Predicting Nitrosation of Individual Amines in Drug Molecules Using Statistical (Q)SAR Models

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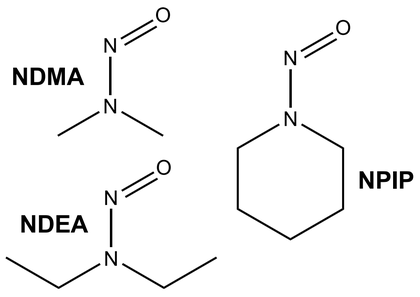
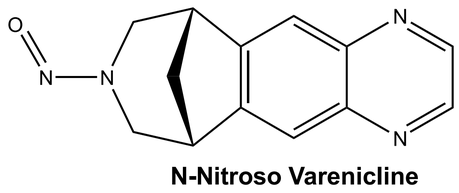
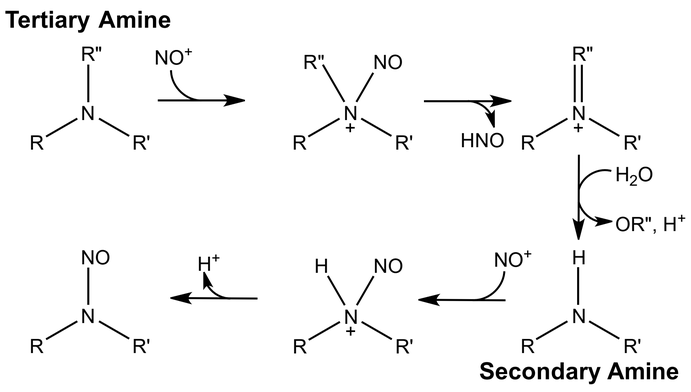
Introduction

Nitrosamines (NA) have been suspected to be carcinogenic for over 60 years. They are particularly dangerous because they can be long-lasting drug impurities that are activated *in vivo* by cytochrome P450. Since 2018, there have been a series of pharmaceutical recalls due to the discovery of *N*-nitrosamine impurities in the drug products.







Secondary amines are typically of the greatest concern because they are nitrosated so easily. Tertiary amines are nitrosated 1000× more slowly but can still be an issue.

Goal

- Use existing nitrosation data to build a statistical model that will predict if an amine is likely to be nitrosated based on a drug's molecular structure

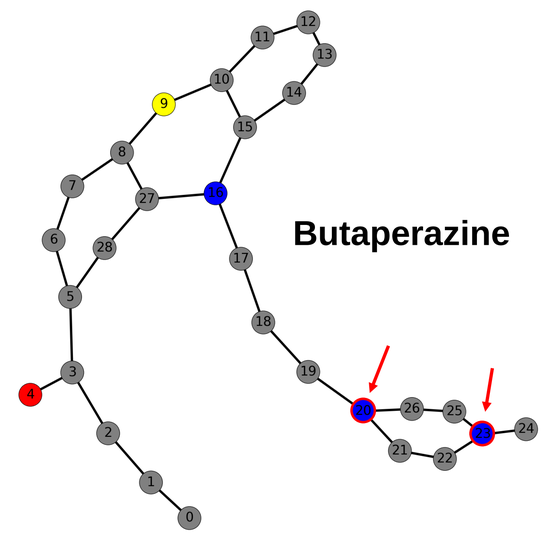
Methods

Dataset

Data was taken from published nitrosation studies that abided by the NAP test.[1] This yielded a dataset of **207 molecules** containing 143 secondary and 182 tertiary amines, as well as 93 other amines.

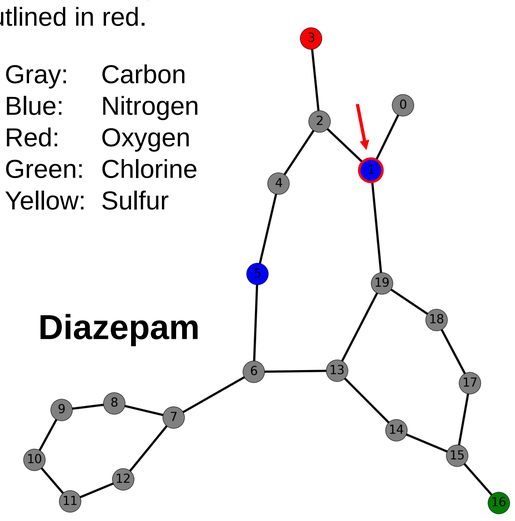
Graph Neural Networks

- Two Models
  - Graph Convolution Network [2]
  - Graph Attention Network [3]
- Node Classification
  - Positive: ≥1% NA yield
    - 110 amines
  - Negative: <1% NA yield
    - 308 amines



Atoms and bonds are represented as nodes and edges. Nitrosated centers are outlined in red.

Gray: Carbon
Blue: Nitrogen
Red: Oxygen
Green: Chlorine
Yellow: Sulfur



Measures of Model Quality

	Positive	Negative
True	TP	TN
False	FP	FN

- **Accuracy**: $(TP + TN)/(TP + FP + TN + FN)$
- **Positive Precision**: $(TP)/(TP + FP)$
- **Negative Precision**: $(TN)/(TN + FN)$
- **Positive Recall**: $(TP)/(TP + FN)$
- **Negative Recall**: $(TN)/(TN + FP)$

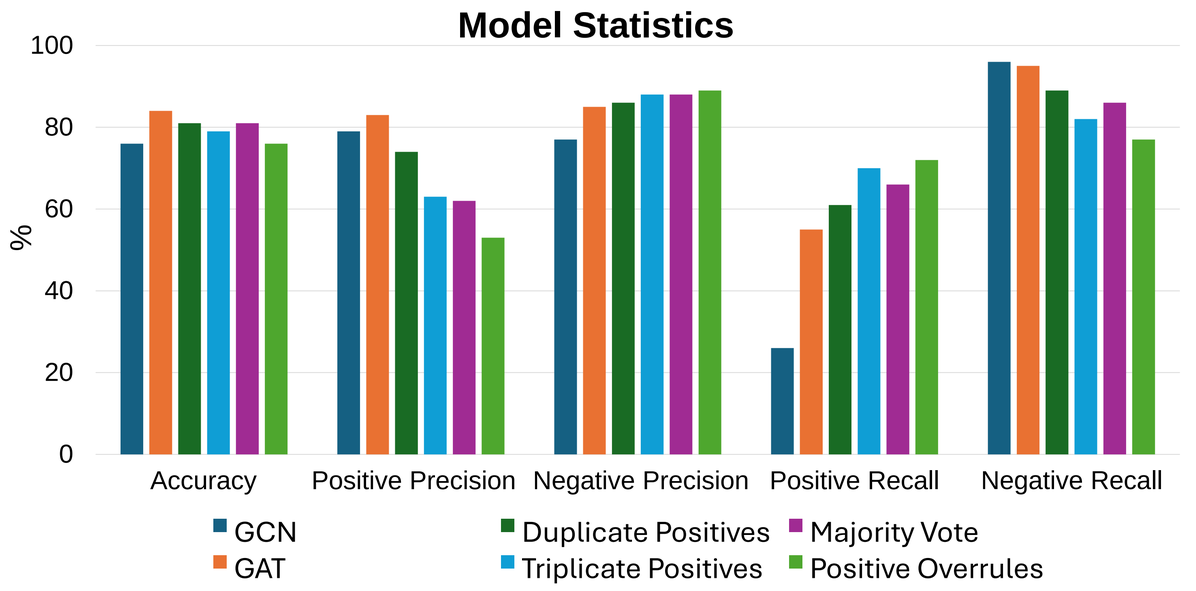
Model parameters were optimized to maximize accuracy, precision and recall of both positive and negative calls.

1. IARC Working Group, IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Some Pharmaceutical Drugs, vol. 24, Lyon: World Health Organization, 1980.
2. T. N. Kipf and M. Welling, "Semi-supervised classification with graph convolutional networks," in ICLR 2017, Toulon, 2017.
3. P. Veličković, G. Cucurull, A. Casanova, A. Romero, P. Liò and Y. Bengio, "Graph Attention Networks," in ICLR 2018, Vancouver, 2018.

Results

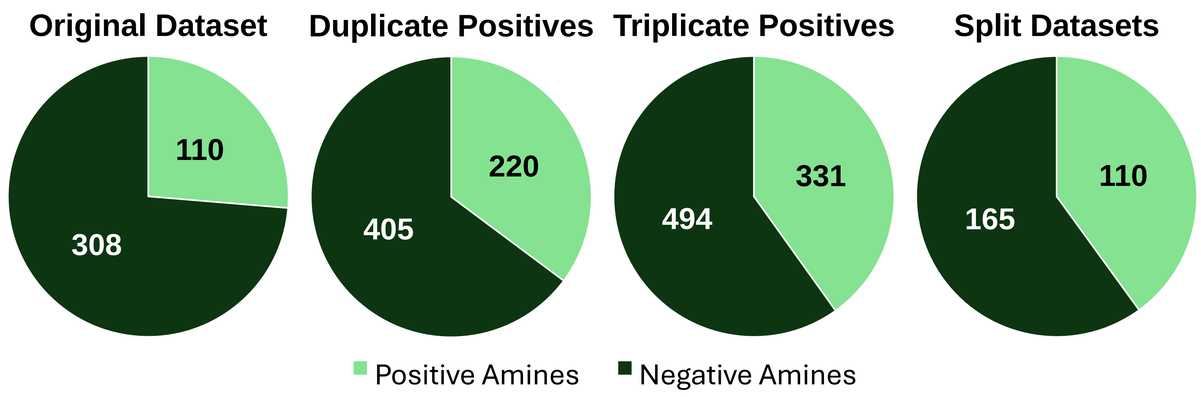
- **Accuracy** was generally high across both models, with GAT performing the best at **~84%**
- **Precision** was on par with overall model accuracy in all models
- **Positive Recall** was low in both model types, with GCN models only recalling between 1/3 and 1/4 of nitrosated amines and GAT models recalling slightly more than 1/2
- **Negative Recall** was nearly **100%** in GCN and GAT models

Overall, these results showed that the models excel at recalling un-nitrosated amines, with **GAT** consistently outperforming GCN.



Balancing the Dataset

- **Duplicating Positives**
  - Molecules with positive amines were duplicated (or tripled) in the training set
  - This improved positive recall, but at the expense of positive precision



- **Splitting the Dataset**
  - The negative molecules were split between three training sets
  - These datasets trained three models which then voted on a final call for each amine using one of two methods
    - **Majority Vote**: Final call is the result of a 2/3 majority
    - **Positive Overrules**: A positive vote from any model produces a positive final call
  - Both voting methods did increase positive recall but had the lowest precision (only 53% for "Positive Overrules")

Conclusion

- GNN models were excellent at detecting un-nitrosatable amines
- The **GAT** model performed the best, correctly identifying both positive and negative amines ~84% of the time
- Further improvements to the models will require a larger dataset with more nitrosatable molecules