**Predict the Stereoselectivity of Chemical Transformation by Machine Learning**

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Introduction:

Stereochemistry plays an essential role in biology. Most biochemical processes in living bodies are extremely sensitive to stereochemistry. For example, our bodies can only digest and make carbohydrates and amino acids of a certain stereochemistry, and all of the proteins that make up our bodies are composed of a single stereoisomer of amino acids. Our bodies can create and digest starch (found in potatoes and bread) but not cellulose (found in wood and plant fibers) despite both being polymers of glucose, however, with different stereochemistry. It is well known in medical practice that stereochemistry is important to drug action. For some therapeutics, single-stereoisomer formulations can lead to improved therapeutic indices because they provide greater selectivity for their biological targets and/or better pharmacokinetics than a mixture of stereoisomers. While one stereoisomer can have positive effects on the body, another stereoisomer may be less effective (D-Isoproterenol vs L-Isoproterenol on the blood pressures or heart rate), ineffective (as in the case of the R enantiomer of ibuprofen), or even toxic (as in the case of thalidomide).

Stereoselectivity or enantioselectivity is the most important aspect of organic transformation. Stereoselectivity can vary greatly in degree depending on reactants, catalysts, and reaction conditions. Quantitatively understanding and controlling the stereoselectivity of a chemical transformation – the relative proportions in which a non-stereospecific chemical transformation generates different stereoisomers under varying reaction conditions – is thus hugely important for organic synthesis. Yet we have only the most basic, qualitative understanding of the stereoselectivity of chemical transformations. We know that the stereoselectivity arises from differences in steric effects and electronic effects in the mechanistic pathways, but we have no rule for accurately, quantitatively predicting stereoselectivity. In addition, the optimizations of asymmetric transformations have been mainly by trial-error. A huge volume of data about the stereoselectivity of chemical transformation has been published over the past 100+ years, and volumes more are now generated. Machine learning has emerged as an effective avenue for taking advantage of these data to build computational models for accurately and quantitatively predicting the stereoselectivity of chemical transformation. In [Reid & Sigman 2019], Reid and Sigman collected the features of 350+ conditions in the CPA chiral phosphoric acid catalysis reaction family, and trained linear regression models for predicting reaction performance. The features include quantitative structure–activity relationships, molecular mechanics, and those derived for iminium, catalysts, and solvents using density functional theory. Why this family of reactions is important?

In this work, we use the dataset provided in [Reid & Sigman 2019] and develop a more sophisticated approach that achieve better performance. A few sentences about how we do it and what the results are.

Some reactions, don’t need to depend on imine

Some reactions, imine > nucleophile

Catalyst features not important

Possible that catalyst features can be well explained by features of imine, nucleophile

Tell people why we do what we want to do (why we use rf over lasso)

Lasso is simple lr, dt and bt capture variance, rf gi

In stereochemical reactions,

Reactions used:

The reactions used were

Methods:

Data Overview

There were 381 total entries in the dataset, collected from 17 sources. Each reaction included a substrate, solvent, catalyst, nucleophile, and imine. Numerical properties of the solvent (160 properties), catalyst (85 properties), nucleophile (15 properties), and imine (22 properties) were identified, as well as a DDG value of each reaction (\_\_\_insert explanation of what ddg double dagger means). Additionally, 64 out of sample reactions collected from 3 sources were used to test the final pipeline.

Early Assessment of Models

Three sets of relatively simple machine learning models were developed for various purposes.

The first set of models were regression models in which the properties of the solvent, catalyst, nucleophile, and imine of a reaction were used to predict the DDG value. The second set of models were machine learning regression models in which the properties of the solvent, catalyst, and nucleophile of a reaction were used to predict the DDG value – imine properties were excluded.

For both sets of models, four separate machine learning models were tested – Lasso, Decision Tree, Boosting Tree, and Random Forest -- and the results of each were compared. Lasso is well suited to capturing linear relationships between features and the Y variable, but may struggle when faced with non linear relationships. Decision Tree and Boosting Tree are able to capture more complex relationships between features. Random Forest improves on decision tree models by reducing overfitting and increasing stability. By implementing three different types of models – linear regression, decision tree, and random forest – we can compare the results and determine the most effective model for the data.

We hypothesized that imine properties could be explained/predicted by the other compounds involved in the reaction, so we also developed a classification model in which the properties of the solvent, catalyst, and nucleophile were used to predict the imine transition state of a reaction (either E or Z).

Training & Evaluation

We trained the models by randomly splitting the dataset 50:50 into a training set and testing set. The trained model was used to make predictions on the test data, and the predicted values were compared to actual test data values to measure accuracy. For regression models in which we predicted numerical values, r^2 was used as the metric of accuracy. The R^2 value measures how much variance in the dependent variable is explained by the model – the closer the r^2 value is to 1, the more accurate the model. For classification models, accuracy was measured simply by dividing the number of correct predictions by the total number of predictions made.

We also observed the feature importance of the models to identify chemical properties that were important and influential to the model’s predictions.

For every type of model we evaluated, we repeated the model creation/training process 100 times, each time with a different random 50:50 split of train/test data. This process ensured that \_\_\_ The mean accuracy/r^2 value over all 100 iterations was calculated and used to determine the accuracy of the model. Similarly, the mean feature importance of each chemical property across all 100 iterations was calculated.

Figure : Results of Random Forest Regression model from second set (excluding iminium properties). The predicted r^2 is 0.933, v and the total r^2 is 0.953

Chart, scatter chart

Description automatically generatedChart, scatter chart

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Figure : Results of Random Forest Regression model from first set (including iminium properties). The predicted r^2 is 0.926, and the total r^2 is 0.957.

Table : Results of models in the first set (including iminium properties)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Models | MSE | Test r2/STD | Train r2/STD | Total r2/STD |
| Lasso |  | Update! |  |  |
| Decision Tree | 0.351993 | 0.883525/0.285952 | 0.997219/0.001423 | 0.940417/0.014141 |
| Boosting Tree | 0.229198 | 0.924112/0.011411 | 0.987517/0.001991 | 0.955898/0.005407 |
| Random Forest | 0.223459 | 0.926373/0.013612 | 0.987074/0.002056 | 0.956674/0.006035 |

Table : Results of models in the second set (excluding iminium properties)

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Models | MSE | Test r2/STD | Train r2/STD | Total r2/STD |
| Lasso | 0.637415 | 0.788066/0.040520 | 0.873554/0.016922 | 0.831636/0.014616 |
| Decision Tree | 0.290518 | 0.903708/0.019526 | 0.976915/0.003481 | 0.940484/0.009601 |
| Boosting Tree | 0.233848 | 0.922961/0.011408 | 0.967222/0.004021 | 0.945171/0.005171 |
| Random Forest | 0.203178 | 0.932761/0.011805 | 0.972154/0.003513 | 0.952569/0.005606 |

Table : Results of models in the third set

|  |  |  |  |
| --- | --- | --- | --- |
| Model | Test acc | Train acc | Total acc |
| Knn | 0.970366 | 0.977737 | 0.974042 |
| Decision tree | 0.960000 | 0.993053 | 0.976483 |
| Random forest | 0.969581 | 0.993474 | 0.984196 |
| Logistic regression | 0.941571 | 0.973789 | 0.957638 |
| lda | 0.954555 | 0.983947 | 0.969213 |

Early Results:

Out of the regression models, the best performing model was the Random Forest model with Hyperparameters [insert description]. The model had a r^2 value on unseen test data of [insert score], and an overall r^2 value on all data of [insert score]. The performance of the other models developed can be found in [insert table].

The most important features in the Random Forest model were mostly properties of the imine and nucleophile of the reaction [reference to above table]. The Natural Bond Orbital C parameter was by far the most influential on the regressor, while other important features identified by our model include [insert features].

Similarly, the strongest model out of the second set of models was a Random Forest model with an r^2 value on unseen test data of [insert score], and an overall r^2 value of [insert score]. The performance of the other models developed can be found in [insert table].

The most important features in the Random Forest model were mostly properties of the nucleophile of the reaction [reference to above table]. The nucleophilic angles H-X-Nu and H-X-CNu were the most influential on the regressor.

The strongest model out of the third set of models was a K Nearest Neighbors Classifier with [insert accuracy] accuracy on unseen training data and [insert accuracy] accuracy on all data. The performance of the other models developed can be found in [insert table].

Analysis:

Firstly, our results indicate a strong correlation between the structural parameters of the various molecules involved in a reaction and the DDG value of the reaction. Our strongest models in both sets of regression models had r^2 values well over 0.9 when making predictions on test data, indicating strong performance, even on data it had not seen yet.

Imine and Nucleophile features seemed to clearly be the most important when predicting DDG values.

Additionally, the strong performance of the second set of models (which excluded imine properties). The Random Forest model (test r^2 = [insert score]) from this set was able to slightly outperform the Random Forest model from the first set (test r^2 = [insert score]), despite its disadvantage in not having information about the iminium involved with the reaction. This was an unexpected finding, as one would expect a decrease in performance after excluding imine properties since properties of the imine were very influential in making predictions in the first set of models. Rather, it was observed that nucleophile properties which were somewhat influential in the first set of models became the most important properties in the second set of models. This shows that while imine properties are important, they aren’t a necessity for strong predictions.

Additionally, the third set of models performed robustly in predicting the transition state of the imine. In addition, most of the important features identified were nucleophile properties that were also important features of the second set of models. This, along with the findings in the earlier paragraph, may signify that imine properties in its transition state can be predicted and/or explained using properties of other substances involved in the chemical reaction, especially the nucleophilic reactant involved.

Another interesting finding was that generally, in all three sets of models developed, solvent and catalyst properties did not seem to play a major role in making predictions about the reaction. A possible conclusion is that catalyst properties can be well explained and predicted based on the imine and nucleophile involved in the reaction

Development of Pipeline

One potential flaw we recognized with our random forest models was in its predictions on the out of sample reactions. While it was very accurate in predicting most reactions, in a few cases it had trouble when the prominent imine or nucleophile properties were in low density areas that the model was unfamiliar with. This was expected, since Random Forest are very effective dealing with data similar to what it was trained on, but it is has trouble extrapolating on completely new data values that fall outside of the training set because it is difficult for it to discover the trends that would allow it to do so. (put example of decision tree in random forest above) When faced with extreme outlying data that is far from the rest of the data, a decision tree may just make a very black and white decision to group it with one side or another of a tree, whereas other models such as linear regression models may be more effective in utilizing captured trends to extrapolate.

This particular flaw was highlighted when the overall random forest model was tested with 64 out of sample data entries. It especially had trouble with (reaction 19) (with a mean average error of \_\_\_), which had unique, unseen imines, and still struggled with (reaction 18) (with a mean average error of \_\_), which had unique, unseen nucleophiles.

One intriguing solution was to develop multiple models as part of an overall pipeline. When a reaction was predicted, the pipeline determined whether the properties of its imine and nucleophile were similar to our training data. Based on that, we chose the most effective model to make the final prediction. Based on our earlier success with the random forest model excluding imine features, we realized that it was possible to exclude parts of the reaction from the model, such as imine and nucleophile, and still produce good results from a random forest model.

Overall, four robust models were used in this pipeline. One was the aforementioned comprehensive random forest model which utilized all features from the reaction (imine, nucleophile, catalyst, solvent). We also developed two other random forest models, one which was imine focused and one which was nucleophile focused. The imine focused model excluded was dominated by imine properties and excluded nucleophile properties, which meant that in reactions with outstanding nucleophiles, the nucleophile would not have an effect on the prediction. In the nucleophile focused model, a similar approach was used in which imine properties were excluded, leading to a model that mostly relied on nucleophile features. Consequently, the model could be applied to reactions with unseen imines and still make accurate predictions. Finally, as a backup, catch all net, we developed a Lasso linear regression model that which could reasonably adapt to both unseen imine and nucleophile properties. While such a linear regression model may not be as accurate as Random Forest models in predicting most data, it would be more effective in extrapolating to new, outlying data than our other Random Forest models would.

To determine which model to use, we utilized Gaussian Mixture Models, probabilistic models which cluster points in Gaussian distributions. We developed two separate gaussian mixture models: one for important nucleophile features, and one for important iminium features. In the nucleophile mixture model, the model determines if the overall nucleophile is in a high or low density area by evaluating important nucleophile properties. Being in a high density area means that the nucleophile is somewhat similar to the nucleophiles that the model has been trained with, it is familiar with the nucleophile in the reaction and will be able to make accurate predictions based off of the nucleophile properties. Meanwhile, being in a low density area means that the training data had none/few nucleophiles that were similar to the nucleophile in the reaction, indicating that perhaps a model that excluded nucleophile features rather than depended on them would be advantageous. A similar imine gaussian mixture model was developed using the imine properties (insert properties) to determine whether the imine was in a high or low density area, and the pipeline used that determination to decide which model to use (including or excluding imine features).

The overall pipeline functioned as such: once a new reaction was fed in to be predicted, both gaussian mixture models were used to determine the log-likelihood score – how well the point fit in the gaussian distributions. A low score indicates that the point does not fit well with the existing gaussian clusters – thus likely placing it in a low density area far from the other data points. On the other hand, a high score indicates that the point fits well with the existing clusters, and is thus in a high density area close to the data. If both the nucleophile and imine gaussian mixture models indicated that the nucleophile and imine were in high density areas, then the overall random forest model was used to make predictions. If the nucleophile GMM indicated that the nucleophile was in a high density area but the imine GMM indicated that the imine was in a low density area, then the imine properties were in a low density area, meaning that attempts to utilize them in the random forest model may cause extrapolation issues. In this case, the nucleophile focused random forest model was utilized, which excluded imine features. If the nucleophile GMM indicated that the nucleophile was in a low density area but the imine GMM indicated that the imine was in a high density area, then the imine random forest model was utilized, which excluded nucleophile features. Finally, if both gaussian mixture models indicated that the nucleophile and imine were in low density areas, then the Lasso model was used to make the prediction.

Training/Evaluation of Pipeline models:

In the actual models used in the pipeline, we used 100% of our in sample data to train it to get the best trained model. However, we still used a similar strategy as above to evaluate the models’ performance, splitting the data 50:50 into train and test and finding the average performance over 100 iterations.

The imine random forest model had a r^2 value of (insert value) on test data, and an overall r^2 value of (insert value) on all total data. The results of the rest of the models can be found above in (insert reference to table)

INCLUDE HYPERPARAMETER TUNING OF MODELS AND GMM SOMEWHERE

Pipeline Results:

The pipeline performed well on the data. For each of the original 381 reactions, the pipeline determined that the overall random forest model would make the best prediction, which was expected since the GMMs were fitted to those reactions.

We were able to see the full capabilities of the pipeline when it made predictions on the out of sample data that had not been included in the original training or testing data. For the (reaction 18) type reactions, the pipeline determined that the imine focused model (excluding nucleophile) was the best model to make the prediction, due to a low nucleophile GMM score indicating low density. This led to a low mean average error of (insert score), which indicates that the prediction was somewhat accurate. For the (reaction 19) tpe reactions, the nucleophile focused forest model was used to make predictions, with a low mean average error of (insert score) - once again, a decent score indicating accuracy and good choice of model. Finally, for the (reaction 20) type reaction, the overall random forest model was used to make prediction with a mean average error of (insert score). Across all 64 out of sample predictions, the r^2 value was (insert value).

Analysis of Pipeline:

The low error scores and the high r^2 value indicate that the pipeline did well in extrapolating out to reactions that it hadn’t been exposed to. Additionally, the strong performance of the imine and nucleophile specific random forest models in the pipeline show that although both sets of imine and nucleophile properties are important in the overall model, it is still possible to make strong predictions in the absence of one or the other.