

A DISTRIBUTED INFRASTRUCTURE FOR DRUG EFFECT DISCOVERY USING 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 billions of 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. When adverse reactions are caused by three or more drugs taken simultaneously, the problem quickly becomes computationally intractable. We previously developed databases for off-label drug effects (OFFSIDES) and drug interactions (TWO SIDES) 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 comprehensive computational framework which forms nSides. The framework includes a front-end web gateway as well as the infrastructure used to populate the back-end database. To handle the large number of computations involved, the back-end database infrastructure is designed to be executed on grid computing systems. We present the necessary code to run the infrastructure on two popular distributed computing platforms: HTCondor and Slurm. Additionally, we present middleware used to communicate between users and the back-end database. 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 diagram of the workflow is shown in Fig. 1.

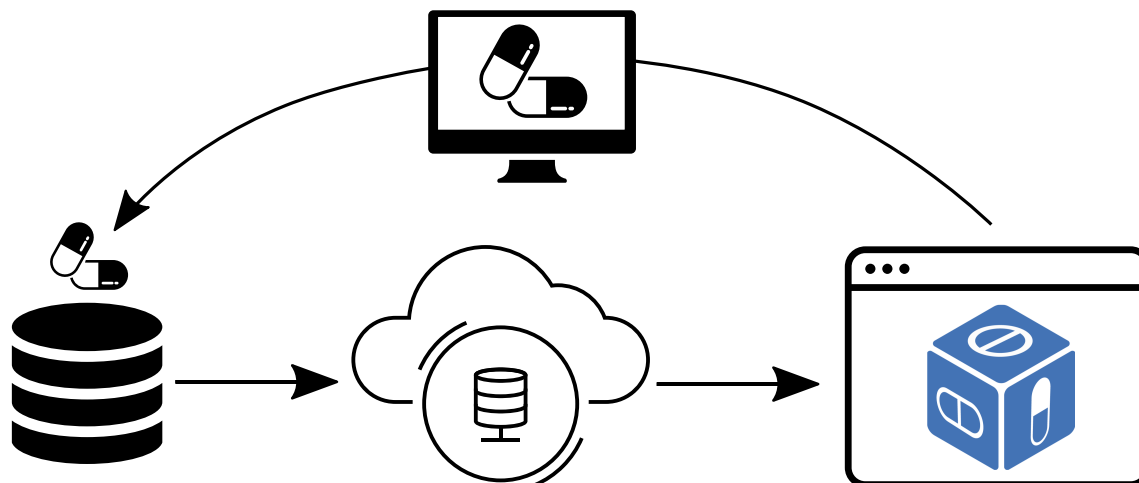


Fig. 1. An image representation of the computational infrastructure presented. Spontaneous reporting system data is processed on grid computing systems to generate an adverse event database (lower left) with a web front-end (lower right) which has an on-demand interface (top center) to request drug combination adverse reactions. User queries are handled by a set of middleware tools and Agave API (bottom center).

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 into the nSides web gateway. Additionally, using 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 can be found on GitHub:

- Front-end <https://github.com/tatonetti-lab/nsides/tree/v1.0-alpha>
- Middleware https://github.com/tatonetti-lab/nsides/tree/v1.0-alpha/job_api
- Back-end <https://github.com/tatonetti-lab/nsides/tree/v1.0-alpha/condor>

2. Data Sources

We built nSides using several data sources. 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 mapping drug names to RxNorm and outcomes to SNOMED-CT—two standardized vocabularies that are widely accepted in informatics. The AEOLUS dataset is publicly available.

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. Furthermore, this strategy facilitates semantic interoperability with other informatics tools, allowing nSides to be more easily incorporated into complex workflows and analysis pipelines.

However, since nSides is designed to work generically on reporting system data, it is not required for the data to use particular vocabularies.

3. Methods

In this paper, we describe the front-end web gateway, the distributed computing setup used to learn and compute the results of nSides, and the middleware used to facilitate communication between the front and back ends. Before describing this setup, we will briefly describe the algorithmic approach used to learn the nSides database.

3.1. *Adverse Event Detection Algorithm*

The algorithm used to develop the databases comprising 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 significantly greater 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 (TWO SIDES) to mitigate confounding biases. Once cases and controls are matched, the PRR for various side effects are calculated. An example is shown in Fig. 2.

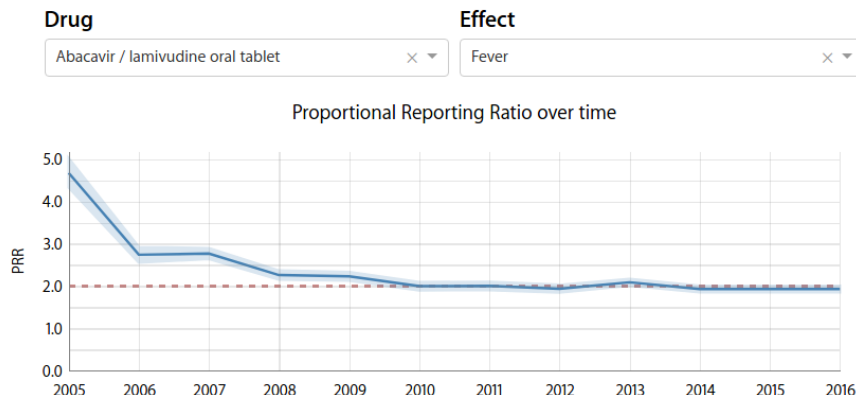


Fig. 2. Example result using the nSides web gateway front-end. Shown is the PRR calculated from all reports dated on or before the year listed on the x-axis.

There are several key differences between the OFFSIDES and TWO SIDES databases and nSides. The updated algorithm uses a deep learning model as well as logistic regression to calculate propensity scores to match cases and controls. By using two algorithms instead of just one, and the increased complexity of deep learning models, the computational power required to populate the nSides back-end database is much greater. Since nSides is not designed to be limited to effects of single and interactions of two drugs, a much more robust computational infrastructure is required.

3.2. Front-end Web Gateway

The public facing front-end web gateway provides access to the nSides results. When a user selects an available drug, a plot of the PRR of the top side effect is shown versus the report year, similar to Fig. 2. The top side effect is defined as the effect having the tightest confidence interval. The top 10 side effects are shown in a drop-down list next to the drug name. The user can type to in the selection box to retrieve the result for any available side effect. To retrieve the result of a drug interaction, the user simply selects multiple drugs in the drug box. If there are no results in the database for that particular combination, it can be requested via an on-demand interface which requests that a model is generated via distributed computing resources. This process is described in Section 3.5.

3.3. 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 we have identified cases and controls, we then needed to calculate PRR values over a range of side

effects. Since the AEOLUS dataset contains $\approx 4,000$ drugs, $\approx 5,000,000$ reports, and $\approx 8,000$ 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 laboratories. The computing infrastructure we present is optimized to work on the OSG to increase the portability of the infrastructure to other spontaneous reporting systems, but our use of Habanero demonstrates that it can be easily adapted to other distributed computing platforms as well.

Initially, we populate the nSides database with single drug effects. To do this, we learn a deep neural network model and a logistic regression model for each of the $\approx 4,500$ unique drugs in the AEOLUS dataset. We learn the models using the two scientific computing libraries TensorFlow and scikit-learn, respectively. The computation involved in generating the deep neural network model is more intensive than that of the more traditional logistic regression model, such as those used in the creation of OFFSIDES and TWOSIDES. As a result, we found it necessary to construct a more robust computational infrastructure.

As mentioned previously, the task of fully populating the back-end database for multiple drug interactions quickly becomes intractable. We show how the number of models to compute for the interaction of two, three, and four drugs scales with the number of total drugs in Fig. 3.

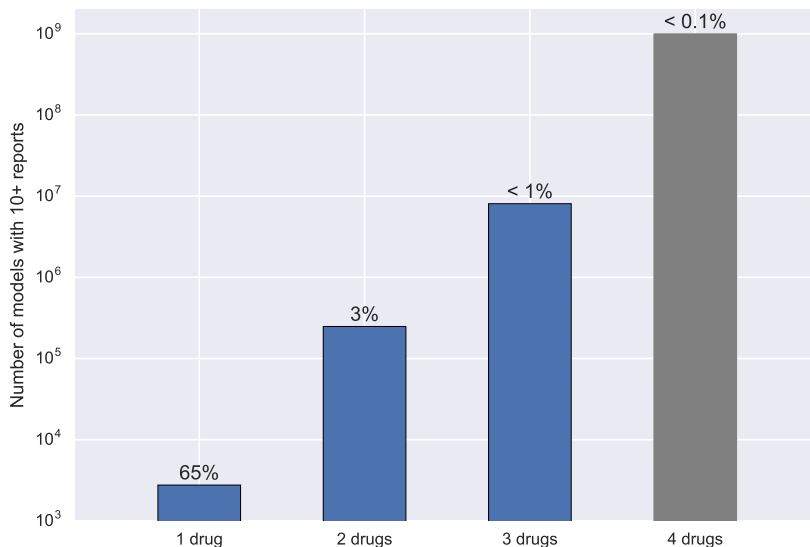


Fig. 3. Plot of the number of drugs in an interaction versus the number of unique drug combinations in AEOLUS with at least 10 reports available. The vertical axis is shown on a logarithmic scale, demonstrating the approximately exponential increase in models to compute in the number of drugs interacting. Values above each bar indicate the “efficiency” of the nSides approach: the percentage of all drug combinations with ≥ 10 available reports. Results for 4 drugs were approximated due to computational complexity.

3.3.1. *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. As mentioned above, we utilized two distributed computing systems to determine the PRR between all pairs of coreported drugs.

The first of these 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 manager⁴ 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 two very common job schedulers, we release code such that the nSides back-end infrastructure can be easily deployed on either, which increases the portability of the infrastructure to other spontaneous reporting systems.

3.4. *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 and logistic regression 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. For comparison, PRR values are also generated without propensity score matching.
- (4) Populate nSides back-end MongoDB database.

Steps (1) through (3) are performed in a grid computing environment in with the DAG strategy, shown in Fig. 4. Step (4) is dependent on the hosting structure of the MongoDB back-end.

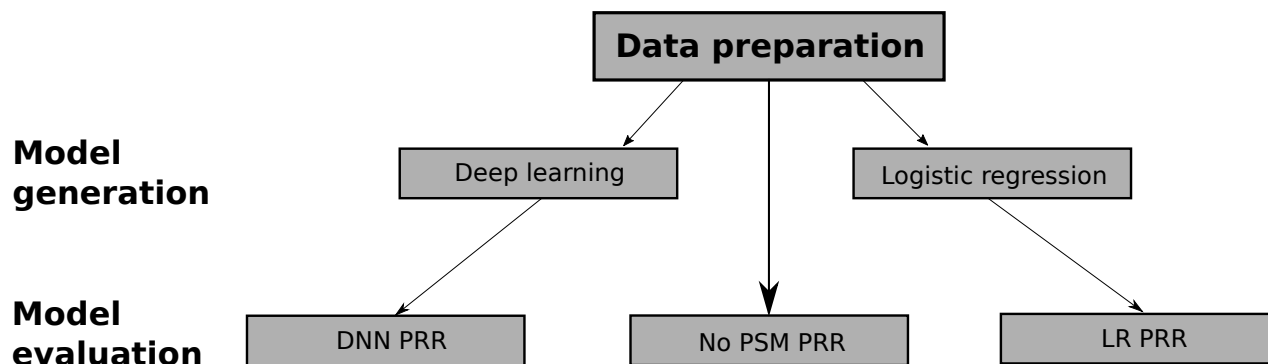


Fig. 4. Computational structure employed on both of the two distributed computing systems. First the data for a particular drug or drug combination is pre-processed, then deep learning and logistic regression models (20 replicates of each) are generated for that specific drug or drug combination, and finally propensity score matching is performed to result in PRR values.

3.5. On-demand Interface

We originally performed testing of our methods manually on the two distributed computing servers using a command line interface and shell scripts. In order to improve the ease of job submission in the future, we developed a robust searchable shared-usage gateway to the OSG resources we 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. We deploy the user interfaces using an application written using the Python Flask framework, which then 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, we bundled the user interface frontend alongside a RESTful Web API (Application Programming Interface) that allows authenticated users to submit jobs programmatically. This API is implemented using the Agave tenant service⁶—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 is 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. As a proof of concept, we were able to compute adverse reactions for the anticoagulant drug dabigatran using EudraVigilance data. This was done by using a subset of the data with randomized report, drug, and outcome

identifiers. The randomized data was then adapted to CSV format and side effect significances were calculated by following the instructions on the nSides back-end GitHub. Due to data licensing restrictions, we are not yet able to include the EudraVigilance results in the public web gateway, although we are currently working on a protocol to allow the inclusion of these elements in future revisions of the gateway.

Using our infrastructure, it is possible for researchers with access to EudraVigilance to compute an adverse event database using all reported drugs to create a separate version of nSides which can be compared to the version made with FAERS data. Furthermore, by randomizing data identifiers in the EudraVigilance dataset, it can also be possible to use large-scale public computing resources to compute the drug models.

The method we present can be used with other types of data. By not using a proprietary data format, the infrastructure presented can be adapted to work with other vigilance systems, claims data, and electronic health records data. By doing these separately, bias of each data type can be assessed by comparison and predictions from spontaneous reporting systems can be corroborated.

Although we have designed nSides to be used by any research group who is interested, we intend to maintain the application and web gateway at <http://nsides.io> permanently. We chose to host the gateway on a dedicated domain, since institutional URLs have a tendency to change over time. The gateway is currently hosted on a virtual Linux server running on Amazon Web Services' EC2 cloud server platform.

The comprehensive nSides framework presented integrates a diverse group of technologies including JavaScript (React and D3.js), distributed computing platforms (HTCondor and SLURM), and cloud-based APIs (Agave). Many of these technologies are intended for a wide array of scientific computing tasks. By making the framework completely open source, we hope to increase awareness of these tools. Additionally, we designed nSides to be agnostic to a specific data source to facilitate drug effect discovery across many systems.

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