USING CONSTRAINT LOGIC PROGRAMMING TO SUPPORT THE CONCURRENT APPLICATION OF MULTIPLE PRACTICE GUIDELINES: ADJUSTING MEDICATION DOSAGES AND RESOLVING REPEATED ACTIONS RELATED TO TREATMENT

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3. Poznan University of Technology
4. McGill University
5. Children's Hospital of Eastern Ontario

Outline

- Clinical practice guidelines (CPGs)
- Issues and a clinical case study
- Overview of mitigation approach
- Extensions to support complex relationships and repeated actions
- Discussion and future work

Clinical Practice Guideline (CPG)

- Clinical algorithm
  - Evidence-based best practice in healthcare
  - Guides decisions and criteria regarding diagnosis, management, and treatment of a *single* condition
  - Used to treat patients
  - Might be represented in multiple different (and not always compatible) formats,
  - Forms a narrative, in a flowchart or decision table
- A valid therapy <u>always</u> exists for a single CPG

Motivation

- 50% of people 65 years old or older have a comorbid condition [Institute of Medicine, 2001]

However…

- Most attention has been paid to an individual CPG instead of adapting the guidelines to manage comorbid condition
  - Creating formal/executable CPG representations
  - Translating unstructured text into formal CPG models
  - Verifying CPG models
  - Using CPG models to assist MD take actions
- Research on combining CPGs is still in its infancy and development of combined CPG is mostly expert-based

Research Questions

Foundations

1. How to represent multiple CPGs associated with comorbid conditions as a single executable model?
2. How to process this model (verify, revise) to ensure a therapy for comorbid conditions exists?

New Extensions

3. How to support complex interactions in these models?
   - Dosing of medications
   - Repeated Actions

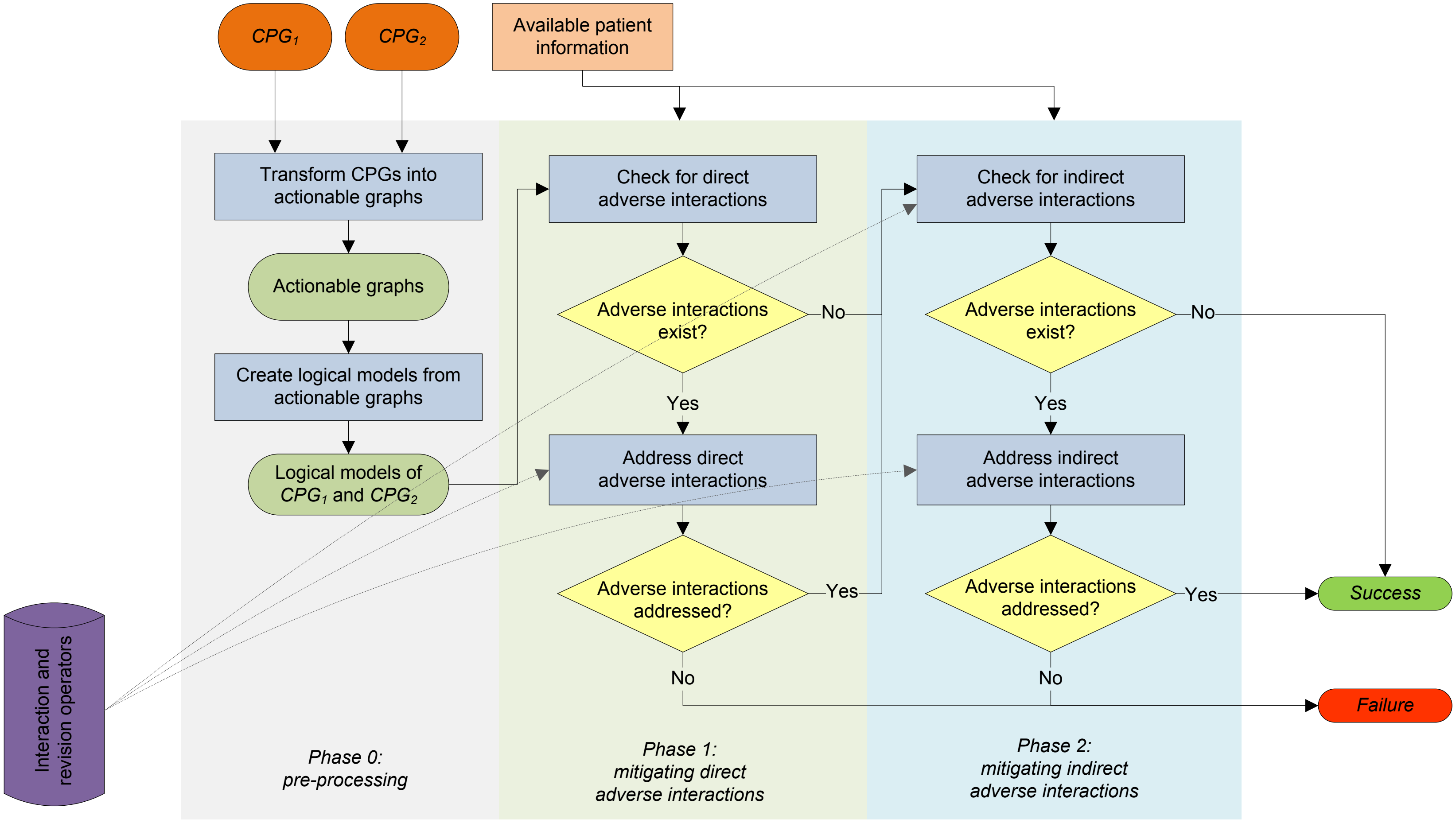
Clinical Case Study

- Concurrent application of CPGs for a patient who is being treated for Wolff Parkinsons White Syndrome (WPW) and suffers an Atrial Fibrillation (AF)
  - Common comorbid condition managed in the ED
  - Overlapping and possibly contradicting treatments
  - Dosages of medication need to be adjusted depending on other measurements
  - Repeated actions that manifest themselves as loops in the CPG
    - Number of iterations is not explicit

Mitigation Approach Overview

- Two CPGs applied to patient with comorbid conditions to obtain combined *therapy*
- Combined therapy does not exist in case of adverse interactions between individual therapies
  - Direct adverse interactions caused by contradictory actions (e.g., to give medication *A*, not to give medication *A*)
  - Indirect adverse interactions caused by drug-drug or drug-disease interactions (e.g., giving medication *A* is forbidden when some disease is present)
- Mitigation (identification and addressing) of adverse interactions requires clinical acumen (experts, textbooks, clinical evidence)
- Clinical acumen encoded in form of operators
  - *Interaction operators* to model adverse interactions
  - *Revision operators* to model revisions

Mitigation Approach Overview (cont.)



CPG_1
CPG_2
Available patient information
Transform CPGs into actionable graphs
Actionable graphs
Create logical models from actionable graphs
Logical models of CPG_1 and CPG_2
Check for direct adverse interactions
Adverse interactions exist?
No
Yes
Address direct adverse interactions
Adverse interactions addressed?
Yes
No
Check for indirect adverse interactions
Adverse interactions exist?
No
Yes
Address indirect adverse interactions
Adverse interactions addressed?
Yes
No
Success
Failure
Interaction and revision operators
Phase 0: pre-processing
Phase 1: mitigating direct adverse interactions
Phase 2: mitigating indirect adverse interactions

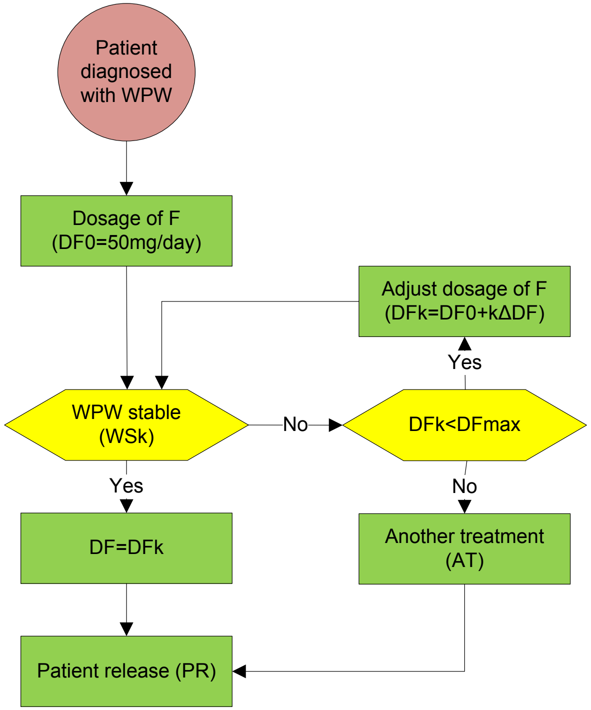
Key Concepts: Actionable Graphs and Paths

- Actionable graph (AG_i) for CPG_i is defined as a directed graph

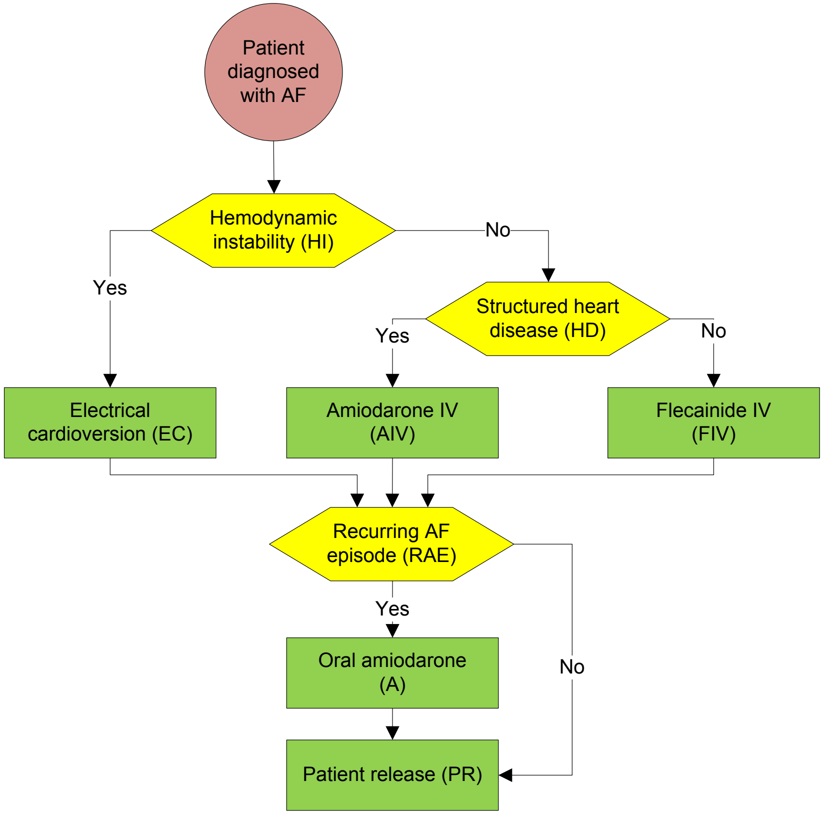
$$AG_i = <N_i, A_i>$$

- N_i = set of context, action and decision nodes
  - Context node provides clinical context, AG_i has a context node as its root, indicating the disease handled by CPG_i.
  - Action node corresponds to an action step from CPG_i
  - Decision node corresponds to a decision step from CPG_i
- A_i = set of arcs representing transitions between nodes
- Inspired by SDA* (*State-Decision-Action*) formalism for health [Isern et al., 2009]

Key Concepts: Actionable Graphs and Paths


Patient diagnosed with WPW
Dosage of F (DF0=50mg/day)
Adjust dosage of F (DFk=DF0+kΔDF)
Yes
WPW stable (WSk)
No
DFk<DFmax
Yes
No
DF=DFk
Another treatment (AT)
Patient release (PR)

Actionable graph for WPW


Patient diagnosed with AF
Hemodynamic instability (HI)
No
Yes
Structured heart disease (HD)
Yes
No
Electrical cardioversion (EC)
Amiodarone IV (AIV)
Flecainide IV (FIV)
Recurring AF episode (RAE)
Yes
No
Oral amiodarone (A)
Patient release (PR)

Actionable graph for AF

All paths enumerated from root to leaves

Key Concepts: Logical Models

- A *logical model* (LM_i) provides a logical representation of an AG_i

$$LM_i = <d_i, V_i, PLE_i>$$

- d_i = label of disease associated with AG_i
- V_i = set of action and decision variables associated with actions and decision nodes in AG_i
- PLE_i is a set of logical expressions representing paths in AG_i

Key Concepts: Logical Models

Logical Model created from AG_{AF}

d_{AF} = AF

V_{AF} = {HI, EC, HD, AIV, FIV, RAE, A, PR}

PLE_{AF} = {(HI = y) ∧ EC ∧ (RAE = y) ∧ A ∧ PR ∧ ¬ FIV ∧ ¬ AIV,
(HI = y) ∧ EC ∧ (RAE = n) ∧ PR ∧ ¬ FIV ∧ ¬ AIV ∧ ¬ A,
(HI = n) ∧ (HD = y) ∧ AIV ∧ (RAE = y) ∧ A ∧ PR ∧ ¬ EC ∧ ¬ AIV,
(HI = n) ∧ (HD = y) ∧ AIV ∧ (RAE = n) ∧ PR ∧ ¬ EC ∧ ¬ FIV ∧ ¬ A,
(HI = n) ∧ (HD = n) ∧ FIV ∧ (RAE = y) ∧ A ∧ PR ∧ ¬ EC ∧ ¬ AIV,
(HI = n) ∧ (HD = n) ∧ FIV ∧ (RAE = n) ∧ PR ∧ ¬ EC ∧ ¬ AIV ∧ ¬ A
}

Example variables and domains

- HI (hemodynamic instability) = {yes, no}
- HD (structured heard disease) = {yes, no}
- RAE (recurring AF episode) = {yes, no}

Key Concepts: Combined Logical Models

- A *combined logical model* ($CLM_{i,j}$) brings together a pair of logical models and information about adverse interactions between underlying CPGs

$$CLM_{i,j} = \langle LM_i, LM_j, ILE_{i,j} \rangle$$

- LM_i & LM_j = individual logical models representing AG_i and AG_j
- $ILE_{i,j}$ = logical expressions that represent indirect adverse interactions between CPG_i and CPG_j

$$ILE_{WPW,\ AF} = \{\neg(A \wedge DF = DF_{max})\}$$

Original Assumptions and Extensions

- Only Boolean variables
  - Requires discretizing decisions and “go/no go” actions
  - Extension: introduce numeric variables
    - Action variables support finer grained details
      - Previously *Flecainide := True / False*
      - Now *Flecainide :=* [*0…500*]
    - Decision variables no longer need discretization
      - Previously *if Flecainide == 150*
      - Now *if Flecanide > 150* $\wedge$ *Flecanide < 300*
- Acyclic AG
  - A node can only be traversed once
    - Unable to support repeated actions (re-testing or monitoring)
  - Extension: allow for algorithmic expressions and conditions
    - Previously $\neg(A \wedge DF)$
    - Now $\neg(A \wedge DF = DF_{max}) \wedge (DF = DF_1 + DF_2 + DF_3 + \ldots)$

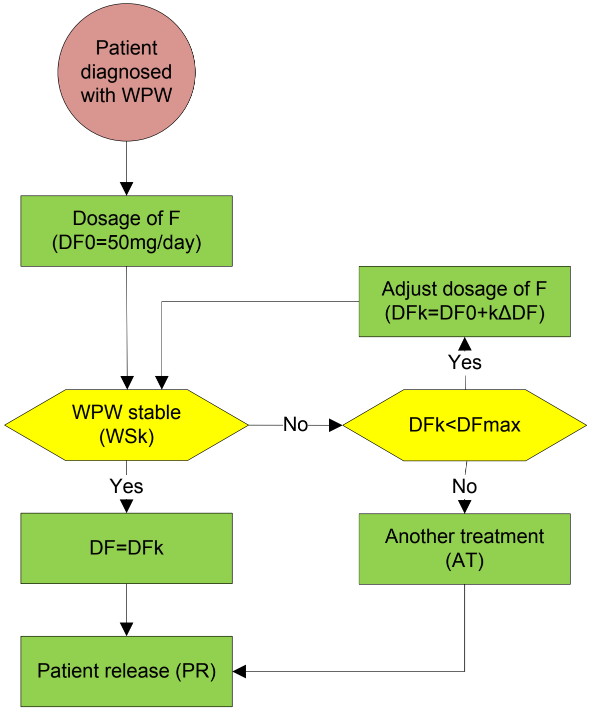
Extensions: Supporting repeated actions

- Find and expand loops in AGs

```
procedure expand(in $AG_i$, in $WorstCase_i$, out $AG_{i\_exp}$)
begin
$Loop_i$ := identify_loop($AG_i$)
$MaxIter_i$ := check_conditions($Loop_i$, $WorstCase_i$)
$ForwardPath_i$ := create_path($Loop_i$, $MaxIter_i$)
$AG_{i\_exp}$ := replace_loop($AG_i$, $ForwardPath_i$)
return $AG_{i\_exp}$
end
```

- $Loop_i$ found using a path-based strong component algorithm (Tarjan’s)
    - Assumes a single loop in the AG
- $WorstCase_i$ is defined according to patient information and secondary knowledge (expert's opinion, evidence, literature, …)
- Supports diseases where therapy involves repeated actions

Extensions: Supporting repeated actions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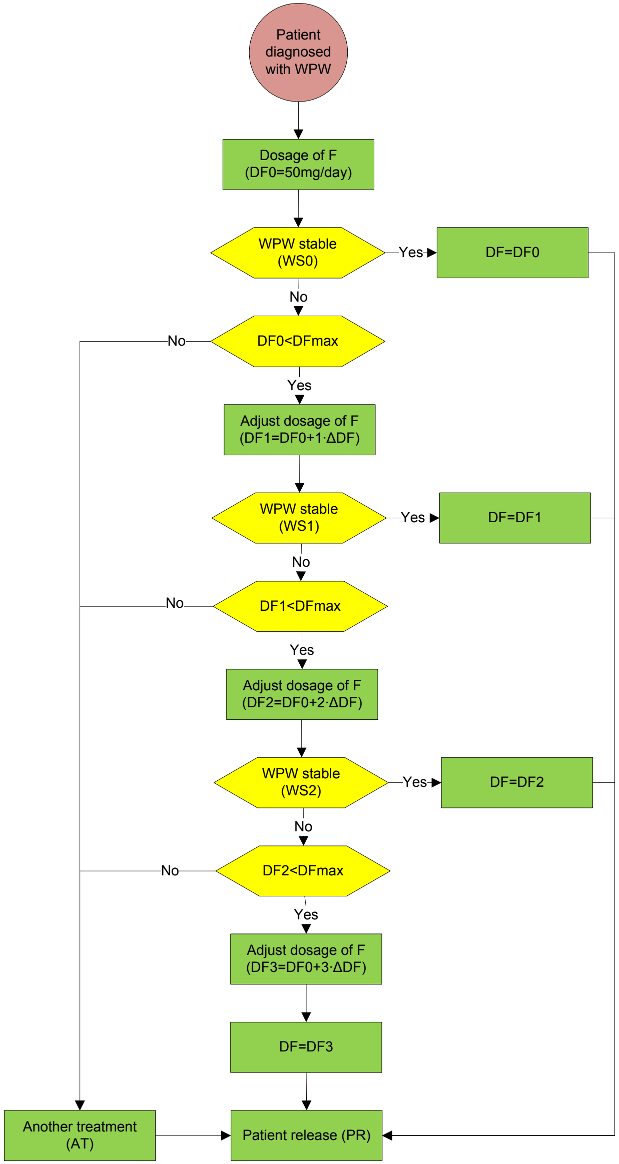
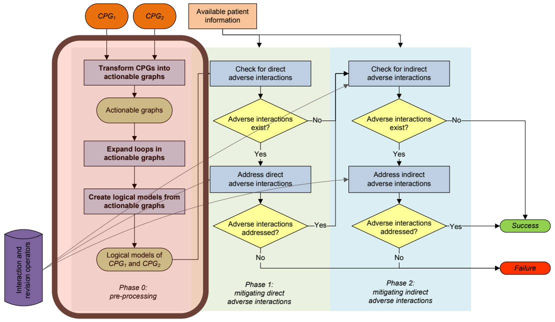
Original AG_{WPW}



Automatically Revised AG_{WPW}

Updated Mitigation Approach



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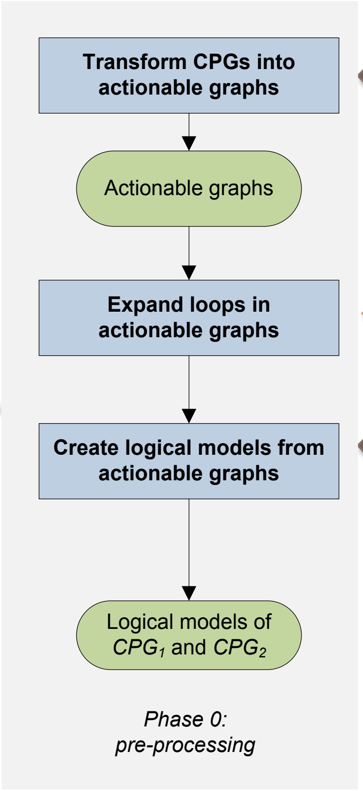

Transform CPGs into actionable graphs

Actionable graphs

Expand loops in actionable graphs

Create logical models from actionable graphs

Logical models of *CPG_1* and *CPG_2*

Phase 0: pre-processing

Modified step to to handle increased complexity associated with numerical variables

New step introduced to handle loops in actionable graphs

Modified step to handle increased complexity associated with numerical variables

Discussion and Future Work

- Contribution: Support complex relationships
- Contribution: Identify and expand repeated actions
- Benefit: Steps towards a comprehensive alerting system for physicians at the point of care
- Benefit: Steps towards wider acceptance on CPGs in clinical practice [Sittig et al. 2008]
- Future Work: Refine inference in handling repeating actions
- Future Work: Modeling temporal aspects of CPGs

Thank you

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