Capstone Project for Machine Learning Engineer Nanodegree

Kaggle's Personalized Medicine Competition

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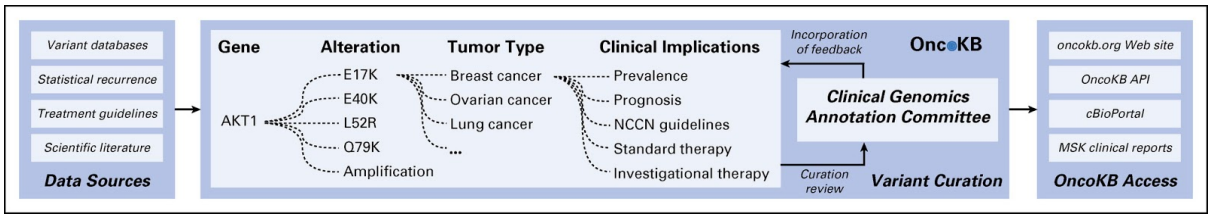
Part I. Proposal

Project Overview

A lot has been said during the past several years about how precision medicine and, more concretely, how genetic testing is going to disrupt the way diseases like cancer are treated. But this is only partially happening due to the huge amount of manual work still required. Once sequenced, a cancer tumor can have thousands of genetic mutations. But the challenge is distinguishing the mutations that contribute to tumor growth (drivers) from the neutral mutations (passengers). The host, Memorial Sloan Kettering Cancer Center (MSKCC) , has been maintaining the database OncoKB [1] for the purpose of knowledge sharing of mutation effects among oncologist. Currently this interpretation of genetic mutations is being done manually. This is a very time-consuming task where a clinical pathologist has to manually review and classify every single genetic mutation based on evidence from text-based clinical literature. Therefore, the task is to develop a Machine Learning algorithm that, using an expert-annotated knowledge base as a baseline, automatically classifies genetic variations.

Since 2004 there are consequent publications trying to address this problem by developing automatic computational methods, and achieved encouraging results, such as CHASM (**C**ancer-specific **H**igh-throughput **A**nnotation of **S**omatic **M**utations) [2,3] (led by Carter et al., published on Cancer Res and Gene Function Analysis respectively), and FIS (Functional Impact Score) [4] (leb by scientists in Computational Biology center, MSK). However, all of these methods requiring strong domain knowledge and high sensitivity to pattern such as protein first and secondary structure characteristics or evolutionary conservation features, while take little use of literature on clinical impacts or pathological mechanism of that variant. On the other hand, the natural language processing tools [5,6,7] in cancer study focus mainly on identifier detection and concepts locating, which are not shrewd enough to predict the functional consequences of a mutant. A NLP based automation method which is able to annotate the functional impact of variants of intense research interest is much needed.

As stated before, variants in those datasets are from real-world cancer cell sequencing, all annotations (labels) are manually added by oncologists based on clinical or molecular studies on the corresponding variant. Text information annotated to each variant are also hand-picked by those domain experts. Given gene AKT1, variant E17K, their workflow according to their official website [1] is like this:



Details of input datasets:

- training_variants - a comma separated file containing the description of the genetic mutations used for training. Fields are ID (the id of the row used to link the mutation to the clinical evidence), Gene (the gene where this genetic mutation is located), Variation (the aminoacid change for this mutations), Class (1-9 the class this genetic mutation has been classified on)
- training_text - a double pipe (||) delimited file that contains the clinical evidence (text) used to classify genetic mutations. Fields are ID (the id of the row used to link the clinical evidence to the genetic mutation), Text (the clinical evidence used to classify the genetic mutation)
- test_variants - a comma separated file containing the description of the genetic mutations used for training. Fields are ID (the id of the row used to link the mutation to the clinical evidence), Gene (the gene where this genetic mutation is located), Variation (the aminoacid change for this mutations)
- test_text - a double pipe (||) delimited file that contains the clinical evidence (text) used to classify genetic mutations. Fields are ID (the id of the row used to link the clinical evidence to the genetic mutation), Text (the clinical evidence used to classify the genetic mutation)
- submissionSample - a sample submission file in the correct format

(Notice that the files above are for stage 1 competition, stage 2 competition has added 5 more files)

Problem Statement

According to the host, they want algorithms to classify genetic mutations based on clinical evidence (text). There are nine different classes a genetic mutation can be classified on. This is not a trivial task since interpreting clinical evidence is very challenging even for human specialists. Therefore, modeling the clinical evidence (text) will be critical for the success of final approach. Both, training and test, data sets are provided via two different files. One (training/test_variants) provides the information about the genetic mutations, whereas the other (training/test_text) provides the clinical evidence (text) that our human experts used to classify the genetic mutations. Both are linked via the ID field. Therefore, the genetic mutation (row) with ID=15 in the file training_variants, was classified using the clinical evidence (text) from the row with ID=15 in the file training_text. Noticebly, the host explicitly mentioned there were machine-generated data to prevent hand labeling. Participants will submit all the results of the classification algorithm develop, but they will ignore the machine-generated samples.

For this natural language based multi classification problem, the two key problems would be: firstly, how to extract most useful features for later model training; and secondly, how to find the most suitable algorithm for that extracted features. To best capture effective features, I need to have deeper understanding of the problem and datasets by asking myself questions such as: what the 9 anonymized labels actually mean? What's the biological relationship of these catagories? Why those papers instead of others, stand out as basis of classification? What are the characteristics of narratives in papers that most convince oncologists in classification? How to reduce the noise and maximize signal-to-noise ratio in text? Then, to find the most suitable algorithms, I should know how big the datasets are and what's the relationship within features. For this specific problem, since each data point is one cancer-related variant, our input are relatively small datasets. While since most features are extracted from text by vectorizer such as bag of words, tfidf etc, I would expect lots of features. I

would try Logistic Regression, Decision Trees, Gradient Boosting, Linear SVM and xgb for this problem, and use log loss for evaluating the performance of my models. (AUC should also work for classification problem here but since log loss is taken by host to calculate rankings I would use only log loss for optimizing the method)

Evaluation Metrics

For this competition, the evaluation metric used is Logarithmic Loss metric. Each observation is in one class and for each observation, there should be a predicted probability for each class. The metric is negative the log likelihood of the model that says each test observation is chosen independently from a distribution that places the submitted probability mass on the corresponding class, for each observation.

$$\text{logloss} = -\frac{1}{N}\sum_{i=1}^{N}\sum_{j=1}^{M} y_{i,j}\log(p_{i,j})$$

where N is the number of observations, M is the number of class labels, loglog is the natural logarithm, yi,jyi,j is 1 if observation ii is in class jj and 0 otherwise, and pi,jpi,j is the predicted probability that observation ii is in class jj.
Both the solution file and the submission file are CSV's where each row corresponds to one observation, and each column corresponds to a class. The solution has 1's and 0's (exactly one "1" in each row), while the submission consists of predicted probabilities.
The submitted probabilities need not sum to 1, because they will be rescaled (each is divided by the sum) so that they do before evaluation.
(Note: the actual submitted predicted probabilities are replaced
with max(min(p,1−10−15),10−15) max (min(p,1−10−15),10−15).)

JUSTIFICATION: Log loss is based on information theory, in which it stands for the cross entropy between the actual labels and predictions. It's used to measure the accuracy of classification, but instead of measuring based on only the predicted most likely class, it measures the calculated probability of each candidate class. Back to this competition, the sample submission is asked to include 9 values for each testing point, which are the predicted confidence of that class to be the actual label. Log loss is a very good choice of metric under this situation.

References for proposal:

[1] *OncoKB: A Precision Oncology Knowledge Base*
[2] *Cancer-specific High-throughput Annotation of Somatic Mutations: computational prediction of driver missense mutations*
[3] *Predicting the Functional Consequences of Somatic Missense Mutations Found in Tumors*
[4] *Predicting the functional impact of protein mutations: application to cancer genomic*
[5] *tmVar: A text mining approach for extracting sequence variants in biomedical literature*
[6] *TaggerOne: Joint Named Entity Recognition and Normalization with Semi-Markov Models*
[7] *GNormPlus: An Integrative Approach for Tagging Gene, Gene Family and Protein Domain*

Part II. Analysis

1.1 Data Exploration

Since the competition is divided into 2 stages, the solution of stage one competition towards stage one test set can be added to training dataset to increase statistic power, I merged `training labels` and `stage1_solution` as final labels `y`; merge `stage2_test, stage2_text` into variable `test`, and merge `filtered solution.ID, training_ text, training_variants, test_test, test_text` into variable `train`. (Basically, I will do both model training and cross validation on `train`. `test` would only be used for leading board submission.) The input `train` variable has only 3 fields: `Gene`, `Variation`, and `Text`. There are in total 401 unique genes and 3921 unique variations for 4675 entries, with the top gene appearing 322 times) and top variation 129 times. Unsurprisingly, some familiar cancer related genes appear in its Gene field: such as BRCA1, the most infamous factor in breast cancer of white women, and PTEN in prostate cancer of men.

In case of non-biology background readers: `Gene` is the unit of DNA. And human DNA are composed of more than 20K of such functional units, each carries special genetic markers that we usually call SNP (Single Nucleotide Polymorphism). SNP is usually harmless, but when it disrupts some key cell signaling pathway it can lead severe consequences as well. Wild type gene is the one with the standard gene sequence which is stored in human gene bank and used as reference when conducting sequencing. Any gene that differs from the reference sequence is taken as a `Variation` (or mutant). If this is a point mutantation, the first alphabet would be the amino acid which this variation change from wild type one, and the last alphabet means the amino acid it changes to. Taking entry 2: Gene CBL, variation Q249E as an example. This entry means the 249 amino acide of gene CBL is mutated from Glutamine (Q) to Glutamic acid (E). You will also find different forms of Variation such as Amplification, Truncation, Epigenetic Silencing and so on. But I cannot elaborate more on them since it would involve deep understanding of epigenetic regulation, which goes beyond the scope of this paper. The readers only need to know that they are simply different variations from wild type form of that corresponding gene.

The `Text` field of each entry is handpicked by domain expert as key literature evidence of classification. A simple googling discovers that they are all from PubMed papers concerning the gene or variation. However, some of them are combined from multiple papers, and some of them are only one single paper and a few of them are just empty (their `Text` field are indicated by `null`). Like this:

```
# Extemely short Text: null values
empty=[(x,len(x.split())) for x in train['Text'] if len(x.split())<10]
print 'Extemely short Texts:'
empty
```

```
Extemely short Texts:

[('null', 1), ('null', 1), ('null', 1), ('null', 1), ('null', 1), ('null', 1)]
```

While these extremely long texts could be as long as 73558 words with the median value to be 6895 words!

```
xlong=[len(x.split()) for x in train['Text'] if len(x.split())>70000]
print 'Extemely long Texts:'
xlong
```

```
Extemely long Texts:

[70447, 76708, 72942, 73558]
```

I can't figure out the reason why their oncologists do that. But these **extreme long or short texts** would potentially affect later processing and modeling. And also, I noticed the distribution of 9 classes is very **imbalanced.**

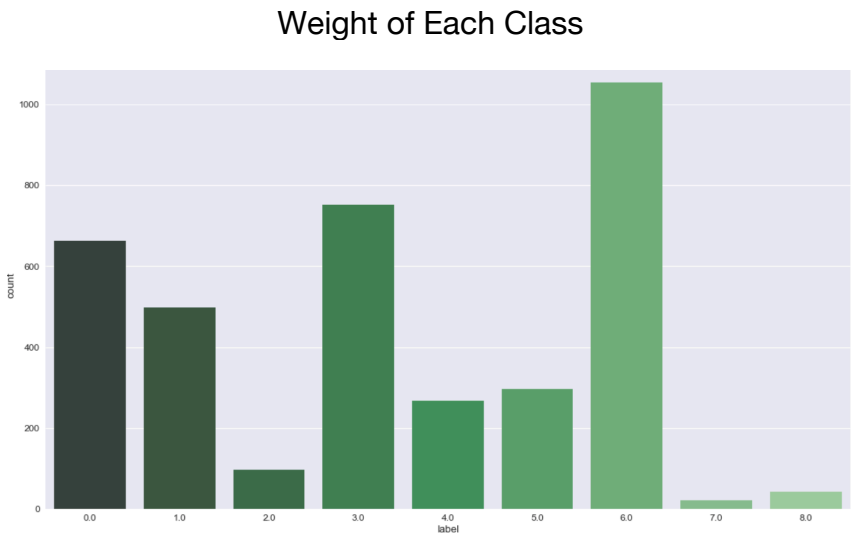


Fig 1.

1.2 Exploratory Visualization

Since there are too few variables in input data and none of them are numerical. I created some numerical variables from original categorical variables by feature engineering. After initial visualization of each variable, I proceed to look at the correlation of them against Class, which would provide important insights for modelling. Here only bivariate analysis is included in this report.

-1. Most Frequent Genes and Class

Fig 2.

First of all, the distribution of gene frequency varies a lot, such as for class 1, TP53 and BRCA1 are much more frequent than other genes. Likewise, top few genes take up a big percentage in class 5, class 6 and class 9, indicated by the great gap of frequency between the top 1 gene and the top 10 gene. While the gene distribution seems more balanced in class 2, class 3 and class 7. Secondly, the most representative group of genes are distinctively different for each class. The most appearing gene for 9 classes are TP53, KIT, BRCA1, PTEN, BRCA1, BRCA2, EGFR, BCOR and SF3B1 respectively, with the only overlap from class 3 and class 6. But once look closer, the two have not only very different combination of first-tier genes but also the distribution of them. In sum, Gene looks like a very promising predictive factor for the label.

-2. Most Frequent Variations and Class

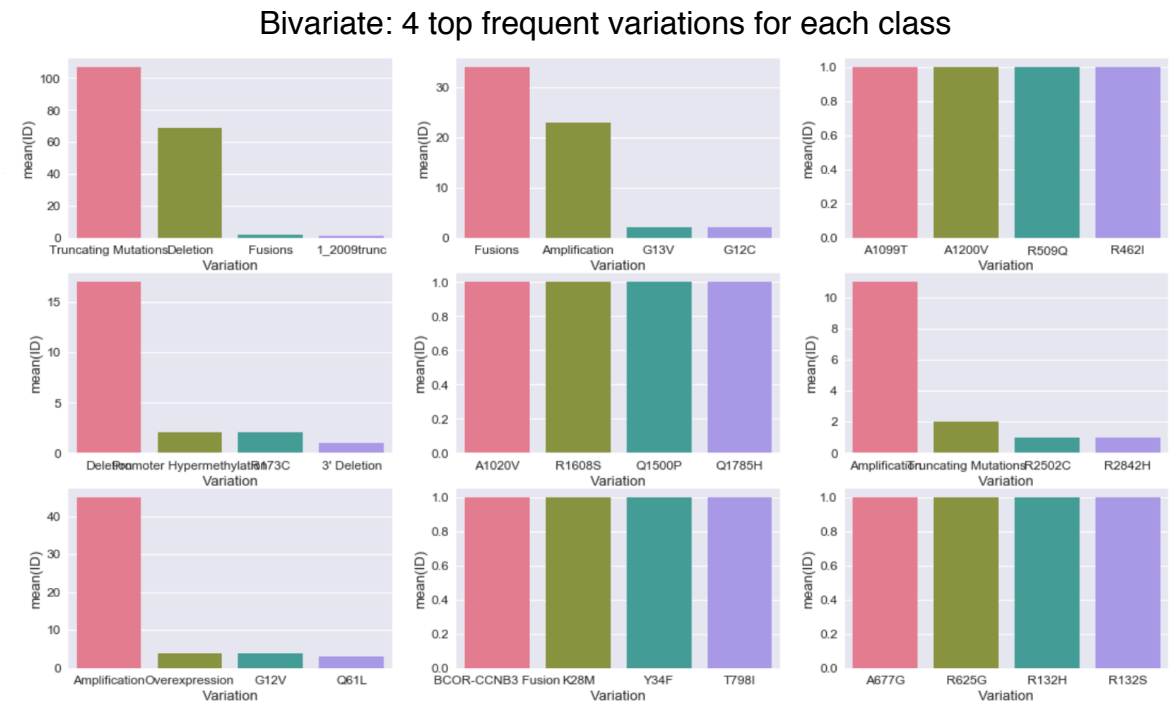


Fig 3.

Noticeably, variations are much more diverse and the frequency of the top variation is much lower than the top gene. This is because we have only limited number of genes (around 20,000 for human beings, among which only less than 10% are cancer related), but almost unlimited possibility of the number of variations. (As we have discussed before, a variation is basically a form of gene which is different from wild type gene. For a specific gene, even assuming it is composed of only 500 amino acids, the possible point mutations only could be as many as 500*20, not to say deletions, insertions and many other forms of variation.) Some classes like as class 3, class 4 and class 9 even don't have a single repeated variation, indicated by the top frequent one having only 1 count. I also want to point out that the top variations in other classes, such as truncating mutations in class 1, deletion in class 4 and amplification in class 7, are actually aggregated form of mutations, meaning themselves do not refer to any specific variation, unlike A1099T, a point mutation which specifically refers to a point mutation from Ala to Thr in 1099 position of this gene, truncating mutations and deletions is a joint name in their cases. Therefore, even Variation also shows some correlation towards Class, I would expect it has less predicting power than Gene does.

-3. Text Length Distribution and Class

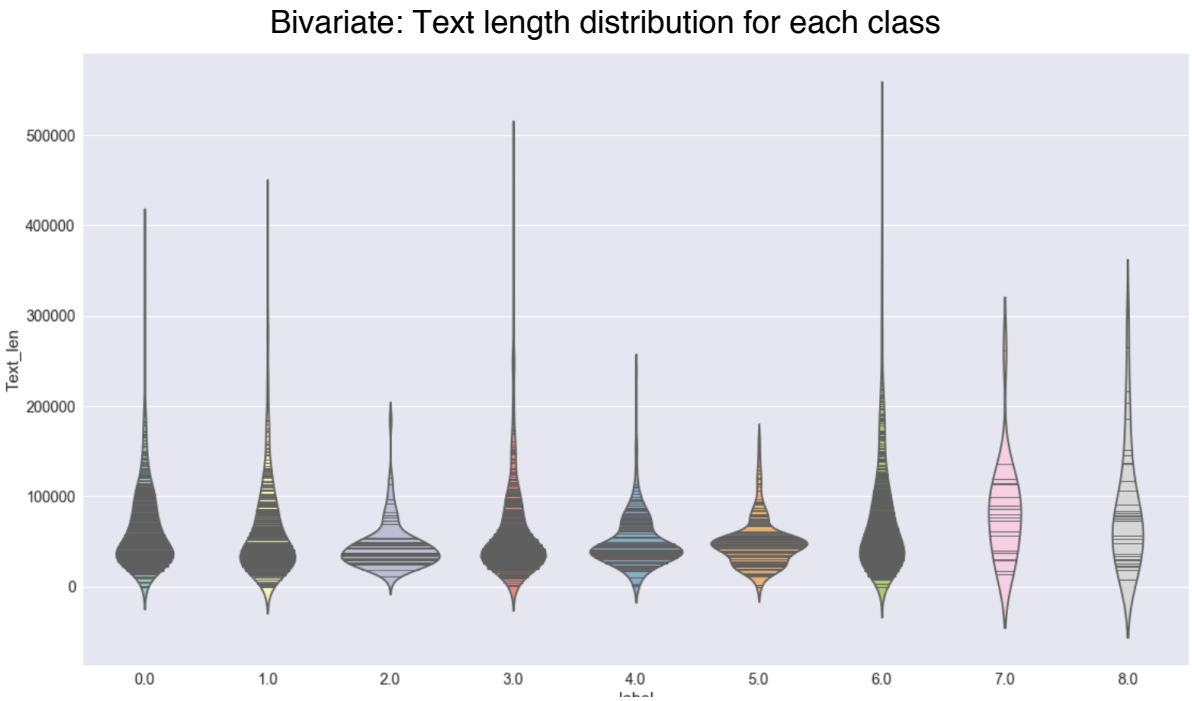


Fig 4.

`Text_len` is a variable created by encoding the character length of Text field. Surprisingly, the distributions of text length are very heterogeneous. Class 3 (label 2.0), for example, has a very narrow distribution, in which almost 95 percent of its text are in range (20K, 80K). In contrast class 8 and class 9 have expanded text length distribution, indicated by the long and narrow spindle shape. Text length also looks like a promising feature for forecasting the class.

1.3 Algorithms and Techniques

I will heavily need pandas, numpy and sklearn libraries and sometimes I need sns to show correlation or feature importance. Since the inputs are separated in 4 files I will combine them and handle it as one file. Primary features are only 3*:* Gene, Variation and Text. For the first two I will implement one-hot-encoding, label encoding, bag of words extraction, encoding length and all (basically as much engineering as I can think of). For Text I will consider more complex way to treat it such word-embedding, topic modeling and tfidf vectorising. But how to improve signal to noise ratio would be major concern. Preprocessing seemingly not necessary here, as most of data are counts, frequency. But it is to be confirmed.

Condering I will need to try different combinations of: ways to engineer features, extract features (tfidf,bow, word2vec,doc2vec,LDA), features selection (PCA, SVD), algorithms (logistic regression, SVM, DecsionTress, GradientBoosting, KNearestNeighbors, LinearDiscriminantAnalysis, XGB), parameters of algorithms etc., I need to build a *pipeline* gives flexibility to try all this. And an automation method GridSearchCV to reduce repeated work of hyper-parameters tuning.

Once I get a few good performing models, I will need to ensemble them for a better solution, by methods such as blending, stacking, bagging. It will be a trade-off that whether using strong performers but less number of ensembling, or weaker performers but greater size is better strategy. And balance the complexity with robustness of the model over unseen data.

JUSTIFICATION: if you have noticed, I have tried and used quite a lot of techniques. That's because in the process of Kaggle, the problem to be addressed is so complicated and the competition is so hectic that it is impossible for participants to foresee which algorithms would work well before actually implementing them. Such as **KNN** is known as a lazy learner which doesn't summarize data much and takes a lot of computation on high dimensional data. It indeed did quite badly (worse than uniform guess), however, taking it out from base estimators unexpectedly weakened the ensemble model. Another example is **SVM**, it looks like a perfect algorithm for this problem in many aspects: the problem is high dimensional text classification; SVM's kernel trick allows expert knowledge via engineering; its maximizes the margin to make the model more robust … however it's not taken in final solution since somehow too much computation time required by it. Third example is **Logistic Regression**, it is known of being vulnerable to dependent input data as well as outliers. As we found out in visualization part, linear correlations are very common among these engineered numerical variables (fig. 5) and the Text field has quite some extremely short or long texts (fig. 4). However, in practice it works well. And more surprisingly, it gives high weight of importance to even related features. And removing any of them weakens its performance.

Considering both the complexity and the workload, I cannot elaborate on each of the algorithms I used and justify their suitability. In fact, some algorithms are chosen not because of their theoretical suitability but their appearance actually improved the model. But I do have reasons on the two key techniques about why I use them for this dataset and why they are suitable. **1. TFIDF**: Tf-idf is the finalized text feature extraction method, which is short for term frequency–inverse document frequency, value of which is intended to reflect how important a word is to a document in a corpus. Since it ignores the position and semantics information it is easy to compute and very straightforward. As we have discussed in data visualization, the top frequent gene and variation names are distinct for each class, which are basically counts of specific words. These findings indicate tf-idf would works well for our problem and it indeed is. **2. XGB**: XGB is a great implementation of a scalable tree-boosting method. It doesn't have independent assumption on input data like LR and it is known to be robust to noise in real-world data as tree algorithm. Besides, it allows users to customize metric function for watchlist and automatically generate the best iteration. (In fact, it has become a rock star in kaggle's winning solutions.) Due to the 3 points I mentioned, XGB is great in predicting as a single model and even greater as a generalizer of the ensemble model.

1.4 Benchmark

For benchmark model, I use gene-encoding features only based on the consensus that variants from same gene should have more related behaviours than those not in terms of functional consequences. According to the formula of metric the host uses for evaluation, the best score is 0.00, meaning 100% hit. The worst possible score is 34.26246 since the host had added a smoothing transformation. Score can be easily improved to 2.1 by simply throwing uniform guesses and it will keep climbing to 1.8 once weights of each class considered. I want to know how much it can improve with only addition of gene one-hot-encoding information. After running Logistic Regression on 1022 gene one-hot encoding features, I got an average

score of 1.21216637352 from 5-fold validation without tuning. This gives the baseline from where the text features should start with.

2.1 Data Pre-processing

(Feature selection and feature transformation will be discussed in Implementation part. Here I will mainly talk about feature engineering and encoding.) As I have mentioned before, due to the nature of this competition being natural language processing, I have only 3 input variables and none of them are numerical, with Text being the richest in information. And I discovered in explorative analysis that the text length distribution is actually characteristic of each class. Therefore, the first thing I do is creating new features regarding Text length. It's a bit tricky about how to encode this information though. Words length is more instinctive than character length as it's widely accepted as the unit of text instead of alphabet. However, word is bigger grain compared with character and the transformation from character to word itself is basically distortion of original input and potentially vulnerable of information loss. Actually, scientific papers use even richer punctuations to secure accuracy in narrative compared to every day text. In the end, I took both of the two ways in encoding, leave the option to the model itself.

Besides, as I have mentioned in the proposal：figuring out how these papers are selected and by what way the signal-to-noise ration can be improved before feeding materials to model might be the key factor in deciding the quality of model. Although the median length of text is as long as nearly 7,000 words, most of them are totally unrelated to the ultimate question we want to answer. After manual check of few texts, I realized the sentences that carry the corresponding Gene or Variation names are more likely to contain the hints of classification. Therefore, I create Gene_txt_len, Gene_txt_words and Variation_txt_len, Variation_txt_words, with each stand for the word length or charater length of sentences containing that Gene or Variation. And of course, I also created another field named `txt`, which unlike original Text, has only joint sentences carrying Gene or Variation names. For some entries of which their Text fields don't contain any of such sentences, I simply fill then with Text. A problem occurred during this process is the inconsistency of naming. Such as gene CCNC could be mentioned in standard form, but cyclin C, or CycC, even hSRB11or SRB11 could also refer to the same gene. I tried to find a tagging tool to tag different names of the same identity to the standard reference number but no current annotation tools accept direct text input (most accept only PMID) and give the expected outcome. I spent quite some time to conquer the first bottleneck， but in the end, I didn't use it for final model due to both time limits and the poor quality of results. I checked the dependence between new numerical variables, and the results are like this:

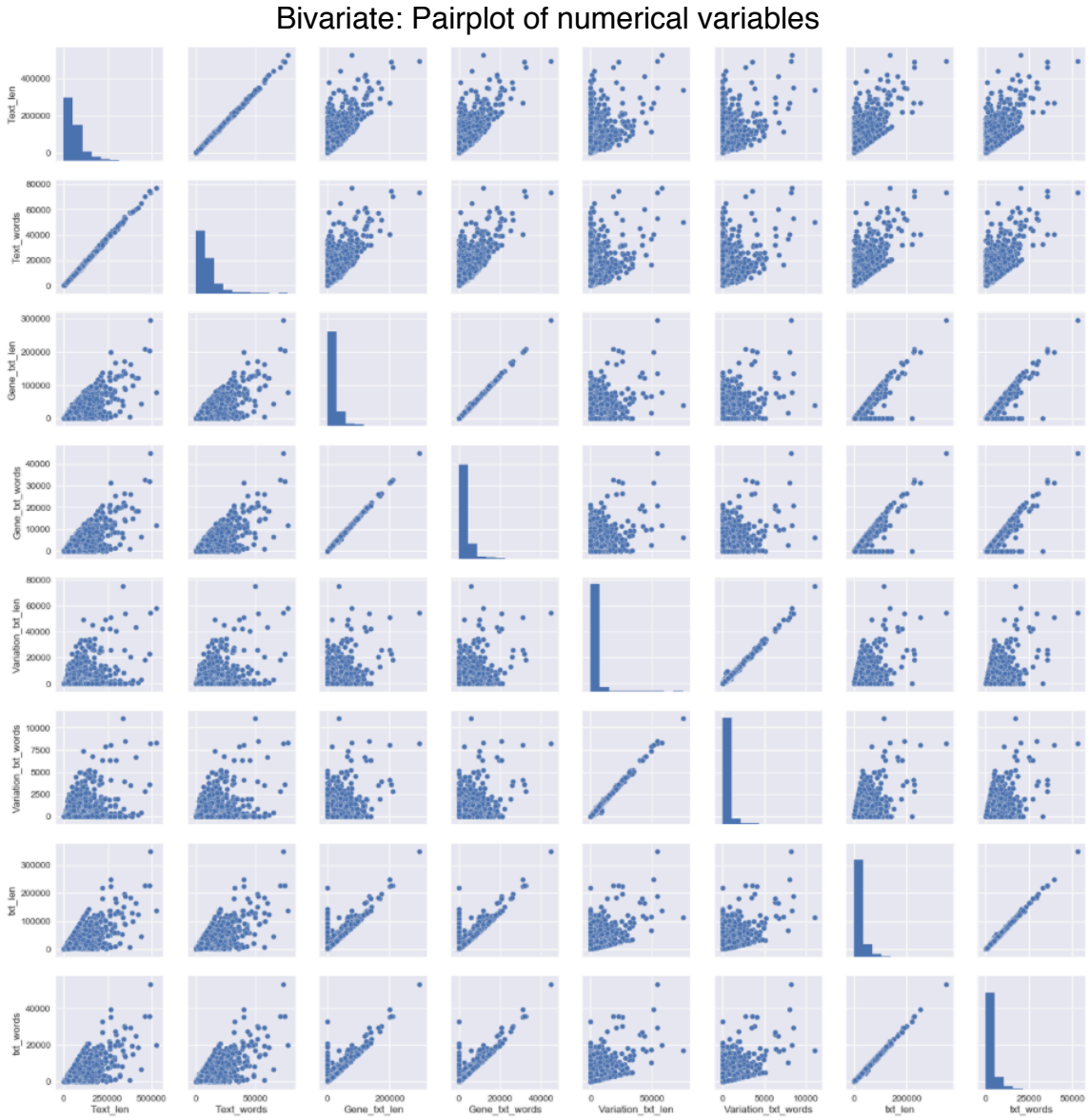


Fig 5.

Word length and character length of the same text are highly linearly correlated. While those of extracted text also shows some linear relationship with the original ones, they are much weaker, which means we successfully introduce a new dimension of variance!

I also did label encoding and one-hot encoding on Gene and Variation. That's because I expect rich information from Gene based on Gene vs Class visualization and since I am not sure which way is a better use of that, I'd better take both and believe the model would take whatever it wants. However, 2 ways of encoding on Variations are perhaps not that worthwhile. I decide to give it a try though. Noticeably, due to the much diversity variation has, I have to aggregate them so that I can have reasonable dimensions of feature after one-hot encoding, by labelling all point mutations as SNP, `*` as null, and such.

2.2 Implementation and Refinement

Feature selection and extraction process is more like a trial and error for me. And depend on what algorithm to choose, the ideal input could be different. For example, I have various text

length features which are linearly correlated with each other as have been shown in the pairplot of last section. Linear Regression perhaps hate them, but tree-based algorithm might love it. Besides I have a couple of ideas about how to vecterize Text variable. To ease the exploration, I build a pipeline for feature selection, reduction and extraction like the one below, which is inspired by the1owl's kernel :

```
fp = Pipeline([('union', FeatureUnion(n_jobs = -1,
                                      transformer_list = [
                                          ('standard', cust_regression_vals()),
                                          ('pi11', pi11),
                                          ('pi12',pi12),
                                          ('Gene_oht', pi21),
                                          ('Variation_oht',pi22),
                                          ('tfidf1',pi31),
                                          ('tfidf2',pi32)
                                      ])
               )])
```

The first sub-pipeline `standard` will take care of all numerical values; `pi1` and `pi2` use CountVecterizer to extract Gene and Variation name features and share one dimension reduction function truncatedSVD; `pi21` and `pi22` for dealing with one-hot-encoding of Gene and Variation names, but each has a feature reduction function; `pi31` and `pi32` are both for extracting and selecting text extracted features by Tf-dif vectorizer and truncatedSVD, except that one from Text, one from `txt`. This allows me to easily test my hypothesis by looking at the individual effect of different groups of variables and trying different combinations of available features. Using non-optimized logistic regression as tentative model, the preliminary results are summarised as below:

Results

Groups of features	numerical features	CountVectorizer on Gene	CountVectorizer on Variation	one-hot-encoding on Gene	one-hot-encoding on Variation	tf-idf on Text	tf-idf on txt
Original dimention no.	14	NA	NA	401	23	5000	5000
Need reduction?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Dropped features	Variation_words, Gene_words	anonymous	anonymous	anonymous	anonymous	anonymous	anonymous
Best dimention no.	12	15	15	120	5	100	200
Logloss based on only this group	0.9978	1.1277	1.5849	1.1223	1.6790	0.9231	0.8717

As expected, algorithm using any group of features alone can give better score than naïve uniform weighted guess that I mentioned in benchmark model part (logloss score = 1.8). However, different groups of features do vary in predicting power. Consistent with explorative visualization, features extracted from variation almost always perform worse than that from gene, as clearly shown by CounterVectorizer (1.1277 versus 1.5849) and one-hot-encoding features (1.1223 versus 1.6790). And surprisingly, tf-idf built on txt, the feature that we engineered by extracting only sentences with target names, performs even better than that on Text, the original feature. Moreover, it takes less than one fifth of the computational time than Text. Therefore, I decide to use the 12+15+15+120+5+0+200=367 features for further exploration.

Actually, for vectorization of Text I have also tried word-embeding method such as word2vec and LDA (LatentDirichletAllocation). However, the biggest problem of using word2vec is the text length. Although word2vec is doing excellently in short text queries, the limit of words is usually within 15. Beyond this length, the key characteristics of the averaged text vector will get averaged and blurred out. The only way out would be compressing the long text into some short sentence which is most representative for this

paper or most useful in classification. I tried two ways: one is trying to find the title for each text and use the title as query to compute the vector for each entry; another is simply using the first sentence that contain the Gene or Variation name, and hopefully it indicates something about classification. However, neither of the two works. For the first one, because the titles of selected papers are removed for anonymization, I have to find their title the other way. Even though I successfully accessed PubMed by their python supportable API entrez, and auto storing titles by querying the first few words in their database but the returned results is unpredictable: sometimes it returns None when you can actually find the paper by manual searching, and sometimes returns a sequence of candidates. And what's even worse is, when I managed to collect these titles and feed them to both pre-trained or locally trained word2vec model, the results are pretty bad. Even the best is only 1.5. This means title itself lacks information for guiding classification. And the same thing happened when I use the first sentence in txt to build word2vec features. I guess there are basically too much noise in this process. As I said before, lots of Text fields are composed of more than one papers, but both methods take only the first paper into account and not to say the many missing values, and dirty characters in it. I have also tried top-based modelling, but unfortunately the preliminary results are too far away from what I want, so I didn't proceed for glove or t-SNE. Finally, I decided to step back to tf-idf vectorization due to time limitation before competition deadline.

With the 367 features I selected, Logistic Regression with a little tuning (C=3) gives 1.05 log loss score from 5-fold validation, which is a major improvement by 0.16 from the benchmark 1.212. And when I change the penalty from default l2 (ridge) to l1 (lasso), which is designed to better handle sparse features, the score is improved to 0.9569! The first time for loss goes below 1. After that logistic regression didn't improve however I changed the parameters combination. For the final model, I decide to use XGB instead of logistic regression since XGB is robust, powerful and very fast. And unlike LR, it's quite resilient to linearly dependent variables. The default XGB gives comparably good results as the best performing LR model. And after tuning, it climbed to 0.8280, another major improvement from 0.9569. Till now I have improved 0.4 from the benchmark model. I did try to use feature importance of this tree-based model to select suitable features for xgb. But it turns out quite to be consistent with that for LR (that's a surprise to me), that's to say adding any extra features besides the 367 reduces the model performance; and reducing of any current features lowers the performance. So now I am happy with the 367 features at hand.

Ensemble is carried after chosen the upper layer model. It's out of the consideration that by pooling together ideas by diverse base estimators, the ultimate model would have become more resistant to random error and algorithm-inherent bias, thus can generalize better on the same data. It is a common practice among Kagglers and usually the last step of model generation. I did this mainly to reduce the risk of overfitting and bias. But before the actual ensemble, it's necessary to choose a bunch of base estimators upon which the generalizer would be built. They should perform fairly well individually but at the same time as different from each other as possible. I tried Logistic Regression, KNeighersClassifier, LinearDiscriminantAnalysis, and GradientBoostingClassifier with different parameters. LR and GradientBoosting always did the best among all the base estimators regardless of various parameters. LDA did fair job. But performance of KNN isn't that good. I wanted to try SVM, but seems the dimensions of data and its sparsity just overwhelmed it, I cannot get results with reasonable time so it's dropped.
Performance and diversity is a trade-off in the case of ensemble, as the top performing models are always similar, and sometimes you have to comprise on one model's performance

due to the different opinion and perspective it brings to the group. The prediction correlation of the 5 classifiers against 9 classes can be found be the graph below:

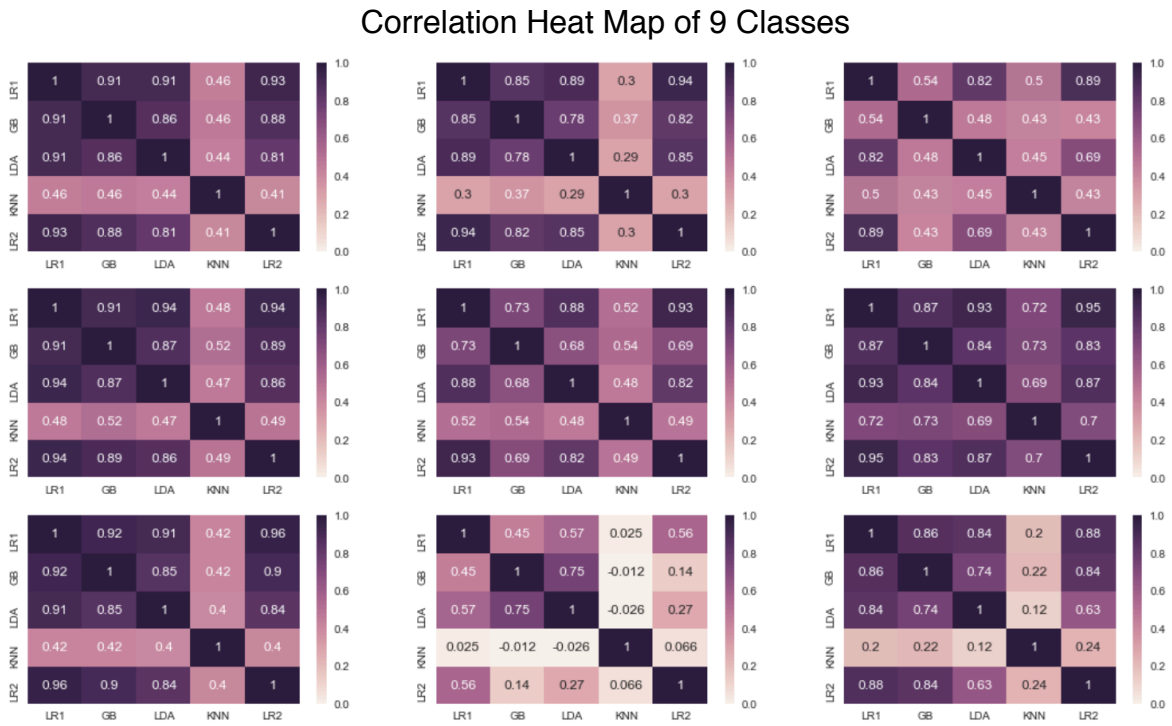


Fig 6.

You can see KNN disagrees with others most of the time. And it seems estimators have formed consensus for deciding class6, but many controversial for class 3 and 8. I used predictions of these 6 base models as meta-input for the top-level generalizer, and formed a model with average local cross validation score to be 0.805329545758 but having a high STD of 0.05508. The performance of this model is highly dependent on the dataset. Such as it predicted quite bad than usual in one of 5 folds, with log loss as high as 0.88, but did awesomely in another fold, and got a lowest ever log-loss score, 0.73. In sum, although not very stable, this model has great potential in performance and might give surprises under some situations. That's why I chose it as one of the two final submissions for this competition.

The second model I choose is the one with most consistently excellent performance across folds. (Mean of log loss score: 0.79839, STD of log loss score, 0.01763). I made this on 4 LR base estimators, 5 GB estimators and one XGB, one LDA, one KNN estimator, in total 12. Due to the high consistency regardless of folds, I expected it to be very dependent and stable, and would perform fair under reasonably disadvantageous situation.

In sum, I can say with confidence that the final model has improved at least by 0.4142 from benchmark model, and is potential to improve another 0.06 on some dataset.

3.1 Model Evaluation and Validation

The 2 final models both perform fairly well, and fined tuned with most appropriated hyper parameters. I have checked the model based on different splitting methods, and also tried different random states for StratifiedShuffleSplit to find the one that can split the dataset most evenly. Choice of random state is not a trivial for this case. As you can easily discover that the entries are not randomly ordered but instead aggregated by some rule. Since variations of the same gene all cluster together. It turns out for random_state=1, the splitting is quite uneven for the specific dataset, as shown by the big STD of log loss scores across folds of almost all classifiers (XGB, LR and GB, etc). While when it was set to 3, the performance of these classifiers consistently improved. Thus, I fix this parameter as 3 for StratifiedShuffleSplit in all the later analysis, to avoid fluctuation of dataset splitting so that it can generalize better on unseen data.

Besides, since I calculated the mean score along with the standard deviation, I have clear idea of the model with regards to its robustness. Small perturbations such as how the dataset is splitted affect my second model very limitedly, as indicated by the small variance it has in different situation. It does affect my first model much more, but that's because I intentionally look for model owning this feature which gives it potential of supernormal performance. In sum, the results are very trustable.

3.2 Justification

The final results are much stronger than the benchmark result. And I have thoroughly analysed and discussed about the final solution. Since Kaggle allows two submissions for final grading and the one with higher grading would be automatically selected to decide your ranking, I decide to take a combined strategy by choosing one consistently excellent performing model along with one model that performs fairly good but has great variance, of which one can guarantee a fair bottom performance and the other challenges the excellence respectively.

4.1 Free-Form Visualization

I would choose **fig 6.** for this Free-Form Visualization section as it shows clearly the consensus and disagreement among estimators. Please refer to **2.2 Implement and Refinement** for more explanation of it.

4.2 Reflection

I found it's really interesting to see how machine learning can help in routine biological study. Actually, there are tons of repetitive work in a junior researcher's career. For me, as my project is using biophysical method to study the structural and functional characteristics of a pathological protein, I am exposed to lots of NMR data every day. It always takes weeks or even months to manually assign amino acid fingerprint son HSQC to its primary structure by comparing their chemical shift with empirical values, which is totally boring and mechanic. Thus, I totally understand why MSK wants to automate this process. I am very interested in applying my knowledge and skills I learned here to change this situation.

The difficulty I encounter here is how to get organized when testing numerous hypothesis and combination of hypothesis. You could have 10 ideas you want to try for each of the single step that you think would perhaps improve the outcome before obtaining the final models, and you might become upset when the model simply doesn't behave as expected and you just want to start from scratch. How to come up with ideas and prioritize them, how to interpret unexpected results and carry on, and how to maintain proper documentation are very important lessons I have learnt from this experience.

I personally don't think it is ready for real-world application yet. The biggest problem is the input papers must come from domain expert. As this model is built on ready-to-use Text instead of open
Database. Picking papers itself could be the most time-consuming among all the procedure, as one has to: read lots of relevant literature, form deep understanding of that field, aggregate them and form ideas about the true functional impact of that gene/ variation, summarize the key evidence by selecting papers and put it in Text field. However, these models do provide a new perspective in understanding literature and perhaps helpful in settling controversial between human experts who always have pre-formed bias.

4.3 Improvement

As I have mentioned before, a bunch of informatics and biology methods could have been added to improve the model. Such as using tagging tools to consistently annotate gene, variation name to a reference, and including primary sequence as features. Besides, a lot of databases, such as COSMIC, Genia and MeSh could also be used here. However, some tools like the one using FIS (Functional Impact Score) to predict functional impact are explicitly mentioned by the host as illegal external data. It's a bit tricky how to take advantage of them while not violating the competition rules. I have tried to collected titles for these anonymized papers from PubMed in attempts of building word2vec vector for Text. Due to lots of limitations, however, I didn't use any external data in my final models, but it's definitely could have been made to improve the model.

References for analysis:

[1] *Personalised Medicine - EDA with tidy R*

[2] *Redefining Treatment*

[3] *Brief insight on Genetic variations*

[4] *Human Genome Variation Society*

[5] *Official external data and pre-trained models thread*

[6] *Key Sentences Extraction ideas*

[7] *KAGGLE ENSEMBLING GUIDE*

[8] *Introduction to Ensembling/Stacking in Python*

[9] *Titanic Top 4% with ensemble modeling*

[10] *Entrez-biopython*