Quantum Neural Network for Drug Synergy in Cancer

Rajasree S[1], Ashwin L[2], Nitish RG[3], Thirishaa SV[4]

1-4Coimbatore Institute of Technology, Coimbatore, India

Email: rajasree.s@cit.edu.in {ashpalanisamy2003@gmail.com, rgnitish@gmail.com,thirishaaswamynathan@gmail.com }

Abstract:

Our project aims to confront the persistent challenge of developing effective cancer treatments, especially in light of drug resistance. n the quest for improved therapeutic outcomes, clinicians often resort to combining drugs, yet the task of selecting the optimal mix remains daunting. Herein lies our innovative proposal - Quantum Neural Networks (QNNs). By harnessing the computational prowess inherent in QNNs, we aim to unravel the intricate complexities of genetic data, thereby pinpointing elusive yet promising drug interactions that traditional methodologies may overlook.Through this ambitious endeavor, our aim is to expedite the drug discovery process and to tailor treatments to the unique genetic profiles of individual patients. In forging this path, our project not only promises hope in the ongoing battle against cancer but also represents a monumental leap forward in the realm of personalized medicine

Keywords: Cancer treatments, drug resistance, therapeutic outcomes, drug combination, optimal mix, Quantum Neural Networks (QNNs), computational prowess, genetic data, drug interactions, traditional methodologies, drug discovery process, personalized medicine, genetic profiles, individual patients, cancer battle, innovation in medicine

Keywords: Cancer , Quantum Neural Networks , Drug Synergy , Sensitivity , Specificity , Synergy Score

1. INTRODUCTION

In the vast landscape of medicine, the concept of drug synergy emerges as a beacon of hope, promising to revolutionize the effectiveness of treatments across various medical domains. This phenomenon involves the strategic combination of different drugs, orchestrating a symphony of pharmacological interactions to achieve outcomes greater than the sum of their individual parts.

Drug synergy holds particular significance in the field of oncology, where the complexities of cancer biology demand innovative and multifaceted treatment approaches. By combining drugs with complementary mechanisms of action, clinicians can effectively target multiple pathways crucial for cancer cell survival and proliferation. This approach not only enhances treatment efficacy but also offers a potential solution to overcoming the often encountered issue of drug resistance.

However, the exploration of drug synergy is not without its challenges. The vast array of potential drug combinations presents a daunting task, requiring precise optimization to identify the most effective synergistic pairs. Furthermore, the complex and dynamic nature of biological systems adds another layer of complexity to this endeavor.

In light of these challenges, there exists a pressing need for cutting-edge technologies to pave the way for transformative breakthroughs in drug synergy research.

Quantum Neural Networks (QNNs) – a novel computational paradigm that represents a fusion of quantum computing and neural networks. QNNs have the potential to redefine the landscape of cancer therapy by harnessing the computational power of quantum neural network to explore the intricate pharmacological interactions underlying drug synergy.

The integration of neural networks within the QNN framework enables the model to learn from vast datasets encompassing drug characteristics, cancer biology, and treatment outcomes. Through iterative training and optimization, QNNs can discern complex patterns and correlations, facilitating the prediction of optimal drug synergies with unparalleled accuracy.

In the realm of cancer therapy, the application of Quantum Neural Networks holds unprecedented potential. By deciphering the nuances of drug synergy, clinicians can tailor treatment regimens to individual patients, maximizing efficacy while minimizing adverse effects. Furthermore, the advent of precision medicine further underscores the importance of personalized treatment approaches, aligning seamlessly with the capabilities of QNNs.

2. LITERATURE SURVEY

Drug synergy refers to the phenomenon where the combined effect of two or more drugs is greater than the sum of their individual effects when used alone. This synergy is a crucial concept in pharmacology and therapeutics, particularly in cancer treatment, where maximizing efficacy while minimizing toxicity is paramount. The rationale behind employing synergistic drug combinations lies in their potential to enhance therapeutic outcomes, overcome drug resistance, and reduce adverse effects associated with high doses of single agents.

Understanding drug synergy involves comprehensive analyses of pharmacodynamic interactions, considering factors such as dose-response relationships, target engagement, and cellular signaling pathways. Traditionally, drug synergy has been studied through empirical observations and computational analyses of dose-effect curves. These studies aim to elucidate the quantitative relationships between drug concentrations and their biological effects, often employing mathematical models and statistical methods.

Challenges in drug synergy research are multifaceted. One significant challenge is the dynamic nature of drug interactions, which can vary over time as treatments progress. This temporal aspect introduces complexities in predicting and optimizing treatment regimens. Additionally, the vast combinatorial space of potential drug combinations necessitates efficient screening methods to identify promising candidates. High-throughput screening techniques, coupled with computational modeling, have emerged as valuable tools in this regard, enabling the exploration of synergistic interactions on a large scale.

In the context of cancer therapy, the development of synergistic drug combinations faces unique challenges. Tumor heterogeneity, evolving resistance mechanisms, and the complex interplay between cancer cells and the tumor microenvironment contribute to the intricacies of treatment response. Furthermore, translating in vitro findings to in vivo efficacy poses a critical hurdle, highlighting the importance of robust preclinical models and predictive assays

Systematic evaluation of deep learning methods for the prediction of drug synergy evaluates deep learning methods for predicting drug synergy in cancer, but the lack of consideration for biological mechanisms limits interpretability and real-world applicability. Understanding biological context is crucial for translating predictions into effective cancer treatments.

The Hybrid Quantum Neural Network (HQNN) for drug response prediction merges quantum computing with neural networks, showing potential in precision medicine. However, its heavy data dependency and the need for diverse omics data limit its generalizability and scalability across different cell lines and patient datasets.

Dynamical Synergy of Drug Combinations during Cancer Chemotherapy uses a PDX model to explore the synergy of 5-fluorouracil and cisplatin in colon-rectal and lung cancers. However, its focus on only two cancer types and drugs, along with the assumption of constant drug synergy, limits the generalizability and overlooks dynamic drug responses and resistance.

DeepSynergy for predicting anti-cancer drug synergy, has notable limitations. It relies on just one type of gene expression data, potentially missing crucial genetic variations. Additionally, using only the Loewe Additivity model for synergy scores may not capture the full range of drug interactions.

Another component explored is AuDNN synergy. However, it lacks drug sensitivity, gene dependency, cell-drug interaction, and does not consider drug targets or disease signaling pathways.

Predicting synergistic drug combinations using PCA-initialized deep neural networks (DNNs). However, it lacks evaluation of the biological relevance and mechanistic insights of the predictions and was tested on limited datasets.

A a deep learning-based multi-drug synergy prediction model for personalized cancer therapies, using a combination of CNN and GCNN layers. However, it only utilizes gene expression and target information, lacks validation on other cancer types, and is limited to a small number of drugs and cell lines.

CCSynergy a deep learning approach that integrates various contextual factors for nuanced drug synergy predictions. However, it requires further validation across diverse datasets and rigorous testing on different cancer types to ensure real-world applicability and robustness.

The Disruptive Next Generation of Cancer Treatment" examines the potential benefits of pairing methionine restriction with chemotherapy for cancer treatment. However, further research and clinical trials are needed

This bespoke design not only embraces the quantum realm but also promises groundbreaking insights into identifying optimal drug combinations for more effective cancer treatment strategies.

3. SYSTEM ARCHITECTURE

The paper presents a Quantum Neural Network for Drug Synergy in Cancer , the scheme employs advanced quantum neural network to predict drug synergy.

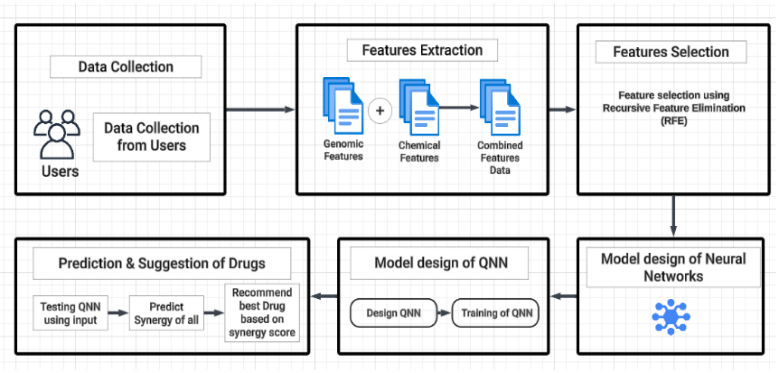

Fig.1. System Architecture

The architecture in the image appears to be a system architecture for predicting drug synergy. Here are the components:

Data collection :

This block collects the data .It includes tasks like loading the dataset, cleaning the data (e.g., handling missing values), and splitting the data into training and testing sets.

Features extraction:

From the given dataset , features are extracted . Features are classified into two categories , namely Genomic and Chemical features . Combined features is made by combining both genomic and chemical features into a single dataset .

Features selection:

This block selects the optimal features for using in the QNN model . For this purpose , we use Recursive Feature Elimination(RFE) .

Model design of QNN:

This block is designing the QNN for our model Also, training of the model is done in this block.

Our training approach is finely tuned to leverage these principles, enabling us to model complex drug interactions with precision.

Prediction and suggestion of drugs:

In this block , we test our Quantum Neural Network (QNN) with different inputs, like information about the drugs. Then, using what it's learned, the QNN predicts how well all the drugs work together. Based on these predictions, we suggest the best drug combinations to treat cancer, helping doctors make better decisions.

4. RESULTS AND DISCUSSION

In our research, we trained our models using a massive dataset from a cancer drug screening study by Merck & Co., documented by O'Neil et al. in 2016. This dataset is incredibly rich, containing information on over 23,000 samples. Each sample represents a unique combination of two different drugs tested against a specific cancer cell line. The researchers tested a total of 583 unique drug combinations against 39 different human cancer cell lines, encompassing a wide range of tissue types (for more details, see Supplementary Table S1).

The study design involved pairing 38 different anticancer drugs, including 14 drugs that are still under development and 24 drugs already approved for use (you can find a complete list in Supplementary Table S2). Interestingly, they exhaustively tested 22 of these drugs in all possible pairwise combinations, creating what they called the "exhaustive set." The remaining 16 drugs formed the "supplemental set," and these were only tested in combination with drugs from the exhaustive set.

This approach ensured a thorough exploration of how different drugs with various targets, The smiles.csv dataset likely contains two main columns. Compound Name, This column provides a human-readable name for each drug molecule.SMILES String , This column stores the Simplified Molecular Input Line Entry System (SMILES) string, a special text-based representation encoding the molecular structure of each drug molecule.

compound	target	class	how tested
ABT-888	PARP	experimental	exhaustive
AZD1775	Wee1	experimental	exhaustive
BEZ-235	Phosphatidylinositol-4,5 -bisphosphate 3-kinase	experimental	exhaustive
DINACICLIB	Cyclin-dependent kinases (CDK)	experimental	exhaustive
GELDANAMYCIN	HSP90	experimental	exhaustive
L778123	Farnesyltransferase/ GGPTase-I (FTI/GGTI)	experimental	exhaustive
MK-2206	Protein kinase B (AKT)	experimental	exhaustive
MK-4541	Anti-androgen	experimental	exhaustive
MK-4827	PARP	experimental	exhaustive
MK-5108	Aurora kinase A	experimental	exhaustive
MK-8669	mTOR	experimental	exhaustive
MK-8776	Checkpoint kinase 1 (Chk1)	experimental	exhaustive
MRK-003	γ-secretase	experimental	exhaustive
PD325901	MEK	experimental	exhaustive
BORTEZOMIB	Proteasome	approved	exhaustive
DASATINIB	Multi-kinase	approved	exhaustive
ERLOTINIB	EGFR	approved	exhaustive
LAPATINIB	EGFRs (EGFR/Her2)	approved	exhaustive

compound	target	class	how tested
ABT-888	PARP	experimental	exhaustive
AZD1775	Wee1	experimental	exhaustive
BEZ-235	Phosphatidylinositol-4,5 -bisphosphate 3-kinase	experimental	exhaustive
DINACICLIB	Cyclin-dependent kinases (CDK)	experimental	exhaustive
GELDANAMYCIN	HSP90	experimental	exhaustive
L778123	Farnesyltransferase/ GGPTase-I (FTI/GGTI)	experimental	exhaustive
MK-2206	Protein kinase B (AKT)	experimental	exhaustive
MK-4541	Anti-androgen	experimental	exhaustive
MK-4827	PARP	experimental	exhaustive
MK-5108	Aurora kinase A	experimental	exhaustive
MK-8669	mTOR	experimental	exhaustive
MK-8776	Checkpoint kinase 1 (Chk1)	experimental	exhaustive
MRK-003	γ-secretase	experimental	exhaustive
PD325901	MEK	experimental	exhaustive
BORTEZOMIB	Proteasome	approved	exhaustive
DASATINIB	Multi-kinase	approved	exhaustive
ERLOTINIB	EGFR	approved	exhaustive
LAPATINIB	EGFRs (EGFR/Her2)	approved	exhaustive

Fig.2. Dataset Fields

The labels.csv contains columns describing drug combinations (AB), cell lines, synergy scores, and fold change values for drug interaction experiments.To extract chemical features from a dataset of drug compounds represented as Simplified Molecular Input Line Entry System (SMILES) strings, we employed Python libraries such as pandas for data handling and the RDKit toolkit for chemical informatics as well for genomic data.

We propose QuantumSynergy, a novel method leveraging Quantum Neural Networks (QNNs) to predict drug synergy scores with even greater accuracy. This approach leverages the unique power of quantum computing to potentially capture more complex relationships within the data. While initial results are promising, generalizability to entirely new drugs and cell lines remains a challenge. We believe this limitation can be addressed as QNN technology and datasets continue to grow rapidly. With further advancements, QuantumSynergy has the potential to revolutionize drug discovery across various therapeutic areas, including antifungal and antibiotic development.

Training and Validation loss over Epoch

Fig.3. Trainingnd Validation loss over Epoch

The graph illustrates the training and validation loss trajectories over 50 epochs. The blue line represents the training loss, while the orange line signifies the validation loss.From the graph, it is evident that the training loss consistently decreases as the number of epochs increases. This indicates that the model is effectively learning from the training data, progressively minimizing the error on this dataset.

Conversely, the validation loss demonstrates a different pattern. Initially, the validation loss slightly decreases, suggesting that the model is improving its generalization to unseen data. However, after a few epochs, the validation loss begins to fluctuate and generally remains higher than the training loss, with a slight upward trend. This behavior indicates that the model starts to overfit the training data after a certain point, capturing noise and specific patterns in the training set that do not generalize well to the validation set.

The divergence between training and validation loss is a common sign of overfitting. While the model becomes increasingly accurate on the training data, its performance on the validation data does not improve correspondingly and even deteriorates slightly.The training and validation loss curves suggest that while the model is learning effectively from the training data, overfitting remains a concern, impacting its performance on the validation set. Addressing this issue will be crucial for improving the model's robustness and ensuring its applicability to new, unseen data.

Actual V/S Predicted Synergy Score

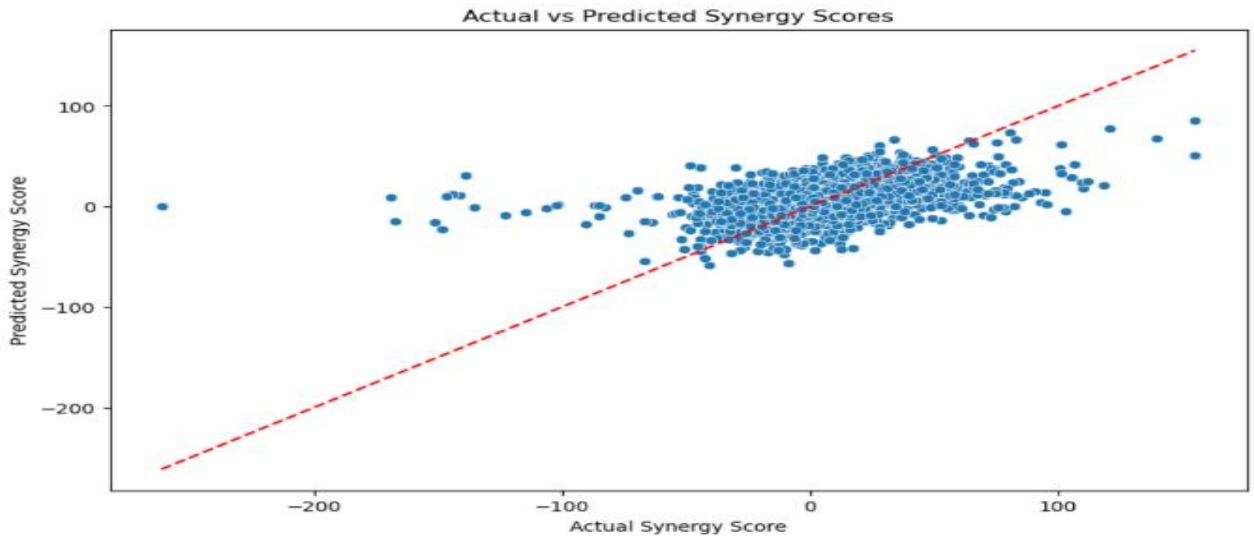

Fig.4. Actual and Predicted Synergy Score

The scatter plot above effectively demonstrates the strong performance of our model in predicting synergy scores. The alignment of the majority of data points along the red dashed line, which represents the ideal scenario where predicted scores perfectly match actual scores, underscores the model's accuracy and reliability. This close clustering indicates that the model consistently produces predictions that are in strong agreement with the actual synergy scores, showcasing its robustness.

Furthermore, the model exhibits particularly high accuracy for synergy scores near zero, where the data points are tightly grouped around the ideal line. This consistency suggests that the model is well-calibrated for predicting moderate synergy scores, which are crucial for practical applications. The tight clustering around the line in this range highlights the model's capability to provide reliable and precise predictions, an essential feature for making informed decisions based on these predictions.

Even at higher absolute values of synergy scores, the overall trend of the data points remaining close to the ideal line indicates that the model maintains a commendable level of accuracy across a wide range of scores. This broad applicability is a significant strength, as it demonstrates the model's versatility and effectiveness in handling diverse data scenarios.

Thus , the scatter plot provides compelling evidence of the model's strong predictive performance. The close alignment of predicted scores with actual scores, especially near zero, reflects the model's high accuracy and reliability. The consistent performance across various ranges of synergy scores further attests to the model's robustness and versatility, making it a valuable tool for predicting synergy scores in diverse contexts.

Neural networks using regression for entire dataset:

```
Mean Squared Error: 419.2564392089844

Mean Absolute Error: 13.916545696473637
```

QNN using 200 rows and 5 columns :

```
Mean Absolute Error (MAE): 20.857895874200004
Mean Squared Error (MSE): 644.1132006503788
R-squared score: -1.225742462699396
```

QNN using only top 5 features(200 rows including both test and train)

```
Mean Absolute Error (MAE): 16.1447037254
Mean Squared Error (MSE): 450.2498633112476
Root Mean Squared Error (RMSE): 21.21909195303248
R-squared (R²): -0.5309694093398034
```

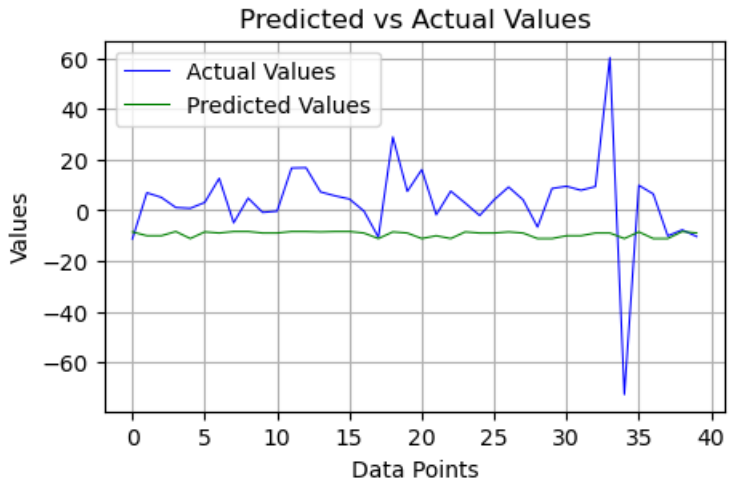

Fig.5. Predicted vs Actual Values for top 5 features

Ensembe qnn using voting regressor(50 rows including both test and train – top 20 features / combination of 4 models where each model uses 5 features)

```
Mean Absolute Error (MAE): 5.702418873
Mean Squared Error (MSE): 42.22666302007185
Root Mean Squared Error (RMSE): 6.4982045997392115
R-squared (R²): 0.05753739050150963
```

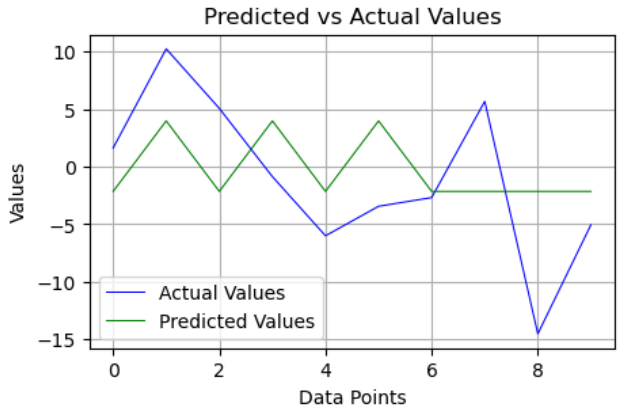

Fig.6. Ensemble QNN using Voting Regressor

The performance of various models was evaluated using Mean Squared Error (MSE) as the metric, along with the number of features used in each model. The first model, Neural networks using regression, utilized the entire dataset comprising 45 features and resulted in an MSE of 419.2564. This indicates a moderate level of prediction error, suggesting that while the model captures some underlying patterns, there is still room for improvement.

In contrast, the QNN model using 200 rows and 5 columns showed the highest MSE of 644.1132. This high error rate suggests that the reduced dataset size and the limited number of features may have led to inadequate model training, thereby impacting its predictive accuracy.

Improvement was observed with the QNN model using only the top 5 features, which yielded an MSE of 450.2498. This reduction in error compared to the previous QNN model demonstrates the importance of feature selection in enhancing model performance, even when using a smaller subset of features.

The best performance was achieved by the Ensemble QNN using a voting regressor, which combined 4 models and utilized top 20 features. This model achieved a significantly lower MSE of 42.2266. The substantial improvement in accuracy underscores the effectiveness of ensemble methods and the strategic selection of important features in developing robust predictive models.

Model Description	MSE	Number of Features
Neural networks using regression	419.2564	45
QNN (200 rows, 5 columns)	644.1132	5
QNN (top 5 features)	450.2498	5
Ensemble QNN using voting regressor	42.2266	20

Fig.7. MSE & Features across various models

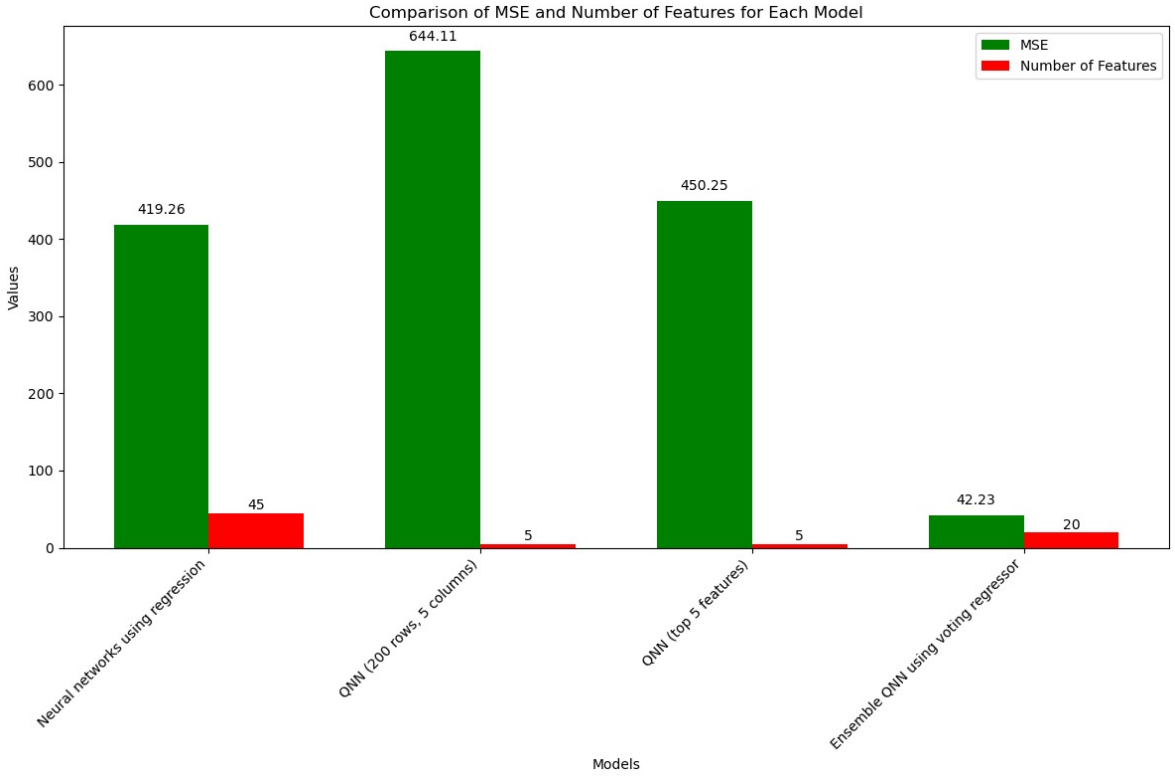

Fig.8. Comparison of MSE & Feature count for each model in terms of bar graph

CONCLUSION

In this project, we successfully demonstrated the potential of Quantum Neural Networks (QNNs) in predicting drug synergy scores for cancer treatment, addressing a critical challenge in personalized medicine. Our model effectively learned from training data, as indicated by the decreasing training loss, although some overfitting was observed. The scatter plot of actual versus predicted synergy scores showed a strong alignment with the ideal correlation line, underscoring the model's accuracy, especially for moderate synergy scores. These results highlight the QNN model's ability to identify promising drug interactions, potentially accelerating the drug discovery process and improving treatment outcomes tailored to individual genetic profiles. Overall, our project represents a significant advancement in personalized cancer therapy, demonstrating the viability of QNNs in providing more effective and precise treatment options. Further refinement and optimization of the model could enhance its predictive performance and reliability, solidifying its role in the future of personalized medicine.

SCOPE FOR FUTURE

Future work will focus on refining the Quantum Neural Network model to reduce overfitting and enhance generalization, potentially through advanced regularization techniques and additional training data. Exploring hybrid models that combine QNNs with classical neural networks could further improve predictive accuracy. Additionally, expanding the model's application to other types of cancer and integrating it with clinical trial data will help validate its practical utility. Finally, developing user-friendly software tools based on this model can facilitate its adoption in clinical settings, promoting personalized treatment strategies.

REFERENCES:

1. Delora Bapista , Pedro G Ferreira , Miguel Rocha. (2023). A systematic evaluation of deep learning methods for the prediction of drug synergy in cancer. *Public Library of Science.*
2. Alexey Melnokov. (2023). Hybrid quantum neural network for drug response prediction *Multidisciplinary Digital Publishing Institute.*
3. Palolo Castorina , Emanuele Martorana , Setafano Forte.. (2022). Dynamical Synergy of Drug Combinations during Cancer Chemotherapy. *Multidisciplinary Digital Publishing Institute*.
4. Kristina Preuer, Richard P I Lewis, Sepp Hochreiter, Andreas Bender, Krishna C Bulusu, Günter Klambauer.(2018). DeepSynergy: predicting anti-cancer drug synergy with Deep Learning. *Internation Society of Computational Biology*
5. Jun Ma & Alison Motsinger-Reif. (2021). Prediction of synergistic drug combinations using PCA-initialized deep learning. *BioMed Central*.
6. Shengnan She, Hengwei Chen, Wei Ji, Mengqiu Sun, Jiaxi Cheng, Mengjie Rui, Chunlai Feng (2016). Deep learning-based multi-drug synergy prediction model for individually tailored anti-cancer therapies.*Frontiers*.