CLINICAL PRACTICE GUIDELINES AND COMORBID DISEASES: A MINIZINC REPRESENTATION OF GUIDELINE MODELS FOR MITIGATING ADVERSE INTERACTIONS

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CPGs and Comorbidity

- Identified as one of the important research themes [Peleg, 2013]
  - Most attention has been paid to an individual CPG instead of adapting the guidelines to manage comorbid condition

- Relevant research
  - Taxonomy of cross-guideline interactions and computational architecture for detecting them – GLINDA [http://glinda-project.stanford.edu/]
  - Merging (via mapping an alignment) of CPGs represented as ontologies – COMET [Abidi and Abidi, 2009]
  - CPG templates and composition operators [Riano and Collado, 2013]

- Our research uses:
  - Graph theory (CPG representation)
  - Constraint logic programming (CPG analysis, safe therapy development)
Problem Statement

How to create an executable model of complex guidelines that can be applied to a patient with comorbidity?

Our goal: Automate the mitigation process (identifying and addressing interactions) and provide a decision tool to support a physician at the point of care.

Note: Research presented today is current, reporting advances since the Medinfo paper submission.
Clinical Case Study

Concurrent application of CPGs for a patient who is being treated for Wolff-Parkinson-White syndrome (WPW) and suffers an atrial fibrillation (AF)

- Relatively common comorbid condition managed in the ED
- Overlapping and possibly contradicting treatments
- Dosages of medication need to be adjusted depending on patient state
- Repeated actions that manifest themselves as loops in the CPG (number of repetitions not explicit)
Mitigation

- Two CPGs applied to patient with comorbid condition to obtain safe therapy
- Safe therapy does not exist in case of adverse interactions
  - Direct ones caused by contradictory actions
  - Indirect ones caused by drug-drug or drug-disease interactions
- Mitigation of adverse interactions requires clinical acumen (experts, textbooks, clinical evidence)
- Clinical acumen encoded in form of operators
  - Interaction operators to model indirect adverse interactions
  - Revision operators to model revisions
Mitigation Algorithm

**Phase 1: Preparation**

- Available patient data

**Phase 2: Mitigation of direct adverse interactions**

- Two CPGs given as actionable graphs
  - Expand loops in actionable graphs
  - Create logical models from actionable graphs
  - Identify and address direct adverse interactions
  - No interactions or interactions addressed
    - Augment combined logical model
    - Identify and address indirect adverse interactions
      - No interactions or interactions addressed
      - Success
        - Report safe therapy
      - Failure
        - Unable to address interactions

- Interaction and revision operators
Phase 1 (Preparation)

Actionable graph ($AG_i$) representing $CPG_i$ is defined as a directed graph with three types of nodes (context, decision, action)

Original $AG_{WPW}$

Revised $AG_{WPW}$

Expanding loops
Phase 1  (Preparation)

A combined logical model \((CLM_{i,j})\) brings together the pair of logical models representing \(CPG_i\) and \(CPG_j\) and information about possible adverse interactions between these CPGs.

\[
CLM_{WPW, AF} = <LM_{WPW}, LM_{AF}, ILE_{WPW, AF}>
\]

\[
LM_{WPW} = \{(DF0 = 50) \land WSO \land PR \land \neg AT \land (DF=DF0) \land \neg (DF1=DF0+\Delta DF) \land \\
\neg (DF2=DF0+2*\Delta DF) \land \neg (DF3=DF0+3*\Delta DF) \land \neg (DF=DF1) \land \\
\neg (DF=DF2) \land \neg (DF=DF3), \\
(DF0 = 50) \land \neg WSO \land \neg (DF0<DF_{max}) \land AT \land PR \land \\
\neg (DF1=DF0+\Delta DF) \land \neg (DF2=DF0+2*\Delta DF) \land \neg (DF3=DF0+3*\Delta DF) \land \\
\neg (DF=DF0) \land \neg (DF=DF1) \land \neg (DF=DF2) \land \neg (DF=DF3), \ldots\}
\]

\[
LM_{AF} = \{HI \land EC \land RAE \land A \land PR \land \neg FIV \land \neg AIV, \\
HI \land EC \land \neg RAE \land PR \land \neg FIV \land \neg AIV \land \neg A, \\
\neg HI \land HD \land AIV \land RAE \land A \land PR \land \neg EC \land \neg AIV, \\
\neg HI \land HD \land AIV \land \neg RAE \land PR \land \neg EC \land \neg FIV \land \neg A, \\
\neg HI \land \neg HD \land FIV \land RAE \land A \land PR \land \neg EC \land \neg AIV, \\
\neg HI \land \neg HD \land FIV \land \neg RAE \land PR \land \neg EC \land \neg AIV \land \neg A\}
\]

\[
ILE_{WPW, AF} = \{\} //Empty in Phase 1
\]
Phase 2 (Mitigation of Direct Adverse Interactions)

Combined logical model is converted into solver-specific model and solved for available patient data

- Initial implementation used MiniZinc
- Current implementation relies on ECLiPSe

```prolog
:- lib(repair).
:- lib(ic).

cardiac(Vars, Conflicts) :-
Vars=[At, Pr, Dfmax, Hi, Ec, Hd, Fiv, Aiv, Lr, A, Df, Ddf, Df0, Df1, Df2, Df3, Ws0, Ws1, Ws2],
Ddf=50, Hi=0, Hd=0, Lr=0, Dfmax=200, Ws0=0, Ws1=0, Ws2=0,
((Df0 $= 50) and Ws0 and Pr and neg(At) and (Df $= Df0) and neg(Df1 $= Df0 + Ddf) and neg(Df2 $= Df0 + Ddf + Ddf) and neg(Df3 $= Df0 + Ddf + Ddf + Ddf) and neg(At)) and neg(Df1 $= Df2) and neg(Df1 $= Df3) and $= 1)
or ((Df0 $= 50) and neg(Ws0) and (Df0 $< Dfmax) and (Df1 $= Df0 + Ddf) and Ws1 and (Df $= Df1) and Pr and neg(At) and neg(Df2 $= Df0 + Ddf + Ddf) and neg(Df3 $= Df0 + Ddf + Ddf + Ddf) and neg(At)) and neg(Df1 $= Df2) and neg(Df1 $= Df3) and $= 1)
or ((Df0 $= 50) and neg(Ws0) and (Df0 $< Dfmax) and (Df1 $= Df0 + Ddf) and Ws1 and (Df $= Df1) and Pr and neg(At) and neg(Df2 $= Df0 + Ddf + Ddf) and neg(Df3 $= Df0 + Ddf + Ddf + Ddf) and neg(At)) and neg(Df1 $= Df2) and neg(Df1 $= Df3) and $= 1)
or ((Df0 $= 50) and neg(Ws0) and (Df0 $< Dfmax) and (Df1 $= Df0 + Ddf) and Ws1 and (Df $= Df1) and Pr and neg(At) and neg(Df2 $= Df0 + Ddf + Ddf) and neg(Df3 $= Df0 + Ddf + Ddf + Ddf) and neg(At)) and neg(Df1 $= Df2) and neg(Df1 $= Df3) and $= 1)
```

Phase 2  (Mitigation of Direct Adverse Interactions)

• Check if solution of solver-specific model exists
• Lack of a solution indicates direct adverse interaction caused by “shared” actions suggested by both CPGs
• Address identified interactions using applicable \textit{revision} operators, for example
  \[ RO^1 = \langle \{\star\}, \{PD\}, \{PD\}, \{SC \land \neg PD\} \rangle \]
Phase 3 (Mitigation of Indirect Adverse Interactions)

- Indirect adverse interactions described by *interaction operators*
  
  \[ IO^1 = \langle \{ WPW, AF \}, \{ A, DF \}, \neg (A \land DF = DF_{\text{max}}) \rangle > \]
  \[ ILE_{WPW, AF} = \{ \neg (A \land DF = DF_{\text{max}}) \} \]

- Check for solution and mitigate possible adverse interactions by applying *revision operator*
  
  \[ RO^2 = \langle \{ WPW, AF \}, \{ A, DF \}, \{ DF = DF_{\text{max}} \}, \{ DF = DF_{\text{adj}} \} \rangle > \]

- If solution exists, then it is used to derive a safe therapy
  
  - Sample solution
    
    \[ [WS0=n, WS1=n, WS2=n, DF0=50, DF1=100, DF2=150, DF3=200, DF=150, HI=y, EC=true, RAE=y, PD=true] \]
  
  - Derived safe therapy
    
    Set dosage of flecainide to 150mg \((DF=150)\), perform electrical cardioversion on the patient \((EC = true)\), discharge to care of family physician \((PD = true)\)
Discussion and Future Work

- **Contribution:** Logic-based approach to mitigate adverse interactions between CPGs
  - One of few attempts to show how to address CPG integration for comorbidity

- **Benefit:**
  - Step towards a comprehensive alerting system for physicians at the point of care
  - Support for comorbidities leading to wider acceptance of CPGs in clinical practice

- **Future Work:** Theoretical foundation for personalized guideline
  - Formalizing all critical issues including time dependence and precedence relations (first-order logic and theorem proving)
Thank you!

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