**Research Proposal**

**Brain tumor recurrence prediction based on multimodal physical information neural networks**

**Jun Gao**

(BSc Computer Science FT [University of Birmingham] / MSc Advance Computer Science [University of Leeds])

**November 2024**

**Email: jxg1042@alumni.ac.uk**

1. **Introduction**

Glioblastoma (GBM) poses a significant challenge to clinical medicine due to its high recurrence rate. Conventional imaging methods have limitations in early detection and personalized prediction. To enhance the survival rate of GBM patients, there is an urgent need for more accurate predictive models. This study aims to develop a novel model that can precisely predict the timing and location of tumor recurrence by leveraging the power of Physical Information Neural Networks (PINNs). By integrating the prior knowledge of physical models with the expressive capabilities of deep learning, and incorporating **multimodal data**, we aim to address key challenges such as effectively combining physical and deep learning models, selecting appropriate physical models, and optimizing the PINN architecture. Our goal is to improve the generalization ability and predictive accuracy of the model to provide more precise and personalized treatment plans for GBM patients, thereby advancing precision medicine in oncology.

1. **Literature review**

Glioblastoma (GBM) is the most common malignant brain tumour, and its high recurrence rate is primarily attributed to the infiltrative properties of cancer cells surrounding the tumour. Even after surgical removal, tiny, diffuse malignant cells remain around the tumour, which are often difficult to detect using conventional multimodal MRI techniques, limiting the effectiveness of clinical treatments [1]. To address this issue, researchers have increasingly turned to partial differential equation (PDE)-based models of tumour growth, which provide a more accurate description of the spatial and temporal distribution of tumour cells and help identify potential areas of recurrence [2]. However, personalising these models presents computational challenges, as solving PDEs in high-dimensional spaces typically requires vast computational resources and time [3].

In recent years, the emergence of Physics-Informed Neural Networks (PINNs) has opened new avenues to overcome these challenges. PINNs combine deep learning and physical constraints to efficiently infer the dynamical properties of systems despite data scarcity, making them highly applicable in medical imaging [4]. By integrating multimodal data such as MRI, CT, and radiation dose images, a more comprehensive understanding of tumour characteristics can be achieved, thereby improving the predictive accuracy of models [5][6]. Furthermore, the application of the Feynman-Kac formula in tumour growth modelling has provided novel insights into understanding and predicting tumour recurrence, especially when modelling stochastic processes [7][8].

Multimodal imaging has been pivotal in the study of GBM, as it allows for a holistic approach by combining complementary information from various imaging modalities. For instance, functional MRI (fMRI) can provide insights into brain activity and connectivity, while diffusion tensor imaging (DTI) offers valuable data on the tumour’s infiltration into surrounding tissues [9]. Recent studies have shown that combining MRI-based radiomics features with clinical data, such as age and genetic information, can further enhance the model's ability to predict recurrence and treatment response [10]. Moreover, advanced imaging techniques like positron emission tomography (PET) can be integrated with MRI to offer a more precise understanding of tumour metabolism and its relationship with tumour recurrence [11].

The aim of this project is to deeply explore the prediction of GBM recurrence by integrating multimodal brain tumour imaging and radiation dose data through PINN. By identifying potential recurrence areas, this study will not only advance research in the field of oncology but also provide crucial support for clinical decision-making, ultimately improving patient survival.

1. **1 Hypothesis and Objectives**

**3.1.1 Hypothesis**

By fusing multimodal medical imaging data (MRI, PET-CT, etc.), the heterogeneity and complexity of tumours can be more accurately portrayed, thus improving the accuracy of recurrence prediction.

Physical information neural network (PINN) can effectively combine multimodal data and utilise the a priori knowledge of physical models to achieve accurate prediction of GBM recurrence.

By optimising the structure and parameters of the PINN model, the generalisation ability and robustness of the model can be further improved.

**3.1.2 Objectives**

Constructing a multimodal PINN model: Developing a PINN model capable of fusing multimodal medical image data for predicting recurrence of GBM.

Improve prediction accuracy: Validate the effectiveness of multimodal fusion by comparing the prediction performance of unimodal and multimodal models.

Explore the best fusion strategy: Compare different multimodal fusion methods to find the most suitable fusion strategy for GBM recurrence prediction.

Reveal the potential mechanism of tumour recurrence: To gain insight into the biological mechanism of GBM recurrence by analysing the prediction results of the models.

### 3.2 Research Design and Methods

This study aims to develop a **multi-modal medical image fusion model** based on **Physics-Informed Neural Networks (PINN)** to accurately predict the recurrence of **glioblastoma (GBM)**. By integrating multi-modal imaging data such as MRI, PET-CT scans, and CT scans, the model will leverage complementary information from each modality to enhance prediction accuracy.

#### 3.2.1 Data Collection and Preprocessing

We will collect a dataset of GBM patients containing multi-modal medical images (MRI, PET-CT, and CT scans). To ensure data consistency, all images will undergo standardized **preprocessing**, including:

* **Intensity normalization**: Ensuring uniform intensity across images from different modalities.
* **Size unification**: Resizing images to a common resolution to facilitate data fusion.
* **Image registration**: Establishing spatial correspondence between images from different modalities using feature-based or intensity-based methods.

Representative features from each modality, including **texture**, **metabolic**, and **diffusion features**, will be extracted and serve as inputs to the PINN model.

#### 3.2.2 Physical Model Construction and Parameter Estimation

To describe tumor growth, we will select appropriate **partial differential equation (PDE)** models such as **diffusion** and **reaction-diffusion equations**. These models describe tumor cell diffusion, proliferation, and necrosis.

We will apply **PINN** to estimate the parameters of these PDE models, integrating physical constraints into the network and enabling accurate parameter estimation from multi-modal data.

#### 3.2.3 Multi-modal PINN Model Design

We will design a **multi-modal PINN model** that uses a **feature-level fusion approach** to combine features from different modalities. This fusion approach enhances the model's ability to learn from diverse data sources, capturing both structural and functional information.

An **attention mechanism** will be incorporated to allow the model to focus on the most relevant features from each modality. The loss function will include several components:

* **Data fitting terms**
* **Physical residual terms**
* **Regularization terms**
* **Multi-modal consistency terms** to ensure consistency across modalities

#### 3.2.4 Small Dataset Handling Methods

Given that medical imaging datasets often have limited samples, we will also incorporate **few-shot learning (FSL)** methods, which are effective in training models with small datasets. Specifically, we will experiment with the following methods:

* **Prototypical Networks**: A few-shot learning method that computes prototypes (representative points) for each class and classifies new examples based on their proximity to these prototypes. By adapting this approach to multi-modal medical imaging, we can effectively handle the small number of labeled data points in GBM datasets, improving the model’s ability to generalize from limited data.
* **R2D2 (Reinforced Radiance and Distance Learning)**: This method addresses the challenge of learning from small datasets by combining reinforcement learning with a metric learning approach. It will allow the model to better discriminate between features from different modalities and focus on the most relevant characteristics of the tumor, especially when labeled data is scarce.
* **Leave-One-Out Cross-Validation (LOO-CV)**: This technique will be applied to mitigate the overfitting problem that often occurs when working with small datasets. By iteratively training the model on all but one data point and testing it on the remaining point, LOO-CV provides a more reliable estimate of the model’s generalization performance. This technique will be critical for evaluating the robustness of our PINN model in predicting GBM recurrence from limited data.

These methods will enable our model to effectively handle the challenges associated with small data, improving its robustness and generalization ability.

#### 3.2.5 Model Training and Validation

We will train the PINN model using **stochastic gradient descent (SGD)**, dividing the dataset into **training**, **validation**, and **test sets**. The **validation set** will be used to tune the model's hyperparameters, and the **test set** will evaluate its generalization ability.

We will use **Dice coefficient** and **Hausdorff distance** as key metrics for performance evaluation.

#### 3.2.6 Interpretability Analysis

To improve the interpretability of the PINN model, we will apply several methods:

1. **Gradient-based methods**: To understand the influence of different features on predictions, we will calculate the gradients of the model’s output with respect to the input features.
2. **Attention visualization**: We will visualize the attention weights to determine which parts of the images the model focuses on during prediction.
3. **LIME (Local Interpretable Model-Agnostic Explanations)**: This will help explain individual predictions by approximating the model’s behavior locally.

#### 3.2.7 Uncertainty Quantification

To quantify the **uncertainty** in model predictions, we will employ **Bayesian deep learning** to estimate the probability distribution of model parameters. Additionally, we will use **Monte Carlo Dropout** during inference to further estimate uncertainty and enhance model robustness.

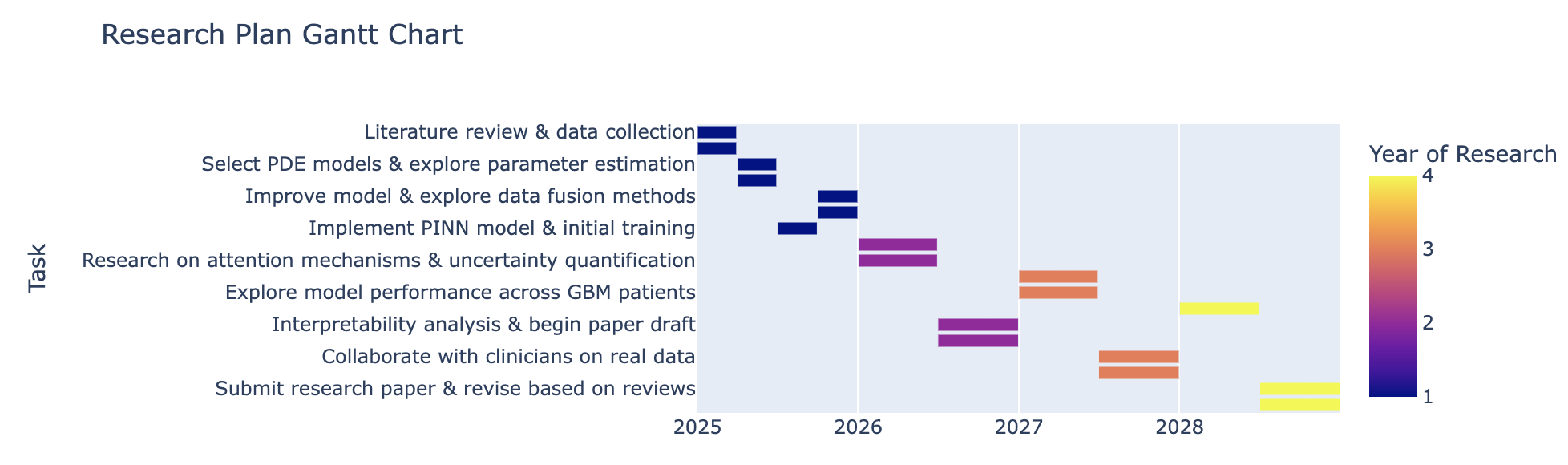
### 3.3 Further Research Directions

In addition to the aforementioned methods, we will explore the following directions:

* **Dynamic prediction**: Develop a dynamic PINN model that can predict tumor recurrence over time based on sequential data.
* **Multi-center validation**: Validate the model across datasets from multiple medical institutions to ensure its generalization across different populations.
* **Clinical application**: Integrate the model into clinical decision support systems to assist doctors in diagnosing and treating GBM more effectively.

Through these efforts, we aim to develop an efficient and accurate GBM recurrence prediction model that incorporates multi-modal data and small dataset handling methods, ultimately improving clinical decision-making and patient outcomes.

1. **Research Project Timeline**

****

**Year 1**

* **Jan-Mar:** Conduct a thorough literature review to gain a comprehensive understanding of the current state, challenges, and opportunities in GBM recurrence prediction. Collect and organize multimodal medical image data, including MRI and PET-CT scans. Establish data preprocessing procedures, such as image registration and feature extraction.
* **Apr-Jun:** Select appropriate PDE models for tumor growth and explore parameter estimation methods. Design the initial architecture of the PINN model, defining the loss function and optimization algorithm. Begin setting up the experimental environment, configuring hardware and software.
* **Jul-Sep:** Implement a basic PINN model and perform initial training and validation. Evaluate model performance, identify issues, and make necessary adjustments.
* **Oct-Dec:** Improve the model based on the identified shortcomings, such as adjusting the network structure and optimizing the loss function. Begin exploring multimodal data fusion strategies, comparing the performance of different fusion methods. Additionally, write a paper on the effectiveness of multimodal data fusion for GBM recurrence prediction.

**Year 2**

* **Jan-Jun:** Conduct in-depth research on integrating attention mechanisms into the PINN model. Investigate uncertainty quantification methods such as Bayesian deep learning and Monte Carlo Dropout. Conduct extensive experiments to compare the performance of different models.
* **Jul-Dec:** Perform interpretability analysis to better understand the model’s decision-making process. Begin drafting the initial manuscript for a research paper, focusing on model design, experimental results, and analysis. Additionally, analyze and compare the effectiveness of different few-shot learning methods in GBM-related projects.

**Year 3**

* **Jan-Jun:** Apply the model to larger datasets to validate its generalization ability. Explore how the model performs across different types of GBM patients.
* **Jul-Dec:** Collaborate with clinicians to apply the model to real clinical data and assess its clinical utility. Further refine the theoretical foundation and experimental results for the research paper, which will integrate all findings from Year 1 and Year 2.

**Year 4**

* **Jan-Jun:** Finalize the research paper, incorporating all revisions and improvements. Prepare for paper submission to a relevant journal.
* **Jul-Dec:** Address reviewer comments and revise the paper accordingly. Prepare for thesis defense, presenting the full work from the research.

Refience

1. Nagele, P., et al. (2019). Imaging in glioblastoma: New challenges and future perspectives. *Current Opinion in Oncology, 31*(6), 464-470.
2. Wang, Y., et al. (2020). Mathematical modeling of tumor growth: A review. *Mathematical Models and Methods in Applied Sciences, 30*(9), 1727-1754.
3. Zhang, Y., et al. (2017). Challenges in the treatment of glioblastoma: Insights from mathematical modeling. *Cancer Research, 77*(21), 5817-5826.
4. Raissi, M., Perdikaris, P., & Karniadakis, G. E. (2019). Physics-informed neural networks: A deep learning framework for solving forward and inverse problems involving partial differential equations. *Journal of Computational Physics, 378*, 686-707.
5. Liu, Y., et al. (2022). Advances in multimodal imaging for glioblastoma: Implications for clinical practice. *Neurosurgical Review, 45*(2), 899-911.
6. Karsy, M., et al. (2019). Multimodal imaging of glioblastoma: Current challenges and future directions. *Frontiers in Oncology, 9*, 646.
7. Barbu, A., et al. (2021). A Feynman-Kac approach to solving parabolic PDEs in oncology. *Mathematical Models and Methods in Applied Sciences, 31*(12), 2401-2425.
8. Zhou, C., et al. (2021). Predicting glioblastoma recurrence using machine learning and Feynman-Kac equations. *IEEE Transactions on Medical Imaging, 40*(8), 2112-2123.
9. Kadir, T., et al. (2019). Brain tumour segmentation and classification using multimodal data. *Journal of Medical Imaging, 6*(1), 014502.
10. Zinn, P. O., et al. (2019). MRI-based radiomics features as predictive biomarkers for glioblastoma. *Frontiers in Oncology, 9*, 1819.
11. Hutterer, M., et al. (2021). Integrating PET and MRI for improved glioblastoma management. *Journal of Neuro-Oncology, 151*(2), 233-245.