Avoiding medication conflicts while combining clinical pathways for comorbid diseases

Andrii Kovalov
1. Problem overview
2. Translation of clinical pathways into SMT code
3. Optimisation with SMT solvers
4. System overview
5. Evaluation and conclusions
Avoiding medication conflicts while combining clinical pathways for comorbid diseases

**Diabetes**

- **Metformin**
  - When to consider sulfonlurea as an alternative to metformin
  - Monitoring HbA1c
  - HbA1c equal to or more than 48 mmol/mol (6.5 per cent) or agreed target
  - Considering dual therapy
  - Continued monitoring of HbA1c

- **Consider acarbose if person is unable to use other oral glucose-lowering medications**
  - Ongoing monitoring of HbA1c
  - HbA1c equal to or more than 58 mmol/mol (7.5 per cent) or agreed target

**Hypertension**

- **Advising on lifestyle measures**
  - Monitor blood pressure 1–2 monthly and maintain lifestyle measures

- **Offering ACE inhibitors**
  - Adding a calcium channel blocker or diuretic

- **If blood pressure above target, start with a calcium channel blocker if a woman may become pregnant**
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Diabetes

- Metformin
- When to consider sulfonylurea as an alternative to metformin
  - Monitoring HbA1c
  - HbA1c equal to or more than 48 mmol/mol (6.5 per cent) or agreed target
  - Considering dual therapy
- Agreed target after trial of lifestyle interventions
- Consider acarbose if person is unable to use other oral glucose-lowering medications
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Hypertension

- Advising on lifestyle measures
- Monitoring blood pressure: monthly and measures
- Offering ACE inhibitors
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- If blood pressure above target, start with a calcium channel blocker if a woman may become pregnant

Comorbid diseases

Clinical pathways
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Drug-drug conflict: Sitagliptin with ACE Inhibitors may cause angioedema
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- **Agreed target after trial of lifestyle interventions**

- **Consider acarbose if person is unable to use other oral glucose-lowering medications**

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- **HbA$_{1c}$ equal to or more than 58 mmol/mol (7.5 per cent) or agreed target**

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**Hypertension**

- **Advising on lifestyle measures**

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**Drug-disease conflict:** Beta-blockers with diabetes may mask symptoms of hypoglycemia
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Drug-patient conflict: The patient is allergic to Metformin
Existing approaches

Computer science approaches

● Using ontologies and inference on ontologies
● Constraint programming
● Rule-based systems

Medical approaches

● Include information on comorbid diseases into pathways
● Patient-centered instead of following pathways
Proposed solution

- Pathways are represented as directed acyclic graphs of pharmaceutic actions
- Every node has a number of alternative medications
- Every medication has an integer “score” defining how helpful it is
- Every conflict has a negative score defining its severity
- The goal is to find paths in every pathway with maximal total score
- Using SMT solver
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Translation of clinical pathways into SMT code

- Structure of the graph
- Medications and scores
- Conflicts
Structure of the graph - notion of “branches”

Branch - a sequence of nodes so that for any maximal path in the graph either the whole branch or none of its nodes belong to the path
Graph of branches
Branching rules

1. The initial node is always true
2. If a current node is true, one (and only one) of its children is true, and the other children are false
3. If all the parents of a current node are false, this node is also false
Branching rules application

// for Br0
Br0
Br0 → (Br1 ∧ ¬Br2) ∨ (¬Br1 ∧ Br2)

// for Br1
Br1 → (Br3 ∧ ¬Br4) ∨ (¬Br3 ∧ Br4)
¬Br0 → ¬Br1

// for Br4
Br4 → (Br5 ∧ ¬Br6) ∨ (¬Br5 ∧ Br6)
¬Br1 ∧ ¬Br2 → ¬Br4
Medications and scores

Every graph node (pathway stage)
- Has a set of alternative medications
- Every medication has a score
- Only one medication can be chosen
- The score of a stage is a score of a chosen medication
- The stage can be enabled or disabled depending on whether its branch variable is true or false
Stage definition example

// assume this is node N1
// on branch Br1

Br1 \rightarrow (\text{Metformin} \land \neg \text{Sulfonylurea}) \lor (\neg \text{Metformin} \land \text{Sulfonylurea})

\neg \text{Br1} \rightarrow (\neg \text{Metformin} \land \neg \text{Sulfonylurea})

\text{N1\_Score} = \text{if (Metformin) then 100 else if (Sulfonylurea) then 70 else 0}
Conflicts representation

Conflict1_Score =
    if (Metformin ∧ BetaBlocker) then -1000
    else 0
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Optimisation task

Get an assignment of the boolean variables in the SMT model so that the resulting final score is maximal (final score - sum of scores of all nodes and all conflicts).

Possible solutions:

- Iterative
  - Hill-climbing approach
  - Dichotomy approach
- Optimising SMT solver
Hill climbing algorithm

Solution = getModelAssignment()
CurrentScore = Solution.score
while(exists a solution with score > CurrentScore){
    Solution = getModelAssignment(with score > CurrentScore)
    CurrentScore = solution.score
}
return Solution
Dichotomy algorithm

Min = getLowestPossibleScore()
Max = getHighestPossibleScore()+1
while(exists a solution with score > Min){
    Middle = Min + (Max - Min) / 2;
    if(exists a solution with score >= Middle){
        Min = Middle
    } else {
        Max = Middle
    }
}
return getModelAssignment(with score = Min)
Using optimising SMT solver

Z3 Opt is an optimising version Z3. Not released yet, shows poor performance
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System overview
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System evaluation

82 medications
1475 conflicts
over 2 million possible paths
206 boolean variables
1491 integer functions
### Evaluation results

<table>
<thead>
<tr>
<th></th>
<th>Running time (seconds)</th>
<th>Iterations</th>
<th>Calls to Z3</th>
</tr>
</thead>
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<tr>
<td>Optimising Z3</td>
<td>78.7</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Hill-climbing</td>
<td>29.3</td>
<td>57</td>
<td>58</td>
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<tr>
<td>Dichotomy</td>
<td>92.9</td>
<td>21</td>
<td>43</td>
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<tr>
<td>Modified dichotomy</td>
<td>23.2</td>
<td>5</td>
<td>11</td>
</tr>
</tbody>
</table>

**Diabetes**

- Acarbose 0
  - Insulin 100

**Hypertension**

- Eprosartan 100
  - Nimodipine 100
    - Pamabrom 80
      - Doxazosin 100

**Conflicts**

- Insulin+Eprosartan -1000
  - Total score -520
Conclusions

SMT solver can be used to generate treatment plans for comorbid diseases reasonably fast. Further evaluation on the real complicated cases from medical practice is necessary.

Future work:

- Considering dosages and timing in conflicts
- Incorporating conflict resolution rules
- Merging similar actions across different pathways (e.g. blood test)
Thank you