Predicting Adverse Drug Reactions Based on Patient Demographics

CSCI 4502 Semester Project

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PROBLEM STATEMENT

Our project will analyze the FDA FAERS data set, specifically examining links between various demographic attributes or drug characteristics and subsequent adverse outcomes. We hope to be able to find interesting correlations and relationships that will lead us to be able to predict the likelihood of a certain groups of people having adverse reactions to specific drugs. This research could be hugely beneficial for medical staff and pharmaceutical companies in allowing them to develop a more nuanced understanding of previously unidentified factors that may contribute to adverse reactions in patients. It could also help identify groups of patients who may have previously been considered low-risk for an adverse reaction to a drug, and correctly reclassify them as higher risk.

LITERATURE SURVEY

Because the FAERS database is readily available and large, it is a good candidate for data mining, and therefore there are good examples of prior work examining this data set.

In many cases, these prior studies have selected a single drug or drug ingredient, and looked at the risk of a specific outcome or set of outcomes occurring across demographic groups. For example, Fadini et al. [2017] examined the link between SGLT2 inhibitors and diabetic ketoacidosis using the FAERS dataset. They also examined outcomes across groups of people, and concluded that diabetic ketoacidosis associated with SGLT2 inhibitor use does not seem linked to specific demographic attributes.

Umetsu et al. [2015] used the FAERS dataset to determine the relationship between selective serotonin reuptake inhibitor therapy and suicidality. They specifically looked at this relationship across patients grouped by age, and discovered a stronger relationship between SSRIs and suicidality in groups age 18 and above using a logistic regression model.

Feng et. al [2013] took a similar approach to their research question, and mined the FAERS dataset to look at the pancreatic cancer risk associated with the use of dipeptidyl peptidase 4 inhibitors. They found a significant risk of pancreatic cancer associated with the use of dipeptidyl peptidase 4 inhibitors, and were able to identify that the combination of an additional drug, metformin, actually correlated with a decreased risk of pancreatic cancer.

Aside from studies linking drug or demographic attributes to specific adverse outcomes, there is also relevant work on the dataset itself. Banda et al. [2016] tried to address common data cleaning issues with the FAERS data set by providing a standardized version of the database with duplicates removed, missing values imputed, and drug names properly mapped. Though we are not using this standardized version of the database for our own research, referencing techniques used by this team could be invaluable as we undertake data

cleaning ourselves. Likewise, Maciejewski et al. [2017] also sought to standardize elements in the FAERS database, choosing to focus specifically on mapping drugs to their ingredients in order to provide a more accurate way to examine drug outcomes.

At a higher level, Sakaeda et al. [2013] published a paper entitled, “Data Mining of the Public Version of the FDA Adverse Event Reporting System” which contains an overview of some data mining algorithms selected for use on FAERS and the algorithms’ ability to detect “signals” in the data, where signals are “a statistical association between a drug and an adverse event or a drug-associated adverse event”. This study also touching on possible shortcomings of this type of analysis, which may help us avoid pitfalls or erroneous conclusions in our own investigation.

PROPOSED WORK

While the studies covered in the literature survey tended to focus either on the mechanics of cleaning the data or on a specific drug-outcome relationship, we want to focus with more granularity on the demographic attributes available in the dataset. Because of the size of the dataset, we may need to focus our efforts on a specific drug, but since the FAERS dataset includes a number of interesting demographic attributes, we have an opportunity to uncover how adverse outcomes correlate with a variety of influencing factors like sex, age, weight, and location. Ideally, this will lead us to interesting predictive analyses.

Data Collection

For this project we will be working with the FAERS dataset in two different forms: firstly through a Postgresql relational database, and secondly by parsing JSON files using Python.

For the first method, FAERS data from 2016 Q1 through Q3 was downloaded using shell scripts, and loaded into seven different tables in a Postgresql relational database. This will allow us to use standard SQL queries to begin to explore the data.

For the second method, data over the same period was downloaded as JSON files, 788 in all. This was achieved using a Chrome batch download extension. The files are named by their numbering in a given set for that quarter, so after initial download, there are multiple files with the same name. Each file will need to be given a unique name to prevent overwrites when inflating the zip archives, which will be done using a shell script.

Having data in two formats will allow us to explore the dataset in different ways, and ideally give us the most flexibility possible as we begin analysis.

Preprocessing

For most of our data manipulation, Python will be the appropriate tool. We will first load the files into a Pandas dataframe in order to use Python for our data preprocessing.

The first step in the preprocessing stage will be data cleaning. We will need to handle null values if they exist, and check for and remove any outliers. As our data set is quite large (on the order of several million data points) we plan to simply delete all rows of data that are missing a value for one or more of the needed attributes as long that this method does not sacrifice the data integrity.

The next step in the cleaning process is to identify any outliers that may be present. For each numerical attribute we will calculate the first and third quartiles as well as the interquartile range and eliminate all data that fall outside of $Q_1 - 1.5 \times IQR$ and $Q_3 + 1.5 \times IQR$.

The next step in preprocessing will be data integration. At this point we only have one source of data, so there will be minimal integration necessary. When querying the relational database, cases are uniquely identified

across tables by a caseid attribute, so we can use that identifier as a way to join data tables, but more intensive data integration efforts are unneeded.

For data reduction we will simply disregard the attributes that are unnecessary and do not add value to our investigation. This will make the mining process easier as there will be no redundant data to deal with. Data transformation will be done by normalizing all numeric attributes using min-max normalization, so they can be analyzed statistically.

DATA SET

The data set can be located in different file formats (JSON, XML and txt) at the following URLs:

- JSON: https://open.fda.gov/tools/downloads/
- XML/.txt: https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html

More information about the Postgresql database we are using for data analysis is available at the following URL:

- https://github.com/CSCI-4502-DataMining Project/Drug_Reactions

We have downloaded a subset of the data available and placed it into tables mirroring tables in the FAERS database. These tables and their row counts are as follows:

- indi (indications) - 7,901,564
- outc (outcomes) - 2,122,914
- reac (reactions/adverse events) - 9,007,602
- rpsr (report sources) - 113,657
- ther (drug therapy start/end dates) - 4,200,330
- demo (patient demographic information) - 3,088,728
- drug (drug/biologic information) - 11,312,890

The next form of the data set exists as JSON files. For each file there are two subsections of the data, meta and results. Meta contains metadata about the query, including a disclaimer, link to data license, last-updated date, and total matching records, if applicable. Results contains an array of matching results, dependent on which endpoint was queried. The data set provides all necessary information about the patient such as age, gender, condition and outcome as well as detailed information about the drug used for treatment including but not limited to drug name, drug substance, dosage and administration method.

EVALUATION METHODS

For data evaluation it may first be useful to match probability distributions to each of the retained attributes in order to learn more about the data. We will attempt to answer questions such as: Do most attributes fit a normal distribution? Is the skew in certain attributes? If so what could be causing it? Next, we will calculate correlation coefficients between each pair of numerical attributes in order to identify significant correlations that may exist in hopes of exploring what demographic attributes may be highly correlated with negative outcomes.

Once we've discovered interesting correlations we can hopefully construct decision trees which support our claims.

Another method of evaluation will be to use the Apriori algorithm to discover sets of factors and reactions in patients which frequently appear together. If we find a significant amount of these conditions, we may be able to conclude with a certain probability that factor x will cause adverse reaction y.

A last method of evaluation will be implementing a classification algorithm. After data cleaning and preprocessing we can construct a training and test set in which we can use methods such as naive Bayesian and

rule-based classification which will ideally lead to some interesting knowledge discovery. After all evaluation is finished it will be important to check the significance of our conclusion using metrics such as P-value, R squared, confusion matrices and F-score.

Ideally, our work will result in predictive analyses that will allow us to forecast adverse drug reactions for certain demographic subgroups. We hope to find interesting and unexpected indications that a subgroup may be more at-risk of an adverse reaction than otherwise anticipated.

TOOLS

We plan to use the following tools to aid in the analysis and evaluation detailed above:

- Python
- Python JSON library
- Pandas
- Numpy
- SciPy
- Sklearn
- Seabourn
- Patsy
- Matplotlib
- MySQL

MILESTONES

Milestones Completed

- Friday, October 26: Finish any data collection for the JSON files. Continue data cleaning and preprocessing efforts for the data in the Postgresql database.
- Friday, November 2: Finish data preprocessing efforts on both the JSON files and Postgres data, and have completed initial investigation of the dataset. Identify some existing patterns and/or correlations.
- Sunday, November 4: Submit progress report.

Milestones Completed Discussion

The first milestone which needed to be completed was all data cleaning, merging and preprocessing. We performed data cleaning and preprocessing steps on both the JSON version of the dataset and the version of the dataset loaded into our Postgresql database. As mentioned earlier, having the data in two formats allows us to have lots of flexibility in our analysis.

Data Cleaning and Preprocessing on JSON Files

A total of 788 JSON files provided by the FDA at https://open.fda.gov/tools/downloads/ and containing all patient information, ranging from patient demographic information such as age, weight and sex, to drugs used for treatment and reactions to those drugs, were downloaded and inflated to an external drive. The data, in JSON format, contained a lot of information in nested dictionaries which needed to be flattened into a table format to allow for querying and numerical manipulation. Using a Python Jupyter notebook, which can be found here https://github.com/CSCI-4502-DataMiningProject/Drug_Reactions, the files were loaded into a pandas data frame. The first nested dictionary structure of each file was flattened and its attributes listed.

Immediately a number of attributes were dropped as they are irrelevant to our project and will not add any value to our investigation. If desired, those attributes can be referenced in the Jupyter notebook. Out of the remaining attributes, two (drug and reaction) contained a further nested data structure needing to be unpacked. This was done by creating two new data frames for each file containing arrays of the drug(s) and reaction(s) associated with each subject. The columns were split by drug and

reaction, then merged with the original data frame.

At this point we wish to start our investigation small, so we have limited our dataset to include only one drug. We have also limited the dataset to include only the first three reactions, and dropped all others. Information on how that drug was selected, and why we've chosen to limit the reactions, is detailed below in the next section. However, we've kept all files stored in case we wish to expand our project.

The next step in the process is to eliminate any outliers. This was done on the following two numerical attributes, age and weight, using the following formula Q1-1.5×IQR and Q3+1.5×IQR, where Q1 and Q3 are the first and third quartiles, and IQR is the interquartile range.

Data Cleaning and Preprocessing on Postgresql Data

The data preprocessing and cleaning steps on the Postgresql database began with us creating several different subsets of the dataset for exploration. We joined the demographic, reactions, outcomes, and drug tables in the database, matching each record by case ID. Case ID is the FDA unique identifier for a particular patient case. We dropped all attributes unhelpful in our analysis, and for now have kept null values. We may handle null values differently as we proceed with our analysis.

In order to focus our investigation, we chose to only analyze the "primary suspect" drug, which is the drug suspected of causing the adverse reaction. The FDA FAERS database denotes the role of a drug with an attribute called "Drug Role Code". Patients, especially chronically ill ones, may be taking multiple drugs at a time, and the FDA FAERS database will have a record of each of these drugs as part of a case report. However, some drugs are not as likely to cause adverse reactions as others. The drug most likely to have caused the reaction has a Drug Role Code of "PS" (corresponding to "primary suspect"). In order to minimize noise, we chose to retain only these "primary suspect" drugs.

Additional data cleaning steps included normalizing date fields to a MM/DD/YYYY format and removing duplicates.

The attributes retained in our data subsets are:

- Primary Suspect Drug Name
- Drug role code
- Case ID
- Age
- Age Group
- Sex
- Weight
- Weight Code (kg/lbs)
- Country
- Event Occurrence Date
- Reaction

These data subsets include:

Subset A

Subset A contains 1.5 million records with the the attributes above. However, it only includes the primary (first) reaction per case. Reactions can be extremely specific and interrelated, so using a primary reaction as a kind of "descriptive" reaction will work well for higher-level analysis. For example, a patient whose primary reaction is listed as "Abdominal pain lower" may also have "Pelvic pain" and the more general "Fatigue" and "Pain" listed as reactions. Using the primary reaction will help us narrow our focus, and will streamline our investigation when we're not interested in breaking analysis out by specific (and sometimes unhelpful) reactions.

Subset B

Subset B contains all the attributes above aside from drug name, and includes all reactions, not just primary reactions, for finer-grained analysis. It contains 18 million records.

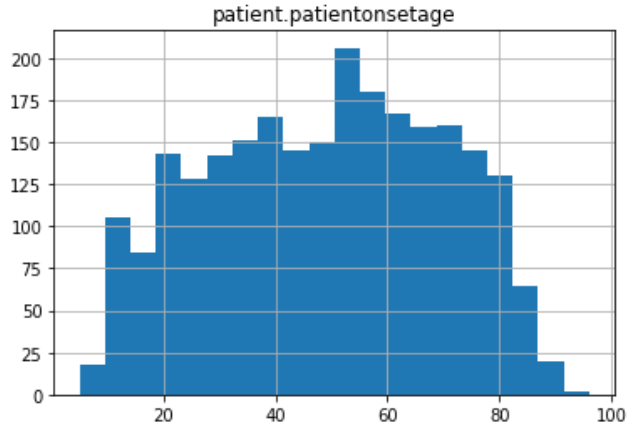
Milestones To Do

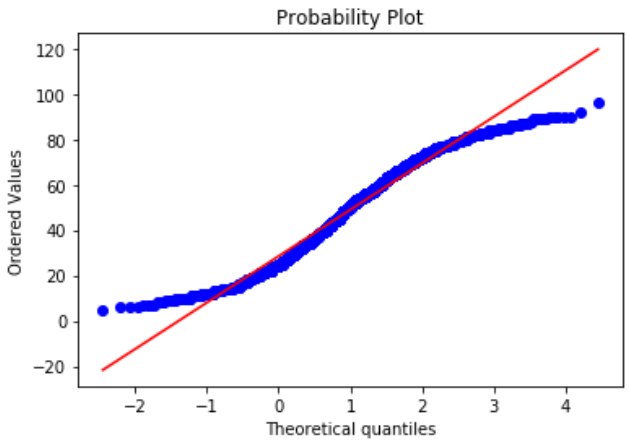
Our next milestones will be to construct our predictive models. We intend to leverage both the Apriori algorithm and naive Bayesian classification to help us build predictive models to determine which patients may be at risk of serious adverse reactions.

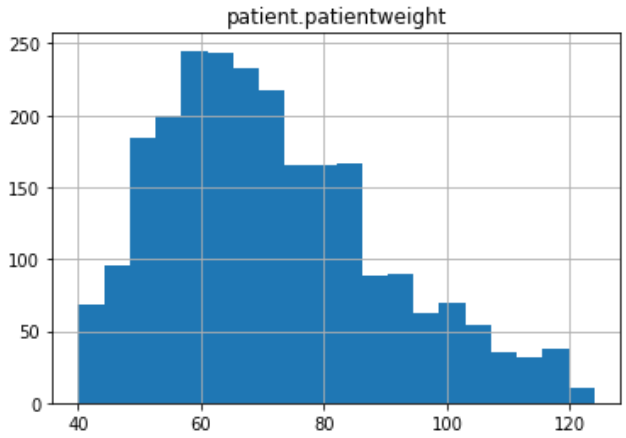
- Friday, November 9: Construct predictive models.
- Friday, November 16: Implement Apriori in python and run on data set.
- Friday, November 23: Construct decision trees based on results.
- Friday November 30: Validate that our findings are accurate using appropriate methods.
- Friday December 7: Finish project code and descriptions and project final report.
- Friday December 14: Finish project presentation.
- Sunday, December 16: Submit Final presentation.

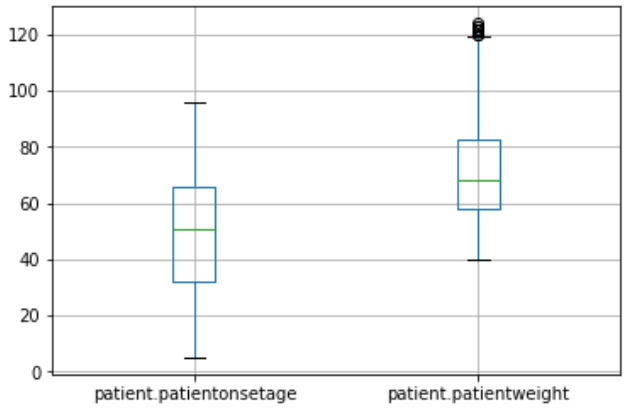
RESULTS SO FAR

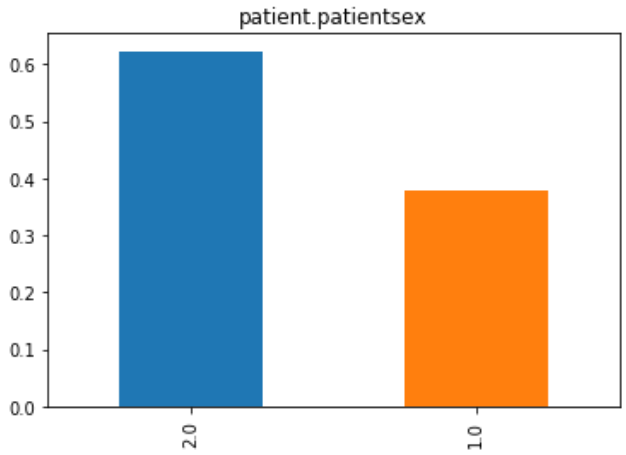
As part of our initial investigation of the data, we plotted histograms of patient demographics. Specifically, patient age, weight and sex were plotted for visual inspection in an attempt to identify any obvious trends and or skews in the data that may exist. Age appears to be evenly distributed, a normal distribution can be verified give the quantile-quantile plot below. There is a slight deviation near the outer ends, however, this can be expected as a result of outlier elimination. Interestingly, patient weight appears to be slightly skewed to the right. This may be an indicator that weight loss is present among a majority of patients in this data set. Using the Scipy statistical analysis tool for Python, the skewness was measured to roughly 0.628 meaning nearly 63% of the weight exists in the left tail of the distribution. In addition a skew test was ran which returned the following result. SkewtestResult(statistic=11.766181724799404, pvalue=5.83041859092924e-32). This will be analyzed in further detail in the near future. Lastly, and for reasons unknown, the number of female patients appears to be greater than the number of male patients in most of the files. A bar chart of overall percentage of males compared to females averaged over 5 files can be reviewed below, where males are given by the number 1 and females the number 2. All plots were also recaptured before any preprocessing was done to verify that these trends are indeed genuine and were not a result of the data cleaning and preprocessing.





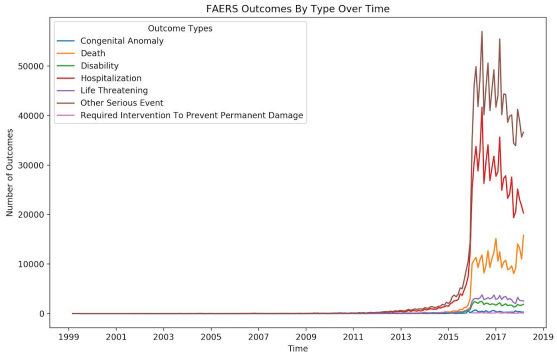






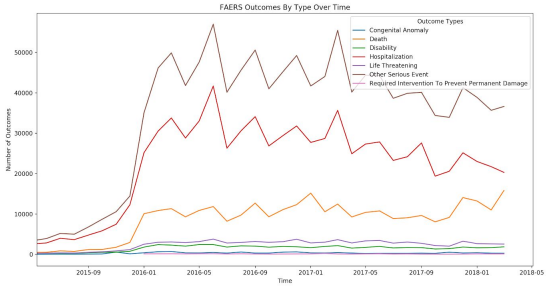
We also examined patient outcomes, which are broken out by the FAERS database into seven types: "Congenital Anomaly", "Death", "Disability", "Hospitalization","Life Threatening", "Other Serious Event", and "Required Intervention". A patient might have multiple adverse reactions per case, but only one outcome.

To explore how the dataset might have changed over time, we created a temporal graph of all outcome reports.



Cumulatively, we can clearly see from the graph that there was a significant increase in reporting starting in 2013.

If we examine this period in greater detail, we can see the beginnings of a pattern, where reporting volume spikes approximately once a quarter, with larger spikes around the first few months of the year. It's possible that the quarterly spikes are due to reporting behaviors by medical staff; perhaps reports tend to get filed around the same time each quarter. It would be interesting to continue to observe outcomes reporting into 2019 and 2020 to see if these patterns continue.



We can see that "Hospitalization" and "Other" are the outcomes categories most commonly used, with "Required Intervention" near the bottom. This is not unreasonable -- since cases only

have one outcome, if a patient is hospitalized at any point, even during a case that “Required Intervention”, their case may get categorized as a “Hospitalization”. This could explain the heavy reliance on categorizing outcomes as hospitalizations.

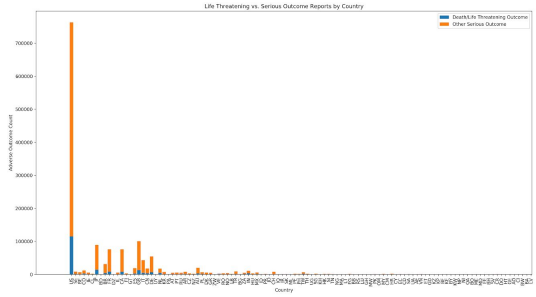
It’s also possible that the person reporting is not the medical staff who treated the patient, and the reporter may have very limited information to base their report on. In that case, “Hospitalization” would be an easy, concrete nominal category to select.

The FAERS database includes the reporter type, which may be illuminating to bring into this analysis. Available types include “Physician”, “Pharmacist”, “Consumer”, and “Lawyer”. It would be interesting to dig deeper into this data to see what percentage of reports come from non-medical reporters, like lawyers and consumers, and if those non-medical reporters are more likely to use the more general outcome categories like “Hospitalization” or “Other”.

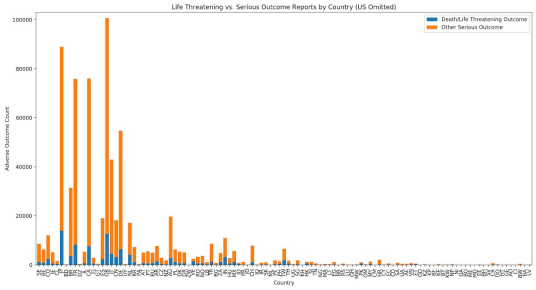
Finally, we looked at outcomes broken out by country. In the FAERS database, “country” is where the adverse reaction occurred. In the graph below, we can see, rather unsurprisingly, that there is an outsize number of reports that occurred in the US.

To create the graph below, we divided outcomes into two categories, rather than the full seven used by the FAERS database. The two categories we used were “Life Threatening/Death” and “Other Serious Outcome”. The first category includes the FAERS cases that were marked as "Death” or "Life Threatening", and the second category includes all other outcomes.

We omitted all countries with less than 20 total outcome reports.



The graph below omits the US, giving us a better view of the other countries.



Japan, Canada, France, Great Britain, and Germany lead the way after the US in terms of reporting numbers. These are not particularly surprising candidates, but there are some potentially interesting questions one could examine based on this data. For example, Great Britain and Japan have roughly the same number of “Life Threatening/Death” reports, but Japan’s total outcome reports are only about 90% of Great Britain’s outcome reports. What might account for the relatively higher “life threatening” reports in Japan?

Our work so far has allowed us to complete data cleaning and preprocessing, to become much more familiar with the dataset, and to unearth some new questions.

Overall, we have made good initial strides in our data investigation. We will continue to dig into factors like age, weight, and occurence country to uncover hopefully useful and compelling

patterns, allowing us to build our predictive models in the next few weeks.

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