Adverse Drug Reaction Discovery

Adverse drug reaction (ADR) discovery is the task of identifying unexpected and negative events caused by pharmaceutical products.

Multiple Self-Controlled Case Series [1]

- Given the time-at-risk window \( L \), for patient \( p \), let \( x_{p,t,d} \) := whether drug \( d \) was prescribed at time \( t \), \( x_{p,t,o} \) := whether outcome \( o \) was observed at time \( t \).
- Define \( \bar{x}_{p,t,d} = \begin{cases} 1, & x_{p,t,d} > 0 \text{ for } s \in \{t-L, \ldots, t-1, t\}, \\ 0, & \text{otherwise}, \end{cases} \)
- as the data with imputed missing elements.
- Model the observation using a Poisson distribution
  \[ x_{p,t,o} \sim \text{Poisson}(\lambda_{p,t,o}). \]
- Parametrize the log-rate of outcome \( o \) for patient \( p \) at time \( t \) as
  \[ \log \lambda_{p,t,o} = b_{p,o} + \sum_{d \in D} w_{o,d} \bar{x}_{p,t,d}, \]
  where \( b_{p,o} \) is an individual-specific baseline rate and the weight \( w_{o,d} \) indicates how predictive drug \( d \) is of outcome \( o \).
- Use convex optimization to learn the parameters.
- Limitations: Assume all drugs share the same time-at-risk window and assume no time-varying drug effect.

Warfarin
Bleeding
Tricyclic Antidepressants
Heart Attack
Figure: Visualization of one patient’s electronic health record

Hawkes Process

- Hawkes Process is a point process model in which past events influence the likelihood of future events.
- Idea: For each drug-outcome pair, approximate the time-varying effect from the drug to the outcome by a weighted sum of some influence functions \( \phi_i \).

Figure: Piecewise constant influence functions that we used in the experiments. Each \( \phi_i \) gives a normalized count of how many events occurred in some time interval in the past.

- Let \( N_p \) be the total number of events observed for patient \( p \).
- Describe his/her \( i \)-th event by the time \( \tau_{p,i} \) and the type \( m_{p,i} \).
- Model the log-rate of the Hawkes process as following:
  \[ \log \lambda_{p,o} (\tau) = b_{p,o} + \sum_{i \in D} w_{o,d,i} \phi_i (\tau - \tau_{p,i}). \]

The weight \( w_{o,d,i} \) indicates how well we may predict outcome \( o \) based on a patient being on drug \( d \) according to the \( k \)-th influence function.

- The log-likelihood for patient \( p \)'s occurrences of outcome \( o \):
  \[ \log L_p (b_{p,o}) = \sum_{i \in D} \log \lambda_{p,o} (\tau_{p,i}) - \int_0^\tau \lambda_{p,o} (\tau) d\tau. \]

Regularized maximum likelihood estimator:

\[ (w, b) = \arg \min_w \sum_{p=1}^P \sum_{o \in O} \log \lambda_{p,o} (\tau_{p,o}) + \lambda \|w\|_1. \]

Solve this convex problem by coordinate descent + FISTA.

Dataset

We employ a de-identified version of Marshfield Clinic health system’s Electronic Health Records. We extracted 10 drug prescription records and 10 diagnosis records based on the definition of OMOP.

<table>
<thead>
<tr>
<th>Table: Summary statistics of the cohort</th>
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<tbody>
<tr>
<td># patients</td>
</tr>
<tr>
<td># adverse health outcomes</td>
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<tr>
<td># drug prescription records</td>
</tr>
<tr>
<td># avg. observation duration</td>
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</tbody>
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References