Application of HiBED to prognosticate Glioma/Glioblastoma

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ABSTRACT

- Glioblastoma is a highly aggressive brain cancer and traditional methods of diagnosis often fall short in predicting patient outcomes.
- HiBED is a model that uses DNA methylation profiles to accurately deconvolve glioblastoma tumor samples into specific brain cell types.
- Involves the creation of a model using HiBED to detect regions of the brain affected by Glioma.

INTRODUCTION

Highly Aggressive Disease:

•Median survival of ~15 months; existing prognostic models struggle with disease's complexity, leading to inaccurate predictions

•HiBED:

• Hierarchical Deconvolution for extensive cell type resolution in the human brain using DNA Methylation
•Approximates proportions of brain cell types (illustrated in Figure 1) within tissue samples by estimating size and re-evaluating by layer. HiBED first determines the proportions of three major cell types: neuronal cells, glial cells, and endothelial/stromal cells (Layer 1). The model employs specialised libraries of CpG sites (particular DNA regions) to precisely identify and quantify each cell type based on its distinct methylation patterns (Table 1).

•Goal: Develop a model to analyze glioblastoma data using HiBED.

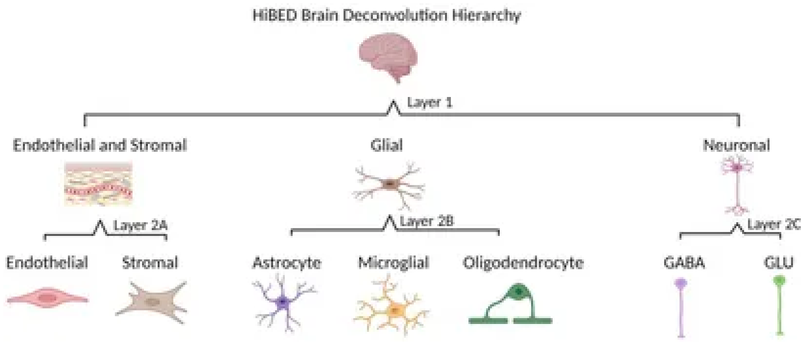
•Experimental Design:

•To identify predictive biomarkers, we used HiBED to deconvolute DNA methylation profiles from glioma/glioblastoma patient samples into specific brain cell types before connecting these cell-type proportions with clinical outcomes.

•Tasks:

- Application of the HiBED model to deconvolute DNA methylation data into distinct brain cell types.
- Comparing deconvolved cell-type proportions to clinical outcomes like median survival and treatment responsiveness.
- A statistical comparison of HiBED-derived prognostic models to existing glioma/glioblastoma prognostic models.

Figure 1:



METHODS

- Data Acquisition

•Obtain glioblastoma data from the Genomics Data Commons (GDC) portal, using the GDC Client for download. This includes the methylation data to discern the cell-type-specific sites to estimate the according proportions.

- Data Types

• Use methylation data to identify chemical alterations to DNA, such as adding methyl groups to CpG sites.
•Using epigenetic characteristics, the model can easily distinguish between cell types in a complicated tumour context.

- Limitations of Existing Methods

• Current prognostic models for glioblastoma frequently use rudimentary statistical methods and struggle to incorporate multiple data sources, resulting in unsatisfactory predictions.
•In comparison, the HiBED model uses methylation data, which is more accurate in predicting cell types seen within the tumour.

RESULTS

Unfortunately, the project wasn't able to be completed by the projected timline, and does not have a set of results to be shown.

Table 1:

Cell type	*N*	Mean age (sd)	*n* Male (%)	Accession	Source	Platform
Astrocyte	6	27.4 (11.2)*	6 (100)*	GSE166845 (29)	GEO	EPIC
Endothelial	12	Newborn	8 (66.7)	FlowSorted.CordTissueAndBlood.EPIC (30)	R package	EPIC
GABA	5	24.6 (5.7)	5 (100)	syn4588488 (24)	Synpase	450 K
GLU	5	24.6 (5.7)	5 (100)	syn4588488	Synpase	450 K
Microglia	18	83 (17.8)	4 (22.2)	GSE191200 (31)	GEO	EPIC
Oligodendrocyte	20	55.7 (15.8)	13 (65)	GSE107729 (32)	GEO	WGBS
Stromal	14	Newborn	10 (71.4)	FlowSorted.CordTissueAndBlood.EPIC	R package	EPIC
Total	80					

*Horvath methylation age was inferred using the ENMIX due to the lack of age information.
*Sex was inferred using the SeSAMe package due to the lack of sex information.

CONCLUSION

•Limitations:

•Time Constraints: Due to imminent summer plans, the project faced significant time limitations, which restricted the depth of analysis and the extent of data integration that could be completed within the available timeframe.
•Technical Limitations: Slow memory and processing speeds of the computational resources limited the efficiency and scalability of data processing and model training, potentially impacting the performance and accuracy of the HiBED model.

•Potential for Clinical Impact:

•HiBED's precise capacity to identify unique cellular compositions in glioblastoma tumours allows for more targeted treatment approaches based on individual tumour profiles, which improves patient outcomes through personalised therapy.
• HiBED improves prognosis by accurately predicting tumour cell type proportions and their correlation with clinical outcomes.
• The model's comprehensive risk profiles can identify patients at high risk for poor outcomes, allowing for timely intervention.

•Refrences:

•Data and Code Availability:

Link to GDC Portal: https://portal.gdc.cancer.gov/projects/TCGA-GBM

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