Event Reporting System. Side effects for a variety of drugs and drug interactions are presented. Additionally, for high order drug combinations, with the support of the Science Gateway Community Institute's Extended Developer Support, we develop a novel system to request new models to be generated using the Open Science Grid on-demand.

I. INTRODUCTION

Spontaneous reporting systems such as the FDA Adverse Event Reporting System (FAERS) are important resources for detecting drug adverse events after a drug is approved (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) that account for these limitations using the novel Statistical Correction for Uncharacterized Bias (SCRUB) [2] algorithm (described below, in II), both of which are publicly available for download. Here, we present a web gateway which acts an interface to a database of drug effects calculated using the previously developed SCRUB algorithm, known as nSides (https://nsides.io). nSides aims to make the database of drug effects accessible to researchers, clinicians, and patients, and contains features related to drug safety. Since it is not feasible to generate models for every possible drug combination, we develop a novel model request system which submits jobs to the Open Science Grid and appends the results to the databases for future access.

Another popular resource for drug effects is SIDER [6], which is generated using data from placebo-controlled clinical trials, biomedical literature, and electronic health records.

nSides makes use of 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) [1]. AEOLUS aims to clean and normalize FAERS data by removing duplicate cases. This is done by mapping to standardized vocabularies and ontologies: RxNorm for drug names and ingredients, and SNOMED-CT for adverse event outcomes. The AEOLUS dataset is publicly available.

The algorithm used to calculate the results present in the nSides gateway is similar to the previously developed OFFSIDES and TWOSIDES databases, which used raw FAERS data [2] instead of AEOLUS. A standard signal detection algorithm involves conducting a disproportionality analysis by comparing the observed reporting frequency of a drug A drug combination and outcome to the expected reporting frequency of all other drugs / drug combinations and the same outcome. This metric is known as the Proportional Reporting Ratio (PRR) of the outcome for a particular drug or drug combination. 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, we reject the null hypothesis. To reduce sampling variance and selection bias, we implemented propensity score matching on the FAERS data 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. nSides extends this methodology to an arbitrary number of drugs, which can be specified by the user.

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https://gateways2017.gshare.com/

the database interactive by allowing the user to search for a single drug or combination of drugs. The top 10 effects associated with the drug(s) (ordered by number of reports in AEOLUS) are presented to the user. The user is also able to retrieve results for other effects. The drug names are mapped to RxNorm identi ers and a remote MongoDB database instance is searched. Effects are returned in the form of 2 plots, showing the PRR and the number of cumulative reports (respectively) in the AEOLUS dataset as functions of the report year. We have populated the nSides database with drug effect results for all single drugs, as well as a number of drug pairs. If results for a combination of n drugs are not present in the database, the user is able to submit a request to have the results computed remotely, as we describe below in V. A schematic of the different components of nSides are shown in Figure 1 and described in the sections below.

IV. DRUG INTERACTIONS

Users can search nSides for outcomes that are statistically associated to 2 or more interacting drugs. When users search for multiple drugs, results of the disproportionality analysis are presented for the drugs in combination. An example job is shown in Figure 2. Additionally, lists of drugs in the same RxNorm classes of each of the drugs searched will appear in order of the number of reports present in FAERS. Effectively, it is possible to see the change in PRR caused by ”swapping” one of the drugs by another in the same RxNorm class. Drug safety – including the possibility of reducing adverse outcomes from combinations of drugs – can be assessed in a data-driven way.

effects and 8,000,000 involving combinations 3 drugs. The nSides database is only initially populated with combinations involving a small collection of drugs. If a combination of drugs is searched that does not have effect results present in the database, the user is given the option to request the computation of a model.

Generating a model is computationally intensive and can take many hours. To optimize this process, we use the Open Science Grid to generate models. When a user requests a model, a job request is submitted to run on the Open Science Grid. When completed, the result is added to the nSides database and is made available for all users. This procedure allows nSides to become populated in a user-driven way.

VI. FRONT-END FRAMEWORK

The nSides web application front-end is implemented using JavaScript (React and D3.js) (Figure 2). We chose these frameworks for their speed and reliability across all modern web browsers. Additionally, we designed the web application to be responsive to screen sizes of both desktop and mobile devices. We also provide an option for users to download the entire database or subsets of interest as CSV les. For job submission to the Open Science Grid, we designed and implemented a user interface to run jobs for custom drug models selected by users.

VII. BACK-END FRAMEWORK

The back-end to the nSides app is implemented in Python (using the Flask web framework), including a fully-featured REST API for querying the remote MongoDB database instance containing computed model results and drug/outcome

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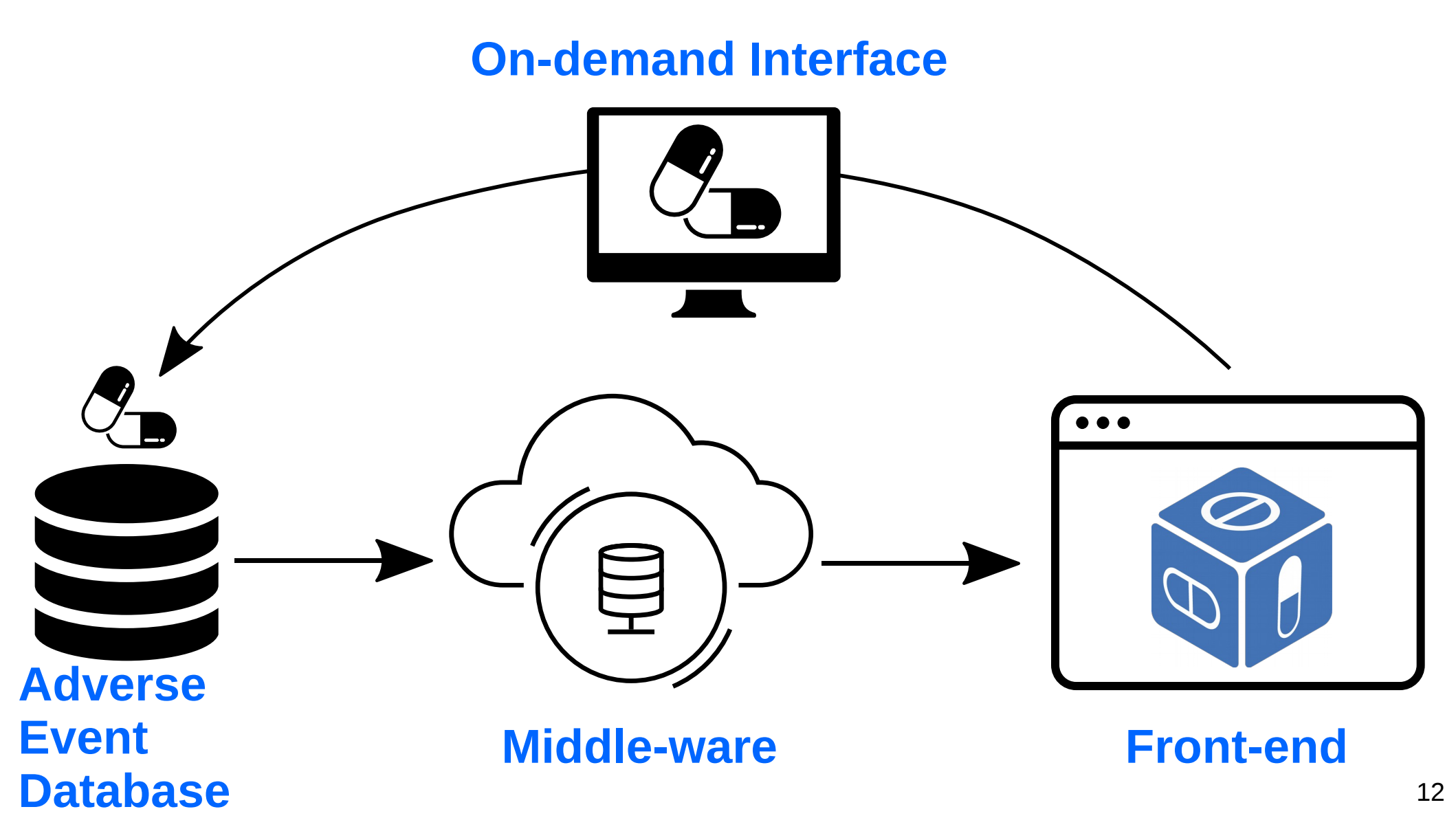
nSides Stack

- Front-end
  - Displays plots, model request system
- Middle-ware
  - Agave Platform to handle model requests, authentication
  - Python Flask framework
- Back-end
  - Models computed via OSG
  - Populated on mongoDB hosted on AWS


On-demand Interface
Adverse Event Database
Middle-ware
Front-end

Summary

- Data-driven analysis of drug effects using FAERS
- Accessible by researchers, clinicians, and patients
- Intended use to be hypothesis generator for further studies
  - See also: http://deltaqt.org
- Initial population done via Open Science Grid
- Novel on-demand job submission system which could be useful for others
- Full stack is open source
  https://github.com/tatonetti-lab/nsides

Future Directions

- PRRs for drugs in same drug class
- Incorporate other data sources
  - Drug structure information
  - Other reporting systems: European Medicines Agency analog: EudraVigilance
- Dynamic analysis on FAERS data
  - Other signal detection algorithms for drug interactions

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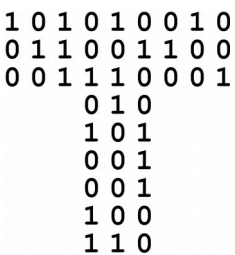

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