

FIRST-ORDER LOGIC THEORY FOR MANIPULATING CLINICAL PRACTICE GUIDELINES APPLIED TO COMORBID PATIENTS: A CASE STUDY

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Outline

- Motivation
- Illustrative clinical scenario
- Related Work
- Our FOL-based approach
- Discussion and future work

Motivation for the Research

- Clinical practice guidelines (CPGs) are *knowledge-based tools for **disease-specific** patient management* [Rosenfeld and Shiffman 2009]
- Concurrent use of multiple CPGs for comorbid (multimorbid) patients is difficult/problematic and “major shortcoming of CPG uptake in clinical practice” [Peleg 2013]
- “The challenge ... to identify and eliminate redundant, contraindicated, potentially discordant, or mutually exclusive guideline based recommendations for patients presenting with comorbid conditions or multiple medications.” [Sittig et al. 2008]
- A new, “combinatorial, logical, or semantic” methodological approach is needed [Fox et al. 2010]

Illustrative Clinical Scenario

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

A physician must mitigate a risk of bleeding for this patient when prescribing aspirin but not a proton pump inhibitor as part of therapy.

Illustrative Clinical Scenario (DU & TIA):

Managing Risk of Bleeding

- A DU patient is prescribed aspirin without a proton-pump inhibitor
 - Increased risk of bleeding
 - Alternative treatments depend on the presence of dipyridamole in the suggested therapy
 - **Not** prescribed dipyridamole: taken off of aspirin and prescribed clopidogrel
 - Prescribed dipyridamole: prescribed a proton-pump inhibitor and the dosage of aspirin is reduced by 50mg
- Issues
 - How to mitigate risk w.r.t. to this specific patient?
 - How to codify medical knowledge regarding alternative treatments not in CPGs?
 - How to revise CPGs for DU and TIA appropriately?

Related Work

- Mostly focused on individual CPG
 - Creating formal/executable CPG representations (e.g., GLIF3, SAGE, Asbru, PROforma, and Arden Syntax)
 - Translating unstructured text into formal CPG models (e.g., GEM Cutter, ERGO project)
 - Verifying CPG models (e.g. UML-based model checking, theorem proving using KIV prover, knowledge-based checking)
 - Using CPG models to assist MD take actions (Model checking using temporal logics, ASTI)
- Development of combined CPG is mostly expert-based
 - GLINDA (GuideLine INteraction Detection Architecture)
 - COMET (Ontology mapping-based approach) [Abidi and Abidi, 2009]
 - CPG templates and composition operators [Riaño and Collado, 2013]
 - Formalizing mitigation using Answer Set Programming [Zhang and Zhang 2014]
 - Transition-based Medical Recommendation (TMR) Model for Clinical Guidelines [Zamborlini et al., 2014]
 - Existing research relies on description logic for manipulating the guidelines and mostly creates a single multi-disease CPG

Our Approach

- Our previous work used constraint logic programming (CLP) paradigm:
 - Limited expressiveness of representation
 - Limited interpretability of generated solutions
 - Unable to control granularity of mitigation
- **Research Question:** How to improve expressiveness of a mitigation framework to increase applicability of CPGs to a broader set of clinical scenarios?

Answer: Revised mitigation framework using First-Order Logic (FOL), Theorem Proving and Model Finding Techniques

Methodology

- *First-order logic (FOL)*
 - Formal system for representing and reasoning about knowledge
 - Logical and non-logical symbols (functions, predicates , ...)
 - Terms, formulas, and sentences
 - A theory D is a collection of sentences (describe CPGs and patient information)
 - A model for theory D is an interpretation I that satisfies all sentences in D , $I \models_m D$ (used to construct therapy)
- *Theorem proving* allows for checking if theory D is *consistent* (used to check for adverse interactions and applicability of revisions)
 - Theory D entails sentence ϕ (denoted as $D \models \phi$), if ϕ is satisfied by all models for D
- If theory is consistent, then its models can be identified using *model finding* techniques (used to suggest appropriate therapies)

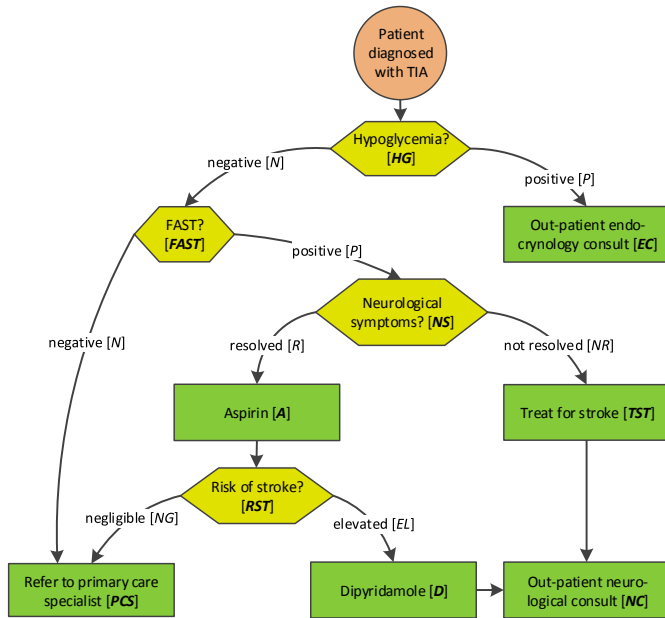
Key Components of Mitigation Framework

Assumptions from our earlier research

1. A CPG represented as an *Actionable Graph* (AG)
 2. Direct and indirect adverse interactions
 3. Secondary domain knowledge encoded using operators
1. A *vocabulary* to construct a FOL-based theory describing a particular mitigation problem and to represent secondary knowledge
 2. A *combined mitigation theory* D_{comb} composed of individual theories that describe universal characteristics of CPGs, disease-specific CPGs and patient information
 3. A set of operators encoding secondary medical knowledge that describe and address interactions between CPGs
 4. A mitigation algorithm that controls the application of operators to D_{comb}

Illustrative Clinical Scenario (DU & TIA):

AG_{TIA} and 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) ∧ value(FAST, N) ∧ executed(PCS)
∧ ¬executed(EC) ∧ ¬executed(A) ∧ ¬executed(TST) ∧ ¬executed(D)
∧ ¬executed(NC))*

*∨ (value(HG, N) ∧ value(FAST, P) ∧ value(NS, R) ∧ executed(A)
∧ value(RST, NG) ∧ executed(PCS) ∧ ¬executed(EC) ∧ ¬executed(TST)
∧ ¬executed(D) ∧ ¬executed(NC))*

*∨ (value(HG, N) ∧ value(FAST, P) ∧ value(NS, R) ∧ executed(A)
∧ value(RST, EL) ∧ executed(D) ∧ executed(NC) ∧ ¬executed(EC) ∧
¬executed(TST) ∧ ¬executed(PCS))*

*∨ (value(HG, N) ∧ value(FAST, P) ∧ value(NS, NR) ∧ executed(TST)
∧ executed(NC) ∧ ¬executed(EC) ∧ ¬executed(A) ∧ ¬executed(PCS)
∧ ¬executed(D))*

*∨ (value(HG, P) ∧ executed(EC) ∧ ¬executed(A) ∧ ¬executed(TST)
∧ ¬executed(PCS) ∧ ¬executed(D) ∧ ¬executed(NC)).*

Based on SDA* formalism [Riaño 2007]
- A computer-interpretable guideline formalism [Peleg 2013]
- Obtainable from others [Hing et al., 2010]

Illustrative Clinical Scenario (DU & TIA): Secondary Knowledge

Interaction operators

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

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

The increased risk of bleeding associated with a drug-disease interaction that occurs when a DU patient is given aspirin (A) without a proton-pump inhibitor (PPI).

Revision operators

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

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

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

Applicable to a patient diagnosed with DU when an increased risk of bleeding is present and dipyridamole (D) is **not** prescribed. The patient is taken off of aspirin and prescribed clopidogrel (CL).

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

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

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

Applicable to a patient diagnosed with DU whose risk of bleeding is partially addressed with aspirin (A) and dipyridamole (D), but without a proton-pump inhibitor (PPI). Revision indicates adding PPI to the therapy and reducing the dosage of A by 50mg.

- Knowledge describing adverse interaction and revisions not encoded in a CPG
 - Adverse interaction coming from evidence-based repositories (e.g. UpToDate, Cochrane)
 - Revisions applied **only** to the part of D_{comb} that represents CPGs

Illustrative Clinical Scenario (DU & TIA):

Patient Information

- Patient information

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

- Patient with DU, tested negative for h.pylori (HP) and positive for Zollinger-Ellison syndrome (ZES)
- Assessment of TIA symptoms gave negative result for hypoglycemia (HG), passed FAST test, has had indicated neurological symptoms (NS) resolved, and has had risk of stroke (RST) evaluated as elevated

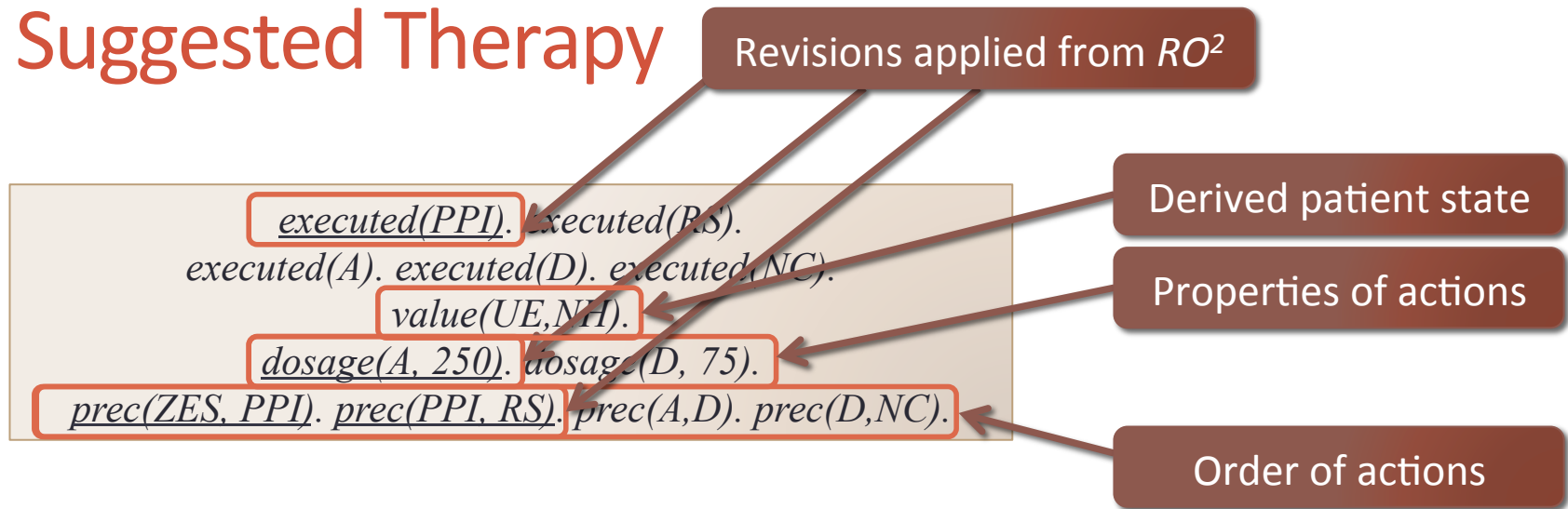
Illustrative Clinical Scenario (DU & TIA):

Mitigation

- Phase 1: Check for direct interactions (shared actions across CPGs)
 - No direct interactions between CPGs (D_{comb} is consistent as a model is found)
- Phase 2: Check for indirect interactions (applying operators)
 - Increased risk of bleeding present since the patient is prescribed aspirin (A) without a proton-pump inhibitor (PPI)
 - $D_{comb} \models \text{diagnosed}(DU) \wedge \text{executed}(A) \wedge \neg \text{executed}(PPI)$
 - Taking patient off of aspirin and prescribing clopidogrel (CL) is not appropriate as patient treatment can include dipyridamole (D)
 - $D_{comb} \not\models \text{diagnosed}(DU) \wedge \text{executed}(A) \wedge \neg \text{executed}(PPI) \wedge \neg \text{executed}(D)$.
 - Prescribing a proton-pump inhibitor and reducing the dosage of aspirin by 50 milligrams is appropriate
 - $D_{comb} \models \text{diagnosed}(DU) \wedge \text{executed}(A) \wedge \neg \text{executed}(PPI) \wedge \text{executed}(D)$
 - $Op^2 = \{ \langle \neg \text{executed}(PPI), \text{executed}(PPI) \rangle, \langle \text{dosage}(A, x), \text{dosage}(A, x - 50) \rangle \}$

Illustrative Clinical Scenario (DU & TIA):

Suggested Therapy



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

- Constructed from a model for D_{comb}
- Focuses on suggested actions and inferred patient states (does not repeat what is already known)
 - Clinical actions to be taken (*executed* and *dosage* predicates) and their order (*prec* predicate)
 - Inference of the possible patient state in light of lack of complete information (*value* predicates not in available patient information)

Discussion

- A FOL-based mitigation framework improves expressiveness and provides explicit representation of properties and relationships in CPGs
 - Dosage associated with a specific CPG action
 - Precedence between CPG actions
 - Provide finer grained control over how to revise therapy
 - Improved interpretability of returned solution
 - Presents interactions, revisions, assumptions of patient state, future actions
 - Divides mitigation process into knowledge chunks [Peleg 2013]
-
- Related work relies on description logic for manipulating guidelines
 - FOL allows to represent properties of domain objects and temporal relationships, and flexibly quantified sentences

Ongoing Research

- Development of new clinical scenarios
 - Represent a broader set of CPGs
 - Parallel paths, temporal actions, loops
 - Support new types of secondary knowledge
 - Interactions between classes of drugs (e.g., antagonists vs. anticoagulants)
- Support patient preferences
 - Consider the patient's preference to select the most preferred revisions and resulting therapy

Thank you!

Current Research Team

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