Mining high-order drug-drug interaction (DDI) induced adverse drug effects (ADEs) from electronic health record (EHR) databases is an emerging area, and few studies have explored the relationships between DDIs. We previously studied a novel pharmacovigilance problem for mining directional drug interaction effect on myopathy [1] using the FDA Adverse Event Reporting System (FAERS) database. Given over 1,500 FDA approved drugs, the number of candidate directional ADE effects between two drug combinations could be prohibitively huge, and many of these drug combinations have zero or very few occurrences in the data. Since different drugs could share similar pharmacological and other properties, grouping similar drugs together and performing group-level analysis instead of drug-level analysis could dramatically reduce the problem dimensionality, boost the drug analysis, and yield high-order directional ADE effect analysis which is defined as $OR = \frac{a \times d}{b \times c}$, where $ATC_1 \rightarrow ATC_2$ is a superset of $ATC_1$, where $ATC_1 \rightarrow ATC_2$ is a superset of $ATC_1$.

Therefore, in this work, we propose to perform high order directional ADE effect analysis at the group level, using the Anatomical Therapeutic Chemical (ATC) classification system.

As shown in Figure 1, we estimated the odds ratio (OR) of the directional myopathy risk from taking ATCC1 to taking ATCC2, U ATCC1, where both ATCC1 and ATCC2 are frequent.

**Figure 1.** The workflow for mining drug interaction effects at the ATC group level.

The odds ratio (OR) of the directional myopathy risk from taking ATCC1 to taking ATCC2 is defined as $OR(a \times d)/b \times c$, where ATCC1 is a superset of ATCC2.

The combination of the ATC codes most present in the odds ratio top findings are shown in Table 1. The top finding S01H, S01A → S01H, S01A, A02B is a two ATC code combination of local anesthetics and combinations with antibiotics which when a drug in the A02B group representing drugs for Peptic Ulcer and Gastro Oesophageal Reflux disease is added produces a drug-drug interaction (DI) that leads to a substantial increase in the risk of myopathy odds ratio = 43.093. This means that the myopathy risk for patients taking the combination of local anesthetics, combinations with antibiotics, and Peptic Ulcer and Gastro Oesophageal Reflux disease is 43 times higher than that for patients taking only local anesthetics and combinations with antibiotics.

**Figure 2.** Drug network visualization. Significant odds ratios associated with baseline $\rightarrow$ two ATC combinations are shown by the edge's transparency within the network. The hub surrounding VOBC, the hub at RO2A, and the hub at HO5A are highlighted and warrant further analysis.

### References
