nodes representing biological entities are more intuitive and substantial for disease diagnosis than edges, that are heuristically-defined.

Formally, we seek to learn a mask $M_V$ such that the induced masked sub-graph $G_s$, (1) is as small as possible, (2) outputs a binary node importance, and (3) provides the same prediction as the original graph. These constraints can be modeled by considering a loss function as:

$$\mathcal{L} = \mathcal{L}_{\text{KD}}(\hat{y}, y^{(m)}) + \alpha_{M_V} \sum_{i} \sigma(M_{V_i}^{(m)}) + \alpha_{\mathcal{H}} \mathcal{H}^c(\sigma(M_{V}^{(m)}))$$  \hspace{1cm} (8)

where, $m$ is the optimization step and $\sigma$ is the sigmoid activation function. The first term is a knowledge-distillation loss $\mathcal{L}_{\text{KD}}$ between $\hat{y} = \mathcal{M}(G)$ and $y^{(m)} = \mathcal{M}(G_s)$ ensuring that $y^{(m)} \approx \hat{y}$. The second term aims to minimize the size of the mask $M_V$. The third term binarizes the mask by minimizing the element-wise entropy $\mathcal{H}^c$ of $M_V$. Following previous work [4], $\mathcal{L}_{\text{KD}}$ is built as a combination of distillation and cross-entropy loss,

$$\mathcal{L}_{\text{KD}} = \lambda \mathcal{L}_{\text{CE}} + (1 - \lambda) \mathcal{L}_{\text{dist}}$$

where $\lambda$ is empirically weighed such that their contributions to $\mathcal{L}$
are comparable. We set $\alpha_{M_V} = 0.005$ and $\alpha_{H} = 0.1$. We learn $M_V$ using Adam optimizer with a learning rate of 0.01. $\mathcal{L}$ is optimized for 1000 steps with an early stopping mechanism, which triggers if the class prediction using $G_s$ is changed. Therefore, $G_s$ and $G$ always predict the same class, i.e., $\hat{t}_m = \hat{t}_m \forall m$.

1.6. Random selection: RANDOM

The RANDOM baseline is implemented using a random nuclei selection. The number of selected nuclei per RoI is given by the threshold value $k \in \mathcal{K}$.

2. BRACS dataset

In this paper, the BRACS dataset is used to analyze CG explainability for breast cancer subtyping. The pixel-level and entity-level statistics of the dataset are presented in Table 1. Training, validation, and test splits are created at the RoI level for conducting the experiments. The details of the class-wise distribution of images in each split are presented in Table 1.

3. Concepts and Attributes

In this paper, we focus on pathologically-understandable nuclear concepts $\mathcal{C}$ pertaining to nuclear morphology for breast cancer subtyping. To quantify each $c \in \mathcal{C}$, we use several measurable attributes $\mathcal{A}_c$. Table 2 presents the list of concepts and corresponding attributes used to perform the proposed quantitative analysis in this work. Also, Table 2 includes the class-wise expected criteria for each concept.

The attributes of the nuclei in a RoI are computed as presented in Table 2. It uses the RoI and corresponding nuclei segmentation map, denoted as $I_{seg}$. Area of a nucleus $x$, denoted as $A(x)$, is defined as the number of pixels belonging to $x$ in $I_{seg}$. $P(x)$, the perimeter of $x$, is measured as the contour length of $x$ in $I_{seg}$. $P_{\text{ConvHull}}(x)$, the convex hull perimeter of $x$, is defined as the contour length of convex hull induced by $x$ in $I_{seg}$. The major and minor axis of $x$, noted as $a_{\text{major}}(x)$ and $a_{\text{minor}}(x)$, are the longest diameter of $x$ and the longest line segment perpendicular to $a_{\text{major}}(x)$, respectively. The chromatin attributes are computed from the normalized gray level co-occurrence matrix (GLCM) [3], which captures the probability distribution of co-occurring gray values in $x$.

4. Quantitative assessment

In this section, we analyze two key components of the proposed quantitative metrics: the histogram construction and class separability scores for threshold set $\mathcal{K}$. Furthermore, we relate the analysis to the class-wise expected criteria for each concept presented in Table 2.

4.1. Histogram analysis

Histogram construction is a key component in the proposed quantitative metrics. Figure 1 presents per-class histograms for each explainer and the best attribute per concept. We set the importance threshold to $k = 25$, i.e., for each RoI, we select 25 nuclei with the highest node importance. The best attribute for a concept is the one with the highest average pair-wise class separability.

The row-wise observation exhibits that GNNEXPLAINER and GRAPHLRP provide, respectively, the maximum and the minimum pair-wise class separability. The histograms for a concept and for an explainer can be analyzed to assess the agreement between the selected important nuclei concept, and the expected concept behavior as presented in Table 2, for all the classes. For instance, nuclear area is expected to be higher for malignant RoIs than benign ones. The area histograms for GNNEXPLAINER, GRAPHGRAD-CAM and GRAPHGRAD-CAM++ indicate that the important nuclei set in malignant RoIs includes nuclei with higher area compared to benign RoIs. Similarly, the important nuclei in malignant RoIs are expected to be vesicular, i.e., high texture entropy, compared to light euchromatic, i.e., moderate texture entropy, in benign RoIs. The chromaticity histograms for GNNEXPLAINER, GRAPHGRAD-CAM and GRAPHGRAD-CAM++ display this behavior. Additionally, the histogram analysis can reveal the important concepts and important attributes. For instance, nuclear density proves to be the least important concept for differentiating the classes.

4.2. Separability score for threshold set $\mathcal{K}$

Multiple importance thresholds $\mathcal{K}$ are required to address the varying notion of important nuclei across different cell graphs and different explainers. Figure 2 presents the behavior of pair-wise class separability for using various $k \in \mathcal{K} = \{5, 10, ..., 50\}$. For simplicity, we present the behavior for the best attribute per concept. In general, the pair-wise class separability is observed to decrease with decreasing $k$. Intuitively, decreasing $k$ results in including more unimportant nuclei into the evaluation, thereby gradually decreasing the class separability.

The degree of agreement between the difference in the expected behavior per concept and the pair-wise class separability in Figure 2, for all pair-wise classifications and various $k \in \mathcal{K}$ can be used to assess the explainer’s quality. For instance, according to Table 2, the difference in the expected nuclear size can be considered as benign–atypical < benign–malignant, and atypical–malignant < benign–malignant. GNNEXPLAINER, GRAPHGRAD-CAM and GRAPHGRAD-CAM++ display these behaviors $\forall k \in \mathcal{K}$. GNNEXPLAINER provides the highest class separability in each pair-wise classification, thus proving to be the best ex-
| Metric                  | Benign   | Atypical | Malignant | Total   |
|------------------------|----------|----------|-----------|---------|
| Number of images       | 1741     | 1351     | 1299      | 4391    |
| Number of pixels (in million) | 3.9±3.54 | 1.62±1.48 | 6.35±5.2  | 3.9±4.3 |
| Max/Min pixel ratio    | 180.1    | 75.3     | 128.6     | 235.6   |

| CG                     |          |          |           |         |
| Number of nodes        | 1331±1134| 635±510  | 2521±1934 | 1468±1642|
| Number of edges        | 4674±4131| 2309±2110| 8591±7646 | 5102±6089|
| Max/Min node ratio     | 312.5    | 128.6    | 2521±1934 | 434.8   |

| Image split           |          |          |           |         |
| Train                 | 1231     | 1008     | 928       | 3163    |
| Validation            | 261      | 162      | 179       | 602     |
| Test                  | 249      | 185      | 192       | 626     |

Table 1. Statistics of BRACS dataset.

| Concept (C) | Attribute (.A) | Computation | Benign | Atypical | Malignant |
|-------------|----------------|-------------|--------|----------|-----------|
| Size        | Area           | $P(x)$      | Small  | Small-Medium | Medium-Large |
|             | Perimeter      | $\frac{P_{\text{C}}(x)}{P(x)}$ | Smooth | Mild irregular | Irregular |
|             | Roughness      | $\frac{a_{\text{min}}(x)}{a_{\text{maj}}(x)}$ |                |            |           |
|             | Circularity    | $\frac{4\pi A(x)}{P(x)^2}$ |                |            |           |
| Shape variation | Shape factor | $\frac{4\pi A(x)}{P_{\text{C}}(x)}$ | Monomorphic | Monomorphic | Pleomorphic |
| Spacing     | Mean spacing   | $\text{mean}(d_y | y \in \text{kNN}(x))$ | Evenly crowded | Evenly spaced | Variable |
|             | Std spacing    | $\text{std}(d_y | y \in \text{kNN}(x))$ |                |            |           |
| Chromatin   | GLCM dissimilarity | $\sum_i \sum_j | i - j|p(i,j)$ |               |           |           |
|             | GLCM contrast  | $\sum_i \sum_j (i - j)^2 p(i,j)$ |               | Hyperchromatic | Vesicular |
|             | GLCM homogeneity | $\sum_i \sum_j p(i,j)^2$ | Light euchromatic | Hyperchromatic | Vesicular |
|             | GLCM ASM       | $\sum_i \sum_j p(i,j)^2$ |               |           |           |
|             | GLCM entropy   | $-\sum_i \sum_j p(i,j) \log(p(i,j))$ |               |           |           |
|             | GLCM variance  | $\sum_i \sum_j (i - \mu_i)^2 p(i,j)$ with $\mu_i = \sum_i \sum_j \mu p(i,j)$ |               |           |           |

Table 2. Pathologically-understandable nuclear concepts, corresponding measurable attributes, and computations are shown in Columns 1, 2, 3, respectively. The expected concept behavior for three breast cancer subtypes is shown in Columns 4, 5, 6, respectively.

5. Qualitative assessment

Figure 3 and Figure 4 present CG explanations produced by GNNEXPLAINER, GRAPGrad-CAM, GRAPGrad-CAM++ and GRAPHLRP for RoIs across benign, atypical and malignant breast tumors. It can be observed that GNNEXPLAINER learns to binarize the explanations, thereby producing the most compact explanations by retaining the most important nuclei set of nuclei with high importance. However, GRAPHGrad-CAM and GRAPGrad-CAM++ produce explanations with more distributed nuclei importance than GNNEXPLAINER.
GRAPHLRP produces the largest explanations by retaining most of the nuclei in the CGs.

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Figure 1. Per-class histograms for different concepts across different graph explainers. For simplicity, histograms are presented for the best attribute per concept at fixed importance threshold $k = 25$. 
Figure 2. Visualizing the variation of pair-wise class separability score (Y-axis) w.r.t. various nuclei importance thresholds in $K$ (X-axis). The analysis is provided for different graph explainers, and for the best attribute per concept.
Figure 3. Qualitative results. The rows represent breast cancer subtypes, and columns represent graph explainers, i.e. GNNEXPLAINER, GRAPHGRAD-CAM, GRAPHGRAD-CAM++, and GRAPHLRP. Nuclei level importance ranges from blue (the least important) to red (the highest important).
Figure 4. Qualitative results. The rows represent breast cancer subtypes, and columns represent graph explainers, i.e., GNNEXPLAINER, GRAPHGRAD-CAM, GRAPHGRAD-CAM++, and GRAPHLRP. Nuclei level importance ranges from blue (the least important) to red (the highest important).