THE USE OF CONSTRAINT LOGIC PROGRAMMING TO RECONCILE PAIRS OF CONCURRENTLY USED CLINICAL PRACTICE GUIDELINES

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Clinical Practice Guideline (CPG)

Systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances

- Motivation for the development and use
  - Variations of clinical practice
  - Significant rates of inappropriate care
  - Need to manage healthcare costs

- Known for 30+ years
  - Initially used by nurses and other ancillary personnel
  - Increasing popularity of computer-interpretable guidelines (CIGs) integrated with CDSSs and EPRs

Development of CPGs

- Consensus-driven and **evidence-based** development process
- Levels of evidence
  - Level A – multiple randomized clinical trials
  - Level B – a single trial or non-randomized studies
  - Level C – consensus opinions of expert
- Confidence in the recommendations of treatments/procedures
  - Class I – evidence or general agreement about usefulness/efficacy
  - Class II – conflicting evidence or divergence of opinions
  - Class III – evidence or general agreement against usefulness/efficacy
CPGs in Practice

• Multiple advantages
  • Improved adherence to standards of practice and quality of care (when applied at the point of care)
  • Increased adoption of evidence-based medicine
  • Positive impact on patient outcomes (e.g., reduced mortality)

• ... But limited adoption
  • Lack of standardization (especially in case of CIGs)
  • Limited interoperability between CIGs and EPRs
  • No support for comorbid conditions (i.e., one or more conditions in addition to a primary one)
Representing CPGs and CIGs

- CPGs → unstructured text with supplementing flowcharts
- CIGs → structured and formalized representations (usually based on a task-network model)
  - Arden Syntax – a syntax for clinical decision rules
  - GLIF3 – a multiple-level representation with conceptual flowcharts and an executable specification
  - SAGE – an complete (event-driven) environment for creating and executing CIGs, integration with EPR via virtual patient record
  - PROforma – a formalism and a set of tools for creating and managing CIGs, one of few commercial applications
  - SDA* – a flowchart-based representation developed for the K4CARE project aimed at automatic execution
Sample CPGs

Diagnosis and Management of Placenta Previa

Abstract

Objective: To review the use of transvaginal ultrasound for the diagnosis of placenta previa and recommend management based on accurate placental localization.

Options: Transvaginal sonography (TVS) versus transabdominal sonography for the diagnosis of placenta previa, route of delivery, based on placental edge to internal os distance; expedient versus sub-optimal anesthesia for cesarean delivery; maternal versus general anesthesia, prenatal diagnosis of placenta previa.

Outcome: Proven clinical benefit in the use of TVS for diagnosis and planning management of placenta previa.

Evidence: MEDLINE search for “placenta previa” and bibliographic review.

Benefits, harms, and costs: Accurate diagnosis of placenta previa may reduce hospital stay and unnecessary interventions.

Recommendations:

1. Transvaginal sonography, if available, may be used to investigate placental location in any time in pregnancy when the placenta is thought to be intraplacental. It is highly accurate and non-invasive, with low maternal discomfort and risk of infection.

2. Sonographers are encouraged to report the actual distance from the placental edge to the internal os at the TVS, using standard terminology of distance away from the internal os or in millimeters. A distance of 20 mm or more is considered adequate for vaginal delivery, whereas a shorter distance may warrant cesarean section.

3. When the placental edge lies between 20 mm and 10 mm from the internal os at TVS, a careful vaginal examination is recommended to confirm the findings.

4. In cases where the placental edge is less than 20 mm from the internal os, a decision on mode of delivery should be made by a multidisciplinary team, considering factors such as maternal and fetal health.

5. In general, any rupture of the third trimester is an indication for Cesarean section, regardless of the route of delivery.

6. Optimal management of placenta previa may be appropriate for patients with a high risk of placental separation, or in cases where there is evidence of pathological adherence of the placenta, delivery should be planned with a multidisciplinary team.

7. There is insufficient evidence to recommend the practice of cervical cerclage to reduce bleeding in placenta previa.

8. Regional anesthesia may be used if the patient's gestational age is less than 36 weeks, in order to minimize maternal discomfort and risk of infection.

9. Women with placenta previa and a prior CS are at high risk for placental separation, and should be evaluated closely for signs of active bleeding.


Comorbid Conditions

- 50% of people 65+ years old have ≥ 3 comorbid conditions, and they account for 90% of the healthcare costs [Medicare, 1999]
- Physician treating a comorbid patient needs to manually reconcile multiple CPGs
  - Reconciliation involves verifying if multiple CPGs can be applied together and introducing necessary revisions
  - Direct application of multiple CPGs may result in adverse interactions, complex regimen and increased cost of care

Our motivation: *to propose an approach to automate the reconciliation process*

Related Research

• Application (and combination) of CPGs for comorbid conditions – one of “grand challenges” for clinical decision support

• Yet, fairly limited research
  • Merging of concurrently used CPGs using ontology alignment techniques
  • Adding “safety rules” to a single CPG
  • Identification of common conditions in a flowchart (SDA*) and their combination
  • Most of these approaches require expert intervention to resolve encountered conflicts


Research Question

1. How to represent multiple CPGs associated with comorbid conditions as a single computable model?
2. How to automatically process this model (i.e., solve, revise) to ensure a treatment plan for comorbid conditions exists?

Practical perspective: our approach as an early alerting system combined with a CPG execution engine
Assumptions and Simplifications

• Secondary knowledge (not available in CPGs) explicitly codified as restriction and mitigation operators
  • Shared repository with operators
  • Operators defined by experts

• Pairs of interoperable CPGs considered at a time
• No temporal aspects
• A single possibility (choice) considered when making a decision
Constraint Logic Programming (CLP)

- Application of logic programming (LP) to a constraint satisfaction problem (CSP)

- Essential elements of a CLP model
  - Set of variables (and their domains – do not have to be Boolean)
  - Set of constraints that restrict the possible combinations of values assigned to variables

- Constraints implemented as clauses (rules) in a logic program

- Querying a program about the provability of a goal produces a solution

- Violated constraints result in the absence of a solution

- *Point of infeasibility* (POI) – a set of variables in violated constraints
CLP Languages and Tools

- Prolog (selected implementations)
  - CLP(FD) library – CLP over Finite Domains

- ECLiPSe ([http://www.eclipseclp.org](http://www.eclipseclp.org))
  - An environment for analyzing and solving CLP models
  - CLP(FD) and CLP(IC) libraries (integer and real variables)

  - A solver-independent constraint modeling language
  - A suite of tools for analyzing and solving constraint models
  - Planned to become a standard language for constraint problems
Proposed Approach

• A patient suffers from two comorbid conditions managed according to associated CPGs (given as actionable graphs)
• Patient state characterized by currently available (possibly incomplete) clinical data

Our approach answers the following questions:

1. Can the considered CPGs be applied concurrently to the patient given her current state?
2. If application of CPGs causes any conflict (manifested by a POI), then
   a) What causes this conflict?
   b) How this conflict can be mitigated?
Schema of the Algorithm

**Phase 1**: Create individual and combined logical models of both CPGs

**Phase 2**: Create a combined CLP model from the combined logical model and solve it

Available patient information

AG$_A$  AG$_B$

Solution exists?

Yes

Outcome 1: Both CPGs can be applied concurrently, no conflicting interaction exits

Outcome 2: Both CPGs can be applied concurrently, there is an conflicting interaction, but it can be mitigated

Outcome 3: Both CPGs cannot be applied concurrently due to unsolvable conflicting interaction

No

Solution exists?

Yes

Restriction operators

Mitigation operators

Repo with secondary knowledge

**Phase 3**: Modify the combined logical models to address the encountered POI

**Phase 4**: Create a combined CLP model from the modified combined logical model and solve it

Restriction operators

(AOI has been encountered)
Actionable Graphs

• An intermediate representation based on a task-network model for better applicability of our approach
• Easily derived from any representation that uses action, decision and context (patient state) steps
• An actionable graph (AG) is a directed graph
  • Action, decision and context nodes corresponding to appropriate steps
  • Arcs corresponding to transitions between nodes
  • A root context node indicating the condition (disease)
Case Study – DVT and HTN

**ag_{DVT} – AG for DVT**
*(deep vein thrombosis)*

- **Patient diagnosed with DVT**
  - History of severe bleeding tendency [sbf]?
    - Present [p] → **Use IVC filter [ivcf]**
    - Absent [a] → **Administer heparin [he]**
  - History of heparin-induced thrombocytopenia? [hit]
    - Absent [a] → **Administer low-molecular-weight heparin [lmwhe]**
    - Present [p] → **Administer alternative anticoagulant agents [aca]**
  - Additional DVT-related risks? [ar]
    - Present [p] → **Administer warfarin [wa]**
    - Absent [a] → **Use IVC filter [ivcf]**

- **Arrange follow-up with family physician [fufp]**

**ag_{HTN} – AG for HTN**
*(hypertension)*

- **Patient diagnosed with HTN**
  - Type of HTN [htn]?
    - Uncontrolled [un] → **Administer IV antihypertensive agents [ivahta]**
    - Controlled [co] → **Administer oral antihypertensive agents [oahta]**
  - Type of uncontrolled HTN [htun]?
    - Emergency [em] → **Administer IV antihypertensive agents [ivahta]**
    - Urgency [ur] → **Administer oral antihypertensive agents [oahta]**

- **Arrange follow-up with family physician [fufp]**
Phase 1 – Individual Logical Models (ILMs)

ILM provides a logical representation of an AG

$$ILM = \langle d, V, PLE \rangle$$

The disease label indicated in the context node of the AG

A set of variables associated with action and decision nodes in the AG.

$$V = V^a \cup V^o \quad (V^a \cap V^o = \{\})$$

A set of logical expressions corresponding to paths in the AG
ILMs for DVT and HTN

\(ilm_{DVT}.d = \text{DVT}\)
\(ilm_{DVT}.V = \{\text{sbt}, \text{hit}, \text{ar}, \text{ivcf}, \text{aca}, \text{he}, \text{lmwhe}, \text{wa}, \text{fufp}\}\)
\(ilm_{DVT}.V^o = \{\text{sbt}, \text{hit}, \text{ar}\}\)
\(ilm_{DVT}.V^a = \{\text{ivcf}, \text{aca}, \text{he}, \text{lmwhe}, \text{wa}, \text{fufp}\}\)
\(ilm_{DVT}.PLE = \{
(sbt = p) \land \text{ivcf} \land \text{fufp} \land \neg \text{aca} \land \neg \text{he} \land \neg \text{lmwhe} \land \neg \text{wa},
(sbt = a) \land (\text{hit} = p) \land \text{aca} \land \text{fufp} \land \neg \text{ivcf} \land \neg \text{he} \land \neg \text{lmwhe} \land \neg \text{wa},
(sbt = a) \land (\text{hit} = a) \land (\text{ar} = p) \land \text{he} \land \text{wa} \land \text{fufp} \land \neg \text{ivcf} \land \neg \text{aca} \land \neg \text{lmwhe},
(sbt = a) \land (\text{hit} = a) \land (\text{ar} = a) \land \text{lmwhe} \land \text{wa} \land \text{fufp} \land \neg \text{ivcf} \land \neg \text{aca} \land \neg \text{he}\}\)

\(ilm_{HTN}.d = \text{HTN}\)
\(ilm_{HTN}.V = \{\text{htn}, \text{htnun}, \text{oahta}, \text{ivahta}, \text{fufp}\}\)
\(ilm_{HTN}.V^o = \{\text{htn}, \text{htnun}\}\)
\(ilm_{HTN}.V^a = \{\text{oahta}, \text{ivahta}, \text{fufp}\}\)
\(ilm_{HTN}.PLE = \{
(\text{htn} = \text{co}) \land \text{fufp} \land \neg \text{oahta} \land \neg \text{ivahta},
(\text{htn} = \text{un}) \land (\text{htnun} = \text{ur}) \land \text{oahta} \land \text{fufp} \land \neg \text{ivahta},
(\text{htn} = \text{un}) \land (\text{htnun} = \text{em}) \land \text{ivahta} \land \text{fufp} \land \neg \text{oahta}\}\)
Phase 1 – Combined Logical Model (CLM)

CLM is a “placeholder” for two ILMs and possible restrictions that prevent conflicting interactions between ILMs

\[
\text{CLM} = <\text{ilm}_A, \text{ilm}_B, \text{RLE}>
\]

- ILMs associated with both AGs (CPGs)
- A set of logical expressions corresponding to restrictions associated with possible conflicting (adverse and contradictory) interactions and introduced by restriction operators
Phase 1 – Restriction Operators (ROs)

RO codifies knowledge about possible interactions

\[ \text{RO} = <D, V, Le> \]

- A set of triggering disease labels (may contain a wildcard – *)
- A set of triggering variables
- A logical expression restricting possible interactions, added to CLM. \( RLE \) by a triggered RO

**Triggering condition**

\[
(\text{RO.}D = \{*\} \lor (\{\text{CLM.ilm}_A.d, \text{CLM.ilm}_B.d\} \cap \text{RO.}D) \neq \{\}) \\
\wedge (\text{RO.}V \subseteq (\text{CLM.ilm}_A.V \cup \text{CLM.ilm}_B.V))
\]
CLM for DVT and HTN

\[ r_1 . D := \{ * \} \]
\[ r_1 . V := \{ htnun, aca \} \]
\[ r_1 . L e := \neg ((htnun = ur) \land aca) \]

\[ r_2 . D := \{ * \} \]
\[ r_2 . V := \{ htnun, he, wa \} \]
\[ r_2 . L e := \neg ((htnun = ur) \land he \land wa) \]

\[ r_3 . D := \{ * \} \]
\[ r_3 . V := \{ htnun, Lmwhe, wa \} \]
\[ r_3 . L e := \neg ((htnun = ur) \land Lmwhe \land wa) \]

\[ CLM_{DVT,HTN} \cdot \text{ilm}_A = \text{ilm}_{DVT} \]
\[ CLM_{DVT,HTN} \cdot \text{ilm}_B = \text{ilm}_{HTN} \]
\[ CLM_{DVT,HTN} \cdot \text{RLE} = \{ \]
\[ \neg ((htnun = ur) \land aca), \]
\[ \neg ((htnun = ur) \land he \land wa), \]
\[ \neg ((htnun = ur) \land Lmwhe \land wa) \} \]

ROs available in the repository (restricting the use of various anticoagulant agents in case of hypertensive urgency)
Phase 2 – Combined CLP Model (CCM)

A CCM is derived directly from a CLM, then implemented and solved using available patient information

\[ \text{CCM} = \langle V, CL \rangle \]

- A set of variables
  \[ \text{CLP}.V = \text{CLM}.iLm_A.V \cup \text{CLM}.iLm_B.V \]

- A set of constraints
  1. Constraints corresponding to \( \text{CLM}.iLm_A.PLE \) and \( \text{CLM}.iLm_B.PLE \)
  2. Constraints corresponding to \( \text{CLM}.RLE \)

**Note:** Due to limitations of available solvers variables shared between ILMs may require special handling (temporary variables and additional constraints)
CCM for DVT and HTN

$ccm_{DVT,HTN}$ (implemented in Minizinc)
Scenario 1 – Easy Case

- A patient with uncontrolled hypertensive emergency and history of bleeding ($htn := un, htnun := em, sbt := p$)
- No POI exists and the $ccm_{HTN,DVT}$ has a single solution ($ivcf := true, ivhta := true, fufp := true, aca := false, wa := false, oahta := false$)

Patient should be fitted with IVC filter ($ivcf$) to manage the DVT and given IV antihypertensive agents ($ivahta$) to manage HTN. A follow-up with a family physician ($fufp$) should be recommended.

- Our algorithm terminates by reporting Outcome 1 (*application of both CPGs is possible*) and the obtained solution
Scenario 2 – Difficult Case

• A patient has uncontrolled hypertensive urgency, no history of bleeding tendency, and a history of heparin-induced thrombocytopenia ($htn := un; htnun := ur, sbt := a; true, hit := p$)

• The $clp_{DVT,HTN}$ model has no solution due to a violated constraint ($\neg((htnun = ur) \land aca)$)

Due to thrombocytopenia ($hit = p$) the patient should be prescribed alternative anticoagulants ($aca$) that are not appropriate in the presence of hypertensive urgency ($htnun = ur$)

• A POI ($poi_{HTN,DVT} = \{htnun, aca\}$) is identified and the algorithm passes to Phase 3
Phase 3 – Migration Operators (MOs)

MO codifies knowledge about changes required in order to mitigate a specific POI

\[ \text{MO} = \langle D, V, le_S, Le_R \rangle \]

- A set of triggering disease labels (may contain a wildcard – *)
- A set of triggering variables
- Logical expressions that describe modifications (search & replace) introduced into CLM.iLm_A.PLE and CLM.iLm_B.PLE

**Triggering condition**
\[
\begin{align*}
(RO.D = \{\ast\} \lor (\{CLM.iLm_A.d, CLM.iLm_B.d\} \cap RO.D) \neq \{\}) \\
\land (RO.V = poi)
\end{align*}
\]
Application of MOs to CLM for DVT and HTN

\[ \text{mo}_1.D := \{\} \]
\[ \text{mo}_1.V := \{\text{htnun, aca}\} \]
\[ \text{mo}_1.\text{Le}_S := (\text{aca} \land \neg \text{ivcf}) \]
\[ \text{mo}_1.\text{Le}_R := (\neg \text{aca} \land \text{ivcf}) \]

\[ \text{mo}_2.D := \{\} \]
\[ \text{mo}_2.V := \{\text{htnun, he, wa}\} \]
\[ \text{mo}_2.\text{Le}_S := (\text{he} \land \text{wa} \land \neg \text{ivcf}) \]
\[ \text{mo}_2.\text{Le}_R := (\neg \text{he} \land \neg \text{wa} \land \text{ivcf}) \]

\[ \text{mo}_3.D := \{\} \]
\[ \text{mo}_3.V := \{\text{htnun, lmwhe, wa}\} \]
\[ \text{mo}_3.\text{Le}_S := (\text{lmwhe} \land \text{wa} \land \neg \text{ivcf}) \]
\[ \text{mo}_3.\text{Le}_R := (\neg \text{lmwhe} \land \neg \text{wa} \land \text{ivcf}) \]

\[ \text{poi}_{\text{HTN,DVT}} = \{\text{htnun, aca}\} \]
Modified CLM for DVT and HTN

\[
ilm^{DVT} \cdot d = \text{DVT}
\]
\[
ilm^{DVT} \cdot V = \{sbt, \text{hit, ar, ivcf, aca, he, lmwhe, wa, fufp}\}
\]
\[
ilm^{DVT} \cdot \text{PLE} = \{(sbt = p) \land \text{ivcf} \land \text{fufp} \land \neg \text{aca} \land \neg \text{he} \land \neg \text{lmwhe} \land \neg \text{wa},
\]
\[
(sbt = a) \land (\text{hit} = p) \land \neg \text{aca} \land \text{fufp} \land \text{ivcf} \land \neg \text{he} \land \neg \text{lmwhe} \land \neg \text{wa},
\]
\[
(sbt = a) \land (\text{hit} = a) \land (\text{ar} = p) \land \text{he} \land \text{wa} \land \text{fufp} \land \neg \text{ivcf} \land \neg \text{aca} \land \neg \text{lmwhe},
\]
\[
(sbt = a) \land (\text{hit} = a) \land (\text{ar} = a) \land \text{lmwhe} \land \text{wa} \land \text{fufp} \land \neg \text{ivcf} \land \neg \text{aca} \land \neg \text{he}
\]

\[
clm^{\text{DVT,HTN}} \cdot ilm_A = ilm^{\text{DVT}}
\]
\[
clm^{\text{DVT,HTN}} \cdot ilm_B = ilm^{\text{HTN}}
\]
\[
clm^{\text{DVT,HTN}} \cdot \text{RLE} = clm^{\text{DVT,HTN}} \cdot \text{RLE}
\]
Phase 4 – Modified CCM

- A modified CCM is constructed from a modified CLM, implemented and solved (as in Phase 2)
- If no solution is found, the next triggered RO is applied
- Changes are not accumulated – MOs are applied to the CLM from Phase 1
Scenario 2 – Continued

• A modified CCM has a solution \((ivcf := \text{true}, \ ohta := \text{true}, \ fufp := \text{true}, \ aca := \text{false}, \ he := \text{false}, \ lmwhe := \text{false}, \ wa := \text{false}, \ ivahta := \text{false})\)

• The resulting management is similar to Scenario 1 (IV anti-hypertensive agents \((ivahta)\) are replaced by the oral ones \((ohta)\))

• The algorithm terminates by reporting Outcome 2 (application of both CPGs requires mitigation) and the identified solution
Discussion

• Automatic reconciliation of pairs of CPGs for treatment of a patient with comorbidities
• Conflicting CPGs revised according to shared secondary knowledge codified in form of mitigation operators
• Assisting, not replacing the physician – the treatment decision ultimately rests with the MD
• Customizing CPGs to comorbid conditions of a specific patient – support for personalized medicine

• Tool for identifying inconsistencies between different CPGs developed for the same condition
Future Work

• Concurrent application of more than two CPGs
• Application of multiple mitigation operators
• Ontology of actions (more general operators)
• Dosages (and other properties) associated with actions
• More complex CPGs/actionable graphs (loops)

• Temporal aspects associated with CPGs (chronic diseases)
• Incorporation of external repositories for (semi-)automatic creation of restriction and mitigation operators
Related Publications

• Published


• Submitted/work in progress


MET Research

http://www.mobiledss.uottawa.ca