Automated Physician Order Recommendations and Outcome Predictions by Data-Mining Electronic Medical Records

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Abstract

The meaningful use of electronic medical records (EMR) will come from effective clinical decision support (CDS) applied to physician orders, the concrete manifestation of clinical decision making. CDS development is currently limited by a top-down approach, requiring manual production and limited end-user awareness. A statistical data-mining alternative automatically extracts expertise as association statistics from structured EMR data (>5.4M data elements from >19K inpatient encounters). This powers an order recommendation system analogous to commercial systems (e.g., Amazon.com’s “Customers who bought this…”). Compared to a standard benchmark, the association method improves order prediction precision from 26% to 37% (p<0.01). Introducing an inverse frequency weighted recall metric demonstrates a quantifiable improvement from 3% to 17% (p<0.01) in recommending more specifically relevant orders. The system also predicts clinical outcomes, such as 30 day mortality and 1 week ICU intervention, with ROC AUC of 0.88 and 0.78 respectively, comparable to state-of-the-art prognosis scores.

Introduction

Electronic medical records (EMR) can improve patient safety and healthcare cost efficiency, but that depends on meaningful use of the data\(^1\). This will require effective clinical decision support (CDS) content, particularly to drive clinical orders (labs, imaging, medications, etc.), the concrete manifestation of clinical decision making. Order sets, risk scores, and similar CDS constructs help reinforce consistency and compliance with best-practices\(^2,3\), but their conventional development is limited by a top-down approach. This approach requires manual production of CDS content, feasible for only a limited number of common scenarios, and often with limited end-user awareness\(^4\). With the progressive digitization of clinical data in EMRs, a Big Data\(^5,6\) approach can instead crowd-source clinical expertise from the bottom-up by data-driven models of clinical expertise, even as it is simultaneously applied to patient care with direct EMR integration.

Background

Prior work in automated CDS content development includes association rules and Bayesian networks between orders and diagnoses, and review of possible order set and corollary order content by subject experts\(^7–10\). With inspiration from analogous problems of information retrieval in recommender systems, collaborative filtering, market basket analysis, and natural language processing, we initiated an item association order recommendation framework\(^11\) analogous to Netflix or Amazon.com’s “Customer’s who bought A also bought B” system\(^12\). Here we update our initial efforts with a much larger dataset that includes non-order data to better define a patient’s clinical context, propose an alternative evaluation metric to identify recommendation methods that highlight items specifically relevant to a given clinical scenario, and use the framework to predict clinical outcomes.

Methods

Deidentified, structured patient data from inpatient hospitalizations at Stanford University Hospital in 2011 was extracted by the STRIDE project\(^13\). Extracted data covers patient encounters starting from their initial (emergency room) presentation until hospital discharge. With >19K distinct patients, the data consists of >5.4M instances of >17K distinct clinical items, with patients, instances, and items respectively analogous to documents, words, and vocabulary items. The clinical items include >3,500 medication, >1,000 laboratory, >800 imaging, and >700 nursing orders. Non-order items include >1,000 lab results, >5,800 problem list entries, >3,400 admission diagnosis ICD9 codes, and patient demographics on age, gender, and date of death. Numerical data was binned into categorical data, particularly lab results, based on “abnormal” flags as established by the clinical laboratory. The ICD9 coding hierarchy was collapsed as necessary into diagnosis codes with a significant number of instances.

The relationship between item instances covered and the top clinical items considered is consistent with the “80/20 rule” in the form of a power law distribution\(^14\). This property allows one to ignore most clinical items with minimal information loss. In this case, ignoring sparsely populated clinical items with <256 instances (0.005% of
all instances) reduces the effective item count from >17K to 1.5K (9%), while only reducing item instance coverage from 5.4M to 5.1M (94%). Computational efficiency of subsequent order recommendations improves significantly with this simplification, given methods requiring $O(m^2)$ space and $O(q * m \log m)$ time complexity, where $m$ is the number of clinical items considered and $q$ is the number of query items for a recommendation.

A pre-computation step collects frequency statistics on clinical item instance co-occurrences from a training set of 16,408 randomly selected patients to build an item association matrix, based on the definitions in Table 1. These statistics drive subsequent recommendations by approximating Bayesian conditional probabilities as in Table 2.

| Notation | Definition |
|----------|------------|
| $n_A$    | Number of occurrences of order A |
| $n_{AB}$ | Number of occurrences of order B following an order A within time t |
| $N$      | Total number of patients |
| $P(A)$   | Number of occurrences of order A / Total number of patients |
| $P(AB)$  | Number of occurrences of order B following an order A within time t / Number of occurrences of order A |
| $P(B|A)$ | Number of occurrences of order B following an order A within time t / Number of occurrences of order A |
| $P(B|A) = P(AB) / P(A)$ | Conditional frequency of B, given A |

| Probability | Estimate | Notation / Notes |
|-------------|----------|------------------|
| $P(A)$      | $n_A / N$ | BaselineFreq(A) |
| $P(AB)$     | $n_{AB} / N$ | $n_{AB}$ (“Support”) only counts directed association where A occurs before B |
| $P(B|A)$     | $n_{AB} / n_A$ | ConditionalFreq(B|A) (“Confidence”) |
| $P(B|A) / P(B) = P(AB) / P(A)*P(B)$ | Frequency of B, given A |
| $P(B|A) / P(B) = P(AB) / P(A)*P(B)$ | $n_{AB}/n_A$ / $n_B/N$ | FreqRatio(B|A). Estimates likelihood ratio. |
| $P(B|A) / P(B) = P(AB) / P(A)*P(B)$ | $n_{AB}/n_A$ / $n_B/N$ | Frequency of B, given A |
| $P(B|A) / P(B) = P(AB) / P(A)*P(B)$ | $n_{AB}/n_A$ / $n_B/N$ | Frequency of B, given A |

Table 1 - Pre-computed frequency statistics for clinical items. Counting repeats allowed.

Table 2 - Bayesian probability estimates based on item frequency statistics.

To generate order recommendations from the above association statistics, query clinical items ($A_1, \ldots, A_q$) are used to select item association pairs from the pre-computed association matrix for all possible target orders ($B_1, \ldots, B_m$). Target orders are ranked by a score such as ConditionalFreq(B|A), the maximum likelihood estimator for the probability of order $B_i$ occurring after query item $A_i$. As previously noted, ranking by ConditionalFreq identifies likely orders, but also tends to yield non-specific orders (e.g., CBC, IV saline) that are common overall, yet not necessarily “interesting.” To identify orders more significantly relevant to the query, recommendations are ranked or filtered by FreqRatio(B|A), comparable to the TF*IDF (term frequency * inverse document frequency) information retrieval concept.

To quantify the significance of item associations, $-2 \log FreqRatio$ can approximate a chi-square statistic or the chi-square statistic can be directly calculated by comparing observed vs. expected occurrence counts. Issues with misinterpreting association strengths in the setting of inadequate data (heuristics advise at least 5 occurrences to be reliable), are mitigated by excluding rare items occurring <0.005% of the time as previously described.

Given $q$ query items, the above method generates $q$ scored lists of all $m$ possible orders. These are aggregated into a single scored recommendation list by taking a weighted average of the component scores, weighted inversely proportional to their respective query item baseline frequencies (lending more weight to less common, more specific query items). Unweighted score averaging and a Naïve Bayes style composite product of the component conditional probabilities (i.e., conditional frequencies) were also attempted, though the weighted average method was retained as it yielded the best results.

While there is no well accepted notion of recommendation quality, accuracy in predicting subsequent items is the most commonly measured, with precision (positive predictive value) and recall (sensitivity) correlating with end-user satisfaction. A test set of 1,903 patients was randomly selected, separate from the training set. For each test patient, all clinical items from the first 4 hours of their hospital encounter were used (average of 29) to query for 10 recommended orders that were compared against the actual subsequent orders within the first 24 hours (average of 15). To quantitatively recognize recommenders that yield results that are more meaningfully relevant to a query and not simply common, we introduce the alternative metrics of inverse frequency weighted precision and recall, based on the following function definition: $TP(i) = \{1$ if recommended item $i$ is a true positive, $0$ if not$\$. Likewise $FP(i)$ for false positives and $FN(i)$ for false negatives. The inverse frequency weighted precision and recall metrics are defined below in summation notation, with components weighted by the inverse baseline frequency of each item $i (n_i/N)$. Note that the common constant factor $N$ can be cancelled out to yield:

| Weighted Precision | $\Sigma (1/n_i)*TP(i) / (\Sigma (1/n_i)*TP(i) + \Sigma (1/n_i)*FP(i))$ |
| Weighted Recall    | $\Sigma (1/n_i)*TP(i) / (\Sigma (1/n_i)*TP(i) + \Sigma (1/n_i)*FN(i))$ |

The association framework was also applied towards “recommending” non-order items to predict outcomes such as patient death and ICU intervention. For the latter, a composite “AnyICU” clinical item was defined as the
occurrence of interventions including mechanical ventilation, vasopressor infusion (epinephrine, norepinephrine, dopamine, phenylephrine, vasopressin, dobutamine), or continuous renal replacement therapy (CRRT). Taking 1,905 test patients separate from the training set, their first 24 hours of clinical items were used to query the association model for the probability (ConditionalFreq(B|A)_{t}) of an outcome event within t time (30 days for death, 1 week for AnyICU) and compared them vs. actual event rates by receiver operating characteristic (ROC) analysis.

**Results**

Table 3 illustrates example order recommendations. Table 4 reports accuracy metrics for different recommendation methods, illustrating the trends toward the best results. Table 5 reports the ROC area-under-curve (AUC) prediction accuracy for outcomes of 30 day mortality and 1 week use of AnyICU. Table 6 illustrates an inverted query example, identifying items commonly *preceeding* an outcome event.

Table 3 – Example orders recommended when query by admitting diagnosis of GI Hemorrhage, ranked by ConditionalFreq(B|A)_{day} and filtering out those with FreqRatio(B|A)_{day} <1. Example interpretation: Given a GI Hemorrhage, 75% of patients receive IV Pantoprazole (standard initial treatment for an acute GI bleed) within 24 hours. This is somewhat more likely (FreqRatio 1.8) than for all patients in general, though even the baseline of 42% is relatively common as IV Pantoprazole is used for non-GI bleed scenarios (e.g., prophylaxis against stress ulcers). For comparison, the Pantoprazole IV continuous infusion is less common (51%), but has a higher relative likelihood (freqRatio 16.0), as it is used almost exclusively in the treatment of GI bleeds.

Pantoprazole is used for non-GI bleed scenarios (e.g., prophylaxis against stress ulcers). For comparison, the Pantoprazole IV continuous infusion is less common (51%), but has a higher relative likelihood (freqRatio 16.0), as it is used almost exclusively in the treatment of GI bleeds.
replacement therapy (CRRT), and mechanical ventilation for ARDS (lung protective ventilation protocol). Inverse
preceded by aggressive life-supporting ICU interventions including vasopressors (norepinephrine), continuous renal
representing reprioritization of care for patients with expected imminent death. Complementary to that are deaths
physician orders and predicts clinical outcomes based on statistics data-mined from electronic medical records. As
time) result in the recommender being distracted by associations that occur outside the relevant 24 hour evaluation
recognizing that lactic acidosis (high lactic acid) and acidemia (low pH) disproportionately precede death.

Table 4.  While standard accuracy metrics favor common items, it is more impressive to correctly predict a rare item
prediction of uncommon items, and future work will explore personalized prediction of lab result
outcome event with minimal incremental effort in future work.

Table 5 reports the association framework’s ability to predict clinical outcomes with ROC AUC of 0.88 for 30
day mortality and 0.78 for requiring ICU intervention within 1 week of hospitalization. These are comparable to
state-of-the-art prognosis scoring systems such as APACHE, MPM, and SAPS with scores ranging from 0.75 to 0.90
for predicting hospital mortality and CURB-65, PSI, SCAP, and REA-ICU with scores ranging from 0.69 to 0.81
for predicting early ICU admission. Other prediction possibilities could include hospital length of stay, readmissions, and many others, though the virtue of the framework is that it can predict any item labeled as an
outcomes with minimal incremental effort in future work.

While the FreqRatio based methods elaborated here help distinguish specifically relevant orders from those that are simply common, a primary concern with this method is favoring common practices that are not actually ideal. With preliminary results on predicting clinical outcomes above, a tempting possibility will link recommendations to favorable outcomes instead of just prevalence, but ultimately this concern will only be proven or disproven by deploying these methods in a prospective clinical trial. Another general concern is that order recommenders may favor over-utilization by encouraging unnecessary orders. The framework can counter-balance this by recommending against uncommon orders, and future work will explore personalized prediction of lab result
pre-test probabilities to recommend against lab tests unlikely to impact clinical care. Another limitation of the current item association method is that it only considers pair-wise associations, thus querying with multiple items assumes independence between the query items. Incorporating more complex models such as Bayesian networks is
possible, but unclear whether significant accuracy would be gained in exchange for the lost computational efficiency of a simpler model.

In closing, this represents another step in ongoing work towards mature clinical decision support systems that will unlock the Big Data potential of electronic medical records. A clinical order recommendation framework is enhanced here with additional non-order data to better define clinical contexts, reporting of significance statistics for individual recommendations to further aid interpretability, multiple evaluation metrics to discern common from specifically relevant items, and application towards predicting clinical outcomes.

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