USING FIRST-ORDER LOGIC TO REPRESENT CLINICAL PRACTICE GUIDELINES AND TO MITIGATE ADVERSE INTERACTIONS

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Motivation for the Research

- Our previous approach to mitigating adverse interactions was based on the constraint logic programming (CLP) paradigm
- Limited expressiveness of representation
  - No properties of objects (e.g., medication dosages)
  - No relationships between objects (e.g., precedence between actions)
- Limited interpretability of generated solutions
  - Need to distinguish between different types of variables (corresponding to actions and decisions)
  - Need to assign real-world semantics to truth-assignments of propositional symbols

Sz. Wilk, W. Michalowski, M. Michalowski, K. Farion, M.M. Hing, S. Mohapatra: *Mitigation of Adverse Interactions in Pairs of Clinical Practice Guidelines Using Constraint Logic Programming*. Journal of Biomedical Informatics, vol. 46, no. 2, 2013, 341-353.

Research Question

1. How to represent CPGs and secondary domain knowledge to address limitations of the CLP-based approach?
2. What techniques to use to "solve" CPGs and to process domain knowledge encoded in a new formalism?

Answer: first-order logic (FOL),
theorem proving and model finding techniques

Assumptions from our previous work

1. Direct and indirect adverse interactions
2. Secondary domain knowledge encoded using operators

FOL Background

- Logical and non-logical symbols (functions, predicates , …)
- Terms, formulas and sentences

- *A theory* $\mathcal{D} =$ collection of sentences
- *An interpretation* $\mathcal{I} = \langle \mathcal{I}_{domain}, \mathcal{I}_{predicate}, \mathcal{I}_{function} \rangle$, where
  - $\mathcal{I}_{domain}$ – a set of objects under consideration
  - $\mathcal{I}_{predicate}$ – a set of interpretation mappings over $\mathcal{I}_{domain}$ that assign meaning to predicate symbols
  - $\mathcal{I}_{function}$ – a set of functions over $\mathcal{I}_{domain}$ that assign meaning to function symbols
- If $\mathcal{I}$ satisfies all sentences in $\mathcal{D}$, then it is called a *model* for theory $\mathcal{D}$ and denoted as $\mathcal{I} \vDash_m \mathcal{D}$

Theorem Proving and Model Finding

- *Theorem proving* allows for checking if theory $\mathcal{D}$ is *consistent* ($i.e.$, there exists at least one model for $\mathcal{D}$)
- If theory $\mathcal{D}$ is consistent, then its models can be identified using *model finding* techniques

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- Theorem proving is also used for checking *logical consequences* (*entailments*) of a consistent theory $\mathcal{D}$
  - Theory $\mathcal{D}$ entails sentence ϕ (denoted as $\mathcal{D} \models \phi$), if ϕ is satisfied by all models for $\mathcal{D}$
  - Entailment $\mathcal{D} \models \phi$ translated into checking if a *new theory* $\mathcal{D} \cup \{\neg\phi\}$ is **not consistent**

Key Components of Our Framework

1. A *vocabulary* to construct a theory describing a particular mitigation problem
2. A *combined mitigation theory* $\mathcal{D}_{comb}$ composed of individual theories that describe various aspects of the mitigation problem (e.g., individual CPGs, patient information)
3. A set of operators encoding secondary knowledge that describe and address interactions between CPGs (→ inconsistencies in $\mathcal{D}_{comb}$)
4. A mitigation algorithm that controls the application of operators to $\mathcal{D}_{comb}$

Vocabulary

Constants, variables and **predicates**, defined under assumption that CPGs are given as *actionable graphs* (AGs)

Predicate	Description
$node(x)$	*x* is a node in AG
$action(x)$	*x* is an action node in AG
$decision(x)$	*x* is a decision node in AG
$executed(x)$	action node *x* is executed
$value(x, v)$	value *v* is associated with decision node *x*
$dosage(x, n)$	action node *x* is characterized by medication dosage *n*
$directPrec(x, y)$	node *x* directly precedes node *y* (there is an arc from *x* to *y*)
$prec(x, y)$	node *x* precedes node *y* (there is a path from *x* to *y*)
$disease(d)$	*d* is a disease to be managed
$diagnosed(d)$	patient has been diagnosed with disease *d*

Combined Mitigation Theory

A combined mitigation theory $\mathcal{D}_{comb} = \langle \mathcal{D}_{common}, \mathcal{D}_{cpg}, \mathcal{D}_{pi} \rangle$, where

- $\mathcal{D}_{common}$ – a shared and reused component of all combined mitigation theories with axioms defining universal character of CPGs, e.g.,
  - $\forall x, y\ directPrec(x, y) \Longrightarrow prec(x, y)$
  - $\forall x, y, z\ prec(x, y) \wedge prec(y, z) \Longrightarrow prec(x, z)$
  - (→ *more axioms in the paper*)
- $\mathcal{D}_{cpg}$ – a union of theories $\left(\mathcal{D}_{cpg}^{d_1} \cup \mathcal{D}_{cpg}^{d_2} \cup \cdots \cup \mathcal{D}_{cpg}^{d_k}\right)$ that represent AGs corresponding to CPGs applied to a comorbid patient ($\mathcal{D}_{cpg}^{d_i}$ associated with AG/CPG for disease d_i)
- $\mathcal{D}_{pi}$ – a collection of available patient data (results of tests and examinations, prescribed therapies, …), a sentence for each data item

Interaction Operators

- An interaction operator $IO^k = \langle \alpha^k \rangle$, where
  - α^k – a sentence describing a specific indirect interaction
- Checking if IO^k is applicable to $\mathcal{D}_{comb}$ (i.e., interaction given by α^k occurs in $\mathcal{D}_{comb}$) through entailment $\mathcal{D}_{comb} \models \alpha^k$

Revision Operators

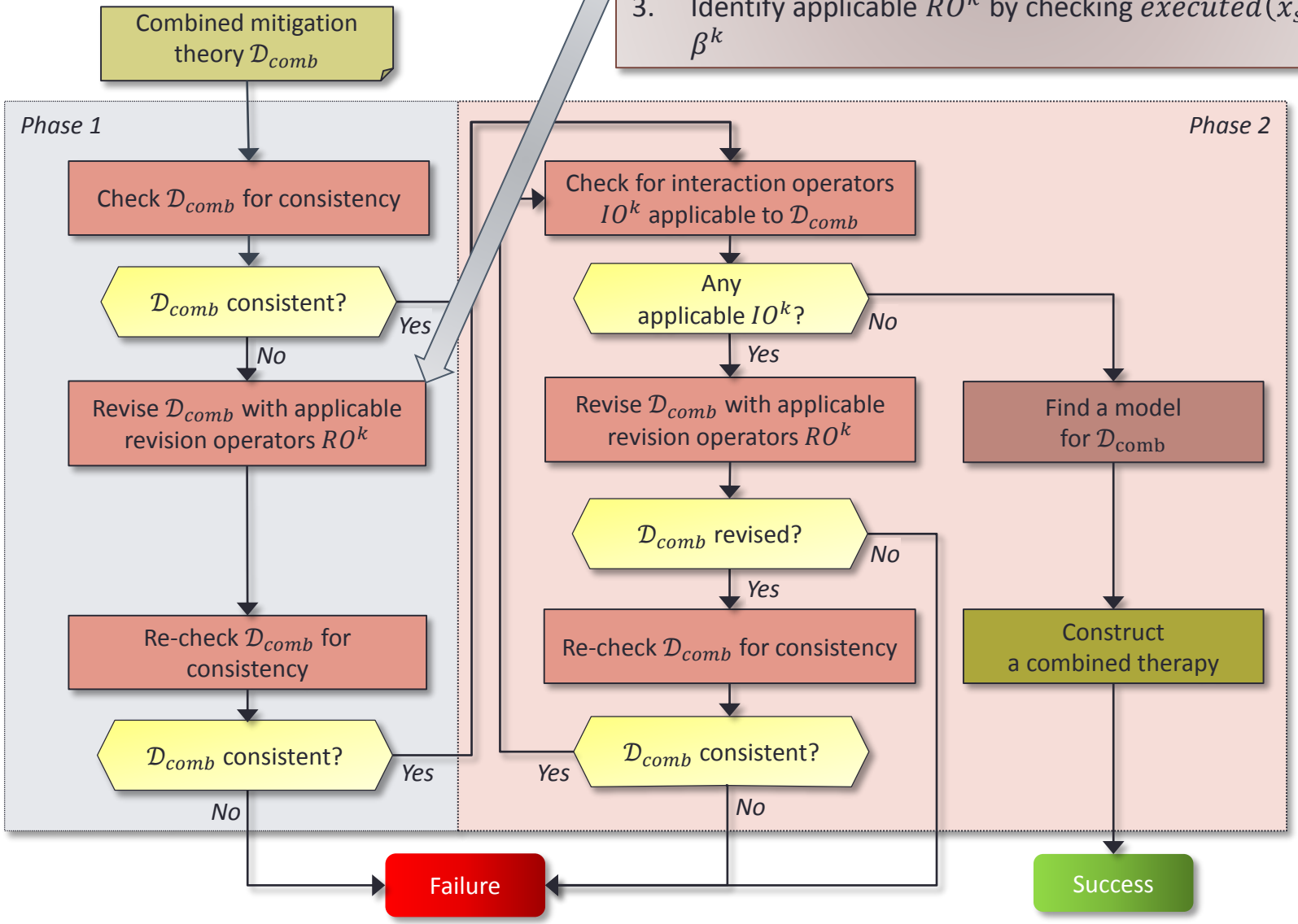
- A revision operator $RO^k = \langle \beta^k, Op^k \rangle$, where
  - β^k – a sentence defining the applicability of the operator
  - Op^k – a description of revisions introduced to $\mathcal{D}_{cpg}$ (only)
- Revisions given as a list of formula pairs $\langle \varphi_i^k, \phi_i^k \rangle$ describing individual *delete*, *add* and *replace* operations on $\mathcal{D}_{cpg}$
  - $\langle \varphi_i^k, \emptyset \rangle$ – φ_i^k is removed from any sentence in $\mathcal{D}_{cpg}$
  - $\langle \emptyset, \phi_i^k \rangle$ – ϕ_i^k is added as a new sentence to $\mathcal{D}_{cpg}$
  - $\langle \varphi_i^k, \phi_i^k \rangle$ – φ_i^k is replaced by ϕ_i^k in any sentence in $\mathcal{D}_{cpg}$

$\emptyset$ – an empty formula

- Unbounded variables in φ_i^k and ϕ_i^k used as "wildcards"
- Checking if RO^k is applicable to $\mathcal{D}_{comb}$ through entailment $\mathcal{D}_{comb} \models \beta^k$

Mitigation Algorithm

1. Identify actions shared across individual theories ($\mathcal{D}_{cpg}^{d_i}$) in $\mathcal{D}_{cpg}$
2. For each shared action x_s check whether $\mathcal{D}_{cpg}^{d_i} \models executed(x_s) \wedge \mathcal{D}_{cpg}^{d_j} \models \neg executed(x_s)$
3. Identify applicable RO^k by checking $executed(x_s) \models \beta^k$



Combined Therapy

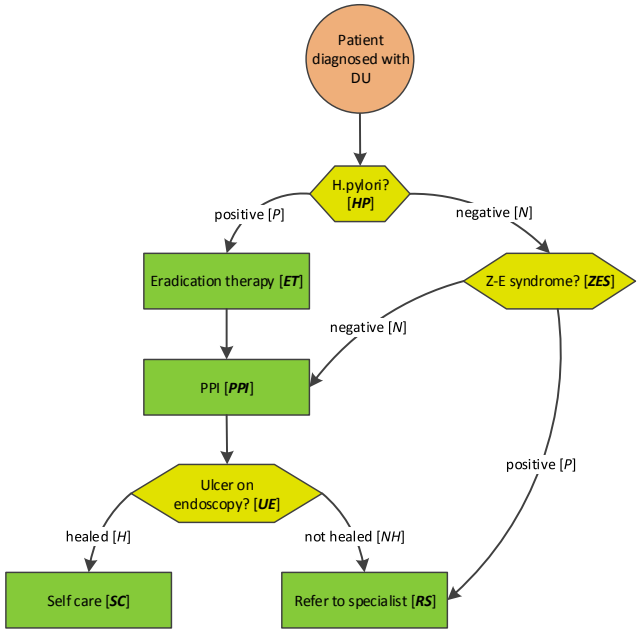
- Constructed from a model for $\mathcal{D}_{comb}$ (its $\mathcal{I}_{predicate}$ component)
- Combined therapy $\mathcal{D}_{th}$ includes
  - Clinical actions to be taken (*executed* and *dosage* predicates) and their order *(prec* predicate*)*
  - Assumptions related to the future patient's state (*value* predicates)
- $\mathcal{D}_{th}$ contains only sentences that do not appear in $\mathcal{D}_{pi}$ → focus on suggested actions and assumed patient states

Illustrative Example

A patient who is treated for a duodenal ulcer (DU), experiences an episode of transient ischemic attack (TIA)

- CPGs for DU and TIA derived from guideline published by NICE and given as AGs (AG_{DU} and AG_{TIA})
- Two considered scenarios
  - Scenario 1 with no adverse interactions
  - Scenario 2 with indirect adverse interactions

AG_{DU} and $\mathcal{D}_{cpg}^{DU}$



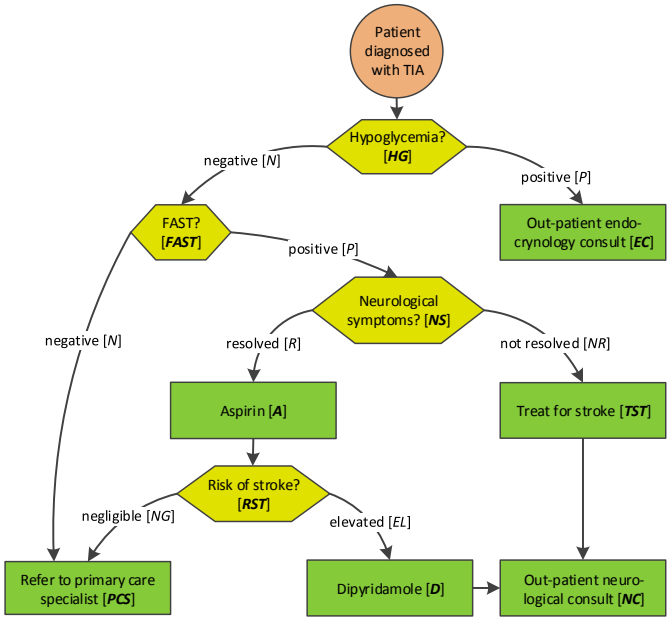
disease(*DU*).

node(*HP*). *node*(*ZES*). *node*(*UE*). *node*(*ET*). *node*(*PPI*). *node*(*SC*). *node*(*RS*).
decision(*HP*). *decision*(*ZES*). *decision*(*UE*). *task*(*ET*). *task*(*PPI*). *task*(*SC*). *task*(*RS*).

directPrec(*HP*, *ET*). *directPrec*(*HP*, *ZES*). *directPrec*(*ET*, *PPI*). *directPrec*(*ZES*, *PPI*).
directPrec(*ZES*, *RS*). *directPrec*(*PPI*, *UE*). *directPrec*(*UE*, *SC*). *directPrec*(*UE*, *RS*).

(*value*(*HP*, *P*) ∧ *executed*(*ET*) ∧ *executed*(*PPI*) ∧ *value*(*UE*,*H*) ∧ *executed*(*SC*)
∧ ¬*executed*(*RS*))
∨ (*value*(*HP*, *P*) ∧ *executed*(*ET*) ∧ *executed*(*PPI*) ∧ *value*(*UE*,*NH*) ∧ *executed*(*RS*)
∧ ¬*executed*(*SC*))
∨ (*value*(*HP*, *N*) ∧ *value*(*ZES*,*N*) ∧ *executed*(*PPI*) ∧ *value*(*UE*,*H*) ∧ *executed*(*SC*)
∧ ¬*executed*(*ET*) ∧ ¬*executed*(*RS*))
∨ (*value*(*HP*, *N*) ∧ *value*(*ZES*, *N*) ∧ *executed*(*PPI*) ∧ *value*(*UE*,*NH*) ∧ *executed*(*RS*)
∧ ¬*executed*(*ET*) ∧ ¬*executed*(*SC*))
∨ (*value*(*HP*,*N*) ∧ *value*(*ZES*,*P*) ∧ *executed*(*RS*)
∧ ¬*executed*(*ET*) ∧ ¬*executed*(*PPI*) ∧ ¬*executed*(*SC*)).

AG_{TIA} and $\mathcal{D}_{cpg}^{TIA}$



$disease(TIA)$.

$node(HG)$. $node(FAST)$. $node(EC)$. $node(NS)$. $node(A)$. $node(TST)$. $node(RST)$. $node(PCS)$. $node(D)$. $node(NC)$.
$decision(HG)$, $decision(FAST)$, $decision(NS)$, $decision(RST)$. $action(EC)$. $action(A)$. $action(TST)$. $action(PCS)$. $action(D)$. $action(NC)$.
$dosage(A, 300)$. $dosage(D, 75)$.

$directPrec(HG, FAST)$. $directPrec(HG, EC)$. $directPrec(FAST, PCS)$. $directPrec(FAST, NS)$. $directPrec(NS, A)$. $directPrec(NS, TST)$. $directPrec(A, RST)$. $directPrec(RST, PCS)$. $directPrec(RST, D)$. $directPrec(D, NC)$. $directPrec(TST, NC)$.

$$
\begin{aligned}
&(value(HG, N) \wedge value(FAST, N) \wedge executed(PCS) \\
&\quad \wedge \neg executed(EC) \wedge \wedge \neg executed(A)\ \neg executed(TST) \wedge \neg executed(D) \\
&\quad \wedge \neg executed(NC)) \\
&\vee (value(HG, N) \wedge value(FAST, P) \wedge value(NS, R) \wedge executed(A) \wedge value(RST, NG) \\
&\quad \wedge executed(PCS) \\
&\quad \wedge \neg executed(EC) \wedge \neg executed(TST) \wedge \neg executed(D) \wedge \neg executed(NC)) \\
&\vee (value(HG, N) \wedge value(FAST, P) \wedge value(NS, R) \wedge executed(A) \wedge value(RST, EL) \\
&\quad \wedge executed(D) \wedge executed(NC) \\
&\quad \wedge \neg executed(EC) \wedge \neg executed(TST) \wedge \neg executed(PCS)) \\
&\vee (value(HG, N) \wedge value(FAST, P) \wedge value(NS, NR) \wedge executed(TST) \wedge executed(NC) \\
&\quad \wedge \neg executed(EC) \wedge \neg executed(A) \wedge \neg executed(PCS) \wedge \neg executed(D)) \\
&\vee (value(HG, P) \wedge executed(EC) \\
&\quad \wedge \neg executed(A) \wedge \neg executed(TST) \wedge \neg executed(PCS) \wedge \neg executed(D) \\
&\quad \wedge \neg executed(NC)).
\end{aligned}
$$

Operators

Increased risk of bleeding

Interaction operators

$IO^1 = \langle \alpha^1 \rangle$

$\alpha^1 = diagnosed(DU) \wedge executed(A) \wedge \neg executed(PPI).$

Two possible ways of revising CPGs to address this risk

Revision operators

$RO^1 = \langle \beta^1, Op^1 \rangle$

$\beta^1 = diagnosed(DU) \wedge executed(A) \wedge \neg executed(PPI) \wedge \neg executed(D).$

$Op^1 = \{<executed(A), executed(CL)>\}$

$RO^2 = \langle \beta^2, Op^2 \rangle$

$\beta^2 = diagnosed(DU) \wedge executed(A) \wedge \neg executed(PPI) \wedge executed(D).$

$Op^2 = \{<\neg executed(PPI), executed(PPI)>, <dosage(A, x), dosage(A, x - 50)>\}$

Scenario 1 – No Interactions

- Patient information $\mathcal{D}_{pi}$

diagnosed(*DU*). *value*(*HP*, *P*). *executed*(*ET*).
diagnosed(*TIA*). *value*(*HG*, *N*). *value*(*FAST*, *N*).

- Mitigation
  - Phase 1
    - $\mathcal{D}_{comb}$ is consistent → no direct interactions
  - Phase 2
    - *IO*[1] is not applicable to $\mathcal{D}_{comb}$ ($\mathcal{D}_{comb} \not\models \alpha^1$) → no indirect interactions
- Combined therapy $\mathcal{D}_{th}$

executed(*PPI*). *value*(*UE*, *H*). *executed*(*SC*).
executed(*PCS*)

Scenario 2 – Indirect Interactions

- Patient information $\mathcal{D}_{pi}$

diagnosed(*DU*). *value*(*HP*, *N*). *value*(*ZES*, *P*).
diagnosed(*TIA*). *value*(*HG*, *N*). *value*(*FAST*, *P*). *value*(*NS*, *R*). *value*(*RST*, *EL*).

- Mitigation
  - Phase 1
    - $\mathcal{D}_{comb}$ is consistent → no direct interactions
  - Phase 2
    - *IO*^{1} is applicable to $\mathcal{D}_{comb}$ ($\mathcal{D}_{comb} \vDash \alpha^1$) → indirect interaction encountered
    - *RO*^{1} is not applicable to $\mathcal{D}_{comb}$ ($\mathcal{D}_{comb} \nvDash \beta^1$)
    - *RO*^{2} is applicable to $\mathcal{D}_{comb}$ ($\mathcal{D}_{comb} \vDash \beta^2$) and successfully revises $\mathcal{D}_{comb}$
- Combined therapy $\mathcal{D}_{th}$

executed(*PPI*). *executed*(*RS*).
executed(*A*). *dosage*(*A*, 250). *executed*(*D*). *dosage*(*D*, 75). *executed*(*NC*).

Discussion and Future Work

- Improved expressiveness of representation and explicit representation of object properties and relationships
- Representation applicable for “hard” representational issues (e.g., loops)
- Improved expressiveness comes at the cost of limited comprehensibility for clinicians

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- Extension of the framework to include patient preferences (support for participatory medicine)
- Generalization of the current framework to include other properties of CPGs (time) and other mitigation scenarios

Thank you!

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