Executive Summary: Pathomic Fusion

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1 Introduction

This project sought to replicate and extend on the findings of the paper 'Pathomic Fusion: An Integrated Framework for Fusing Histopathology and Genomic Features for Cancer Diagnosis and Prognosis' by Chen et al., hitherto referred to as the original paper [1]. The original paper explored integrating histology, genomic and transcriptomic data using new approaches to extract features from the individual modalities and fuse the results to improve cancer grading and prognosis in two types of cancer: glioma (brain cancer) and clear cell renal cell carcinoma (ccRCC, a kidney cancer). Clinical data was added as an additional modality for ccRCC to extend on the original paper. Due to the complexity and heterogeneity of cancer, the goal of the original paper was also to improve patient stratification which is important for personalised therapeutic treatment. Digital pathology has enabled the application of machine learning to extract features from histology slides, such as cell density and nuclear morphology, crucial for diagnosis and prognosis [2, 3]. Genomic data, including mutation status and copy number variation, provide insights into the genetic alterations driving cancer [4]. Transcriptomic analysis enables the evaluation of RNA expression levels to understand the functional impact of these genetic changes [4]. Brain tumors, or gliomas, are broken down into molecular subtypes based on their origin and genetic markers, and these subtypes are highly correlated with patient survival outcomes [5]. ccRCC has various grading and staging methods, including the Fuhrman grade [6]. However, for both of these diseases there is a need for more precise patient stratification using a combination of modalities for improved prognosis and stratified treatment.

2 Methodology

The source of the data was The Cancer Genome Atlas (TCGA), which provides paired whole-slide images, and genomic, transcriptomic, and clinical data with survival and grade labels [7]. The study employed different neural network architectures to extract features for each data type. A VGG19-based convolutional neural network (CNN) was used to extract features from histology images with pretrained weights from ImageNet. A graph convolutional neural network (GCN) was utilized to capture cell spatial relationships from the histology images, using nuclei segmentation to define graph nodes. Cell features were then extracted both manually and using a self-supervised learning technique called contrastive predicted coding. Genomic and transcriptomic features were learned using a self-normalizing network (SNN), which is a feedforward neural network designed to maintain normalized activations throughout the network to prevent overfitting. For kidney cancer, clinical data was incorporated using the same SNN architecture as the genomic SNN instead of the histology GCN. Features from different data types were combined using a gating-based attention mechanism followed by a matrix outer product known as a Kronecker product. This method reduces feature space collinearities and captures interactions across data modalities, enhancing the model's predictive power [1]. The study trained the unimodal models, as well as the bifusion models of two modalities and the trifusion models of three modalities. The models were evaluated using common statistical metrics. For grade classification, Area Under the Curve (AUC), Average Precision (AP), and F1-Scores were used to measure performance. For predicting survival, Concordance Index (c-index) was utilised as the primary metric. Kaplan-Meier curves were plotted to show how well the model could separate patients into different risk groups, and log-rank tests checked if these separations were statistically significant. Additionally, integrated gradient attribution was performed to understand which genomic and clinical features contributed most to the genomic SNN and clinical SNN. A summary of the methodology is displayed in figure 1.

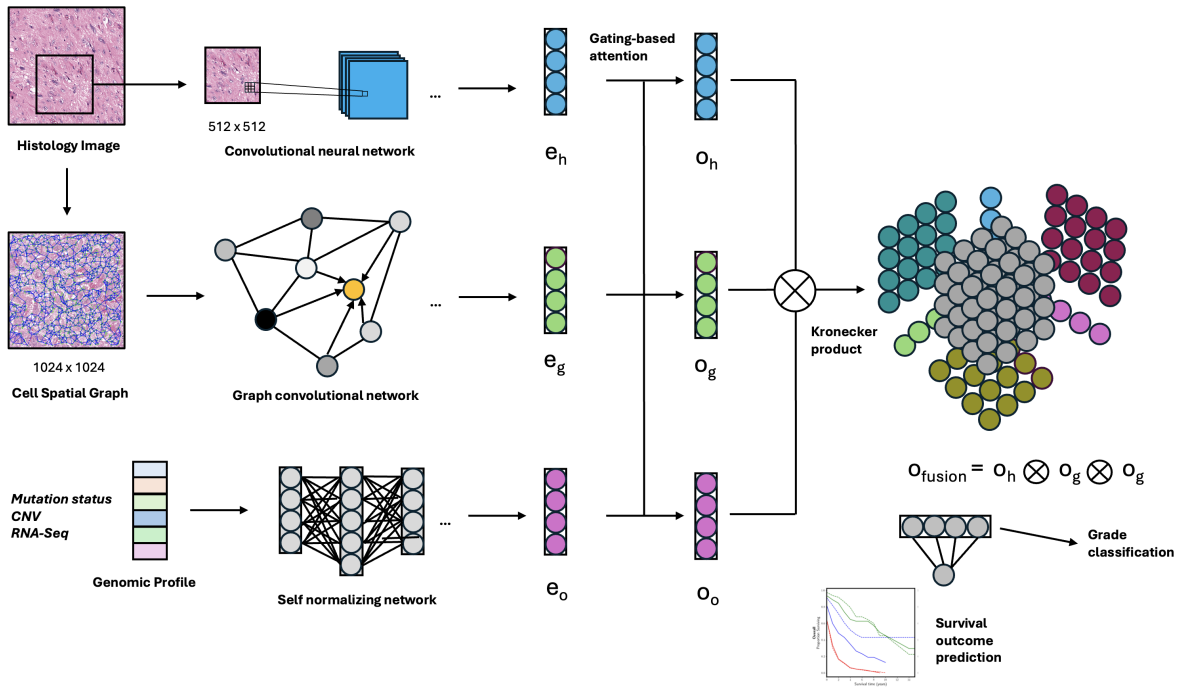

Figure 1: Summary of the methodology for pathgraphomic fusion (CNN+SNN+GCN) modified from figure 1 from the original paper. Unimodal features are extracted using a histology CNN, histology GCN, and genomic SNN. For the trimodal networks, the features are fused together using gating-based attention followed by a Kronecker product and then used for survival outcome prediction or grade classification.

3 Results & Discussion

The study's results for glioma grade classification showed that the pathgraphomic fusion model (CNN, GCN, and SNN fusion) achieved the highest performance across most metrics, except for AP, where a simpler pathomic fusion model (CNN+SNN) outperformed it. Larger standard deviations compared with the replication study were attributed to methodological differences, including the use of a single random 512 x 512 patch per histology image for each patient for evaluation. The histology CNN outperformed other unimodal networks, highlighting the critical role of histology in grade analysis. For survival prediction, the pathomic fusion model (CNN+SNN) demonstrated superior performance compared to individual models and other fusion types. However, the performance of the pathgraphomic fusion model (CNN+SNN+GCN) was very similar and it still achieved a very high c-index. As with the grade analysis, the difference in this performance could be accounted for by the slightly different evaluation methodology in the replication. The stratification by the pathgraphomic fusion model (CNN+GCN+SNN) was the most similar to the stratification by the molecular subtype which highly correlates with survival outcomes for gliomas [5]. The use of integrated gradients for feature attribution provided insights into which genomic features contributed most to the model's predictions. Canonical oncogenes, which are genes known to drive cancer progression when mutated or overexpressed, were shown to have high attribution [8].

For ccRCC, the clinical SNN significantly performed the best out of all the models and also appeared to stratify the patients best based on Kaplan-Meier curves. As in the original paper, the c-indices for the ccRCC models were much lower than those for glioma and the genomic SNN model performed the best out of the unimodal models other than the clinical model. There was again some discrepancy between the reproduced results and the results of the original paper, which may also be explained by the difference in the evaluation methods.

Overall, this study replicated and extended upon the findings of the original paper, confirming the efficacy of multimodal Kronecker product fusion approaches in cancer grade and survival analysis for glioma. It also demonstrated the merit of clinical data in survival analysis but different fusion approaches may need to be utilised to integrate this data more effectively, such as concatenating the embedding with the genomic embedding, rather than incorporating it directly as its own embedding within the Kronecker product. The integration of histology, genomic, and clinical data through unimodal architectures, including GCNs, and fusion strategies, such as the Kronecker product, holds promise for more accurate and personalised cancer prognosis and treatment.