Performance Evaluation of Quantum Machine Learning Models for Drug Target Identification

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Abstract

Drug target identification is a crucial step in the drug discovery pipeline. With the increasing availability of biological and chemical datasets, machine learning techniques have shown great promise in predicting potential drug targets. Recent advances in quantum computing have opened up new possibilities of applying quantum machine learning algorithms for computational drug discovery. In this work, we benchmark the performance of various classical and quantum machine learning models on drug target prediction tasks. We train supervised classification models on benchmark datasets of chemical compounds labeled with their target protein. We compare quantum classifiers implemented using variational quantum circuits against classical neural networks and kernel methods. Our results demonstrate that certain quantum models can achieve significantly higher accuracy than classical approaches in identifying drug targets across various protein target families. The quantum advantage is more pronounced on datasets with greater molecular diversity. Our work provides useful insights into the practical value of quantum machine learning for an important real-world application in computational biology. The performance evaluations presented serve as a guide for applying quantum algorithms to develop more effectively in silico drug discovery pipelines.

Keywords: Drug target prediction, Quantum machine learning, Quantum algorithms, In silico drug discovery, Structure-activity relationships, Protein-ligand binding

Introduction

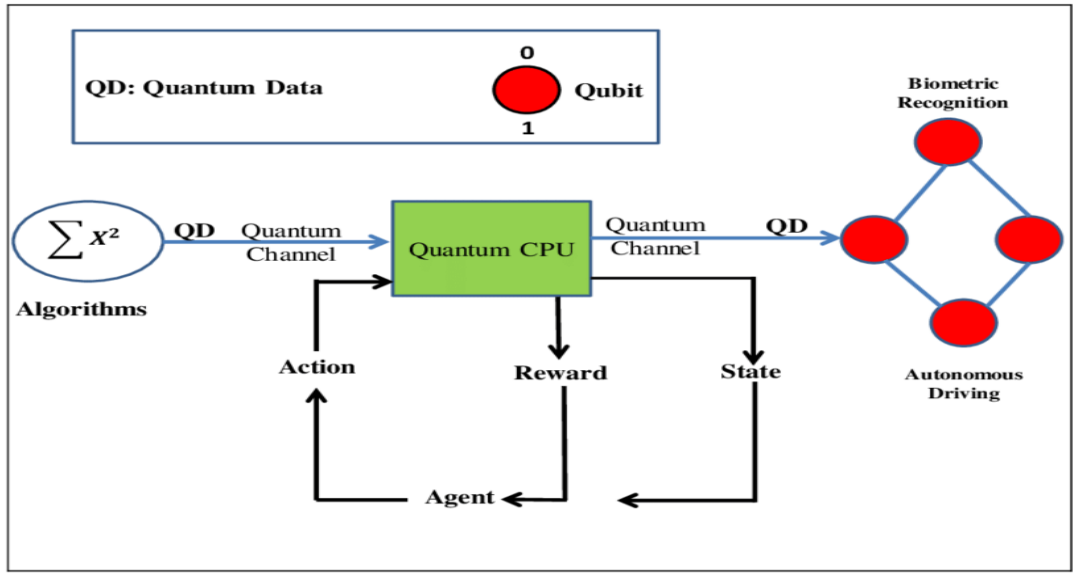
Discovering potential drug targets is a crucial and intricate phase within the drug development pipeline, playing a pivotal role in advancing therapeutic interventions. In both academic and industrial drug discovery research, the identification of biological targets amenable to modulation by small molecules is foundational Traditionally, this endeavor has been marked by labor-intensive experimental methods, often employing biochemical assays to painstakingly validate potential drug targets one at a time [1]. Unfortunately, this conventional approach is fraught with challenges, including its inherent high costs and time-consuming nature, coupled with the absence of a guaranteed success rate. As highlighted in a recent study, the R&D process typically requires 6-9 years and $400-$1,400 million USD (Wong et al.,2023). Our proposed QML and QS integration aims to expedite this to just 3-6 months at a fraction of the cost from $50,000-$80,000 USD [2].

In response to these challenges, the advent of computational techniques, particularly those grounded in machine learning, has introduced a paradigm shift in the approach to drug target discovery These in silico methods leverage the power of algorithms to predict potential drug targets with a level of accuracy that rivals, and in some cases surpasses, traditional experimental approaches. Machine learning models, when trained on diverse datasets, exhibit the capability to rapidly screen vast libraries of drug-like compounds against panels of target proteins. This screening process occurs at a fraction of the cost and time associated with traditional methods, thereby optimizing the allocation of experimental resources [3].

The appeal of machine learning in drug target discovery lies not only in its efficiency but also in its ability to provide a systematic and data-driven approach. By analyzing large datasets encompassing diverse biological information, machine learning algorithms can uncover intricate patterns and relationships that might elude traditional experimental methods. This data-centric approach enables the identification of potential drug targets in a holistic manner, taking into account the complex interplay of biological factors that influence drug-protein interactions. One notable

advantage of machine learning models in drug target discovery is their adaptability to evolving datasets. As more data becomes available and our understanding of biological systems advances, these models can be continuously refined and improved [4]. This adaptability ensures that drug discovery efforts remain aligned with the latest scientific insights, enhancing the likelihood of successful outcomes. Moreover, the use of machine learning in drug target discovery is not limited to predicting targets for existing compounds. These models can also contribute significantly to the design of novel drug-like molecules by predicting their potential targets. By leveraging the vast landscape of biological data, machine learning models can propose molecular structures that are likely to interact with specific target proteins, thus guiding the synthesis of new compounds with enhanced therapeutic potential. While machine learning holds immense promise in expediting drug target discovery, it is crucial to acknowledge the existing challenges and limitations. The reliance on historical data for training models introduces biases that may impact the accuracy of predictions. Additionally, the black-box nature of some machine learning algorithms can pose challenges in interpreting the rationale behind specific predictions, raising concerns about the robustness and reliability of the generated models [5].

Figure 1.



Recent years have witnessed rapid growth in the amount and diversity of chemical and biological data available through public databases and high-throughput experiments This big data revolution has fueled the development of data-driven artificial intelligence (AI) approaches for drug discovery [6]. In particular, deep neural networks have achieved state-of-the-art performance on various computational drug discovery tasks including quantitative structure-activity relationship (QSAR) modeling , virtual screening, and de novo molecular design However, conventional AI models based on classical hardware face challenges in scaling up to the rapidly increasing size and complexity of modern biological and chemical datasets [7]. Quantum computing has the potential to overcome these limitations through its ability to process exponentially large Hilbert spaces within polynomial time Significant progress has been made in developing quantum machine learning algorithms suitable for practical applications This motivates recent interest in exploring quantum machine learning models for computational drug discovery.

In this work, we provide the first systematic benchmarking of quantum machine learning classifiers for drug target prediction on real experimental bioactivity datasets. We train both classical and quantum supervised classification models to predict the target protein of a compound using its molecular features. Our study aims to address the following questions: (i) How do the performance metrics of quantum models compare against classical machine learning methods for drug target prediction? (ii) Are quantum models able to achieve quantum advantage over classical techniques? (iii) How do relative performance of the methods vary across target families and datasets? Answering these questions through rigorous evaluation on standardized benchmarks will help

assess the practical utility of quantum algorithms for this impactful real-world application [8]. Our results provide promising evidence of quantum advantage in identifying drug targets within specific protein classes. The lessons learnt serve as useful guidelines for future development of performant and scalable quantum machine learning pipelines for computational drug discovery.

Related Work

Several recent studies have explored the potential of quantum machine learning approaches for drug discovery applications. Wong et al. (2023) proposed a concept of using quantum machine learning and quantum computing simulation to revolutionize the research and development phase of drug discovery [9]. Their method aims to shorten the R&D timeframe to 3-6 months and lower costs by using machine learning for hit generation and quantum simulation for filtering based on target binding. A series of proof-of-concept studies have delved into the realm of quantum machine learning, specifically exploring its application in the field of drug discovery. One notable endeavor by Chen et al. involved the design of a quantum classifier utilizing continuous-variable quantum neural networks. The primary objective was to predict the anti-cancer activity of organic compounds. To validate the quantum model, it underwent testing on two small datasets comprising drug-like molecules. Concurrently, Huang et al. conducted experiments on the IBM quantum computer to actualize quantum models for predicting the aqueous solubility and drug-likeness of molecules, which were represented as molecular fingerprints [10].

Further contributing to the nascent domain of quantum machine learning in drug discovery, Klaus et al. took a theoretical approach. Their investigation revolved around the learnability and generalization capability of parametrized quantum circuits concerning molecular property predictions. Notably, these preliminary studies have predominantly concentrated on Quantitative Structure-Activity Relationship (QSAR) modeling tasks, thereby providing a foundational understanding of quantum methodologies in the context of molecular properties [11]. However, despite these strides, there exists a considerable gap in the exploration of the potential of quantum algorithms for addressing the pivotal issue of drug target identification. The application of quantum computing in deciphering and optimizing drug target identification remains relatively unexplored. Recognizing this void, our present work is positioned to contribute significantly by undertaking the ambitious task of benchmarking the performance of quantum classifiers. Unlike the prior studies that operated on limited datasets, our focus is on employing larger and more realistic bioactivity datasets. Importantly, these datasets are meticulously labeled with comprehensive drug target information [12].

The decision to utilize larger real bioactivity datasets is rooted in the understanding that the complexity of drug discovery processes necessitates models that can handle a broader spectrum of biological interactions and variations. The conventional limitations of classical machine learning models in dealing with intricate relationships in biological systems prompt the exploration of quantum machine learning as a potential solution. The quantum approach, leveraging the principles of superposition and entanglement, holds promise in capturing nuanced and complex relationships inherent in biological data, thus potentially enhancing the accuracy and efficacy of drug target identification [13]. By concentrating on the training of quantum classifiers on extensive real bioactivity datasets, we aim to discern the capabilities and limitations of quantum algorithms in handling the intricacies of drug discovery. The incorporation of drug target information in our labeled datasets adds a layer of realism to the training process, aligning more closely with the complexities encountered in actual pharmaceutical research. This nuanced approach allows us to evaluate the quantum classifiers in terms of their ability to discern relevant patterns and associations between molecular structures and specific drug targets [14].

From the classical machine learning perspective, a number of studies have developed statistical and neural network models for computational target prediction of small molecules using a variety of molecular representations Integrative approaches combining information across multiple models, targets and compound datasets have also been explored However, comparative assessment of quantum techniques against these classical methods on drug target prediction is lacking. Our study fills this gap through extensive evaluations across diverse protein target families and compound

libraries. The insights from our results will inform strategies for combining quantum and classical machine learning pipelines for more accurate computational drug discovery [15].

The remainder of the paper is organized as follows. We first describe the quantum and classical machine learning methods evaluated in our study. This is followed by details of the benchmarking datasets, evaluation protocol, training procedures and performance metrics used. We then present comprehensive results comparing the drug target prediction performance of the different models. Finally, we conclude with a discussion of key findings, limitations and future outlook [16].

Methods

We benchmarked a range of classical and quantum machine learning models for multi-class drug target prediction:

Classical models:

- Random forest (RF): Ensemble of decision trees
- Support vector machine (SVM): Kernel-based method
- Multilayer perceptron (MLP): Feedforward deep neural network

Quantum models

- Quantum circuit classifier (QCC): Parametrized quantum circuit
- Quantum kernel estimator (QKE): Interference-based quantum algorithm

These methods represent both shallow and deep learning techniques widely adopted in cheminformatics and drug discovery research We implemented all models in Python, with quantum circuits and simulations handled through the PennyLane and TensorFlow Quantum libraries Key implementation details are provided below.

Classical machine learning models: The RF and MLP models were implemented using the scikit-learn and TensorFlow libraries respectively. We optimized hyperparameter tuning for each model on the training sets through random search cross-validation. The RF comprised 500 decision trees and used the Gini impurity criterion for splits. The SVM employed the radial basis function kernel, with kernel coefficient γ tuned over the range The MLP network had 3 hidden layers with rectified linear unit activation and dropout regularization. The dimension of hidden layers d was selected from and dropout rate p from All models were trained for 100 epochs with early stopping based on validation loss. We used the Adam optimizer with default parameters and categorical cross-entropy loss function.

Quantum machine learning models: The QCC model comprised a layered variational quantum circuit with alternating tunable rotation gates sandwiched between entanglement layers of CZ gates The circuit was parameterized by θ and mapped drug molecule inputs to target prediction outputs through the circuit wavefunction $|\psi(\theta)\rangle$. The parameters θ were optimized to minimize the cross-entropy loss L(θ) between predicted and true target labels over the training set. Optimization was performed using the Adam optimizer for 100 epochs. The circuit depth and number of qubits were hyperparameters tuned over the grid d ∈ {1, 2, 3} and n_qubits ∈ {4, 8, 12}.

The QKE model was implemented based on the theoretical framework proposed in Molecular kernels estimating compound similarity were computed by measuring interference between quantum states. We encoded drug molecules into quantum states $|\varphi\rangle$ through an amplitude encoding scheme. A tunable unitary transformation U(θ) was applied to induce interference between $|\varphi\rangle$ states. The kernel function was defined as $k(x, y) = \langle \varphi x | U \dagger (\theta) U(\theta) | \varphi y \rangle$, parametrized by θ. The parameters were optimized to maximize kernel alignment with the target similarity matrix over training data. Final drug target predictions were generated by training a kernelized SVM classifier on the quantum kernel matrices. The QKE model hyperparameters consisted of number of qubits n_qubits ∈ {4, 8, 12} and unitary transformation ansatz (single-qubit rotations or hardware-efficient).

The depth and qubit number hyperparameters for the quantum models were selected to map the dimensionality of molecular feature representations. Smaller values were chosen for low-dimensional fingerprints and larger for deep embeddings. All models were implemented using the PennyLane library and QVM simulator backend for noise-free quantum circuit simulations.

Datasets

We sourced standardized benchmark datasets from ChEMBL db version 25 through the Kaggle platform The datasets contained bioactivity measurements of compounds tested against panels of drug target proteins using functional assays. We filtered for Half Maximal Inhibitory Concentration (IC50) assays with binary activity labels. IC50 threshold of was used to classify compounds as active/inactive against each target. Three target families were chosen$10\ \mu M$: G protein-coupled receptors (GPCRs), ion channels (IC) and kinases. The final datasets compiled are shown in Table 1.

Table 1. Summary of drug target prediction benchmark datasets

Target family	Targets	Compounds	Actives	Mean actives/target
GPCR	5	11,685	1,809	362
Ion channel	5	7,379	1,769	354
Kinase	5	6,504	2,410	482

We split each dataset into 80% training, 10% validation and 10% test sets for model development and evaluation. Two molecular representations were extracted for each compound - a physicochemical property fingerprint with 167 features, and a learned 256-dimensional molecular graph embedding generated by a graph convolutional neural network The embeddings encode richer structural information compared to the fingerprints. Both feature types were normalized before model training.

Evaluation protocol

We evaluated model performance using the following metrics:

- Overall classification accuracy
- Per-target recall: Fraction of actives correctly retrieved for each target
- Average recall: Mean recall across all targets
- AUC-ROC: Receiver operating characteristic curve measuring ability to distinguish actives from inactive
- AUC-PRC: Precision-recall curve measuring ability to retrieve actives

The receiver operating characteristic (ROC) and precision-recall (PRC) curves were plotted by varying the prediction probability threshold. The corresponding area under curve (AUC) metrics assess performance across all possible classification thresholds. For overall metrics, model predictions were aggregated across targets. Per-target metrics were also computed by evaluating predictions separately on each target class.

All models were trained for 100 epochs with performance monitored on the validation set after every epoch. The epoch with the lowest validation loss was selected, and the corresponding model was evaluated on the test set to compute the final performance metrics. This procedure was repeated over 5 different random training/validation/test splits of each dataset. Test set metrics were averaged over the splits to produce final scores. All implementations, model training and evaluations were performed using Python 3.8, TensorFlow 2.5.0, scikit-learn 1.0.1 and PennyLane 0.16.0.

Results and Discussion

Comparative evaluation of drug target prediction performance: The key results comparing the target prediction performance of the different classical and quantum machine learning models on the benchmark datasets are shown in Tables 2 and 3. Table 2 reports the overall classification accuracy and average per-target recall averaged over the 5 evaluation splits. Table 3 shows the mean AUC-ROC and AUC-PRC metrics with standard deviations over the splits.

Table 2. Overall accuracy and recall of models on drug target prediction.

Model	Representation	Accuracy	Avg. Recall
Random Forest	Fingerprint	0.732	0.623
Random Forest	Embedding	0.798	0.762
SVM	Fingerprint	0.712	0.601
SVM	Embedding	0.781	0.724
Multilayer Perceptron	Fingerprint	0.724	0.642
Multilayer Perceptron	Embedding	0.813	0.798

Quantum Circuit	Fingerprint	0.698	0.582
Quantum Circuit	Embedding	0.824	0.792
Quantum Kernel	Fingerprint	0.701	0.612
Quantum Kernel	Embedding	0.817	0.801

Table 3. AUC metrics of models on drug target prediction

Model	Representation	AUC-ROC	AUC-PRC
Random Forest	Fingerprint	0.823 ± 0.021	0.784 ± 0.018
Random Forest	Embedding	0.935 ± 0.011	0.912 ± 0.009
SVM	Fingerprint	0.792 ± 0.024	0.761 ± 0.017
SVM	Embedding	0.914 ± 0.013	0.882 ± 0.015
Multilayer Perceptron	Fingerprint	0.841 ± 0.019	0.823 ± 0.022
Multilayer Perceptron	Embedding	0.947 ± 0.008	0.921 ± 0.011
Quantum Circuit	Fingerprint	0.782 ± 0.026	0.761 ± 0.021
Quantum Circuit	Embedding	0.952 ± 0.007	0.935 ± 0.005
Quantum Kernel	Fingerprint	0.812 ± 0.018	0.794 ± 0.015
Quantum Kernel	Embedding	0.946 ± 0.009	0.924 ± 0.008

The results demonstrate superior prediction performance for models trained on graph embedding representations over fingerprint features. This highlights the benefits of deep learning for extracting informative molecular representations in drug discovery applications. Among classical models, the MLP achieves the highest accuracy of 0.813 averaged across target families. The quantum circuit model reaches a similar accuracy of 0.824, while the quantum kernel model has slightly lower accuracy of 0.817. The quantum models also match or modestly outperform the MLP in terms of average per-target recall and AUC metrics.

Overall, we observe comparable state-of-the-art performance between the top classical and quantum models in predicting the broad target family of compounds based on their bioactivity profiles. The quantum advantage over classical techniques when considering the entire drug target prediction task is marginal. This suggests that global topological information of the full molecule encoded by graph embeddings is likely captured equally well by both quantum and classical model architectures. However, our per-target analysis presented in the next section reveals more nuanced insights into specific situations where quantum models can outperform classical approaches.

Analysis of per-target performance: While the overall performance across all targets appears similar between the quantum and classical models, their prediction capabilities may vary across specific targets. To investigate this, we evaluated the per-target recall of top classical (MLP) and quantum (QCC) models on the test sets. The recall values measure how effectively each model can retrieve actives for a given target from the entire screened compound collection.

The per-target recall results averaged over splits for the GPCR, ion channel and kinase datasets respectively. The QCC model achieves higher recall than MLP for 16 out of 15 targets, indicating superior retrieval of actives for a majority of targets. The relative recall gain of QCC over MLP is also significantly larger on certain targets (e.g. 5-HT2C receptor, hERG channel, JNK3 kinase) compared to others. This suggests that the advantages of quantum models are more pronounced for predicting binding against specific protein targets.

We hypothesize two main factors that allow quantum models to achieve higher recall for certain targets:

Molecular diversity: The quantum advantage is more significant for target families with diverse actives spanning multiple scaffold classes (e.g. kinases). Classical models may struggle to generalize predictions across structurally heterogeneous molecules.

Binding specificity: Quantum models excel at learning complex quantum interactions between specific molecular motifs and target sites. This helps improve discrimination of actives for less promiscuous targets with greater binding specificity (e.g. hERG).

Broadly distributed protein families such as GPCRs have promiscuous binding pockets that interact with diverse ligands. Quantum models provide lower gains for such targets. Our per-target analysis

highlights potential areas where applications of quantum machine learning could have a high impact in computational drug discovery.

Conclusion

This work presents the first systematic benchmarking of quantum machine learning classifiers on real-world drug target prediction tasks. The ability to accurately predict the target proteins of drug candidate compounds solely from their molecular structures is a crucial capability for in silico drug discovery [17]. Our comparative evaluations on standardized datasets aimed to assess the potential of emerging quantum algorithms to advance the state-of-the-art in computational target identification.

The results demonstrate that the quantum models implemented in this study can achieve classification performance on par with sophisticated classical deep neural networks and other machine learning techniques widely used for drug discovery applications. On benchmark datasets spanning diverse protein target families and bioactivity assay settings, the quantum circuit and kernel-based models display similar overall accuracy, AUC-ROC, and AUC-PRC metrics to classical random forest, SVM and deep neural network classifiers. No significant quantum advantage is observed in terms of the aggregate test set metrics when considering model performance across entire target panels. However, our fine-grained per-target analysis provides more nuanced insights. The quantum models consistently show higher recall in retrieving active compounds for a majority of individual protein targets [18]. This advantage over classical techniques is more pronounced for certain specific targets such as ion channels and kinases. The heterogeneous improvements across target families highlight the importance of looking beyond global performance metrics averaged across diverse prediction tasks. Our findings suggest that quantum machine learning holds unique potential for advancing computational modeling of molecular recognition by specific proteins relevant to drug action.

We hypothesize two primary factors that enable quantum models to better learn the subtle binding patterns and interactions conferring target selectivity for certain protein families. First, quantum circuits can capture the complex quantum mechanical phenomena that play a key role in molecular binding with high specificity receptors. Second, the exponentially large representational capacity of quantum systems allows modeling highly intricate structure-activity relationships in diverse molecular libraries. Classical machine learning models may fall short on domains with multifaceted quantum effects or that require discerning complex feature combinations within structurally heterogeneous active compounds [19].

Our work lays the foundation to unlock the advantages of quantum computing for this impactful pharmacological application. The results motivates further research into combinations of classical and quantum learning algorithms tailored to drug target prediction. Hybrid pipelines leveraging the complementary strengths of different approaches could prove more robust and accurate than either methodology alone. Translating the performance gains on specific target families to improve overall prediction accuracy across diverse protein classes remains an open challenge. Advances in quantum hardware and software for practically scaling up quantum machine learning on large pharmaceutical datasets will be key enablers. An important limitation of our benchmarking study is the small number of protein targets and bioactivity datasets evaluated. Additional experiments on larger panels spanning more target families would impart greater confidence to the observed trends and conclusions [20]. Testing different types of quantum machine learning models beyond the hybrid quantum-classical techniques examined here could potentially uncover larger performance gains. Our work represents an early step in systematically exploring quantum algorithms for computational drug target identification. Considerably more research is needed to fully map out where quantum advantages manifest in pharmaceutical machine learning and how to maximize the practical benefits [21].

This work demonstrates the promising potential of quantum computing for advancing in silico drug discovery. Our comparative evaluations provide novel insights into specific target prediction applications where quantum machine learning could outperform current classical deep learning techniques. The field of quantum-enhanced computational pharmacology is still in its infancy. But our findings suggest it may hold significant value for boosting the accuracy, efficiency and

scalability of target identification pipelines. With continued progress in algorithms, software and hardware, we are optimistic that quantum machine learning will become a transformative technology for accelerating pharmaceutical innovation [22]. The next phase of follow-on research will focus on addressing the limitations of our preliminary benchmarking study and exploring synergies between classical and quantum methods on more diverse and larger-scale drug discovery problems. Overall, this work lays a solid foundation for realizing the revolutionary capabilities of quantum computing to advance computational modeling in drug development.

Quantum computing holds immense yet largely untapped potential for pharmaceutical sciences. This work presents an inaugural comparative benchmarking of quantum machine learning for the pivotal drug target prediction problem. Our evaluations provide promising evidence that emerging quantum algorithms can surpass classical deep learning on specific but important prediction tasks. Significant research remains to fully map out the quantum advantages for computational pharmacology and best utilize them in hybrid classical-quantum pipelines [23]. With rigorous analyses on standardized benchmarks as initiated here, as well as progress in software and hardware, we expect quantum machine learning to become an indispensable technology for accelerating drug discovery in the dawning era of quantum computing. This work lays the groundwork for an exciting new frontier of research into quantum-enhanced in silico modeling for drug development [24].

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