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A UNIFIED DEEP LEARNING PIPELINE FOR PLACENTAL MORPHOMETRIC AND PHENOTYPIC MAPPING IN GESTATIONAL DIABETES

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ABSTRACT

This study investigated morphometric differences in placentas from gestational diabetes mellitus (GDM) pregnancies by integrating deep learning with quantitative statistical analysis. Whole slide images (WSIs) of placentas from four pathological groups: small-for-gestational-age (SGA), appropriate-for-gestational-age (AGA), large-for-gestational-age (LGA), and non-GDM pregnancies were analyzed to evaluate cell type distributions, morphology, and connectivity. A state-of-the-art benchmark model was used for comparison. This pipeline produced plausible cell maps and revealed significant cell-type-specific differences across groups. SGA placentas showed reduced vascular myocyte connectivity, and AGA placentas maintained robust cellular interactions. LGA and non-GDM placentas showed intermediate or compensatory remodeling patterns. These results highlight the potential of morphometric analysis as a biomarker discovery tool for placental dysfunction and suggest that deep learning-based cellular mapping can provide clinically relevant insights into pregnancy outcomes.

Index Terms—deep learning, biomedical imaging, placenta, gestational diabetes, morphometric analysis, whole-slide imaging

1. INTRODUCTION

Gestational diabetes mellitus (GDM) is a common pregnancy complication (about 5–10% of pregnancies) associated with adverse maternal and fetal outcomes. One of its effects is altered placental morphology [16], which can disrupt nutrient and oxygen exchange and thereby impact fetal growth and pregnancy outcomes. Quantitative characterization of these morphological changes is critical for understanding the mechanisms of placental dysfunction and for identifying potential biomarkers.

Histopathological analysis [18] of placental tissue provides an opportunity to examine cell type distributions, morphology, and interactions at cellular level. Traditional studies have relied on manual or semi-automated assessments, which are labor-intensive and time-consuming to observer variability. Recent advances in deep learning (DL) [20] have enabled more accurate and scalable cellular

analysis in WSIs. The HAPPY study established an important reference framework for placenta cell classification.

This study presents an integrated pipeline that combines DL-based cell classification with statistical morphometry for comprehensive analysis of placental tissue. And this study aims to compare the proposed approach with the HAPPY’s model for classification performance and investigate morphometric differences across pregnancies complicated by GDM with SGA, AGA, LGA, and non-GDM. The results of this study reveal biologically plausible spatial distributions and group-specific alterations in cell type connectivity, highlighting the potential of morphometric analysis as a tool for uncovering biomarkers of placental dysfunction.

2. METHODS

2.1. Data preparation

The primary dataset consisted of WSIs from placental tissues collected by School of Medicine, University of Leeds from GDM and Non-GDM patients and divided by fetal growth outcome: SGA (9 patients), AGA (8), LGA (8) and Non-GDM (7) for control. All samples were hematoxylin and eosin (H&E) stained and divided into non-overlapping tiles of 2048×2048 pixels to enable efficient processing.

To support training, the CoNSeP dataset [1] with annotated colorectal nuclei was used for segmentation, and the HAPPY dataset [2] which includes manual annotations of 11 distinct placental cell types: leukocytes (WBC), vascular myocytes (VMY), vascular endothelial cells (VEN), syncytiotrophoblast (SYN), mesenchymal stromal cells (MES), maternal decidua (MAT), syncytial knots (KNT), Hofbauer cells (HOF), fibroblasts (FIB), extra villous trophoblasts (EVT), and cytotrophoblasts (CYT). This dataset enabled supervised training of the classification network and provided a standardized reference for benchmarking.

The overall pipeline (Fig. 1) for cell classification and morphometric analysis is illustrated in Fig. 1 and consists of four main stages: (i) image tiling and villous/non-villous classification, (ii) nuclei segmentation and cell classification,

(iii) morphometric extraction and statistical testing, and (iv) connectivity analysis and biomarker identification.

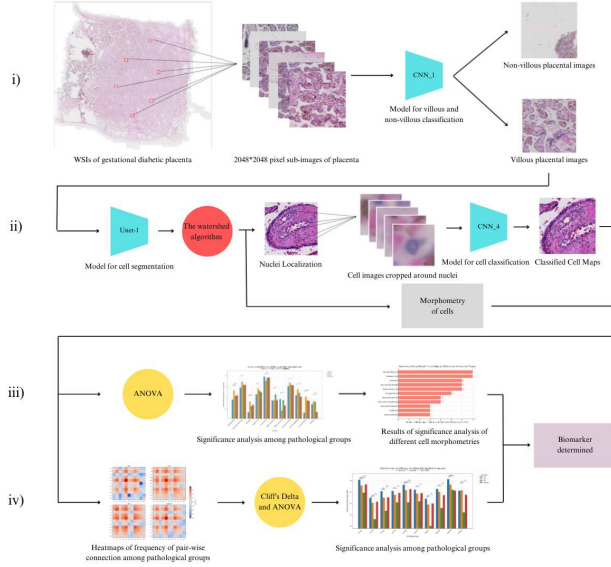


Fig. 1. Workflow of the study. Starting by filtering villous placental images out of extracted sub-images from WSIs of placentas, then using a U-net models and watershed algorithm for nuclei localization, morphometrics extraction and cell maps generation, ending in biomarker identification by statistical analysis.

2.2. Images classification (villous vs. non-villous)

From each WSI, 500 sub-images were randomly sampled and annotated as villous or non-villous. Images were resized to 256×256 pixels and split into training (60%), validation (25%), and test (15%) sets. Standard augmentation (rotation, flipping, zooming, brightness/color adjustment) was applied using the *Augmentor* library, with each training/validation image augmented tenfold.

2.3. Cell segmentation and classification

For nuclei segmentation, a U-Net model [4] was trained on the CoNSeP dataset with augmentation (random cropping, flips, rotations, color jittering) to improve robustness. A watershed algorithm [3] was applied for separating touching nuclei.

For cell classification, the HAPPY dataset was balanced by undersampling abundant classes and augmenting underrepresented ones through noise injection, rotation, flipping, and zooming, yielding 1500 training and 300 validation samples per class. Images were resized to 200×200 pixels. A CNN with four convolutional blocks, global average pooling, and a SoftMax output was trained with Adam [5] and categorical cross-entropy. This pipeline produced fully labeled cell maps across villous tissue.

2.3. Morphometric analysis

From the labeled cell maps, morphometric features were extracted by using function Region Properties (Regionprops) in the scikit-image Python package [8] for each cell type,

including area, perimeter, solidity (area/convex hull area), aspect ratio (major/minor axis length), and frequency. One-way analysis of variance (ANOVA) with Tukey's HSD [9] was applied to test for group-level differences with $p = 0.05$.

2.4. Connectivity analysis

Pairwise connections heatmaps were generated to capture cell-type connectivity patterns across pathological groups. Effect sizes of pairwise connections were measured with Cliff's delta [10] and then connections with high-level effect sizes were performed using ANOVA to identify specific group differences to determine significant alterations.

3. RESULTS

3.1. Classification accuracy for villous images

The model's performance was assessed by evaluating approaches on unseen test sets, such as the confusion matrix and the built-in prediction function in Keras. The evaluation results of the model for classifying villous and non-villous images indicated that the model accurately identified all 41 non-villous images, achieving a 100% accuracy rate for this category. The model correctly predicted 33 out of 34 images for villous images, resulting in only one misclassification. Overall, the accuracy of predictions on the unseen test set reached 98.67%.

3.2. Cell segmentation

The model for cell segmentation allowed the generation of segmented cell maps with 3 channels from placental images and then using the watershed algorithm [3] to delineate individual cells in dense placental tissue samples. Nuclei were detected based on the segmented cell map; a cell map was to be generated by predicting cell classes on cell images cropped around the nuclei using the model for cell classification. This method can automatically annotate different cells in the placental images and focus on cellular studies.

3.3. Classification accuracy for cells vs. benchmark

This study evaluated performance on 2743 cells across 11 types. The confusion matrix (Fig. 2) revealed high accuracy for several categories, including KNT (93.8%), WBC (94.1%), MAT (88.6%), and EVT (88.2%). However, misclassifications were notable in HOF (57.8%), FIB (67.0%), and CYT (65.8%). For example, FIB often overlapped with VMY and VEN, while CYT was frequently misclassified as SYN. Other classes, such as VMY (79.4%), VEN (85.7%), SYN (81.9%), and MES (80.9%), showed relatively strong performance. Overall classification accuracy was 80.1%.

A comparison with the HAPPY benchmark [2] (Fig. 3) highlighted differences in class balance. The proposed model performed reliably for abundant cell types (SYN, VMY, WBC) but showed higher confusion among morphologically similar cells. In contrast, HAPPY achieved more consistent precision across FIB, VEN, and CYT. Both models struggled with HOF and MES, reflecting annotation challenges and visual overlap in H&E slides.

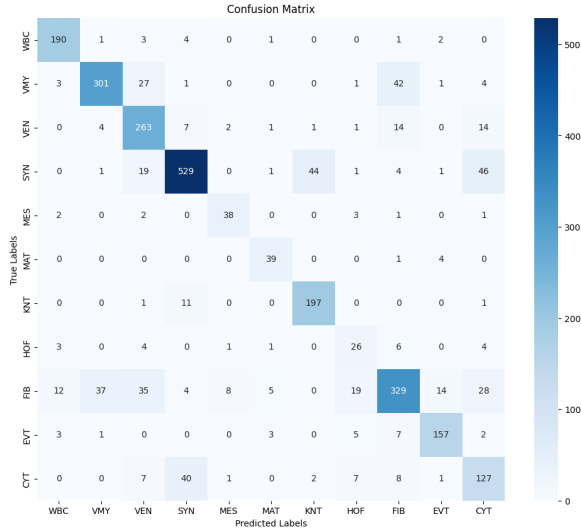


Fig. 2. Confusion matrix of the proposed model across 11 placental cell types.

In addition to quantitative evaluation, visual inspection of the generated cell maps provides further insight into differences between the models.

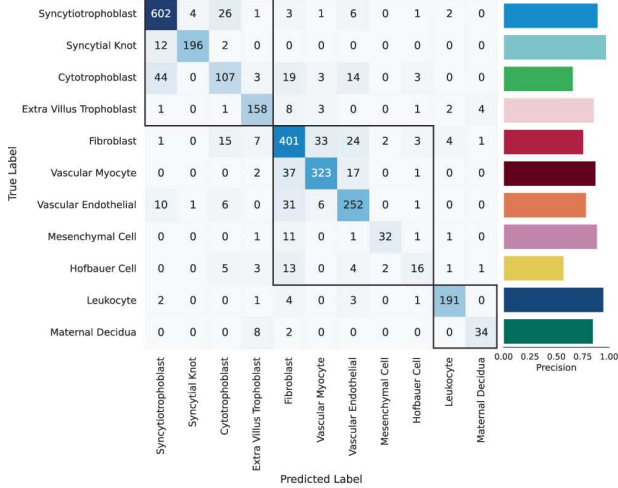


Fig. 3. Confusion matrix of the HAPPY benchmark model (Vanea et al., 2024).

As shown in Fig. 4, both models placed SYN (blue) and KNT (pink) along the villous borders, consistent with placental structure. However, the HAPPY benchmark (b) produced a much denser accumulation of these cell types, leading to crowding along the border. In contrast, the proposed model (a) yielded a sparser and more evenly distributed pattern, which more closely resembles the expected histological organization. These differences suggest that, while HAPPY emphasizes boundary coverage, the proposed approach captures a more biologically realistic balance of cell localization.

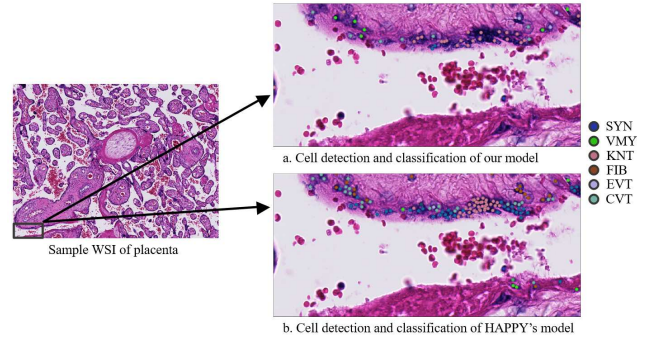


Fig. 4. Comparison of cell detection, where both models localized SYN (blue) and KNT (pink) to the border, but the HAPPY benchmark showed denser accumulation than the proposed model's sparser, balanced distribution.

3.4. Morphometric analysis

To identify cell-type-specific morphological signatures across placental pathologies, we compared eight attributes (frequency, area, perimeter, extent, solidity, major axis length, minor axis length, aspect ratio) among SGA, AGA, LGA, and non-GDM groups using one-way ANOVA with Tukey's HSD ($p \leq 0.05$).

SGA placentas consistently showed significant divergence from other groups, particularly in trophoblasts, stromal cells, and vascular populations. For example, cytotrophoblasts (CYT) displayed significant frequency differences across all group comparisons, and vascular myocytes (VMY) exhibited broad alterations in area, perimeter, solidity, and axis lengths ($p < 0.01$). Hofbauer cells (HOF), syncytial knots (KNT), and maternal decidua (MAT) also showed reductions in size-related features, especially in SGA vs. AGA or non-GDM. Structural compactness (solidity, extent) was disrupted in EVT, HOF, and VMY, while aspect ratio changes indicated altered elongation in HOF, EVT, and VMY.

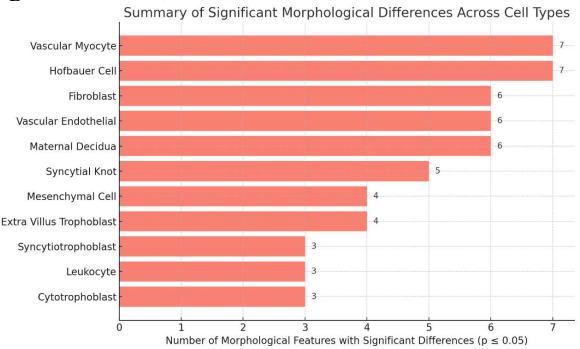


Fig. 5. Summary of significant morphological differences across cell types among four pathological groups.

Overall, Fig. 5 summarizes the extent of remodeling across cell types. HOF and VMY emerged as the most responsive populations, with significant alterations in seven features, suggesting their potential as sensitive biomarkers

of pathological insult. MAT, VEN, and FIB also showed consistent changes, while CYT, SYN, and WBC were less affected. These results highlight distinct remodeling signatures in SGA placentas, supporting the diagnostic utility of quantitative morphometry.

3.5. Connectivity Analysis

As placental cells function in networks, this study examined cell-cell connectivity across the four groups. Heatmaps of interaction frequencies (Fig. 6) and Cliff's delta were computed on the interactions across 4 groups. The top altered interactions included CYT-FIB, FIB-VMY, VMY-VMY, CYT-VMY etc., with several reaching strong effect sizes ($|\delta| > 0.7$).

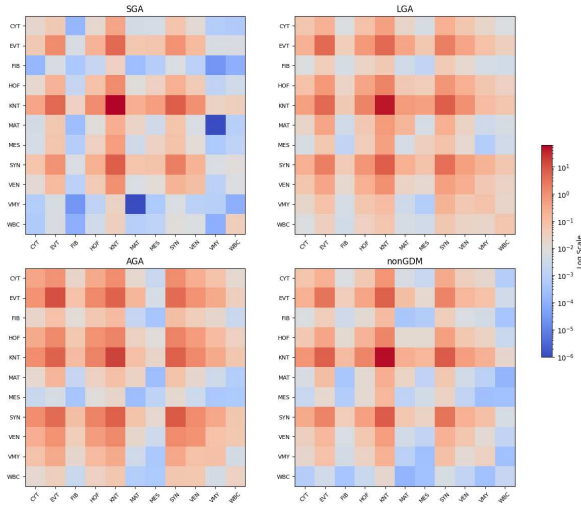


Fig. 6. Heatmaps of frequency of cell connections across pathologies in a logarithmic scale

ANOVA with Tukey's HSD confirmed significant group-level differences ($p \leq 0.05$) across these key pairs. As summarized in Fig. 7, AGA placentas exhibited the highest interaction frequencies, reflecting preserved architecture, while SGA showed marked reductions, particularly in trophoblast-stromal-vascular interfaces. LGA and non-GDM placentas displayed intermediate or partially compensatory patterns, with non-GDM showing elevated EVT-FIB and stromal interactions.

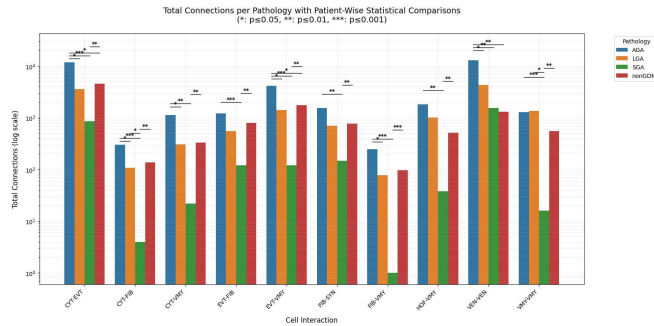


Fig. 7: Significance analysis of cell interactions across four pathological groups

These findings demonstrate that pathological remodeling was not uniform across cell types but instead targets specific connections central to villous organization.

Reduced connectivity in SGA highlights impaired microenvironmental integrity, while preserved or elevated connections in AGA, LGA, and non-GDM suggest adaptive or compensatory remodeling mechanisms.

4. DISCUSSION AND CONCLUSION

This study introduced a deep learning-based pipeline [6][20] that integrates villous image filtering, nuclei segmentation, cell classification, and quantitative morphometry to investigate placental remodeling in gestational diabetes and related growth pathologies. Compared with the HAPPY benchmark [2], our model achieved competitive classification accuracy, generated spatial cell maps with morphological features.

Morphometric analysis revealed cell-type-specific remodeling signatures, with Hofbauer cells and vascular myocytes showing the greatest sensitivity across multiple features. Connectivity analysis further demonstrated that SGA placentas exhibit markedly reduced interactions among trophoblasts, stromal, and vascular compartments, suggesting impaired microenvironmental integrity. In contrast, AGA placentas preserved robust connectivity, while LGA and non-GDM groups displayed partially compensatory remodeling patterns.

These findings highlight the potential of quantitative morphometry and spatial analysis as diagnostic tools for placental dysfunction. Although the findings indicate promising biological trends, the present work is intended as a methodological study, and further external validation is required before any clinical interpretation can be made. Future work will focus on expanding sample size, incorporating multi-modal data, and improving minority class performance through targeted augmentation. Together, this study provides a framework for linking computational pathology with clinically relevant biomarkers in placental disease.

5. COMPLIANCE WITH ETHICAL STANDARDS

This study utilized both open-access datasets and institutional data. The open-access datasets were used under their respective licenses and no ethical approval was required. The institutional data were collected with approval from the London - Riverside Research Ethics Committee (REC reference: 18/LO/0067, IRAS project ID: 234385) in accordance with the Declaration of Helsinki.

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