Traditional ways providing alerts for excessive dose

**Static threshold:**
- Easily available, and commonly used in CPOE.
- Medication doses occasionally exceed as a result of taking a patient’s conditions into account.
- It may lead physician's alert fatigue.

**Rule based threshold:**
- “IF serum-creatinine > 2.5mg/dl & candesartan dose > 8 mg THEN“
- Rule-based approach has problem with cost and maintenance, because of complexity and comprehensiveness of the rule building for thousands of drugs.
Hypothesis

- If we can estimate a dose of medication according to the patient similarity, it seems to be reasonable to set an alert threshold based on the estimated dose, because similar medication for a similar patient must be safest one.

- If the patient similarity is measured by their demographics and registered diseases, we can develop a prediction model of a medication dose using these features, and CPOE can compute the threshold based on the prediction model at the time of a medication.
Materials and Methods

1. Collecting medication record:
   - Eight frequently alerted drugs (Carvedilol, Pravastatine, ..etc)
   - Health insurance claims for 5 years.

2. Developing prediction models:
   - Applied Random Forests (RF) to estimate the medication dose.
     ✓ Comparing the performance of RF with Bagging and CART.
     ✓ Showing variable importance measures features contributions.

3. Determining thresholds:
   - Applied boxplot for the RF predictions.
     ✓ Comparing the boxplot’s thresholds with traditional static one.
1-1. Methods: Collecting medication records

- **Experiment settings**
  - The University of Tokyo Hospital: 1,200 beds, 750,000 visits annually.
  - Insurance claims of inpatients and outpatients from Jan 2007 to Dec 2011.
  - Multiple medication records for the same patients prescribed during different visits or different days were allowed.

Used 1500 out of 13000 diseases ranked by frequency

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dose (tabs)</th>
<th>Gender</th>
<th>Age</th>
<th>Chr. Heart failure</th>
<th>Dilated cardiomyopathy</th>
<th>Old Myocardial Infarction</th>
<th>...</th>
<th>...</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carvedilol 2.5mg</td>
<td>3</td>
<td>M</td>
<td>47</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Carvedilol 2.5mg</td>
<td>2</td>
<td>F</td>
<td>51</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carvedilol 2.5mg</td>
<td>4</td>
<td>F</td>
<td>76</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Carvedilol 2.5mg</td>
<td>2</td>
<td>M</td>
<td>81</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
</tbody>
</table>
1-2. Methods: Why we used 1500 disease

The top 1500 types of diseases account for 90% of the total frequency.

<table>
<thead>
<tr>
<th>Types of Diseases</th>
<th>Frequency of Occurrence in the Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>&lt;= High Frequency</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td></td>
</tr>
<tr>
<td>Atheroma</td>
<td>Low Frequency =&gt;</td>
</tr>
<tr>
<td>Mushroom Poisoning</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Type</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>13000</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1500</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13000</td>
</tr>
<tr>
<td>Atheroma</td>
<td>1500</td>
</tr>
<tr>
<td>Mushroom Poisoning</td>
<td>13000</td>
</tr>
</tbody>
</table>
2-1. Methods: Random Forest *(L. Breiman, 1999)*

Decision Tree (CART) + Ensemble learning + Random feature sampling

- **Bootstrap sampling**
- Developing CART with **random feature sampling**
- Ensemble vote *(majority / mean)*

Training Data

- Sample 1
- Sample 2
- ...
- Sample N

CART 1
- Prediction 1

CART 2
- Prediction 2
- ...

CART N
- Prediction N

Final prediction
2-2. Methods: Developing and evaluating the model

- For 8 Drugs

30000 Records
Random Selection

Repeated increasing the number of the features (from 10 to 1500)

Testing models 10000 records

Developing models 20000 records

Predict dose
Actual dose

CF = 0.82

- Random Forest: 200 trees
- Bagging: 200 trees
- CART: Single tree

Decision Tree
Ensemble learning
Random Feature sampling
2-3. Results: Performance among the algorithms

- **Carvedirol 2.5 mg Tab**
  - Highest point at 200 features: 0.89

- **Loxoprofen 60 mg Tab**
  - 0.51

- **Brotizolam 0.25 mg Tab**
  - 0.68

- **Sennoside 12 mg Tab**
  - 0.80

- **Pravastatin 10 mg Tab**
  - 0.95

- **Nifedipine 20 mg Tab**
  - 0.90

- **Ursodeoxycholic acid 100 mg Tab**
  - 0.88

- **Famotidine 20 mg Tab**
  - 0.81
2-4. Results: Variable importance in RF (a feature’s contribution)

**Carvedilol 2.5 mg Tab**
- Age
- Idiopathic Cardiomyopathy
- Myocardial Infarction
- Diabetes
- Hypertension
- Gastric Ulcer
- Chr. Atrial Fibrillation
- Congestive Heart Failure
- Ventricular Tachycardia
- Ventricular Extrasystole

**Nifedipine 20 mg Tab**
- Age
- Chr. Renal Failure
- Acute Aortic Dissection
- Diabetes
- Renovascular Hypertension
- Osteoporosis
- Reflux Esophagitis
- Hypertension
- Gastric Ulcer

**Famotidine 20 mg Tab**
- Age
- Gastric Ulcer
- Chr. Gastritis
- Reflux Esophagitis
- Metastatic Liver Cancer
- Hepatocellular Carcinoma
- Angina Pectoris
- Acute Gastritis
- Rheumatoid Arthritis

**Pravastatin 10 mg Tab**
- Familial Hyperlipidemia
- Age
- Coronary Heart Disease
- Hyperlipidaemia
- Neurosis
- Chr. Glomerulonephritis
- Cerebral Infarction
- Carotid Atherosclerosis
- Hypothyreoidism
- Ischaemic Heart Disease
3-1. Methods: How to Determine thresholds

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Gender</th>
<th>Age</th>
<th>Diabetes</th>
<th>Colon cancer</th>
<th>Hyper tension</th>
<th>...</th>
<th>Dose(tabs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nifedipine 20mg Tab</td>
<td>M</td>
<td>47</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>...</td>
<td>6</td>
</tr>
</tbody>
</table>

Getting RF votes from the developed forest

1.5, 1.5, 2.0, 2.5, 2.5, 2.8, 3.2, 3.2, 3.5, 3.8, 4.2, 4.5, 5.5, 7.2,…

Drawing a boxplot for the votes

![Boxplot Diagram]

IQR = Interquartile Range

Outlying!
3-2. Results: Comparing thresholds - Carvedilol

Among 10000 medications, 602 cases were detected by either or both of the thresholds.

- 57 cases detected by both of the thresholds
- 317 cases detected only by static thresholds
- 228 cases detected only by proposed thresholds
### 3-3. Results: Comparing thresholds – overall

<table>
<thead>
<tr>
<th></th>
<th>Number of the cases detected by thresholds</th>
<th>Reduction (Proposed/Static)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Cases</td>
<td>by Both Thresholds</td>
</tr>
<tr>
<td><strong>Ursodeoxycholic acid</strong></td>
<td>949</td>
<td>113</td>
</tr>
<tr>
<td><strong>Carvedilol</strong></td>
<td>602</td>
<td>57</td>
</tr>
<tr>
<td><strong>Sennoside</strong></td>
<td>327</td>
<td>29</td>
</tr>
<tr>
<td><strong>Loxoprofen</strong></td>
<td>505</td>
<td>15</td>
</tr>
<tr>
<td><strong>Brotizolam</strong></td>
<td>1167</td>
<td>300</td>
</tr>
<tr>
<td><strong>Nifedipine</strong></td>
<td>627</td>
<td>37</td>
</tr>
<tr>
<td><strong>Famotidine</strong></td>
<td>183</td>
<td>8</td>
</tr>
<tr>
<td><strong>Pravastatin</strong></td>
<td>53</td>
<td>0</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>4413</td>
<td>559</td>
</tr>
</tbody>
</table>
Discussions 1

- **Dose prediction based on patient similarity**
  - The performances of RF prediction was high except for 2 drugs.
  - The patient similarity measured by the demographics and registered diseases are useful for estimation of medication dose.

- **Significance of the thresholds**
  - We showed the proposed thresholds would reduce the alerts by a half of those when using the static thresholds.
  - Of course, merely discussing the increase or decrease in the number of alerts is not significant, we should discuss the trade-offs between what can be obtained and what can be lost.
  - However, our approach, which relies on past medications that were assured as appropriate for a patient’s condition, would have a certain level of evidence.
Advantages of the prediction thresholds

- It can detect inappropriate medications even if the cases are under the static threshold.
- In terms of adaptivity, our approach can be easily adopted in other hospitals because the health insurance claims that we used as the source for prediction model are commonly available.

Limitations

- We need to clarify how many prescription are enough to build the prediction model for applying the other drugs.
- We also need to evaluate a physician's compliance for those alerts in the clinical setting while clarifying the outcomes responsible for those alerts.
Conclusions

1. We presented a prediction-based approach to determine thresholds for the medication alert.

2. Although the significance of the thresholds should be discussed in different ways, our approach, which relies on physicians’ collective experiences, had some practical advantages.

3. In future work, we should evaluate a physician's compliance for those alerts in a clinical setting.
Thank you!

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