

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

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

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 (\rightarrow 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.,
 - $\forall x, y \text{ directPrec}(x, y) \Rightarrow \text{prec}(x, y)$
 - $\forall x, y, z \text{ prec}(x, y) \wedge \text{prec}(y, z) \Rightarrow \text{prec}(x, z)$
 - (\rightarrow more axioms in the paper)
- \mathcal{D}_{cpg} – a union of theories $(\mathcal{D}_{cpg}^{d_1} \cup \mathcal{D}_{cpg}^{d_2} \cup \dots \cup \mathcal{D}_{cpg}^{d_k})$ 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 $\mathcal{D}_{comb} \models \alpha^k$

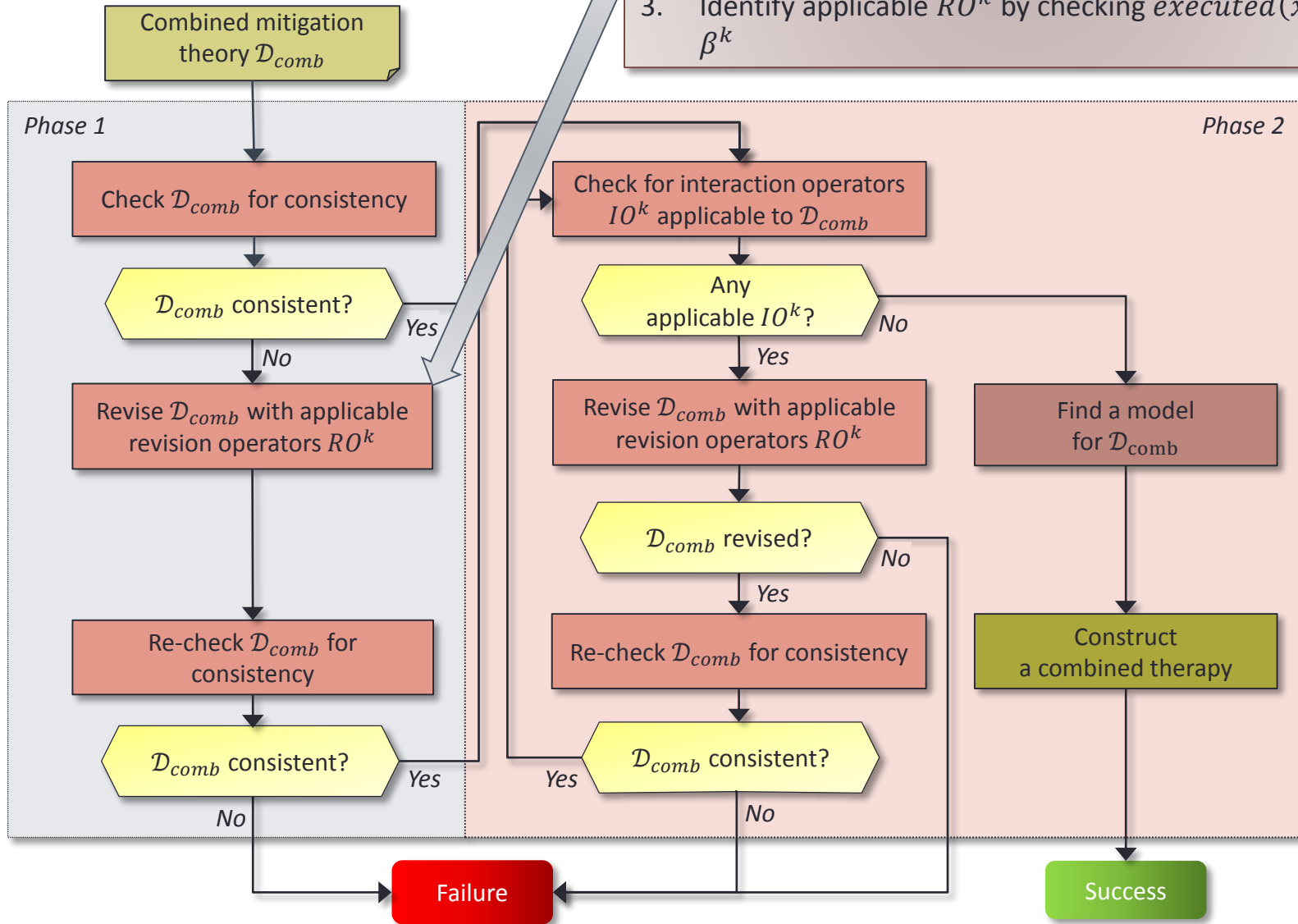
Revision Operators

- 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}
- 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
 $\mathcal{D}_{comb} \models \beta^k$

\emptyset – an empty formula

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

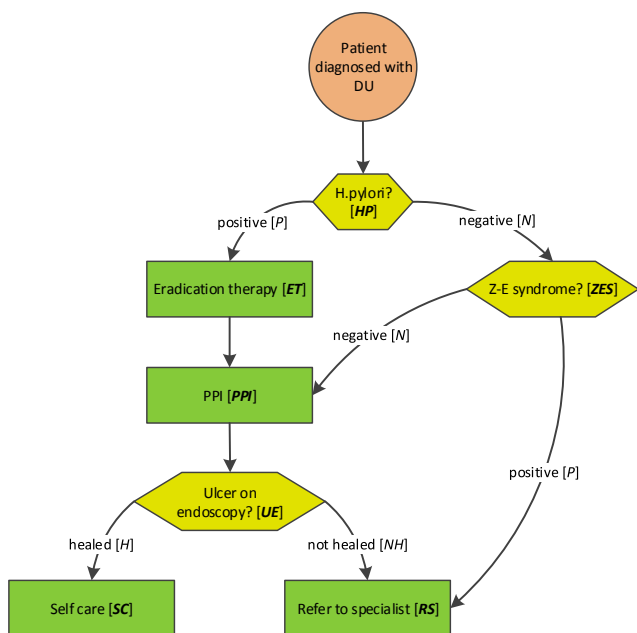
- Constructed from a model for \mathcal{D}_{comb} (its $\mathcal{I}_{predicate}$ component)
- Combined therapy \mathcal{D}_{th} includes
 - Clinical actions to be taken (*executed* and *dosage* predicates) and their order (*prec* predicate)
 - Assumptions related to the future patient's state (*value* 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).

$(value(HP, P) \wedge executed(ET) \wedge executed(PPI) \wedge value(UE, H) \wedge executed(SC) \wedge \neg executed(RS))$

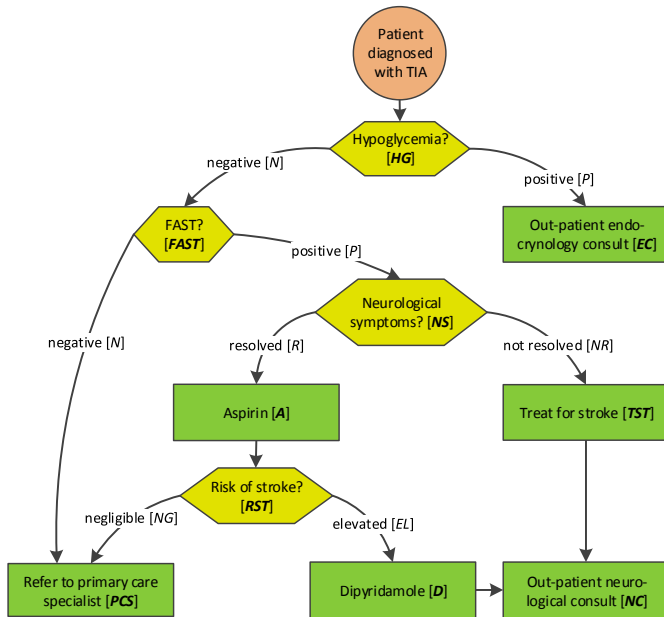
$\vee (value(HP, P) \wedge executed(ET) \wedge executed(PPI) \wedge value(UE, NH) \wedge executed(RS) \wedge \neg executed(SC))$

$\vee (value(HP, N) \wedge value(ZES, N) \wedge executed(PPI) \wedge value(UE, H) \wedge executed(SC) \wedge \neg executed(ET) \wedge \neg executed(RS))$

$\vee (value(HP, N) \wedge value(ZES, N) \wedge executed(PPI) \wedge value(UE, NH) \wedge executed(RS) \wedge \neg executed(ET) \wedge \neg executed(SC))$

$\vee (value(HP, N) \wedge value(ZES, P) \wedge executed(RS) \wedge \neg executed(ET) \wedge \neg executed(PPI) \wedge \neg executed(SC)).$

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).

$(value(HG, N) \wedge value(FAST, N) \wedge executed(PCS))$

$\wedge \neg executed(EC) \wedge \neg executed(A) \wedge \neg executed(TST) \wedge \neg executed(D)$
 $\wedge \neg executed(NC))$

$\vee (value(HG, N) \wedge value(FAST, P) \wedge value(NS, R) \wedge executed(A) \wedge value(RST, NG)$
 $\wedge executed(PCS))$

$\wedge \neg executed(EC) \wedge \neg executed(TST) \wedge \neg executed(D) \wedge \neg executed(NC))$

$\vee (value(HG, N) \wedge value(FAST, P) \wedge value(NS, R) \wedge executed(A) \wedge value(RST, EL)$
 $\wedge executed(D) \wedge executed(NC))$

$\wedge \neg executed(EC) \wedge \neg executed(TST) \wedge \neg executed(PCS))$

$\vee (value(HG, N) \wedge value(FAST, P) \wedge value(NS, NR) \wedge executed(TST) \wedge executed(NC)$
 $\wedge \neg executed(EC) \wedge \neg executed(A) \wedge \neg executed(PCS) \wedge \neg executed(D))$

$\vee (value(HG, P) \wedge executed(EC))$

$\wedge \neg executed(A) \wedge \neg executed(TST) \wedge \neg executed(PCS) \wedge \neg executed(D)$
 $\wedge \neg executed(NC)).$

Operators

Increased risk of bleeding

Interaction operators

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

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

Revision operators

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

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

$$Op^1 = \{ \langle \text{executed}(A), \text{executed}(CL) \rangle \}$$

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

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

$$Op^2 = \{ \langle \neg \text{executed}(PPI), \text{executed}(PPI) \rangle, \langle \text{dosage}(A, x), \text{dosage}(A, x - 50) \rangle \}$$

Two possible ways of revising CPGs to address this risk

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 \rightarrow no direct interactions

- Phase 2

- IO^1 is not applicable to \mathcal{D}_{comb} ($\mathcal{D}_{comb} \not\equiv \alpha^1$) \rightarrow 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 \rightarrow no direct interactions

- Phase 2

- IO^1 is applicable to \mathcal{D}_{comb} ($\mathcal{D}_{comb} \models \alpha^1$) \rightarrow indirect interaction encountered
 - RO^1 is not applicable to \mathcal{D}_{comb} ($\mathcal{D}_{comb} \not\models \beta^1$)
 - RO^2 is applicable to \mathcal{D}_{comb} ($\mathcal{D}_{comb} \models \beta^2$) 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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