DRUG EFFECT DISCOVERY USING THE SPONTANEOUS REPORTING SYSTEMS

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Adverse drug events are a leading cause of morbidity and mortality around the world. Regulatory agencies, such as the Food and Drug Administration (FDA), maintain large collections of adverse event reports, providing an opportunity to retrospectively study drug and drug combination effects. We mined the FDA Adverse Event Reporting System (FAERS) for significant adverse reactions and developed a database of drug effects, known as nSides. FAERS contains millions of reports covering thousands of drugs and thousands of effects, requiring the computing of approximately X billion models. We present a scalable, distributed, on-demand computational infrastructure which can be used with spontaneous reporting systems to calculate side effect significances from drug combinations. Even though nSides is based on FAERS data, the presented infrastructure is portable can be applied to any spontaneous reporting system.

1. Introduction

Spontaneous reporting systems such as the FDA Adverse Event Reporting System (FAERS) and EudraVigilance are important resources for detecting drug adverse events during and after the drug approval process (pharmacovigilance). However, pharmacovigilance algorithms often lead to many false positive and false negative findings due to issues of confounding, and detection of drug-drug interactions is an even greater challenge. We previously developed databases for off-label drug effects (OFFSIDES) and drug interactions (TWOSIDES) using FAERS that account for these limitations using a novel Statistical Correction for Uncharacterized Bias (SCRUB).[1] We re-mined FAERS with an updated algorithm to populate a new version of the databases, known as nSides. nSides also contains a front-end component consisting of a web gateway (http://nsides.io/) accessible to researchers, clinicians and patients alike.

We present the computational infrastructure used to populate the nSides back-end database. Additionally, we present middleware used to communicate between users and the back-end database population. The communication is done via an on-demand interface where users can request the nSides back-end database be populated with a specific drug combination. Drug combinations must be calculated on an on-demand basis due to the very high number of drug combinations possible in spontaneous reporting systems. The goal is to populate the back-end database within 24 hours of a user request.

A key feature of the computing infrastructure presented is portability to other spontaneous reporting systems, such as EudraVigilance. This allows researchers to create their own version of the back-end database for any use, including incorporation in the nSides web gateway. Additionally, using the consistent algorithms across spontaneous reporting systems allows researchers to evaluate drug effect differences and bias due to drug approval process differences.

The computational infrastructure with instructions is located on GitHub: https://github.com/tatonetti-lab/nsides

2. Data Sources

There are several data sources which are involved in nSides. We use a curated version of the FDA Adverse Event Reporting System (FAERS) known as Adverse Event Open Learning through Universal Standardization (AEOLUS).[2] AEOLUS aims to clean and normalize the data by removing duplicate cases. This is done by applying standardized vocabularies in the form of RxNorm to map drug names and SNOMED-CT to map outcomes. The AEOLUS dataset is publicly available.

By using standard vocabularies for drug names and outcomes allows other spontaneous reporting systems to be adapted to a consistent format used on the AEOLUS dataset.

3. Methods

3.1. *Algorithm*

The algorithm used to develop the databases used for nSides is an updated version of the one used to populate the OFFSIDES and TWOSIDES databases. These databases contain side effect

significances calculated using raw FAERS data.[1] Generally, a standard signal detection algorithm involves conducting a disproportionality analysis by comparing the observed reporting frequency of a drug and outcome to the expected reporting frequency of all other drugs and the outcome. The metric is known as a Proportional Reporting Ratio (PRR). If the outcome occurred by chance, the frequencies will be equal and the PRR will be one. If the PRR is much larger than one, the null hypothesis is rejected. To reduce sampling variance and selection bias, propensity score matching is implemented to form the groups used in the disproportionality analysis. This procedure, known as SCRUB, matches cases and controls between patients exposed and not exposed to a particular drug (OFFSIDES) or two drugs (TWOSIDES) to mitigate confounding biases. Once cases and controls are matched, the PRR for various side effects are calculated.

There are several key differences between the OFFSIDES and TWOSIDES databases and nSides. The updated algorithm uses a deep learning model instead of logistic regression to calculate propensity scores to match cases and controls. As a result, the computational power required to populate nSides is much greater. Additionally, nSides is not designed to be limited to effects of single and interactions of 2 drugs.

3.2. *Computational Challenge*

Populating the nSides database requires the SCRUB procedure to be run for each drug or combination of drugs individually to identify appropriate cases and controls. Once cases and controls are identified, PRR values need to be calculated over a range of side effects. Since the AEOLUS dataset contains ≈4,000 drugs, ≈5,000,000 reports, and ≈8,000 effects to analyze, a computational challenge emerges. To deal with this challenge we employ resources made available by the Open Science Grid (OSG) and Columbia University's computing cluster, Habanero. The OSG provides access to computing resources for research in the United States, free of charge. The computing facilities are located at over 100 sites spanning the United States, primarily at universities and national labs. The computing infrastructure presented is optimized to work on the OSG to increase the portability of the infrastructure to other spontaneous reporting systems.

The nSides back-end database is initially populated with single drug effects. To do this, a deep neural network model is generated for each unique ≈4,500 drugs in the AEOLUS dataset. The models are generated using the TensorFlow machine learning library. Because the computation involved in deep neural network model generation is more intensive than the logistic regression models used for the creation of OFFSIDES and TWOSIDES, a more complicated computational infrastructure is used.

TODO: Figure with number of drugs (x-axis) and number of models that need to be computed (y-axis)

3.2.1. *Distributed Computing Strategy*

The combinatorial complexity of running all jobs scales on the order of $\Theta(N^2)$ in the number of drugs. Given that a single job running on an OSG node takes 4-10 hours to complete, a distributing computing strategy is necessary to make the total runtime practical. We utilized

two distributed computing systems to determine the PRR between all pairs of coreported drugs, as described below.

The first of these, as mentioned above, was provided by the OSG. The OSG uses the HTCondor job submission software,[3] which handles allocation of computing resources to jobs submitted by the user. The other distributed computing system we utilized was Columbia University's scientific computing cluster, named Habanero. Habanero, like the OSG, uses a job submission management system, but unlike the OSG, Habanero uses the Slurm workload manager[4] for user-submitted jobs. We used both HTCondor and Slurm to submit jobs in a directed acyclic graph (DAG) configuration, supported using native extensions to HTCondor and Slurm.[5] In short, the DAG strategy allows users to take advantage of the fact that many distributed computing workflows consist of jobs containing common elements, such as initial data preparation. In a simplified example, a workflow may consist of one invariant data preparation stage followed by two sequential machine learning models, where each step relies on the previous step, and the machine learning models accept variable parameters. Here, the DAG capabilities of HTCondor and Slurm will only run the first stage one time, and sequentially pass the results of each stage to the next stage with the appropriate parameters as the results of the previous stage are available. This approach allows us to substantially reduce the combinatorial complexity of running all jobs to a manageable level.

Since HTCondor and SLURM are the two most common job schedulers, we release code such that the nSides back-end infrastructure can be easily deployed on either. This is done to increase the portability of the infrastructure to other spontaneous reporting systems.

3.3. *Computational Structure*

Generating a model for an individual drug or drug combination involves the following:

(1) Data preparation: Dimensional reduction of the complete AEOLUS dataset to reduce computational complexity of generating models. To do this, we only consider co-reported drugs that appear in at least 1 report
(2) Model generation: Generate 20 deep learning models per drug using different subsets of exposed and non-exposed reports. This is done to increase generality of the model.
(3) Model evaluation: Use scores generated by models to perform propensity score matching, use propensity score matched cases and controls to calculate side effect PRR values.
(4) Populate nSides back-end MongoDB database.

Steps (1) through (3) are performed in a grid computing environment and (4) is dependent on the hosting structure of the mongoDB database back-end.

TODO: DAG Figure to be referenced in Distributed Computing Strategy and Computational Structure

3.4. *On-demand Interface*

The original testing of our approach was performed manually on the distributed computing servers using a command line interface and shell scripts. In order to improve the ease of job submission in the future, we have developed a robust searchable shared-usage gateway to

the OSG resources we have described previously. The gateway uses a three-tiered architecture consisting of browser-based user interfaces on the frontend, the OSG job submission system on the backend, and middleware to facilitate communication between the other two components. The user interfaces are deployed using the Python Flask framework, and they access a variety of web services that constitute the middle tier of the gateway. These web services are arranged in a way that allows a heterogeneous collection of resources to be accessed remotely in a uniform fashion.

Additionally, the user interface frontend is bundled alongside a RESTful Web API (Application Programming Interface) that allows authenticated users to submit jobs programmatically. This API is implemented using the Agave tenant service[6]—a cloud-based API system designed for developing APIs to be used for scientific computing. The Agave job API manages all aspects of job execution and management, including data staging, job submission, job monitoring, output archiving, event logging, sharing, and notifications.

4. Discussion

Creating an open-source computing infrastructure for mining and presenting side effect significances from spontaneous reporting systems has great potential for improving pharmacovigilance. By using the same algorithm across many systems, it can be possible to evaluate drug effect significance differences which can be used to reduce the potential of adverse drug effects.

Due to dataset restrictions, it is not always possible to incorporate spontaneous reporting system data other than FAERS directly. For example, EudraVigilance data is only available to academic institutions within the European Union. With the infrastructure presented, it is possible for researchers with access to the EudraVigilance to form a separate version of nSides which can be compared with the version made with FAERS data.

References

1. N. P. Tatonetti, P. P. Ye, R. Daneshjou and R. B. Altman, *Science Translational Medicine* **4**, 125ra31 (2012).
2. J. M. Banda, L. Evans, R. S. Vanguri, N. P. Tatonetti, P. B. Ryan and N. H. Shah, *Scientific data* **3** (2016).
3. T. Tannenbaum, D. Wright, K. Miller and M. Livny, Condor – a distributed job scheduler, in *Beowulf Cluster Computing with Linux*, ed. T. Sterling (MIT Press, October 2001)
4. M. Jette and M. Grondona, Slurm: Simple linux utility for resource management, in *ClusterWorld Conference and Expo*, JUN 2003.
5. P. Couvares, T. Kosar, A. Roy, J. Weber and K. Wenger, Workflow in condor, in *Workflows for e-Science*, eds. I. Taylor, E. Deelman, D. Gannon and M. Shields (Springer Press, JAN 2007)
6. R. Dooley, M. Vaughn, D. Stanzione, S. Terry and E. Skidmore, Software-as-a-service: The iplant foundation api, in *5th IEEE Workshop on Many-Task Computing on Grids and Supercomputers*, NOV 2012.