CT6039 Dissertation

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**Developing an explainable deep learning model for drug-drug interaction prediction**

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# **1. Abstract**

An overview of what the paper contains

# **2. Introduction (374 words)**

**Overview:**

This research endeavours to address the challenge of enhancing the interpretability of deep learning algorithms in the field of drug-drug interaction prediction, to increase trust in models, and enable wider adoption by healthcare practitioners. This will reduce risk to human life, and costs for pharmaceutical companies performing clinical trials.

**Aim:**

The aim is to develop an accurate deep learning model for drug-drug interaction prediction while emphasizing explainability in the results. This entails leveraging both the predictive power of deep learning algorithms and explainable AI methods to enhance the models explain-ability.

**Problem statement:**

How to increase explainability of deep learning algorithms for drug-drug interaction prediction, to improve reliability and reduce patient risk?

**Objectives:**

* To investigate current deep learning approaches for drug-drug interaction prediction.
* To develop a new explainable machine learning model for drug side effect prediction.
* To evaluate the developed model, measuring its accuracy and explainability.
* To validate the developed model on unseen data.

**Research questions:**

* What are the current deep learning models used for drug-drug interaction prediction?
* How can deep learning models be made more explainable?
* What are the best methods of measuring accuracy and explainability in deep learning models?
* How can a deep learning model be made more robust to unseen data?

**Scope:**

This research will primarily focus on developing a hybrid machine learning model that emphasizes explainability in its results. This will be achieved by combining deep learning and traditional methods. Multiple data sources will be used to train the model, including chemical structures, and chemical properties (molecular weight, no. bonds, atom count, etc).

For the purpose of creating a working proof of concept, predictions will be limited to drug-drug interactions, and will not include prediction of side effects from interaction between more than two drugs. A user-friendly interface and visualization tools will present the model's predictions, aiming to make it understandable by both researchers and healthcare practitioners. The models performance will be evaluated using appropriate metrics and cross-validation techniques, as well as comparison to traditional methods, and other hybrid model case studies found in the literature review.

**Conclusion:**

Through these components, this research aims to contribute to the advancement of drug-drug side effect prediction by creating a model that combines deep learning predictive capabilities with a high degree of explainability.

# **3. Literature Review**

## **3.1 Brief History**

To understand the current landscape of the pharmaceutical industry, it is useful to first look to the past. When discussing side effects and adverse reactions from drugs, the most notable example in history is the Thalidomide incident that occurred in the late 1950’s to early 1960’s. Initially approved and marketed as anti-nausea medication, pregnant women who had taken the drug gave birth to children with severe birth defects. Less severe side effects were also noted, consisting of rash, fatigue and constipation. This was a turning point in the pharmaceutical industry, causing clinical trials to become stricter, and testing for adverse drug reactions (ADR’s) more thoroughly.

Add a source to back up the info on the Thalidomide crisis?

Regardless of stricter regulations, traditional methods of detecting ADR’s fail to provide a fully comprehensive solution alone. Methods such as post-marketing surveillance and adverse event reporting help to identify ADR’s, however these are reactive solutions which only provide this information after potentially causing significant damage to large groups of patients (Yang and Kar, 2023, p. 1).

The collection of adverse drug reaction data into organised databases opened up the possibility for deeper data analysis, and eventually machine learning, to be applied. The more information that is gathered about drugs properties and interactions, the more we understand them. Databases such as SIDER provide information on drug-ADR pairs, gathered from drug labels, academic research, and post-marketing surveillance (Kuhn *et al.*, 2016, p. 1). This data ranges from specific information about the drugs, to frequency and severity of their ADR’s.

When trying to predict ADR’s, multiple factors may be considered. These factors can be categorised in one of four categories, patient, social, drug or disease (Alomar, 2013, p. 85). Patient factors include age, gender, weight, genetics, and allergies. These can be some of the hardest to gather large datasets for, often leading to them being left out of generalised predictive models. The same can be said for social factors, such as drinking or smoking. The most common factors used to predict ADR’s are drug related factors, such as dose or frequency of use. Polypharmacy, taking multiple drugs together, is a significant drug related factor which contributes to adverse reactions. Disease factors relate to when drugs are used to treat one disease, and worsen another that was already present.

*Add a reference at the end for diseases worsening ADR’s?*

*Add a source talking about the expenses of clinical trials and drug discovery?*

## **3.2 Early Machine Learning Research**

Early usage of machine learning for ADR prediction was focused on the interaction of single drugs with existing protein structures within the body. This allowed researchers to create drugs which avoided interaction with those proteins. One such study found that Support Vector Machines (SVM’s) could identify and associate ADR related protein structures with a high degree of accuracy, correctly classifying 93.9% of the proteins related to known ADR’s (Ji *et al.*, 2012, p. 319). It should be noted however that the data used was limited in its diversity, and the model therefore would not generalise well to new datasets or less common ADR related protein structures. In addition to this, as it has been established, while protein interaction can cause ADR’s they are not the only factor involved. Research into protein structures paved the way to exploring other factors, primarily drug related, as they had the largest quantity of data available.

As the field of ADR prediction grew, the next logical step was to begin incorporating multiple types of data and ADR factors into machine learning models. Researchers creating models which utilised chemical structure and biological information such as protein targets, noted that they were able to achieve a significantly higher accuracy when incorporating multiple types of data in comparison to only using chemical structures (Liu *et al.*, 2012, p. 32). A comparison of five models (logistic regression, naïve Bayes, K-nearest neighbor, Random Forest, and SVM) with fivefold cross-validation revealed better performance by SVM and Random Forest across all metrics. The results achieved in this study prove that using a hybrid fusion of multiple data types helps increase accuracy when predicting ADR’s.

Some studies chose to focus on patient related factors, such as Valeanu *et al* (2020, p. 1), who created a patient tailored model. This allowed patients to enter information about themselves, and the drugs they are taking, and a report would be generated to highlight their likelihood of experiencing ADR’s. The report included a severity profile which assessed the risk to the patients health, as well as a list of probabilities for each ADR they may experience. This model is especially significant, because in addition to patient factors it considers polypharmacy, a major factor which causes ADR’s, and one that has limited data and studies which focus on it. Perhaps the most notable part of the model, it was presented in a web application, with a user friendly GUI. This is less commonly seen and focused on in studies which aim to create predictive models for ADR’s, even in the present day. However for models to adopted by pharmaceutical and medical practitioners this is extremely important, as it promotes trust in the model.

*I put this case study here, but honestly, I have no idea why.*

[Prediction of adverse drug reactions based on knowledge graph embedding](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7863488/#:~:text=There%20is%20a%20large%20body,Dey%2C%20et%20al.)

## **3.3 Deep Learning Research**

**Look next at reviews which identify the most dangerous sources of ADR’s, leading to DDI prediction, and how deep learning has been applied to that**

* *Introduce the study which created the Decagon model, which was used to gather the data I’ll be using*

[Modelling polypharmacy side effects with graph convolutional networks](https://academic.oup.com/bioinformatics/article/34/13/i457/5045770?login=false)

* *Use this study to relate which machine learning models are most commonly used with which data sets*

[Analysing adverse drug reaction using statistical and machine learning methods](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9276413/)

* *Discuss this case study, where they identify ADR related data sources, as well as talk about the issue of interpretability.*

[A survey on adverse drug reaction studies: data, tasks and machine learning methods](https://academic.oup.com/bib/article/22/1/164/5678053)

* *Use this study to back up that DDI is important, needs deep learning, and lacks interpretability. This study also covers the current models being used for DDI. It also discusses an example where they just used structure to predict, and why diversifying data is important.*

[Prediction of drug adverse events using deep learning in pharmaceutical discovery](https://academic.oup.com/bib/article/22/2/1884/5826453)

**Review models which include deep learning, and how they are more accurate**

* *Discuss the CNN-BiLSTM case study, which provides descriptive predictions of ADR’s by chemical structure. Has an interesting way of describing side effects with natural language.*

[Descriptive prediction of drug side-effects using a hybrid deep learning model](https://onlinelibrary.wiley.com/doi/full/10.1002/int.22389?casa_token=wFyukhmhKR8AAAAA%3AaUR1UKic6M0-KVysyeR4GLpuOiXFWigvZcZqZj7NjjfEAqrPDx_a2ACmI1_2PfPC-Ux2tuEtRdScx6rU)

* *Look at this case study’s methods of evaluating model accuracy. For future work, it suggests combining the LSTM model that evaluates ADR data, with a model that evaluates structure data. This promotes the idea of a hybrid model.*

[An Attentive LSTM based approach for adverse drug reactions prediction](https://link.springer.com/article/10.1007/s10489-022-03721-y)

* *Use this case study to justify using SMILES strings with deep learning. Also explore the possibility of using hypergraph neural networks, as it achieved a high accuracy.*

[HyGNN: Drug-Drug Interaction Prediction via Hypergraph Neural Network](https://arxiv.org/abs/2206.12747)

* *Explore this study into knowledge graph for polypharmacy prediction.*

[SimVec: predicting polypharmacy side effects for new drugs](https://jcheminf.biomedcentral.com/articles/10.1186/s13321-022-00632-5#:~:text=The%20SimVec%20model%20allows%20predicting,side%20effect%20with%20another%20drug.)

* *Use the references from this study’s DDI section to get a timeline of noteworthy deep learning models for drug discovery.*

[Deep learning in drug discovery: an integrative review and future challenges](https://link.springer.com/article/10.1007/s10462-022-10306-1)

* *Review this study, that goes through successful deep learning models for DDI. It also mentions Decagon, which gathered the dataset I’m using.*

[Recent development of machine learning models for the prediction of drug-drug interactions](https://pubmed.ncbi.nlm.nih.gov/36748027/)

* *Look at knowledge graphs, and this study which uses a deep learning model that incorporates both chemical structure and a knowledge graph of chemical features.*

[Multi-view feature representation and fusion for drug-drug interactions prediction](https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-023-05212-4#:~:text=We%20present%20a%20multi%2Dview,features%20from%20bio%2Dmedical%20KG.)

## **3.4 Limits of Current Models**

One of the prevailing limitations highlighted in deep learning research for ADR prediction is the lack of interpretability and explainability in models. While they provide high accuracy, deep learning models introduce a level of uncertainty as to why predictions have been made. This causes a lack of trust, which impedes the adoption of machine learning for ADR prediction. Interpretable models are therefore especially important in medical and pharmaceutical fields, where lives are at risk if wrong predictions are made.

Deep learning models can be considered a “black box”, meaning data is given as input to the model and it outputs a prediction, while the internal processes which govern the models decision making process are obscured (Lee and Chen, 2019, p. 1340). The case has been made that both doctors and patients would be less likely to trust the predictions of an algorithm which doesn’t provide reasoning for its predictions and, arguably more importantly, models become much harder to debug when they fail or make incorrect predictions (Vamathevan *et al.*, 2019, p. 474).

*Use this as a supporting reference for the issue of interpretability?*

[Machine Learning in Drug Discovery: A Review](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8356896/)

## **3.5 Existing Interpretable Methods**

**Explain the current methods of increasing interpretability in models, and the challenges that comes with doing so (lower accuracy)**

* *Discuss this interpretable deep learning model that uses neural fingerprints.*

[Predicting adverse drug reactions through interpretable deep learning framework](https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-018-2544-0)

* *Looks at this review of explainable AI in DDI. Has good sources for different XAI techniques, as well as mentioning the issue of reduced predictive power.*

[On the road to explainable AI in drug-drug interactions prediction: A systematic review](https://pubmed.ncbi.nlm.nih.gov/35832629/#:~:text=In%20this%20review%2C%20a%20comprehensive,prediction%2C%20the%20modeling%20methods%2C%20is)

* *Discuss XSMILES, to give inspiration for my own models interface, which will represent SMILES strings in a similar way.*

[XSMILES: interactive visualization for molecules, SMILES and XAI attribution scores](https://jcheminf.biomedcentral.com/articles/10.1186/s13321-022-00673-w)

* *Discuss this study which explores methods of measuring explainability, which will be important for my evaluation.*

[An objective metric for Explainable AI: How and why to estimate the degree of explain ability](https://www.sciencedirect.com/science/article/pii/S0950705123006160)

* *Discuss the issue of interpretability brought up in this paper, and the deep learning methods which are easiest to make more explainable.*

[Deep learning in drug discovery: an integrative review and future challenges](https://link.springer.com/article/10.1007/s10462-022-10306-1)

* *Discuss the weighted drug-drug network method of improving accuracy, could counteract accuracy loss from interpretability methods?*

[How could a weighted drug-drug network help improve adverse drug reaction predictions? Machine learning reveals the importance of edge weights](https://dl.acm.org/doi/abs/10.1145/3579375.3579409)

*Add something in here about LIME? If I decide to use it.*

## **3.6 Proposed Solution**

Given the gaps in the current research which have been highlighted it is clear that, while deep learning models achieve high levels of accuracy when predicting ADR’s, deep learning cannot be fully adopted in ADR prediction or the drug discovery pipeline as a whole until the issues of explainability are addressed. Additionally, the models must be presented in an easy to use interface, to promote trust among the researchers and medical staff who would be utilising them. Few existing models seem to target polypharmacy predictions, due to a lack of datasets. There is therefore a clear need for a high accuracy, high explainability deep learning model, which can predict ADR’s that result from drug-drug interactions, and provides a clean user interface for researchers to interact with.

Recent work by Zhong *et al* (2023, p. 1) utilises Graph Convolutional Networks (GCN’s) for this purpose, improving their explainability while maintaining a high level of accuracy.

*Talk about the paper that did my idea*

*Discuss how I could do the 3d structure representations, maybe explainability representation with that?*

*Discuss adding extra tabular data to that? Or perhaps use the GCN in a hybrid model architecture?*

*Discuss using graph autoencoders for reduced feature complexity as an alternative to Sparseshift?*

*Discuss also using molecular fingerprints?*

# **4. Methodology**

## **4.1 Dataset Collection**

-Describe my datasets and other potential sources of ADR data.

## **4.2 Feature Selection**

-Explain which features I’m selecting from my combined datasets, and why.

## **4.3 Techniques**

-Explain each of the techniques and models I’m using in the project.

## **4.4 Evaluation Metrics**

-Explain how I am going to evaluate the success and accuracy of the model.

# **5. Data Pre-processing & Analysis**

## **5.1 Data Pre-processing**

-Go through how I cleaned, merged and prepared the datasets for analysis. Provide relevant screenshots and link papers which use the same analysis tools I do.

-Start with the decagon dataset

-Then how I found the PUG REST API for PubChem, which links to the ID’s from the decagon dataset. Discuss things I had to consider such as the rest limit for the API (5 requests a second), and how I accounted for it.

-Talk about my solution for the amount of API requests I would need to make, around 2 million, and how I managed to reduce that number significantly by adding in a check that re-uses past information.

-Talk about the specific information I gathered, atoms, bonds, coordinates and charges, as well as regular SMILES strings.

-Discuss how I tested the data gathering with aspirin first, to get the format right.

-Also discuss any calculations I needed to do, such as calculation bond length, bond angles and Dihedral angles.

## **5.2 Data Analysis**

-Give statistics and visual analysis of the data.

-Describe any further feature engineering done.

# **6. Benchmarking**

-Create 3 or 4 of the models from the literature review, the ones that got the best results. Fit them to my data, and see how they perform.

-For training, use five-fold cross-validation method. This means that the data is split into five parts, and the model is trained and validated on different combinations of these parts. This helps to find the best hyperparameters for the model.

-Evaluate their performance via accuracy, precision, recall, F1 score, k-fold cross-validation and other metrics laid out in the methodology.

# **7. Hybrid Model Development**

-Explain the design and architecture of my model.

-Detail the models training process, hyperparameter tuning and cross validation techniques used.

-Evaluate the models performance via its accuracy, precision, recall, F1 score, k-fold cross-validation and other metrics laid out in the methodology.

# **8. Evaluation**

-Analyse the results I got from my model, and compare them to the existing classical models.

-Discuss improvements or limitations that might have held my model back.

-Predict severity of ADRs

-Include patient data for enhanced accuracy

-Multi-label prediction rather than single-label

-Answer the research questions I wrote in the introduction.

# **9. Validation**

# **10. Conclusion**

-Summarise my findings in the project, and how it has contributed to ADR prediction.

-Identify future improvements to my work, and other potential areas.

# **11. Bibliography**

Alomar, M.J. (2013) ‘Factors affecting the development of adverse drug reactions (Review article)’, *Saudi Pharmaceutical Journal : SPJ*, 22(2), pp. 83–94. Available at: https://doi.org/10.1016/j.jsps.2013.02.003.

Ji, Z.L. *et al.* (2012) ‘Prediction of Putative Adverse Drug Reaction-Related Proteins from Primary Sequence by Support Vector Machines’, *International Journal of Pharmaceutical Medicine*, 19(5), pp. 317–322. Available at: https://doi.org/10.2165/00124363-200519050-00009.

Kuhn, M. *et al.* (2016) ‘The SIDER database of drugs and side effects’, *Nucleic Acids Research*, 44(Database issue), pp. D1075–D1079. Available at: https://doi.org/10.1093/nar/gkv1075.

Liu, M. *et al.* (2012) ‘Large-scale prediction of adverse drug reactions using chemical, biological, and phenotypic properties of drugs’, *Journal of the American Medical Informatics Association*, 19(e1), pp. 28–35. Available at: https://doi.org/10.1136/amiajnl-2011-000699.

Valeanu, A. *et al.* (2020) ‘The development of a scoring and ranking strategy for a patient-tailored adverse drug reaction prediction in polypharmacy’, *Scientific Reports*, 10, p. 9552. Available at: https://doi.org/10.1038/s41598-020-66611-8.

Vamathevan, J. *et al.* (2019) ‘Applications of machine learning in drug discovery and development’, *Nature Reviews Drug Discovery*, 18(6), pp. 463–477. Available at: https://doi.org/10.1038/s41573-019-0024-5.

Yang, S. and Kar, S. (2023) ‘Application of artificial intelligence and machine learning in early detection of adverse drug reactions (ADRs) and drug-induced toxicity’, *Artificial Intelligence Chemistry*, 1(2), p. 18. Available at: https://doi.org/10.1016/j.aichem.2023.100011.

Zhong, Y. *et al.* (2023) ‘DDI-GCN: Drug-drug interaction prediction via explainable graph convolutional networks’, *Artificial Intelligence in Medicine*, 144, p. 9. Available at: https://doi.org/10.1016/j.artmed.2023.102640.

# **12. Appendix**