Computer Interpretable Clinical Guidelines: Generalities and the GLARE approach

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Summary

- Introduction: clinical guidelines and advantages of an ICT support

- An example: GLARE
  - representation formalism
  - acquisition & execution

- Advanced Artificial Intelligence support in GLARE
  - Verification support
  - Decision making support
  - Temporal reasoning
  - Comorbidities
Introduction

Clinical guidelines are a means for specifying the “best” clinical procedures and for standardizing them.

**USA Institute of Medicine**: “sistematically developed statements to assist practitioner and patient decisions about appropriate health care in specific clinical circumstances”.

Thousands of clinical guidelines (e.g., ~6500 in the G-I-N Network http://www.g-i-n.net)
Introduction
Advantages of Clinical Guidelines (GL)

1. **patients**, granting them that they will receive the best quality medical treatments (since GLs are a way of putting *evidence-based medicine* into practice);

2. **physicians**, providing them with a *standard* reference which they may consult, with a way of *certifying the quality* of their activity (e.g., for insurance or legal purposes), as well as with *advanced support to their decision-making* activity;

3. **hospitals** and **health-care organizations**, providing them with tools to grant the *quality* and the *standardization* of their services, a mean to evaluate quality, and to *optimize* costs and resources.
Clinical guidelines have not reached all their expected impact

Two main reasons:

(1) Difficult to interpret (formalization problems)

(2) Difficult to apply on the specific patient
Introduction

(1) Difficult to interpret (formalization problems)

text (natural language) is informal and ambiguous
Introduction

(1) Difficult to interpret (formalization problems)

even control-flow graphs may be ambiguous
Introduction

(1) Difficult to interpret (formalization problems)

even control-flow graphs may be ambiguous
Introduction

(2) Difficult to apply on the specific patient
Introduction

Adopting (computer-based) clinical guidelines allows to overcome the above problems

(1) Acquisition: user-friendly tools to acquire a FORMAL representation of the guidelines
(2) Execution: user-friendly tools to “customize” the general guideline to the data of the patient, and to support physicians’ decisions.
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Many different computer systems managing clinical guidelines
(e.g., Asgaard, GEM, Gliff, Guide, PROforma, ..., GLARE)

- Task-Network Model
- Acquisition & Execution Tools
GLARE
(Guideline Acquisition Representation and Execution)

-Joint project (since 1997) with:
Gianpaolo Molino, Mauro Torchio
Laboratorio di Informatica Clinica, Azienda Ospedaliera S. Giovanni Battista,
Molinette, Torino, Italy

Stefania Montani, Alessio Bottrighi, Luca Anselma, Gianluca Correndo, Luca
Piovesan

- Domain independent (e.g., bladder cancer, reflux esophagitis, heart
  failure, ischemic stroke, alcohol-related disorders)

- Physician-friendly (the specifications of GLARE provided by physicians)

Paolo Terenziani, Gianpaolo Molino, Mauro Torchio:
A modular approach for representing and executing clinical guidelines. Artificial Intelligence in
Medicine 23(3): 249-276 (2001)
GLARE (Guideline Acquisition, Representation and Execution)

Representation Formalism

Tree of graphs
Representation Formalism

Tree of graphs

Atomic actions
Representation Formalism

Tree of graphs

Atomic actions

Composite actions (plans)
Representation Formalism

Tree of graphs

Atomic actions

Composite actions (plans)

Control relations between actions:
- sequence
Representation Formalism

Tree of graphs

Atomic actions

Composite actions (plans)

Control relations between actions:
- sequence
- “controlled” (e.g., during)
Representation Formalism

Tree of graphs

Atomic actions

Composite actions (plans)

Control relations between actions:
- sequence
- “controlled”
- alternative
Representation Formalism

Tree of graphs

Atomic actions

Composite actions (plans)

Control relations between actions:
- sequence
- “controlled”
- alternative
- repetition (e.g. “3 times each 2 days for a month”)
Representation Formalism
Hierarchy of Action Types

- Plan
  - Clinical action
- Work action
  - Pharmacol. prescription
- Query
- Decision
  - Diagnostic decision
- Conclusion
  - Therapeutic decision
Representation Formalism
description of a clinical action

basic description

name
description (text)

preconditions

logical
must include
may include
must exclude
may exclude
cost
conflicts

contextual
time
resources

goals (text)

repetitions

frame time
action-time
delay time
1-time
execution time
frequency
exit_condition
Therapeutic decisions

Fixed set of parameters (effectiveness, cost, side-effects, compliance, duration)

Treatment choice for symptomless gallbladder stones

- Surgical treatment
- Expectant management
- Litholitic therapy
Local information associated with treatment choice
(in the symptomless gallbladder stones guideline)

<table>
<thead>
<tr>
<th>Strategy</th>
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<td>++</td>
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Diagnostic Decisions

* Decision parameters
  <finding, attribute, value>

* Decision criteria
  score-based mechanism

  For each alternative
    For each parameter
      ⇒ score
      ⇒ (additive) threshold range
Diagnostic Decisions
(Gastro Esophageal Reflux Disease)

PARAMETERS: heartburn absent (“no-hb”), heartburn lasted not more than 3 months (“hb=<3”), heartburn r lasted more than 3 months (“hb>3m”); dysphagia absent (“no-dys”); dysphagia present (“dys”); occurrence of weight loss (“wl”) or non-occurrence (“no-wl”); hemathemesis absence (“no-hem”); hemathemesis presence (“hem”); postural reflux absent (“no-ref”), postural reflux lasted not more than 3 months (“ref=<3”); postural reflux lasted more than three months (“ref>3m”). THRESHOLD: >9.
(One should conclude “no GERD” only if heartburn, dysphagia, weight loss, hematemesis and postural reflux are all absent.)
Architecture of the system
(Acquisition part)

Clinical DB
Pharmac. DB
Resource DB
ICD-9-CM DB

Expert Physician

Acquisition Interface

Knowledge Manager

Guidelines DB
Acquisition
Graphical Interface
Acquisition

“Intelligent” helps (syntactic & semantic checks)

- Interaction with the clinical DB (“vocabulary”)
- “legal” names & “legal” values for attributes
- “logical” design criteria (no unstructured cycles, well-formed alternatives & decisions)
- “semantic” checks: consistency of temporal constraints
Execution: Architecture of the system

- Clinical DB
- Pharmac. DB
- Resource DB
- ICD DB

Acquisition Interface

Knowledge Manager

Expert Physician

Guidelines DB

Instantiation DB

Patient DB

Execution Module

User Physician

Guidelines Instantiation DB
Clinical Guidelines Execution Module

“Instantiate” a general guideline on a specific patient

Semi-automatic generation of the instance of the general LG appropriate for the patient’s (given the patient clinical record)
**Agenda-based execution**

In the agenda

- next actions to be executed
- execution time (earliest and latest e.t.)

- “On-line” execution: wait until the next e.t.  
  (support physician in clinical activity)

- “Simulated” execution: jump to the next e.t.  
  (education, critique, evaluation)
GLARE: Architecture of the system

Temporal Reasoning Module

Contextualization Module

Update Module

GLARE KERNEL

Decision-Making Module

Model-Checking Module

SPIN
GLARE: Contextualization

Temporal Reasoning Module

Contextualization Module

Update Module

GLARE KERNEL

Decision-Making Module

Model-Checking Module

SPIN
Artificial Intelligence supports in GLARE:

MAIN MESSAGE:

- Representation is not enough
- Reasoning is fundamental

An example: temporal constraints & temporal reasoning

GLARE: Temporal Reasoning

Temporal Reasoning Module

Contextualization Module

Update Module

GLARE KERNEL

Decision-Making Module

Model-Checking Module

SPIN
Need for “reasoning”: Temporal Constraints

Representation:

Intended meaning:
Need for “reasoning”: Temporal Constraints

Representation:

A \rightarrow B \rightarrow C

Intended meaning:
- It is not possible to execute without violating some constraint
- Temporal inconsistency
Need for “reasoning”: Temporal Constraints

Inside the computer:

Reasoning is NECESSARY to identify the inconsistency

…. and, in general, to provide the intended meaning to a representation within a computer !!
Temporal constraints are an intrinsic part of clinical knowledge (e.g., ordering of the therapeutic actions)

Different kinds of temporal constraints, e.g.,

- duration of actions (min / max)
- qualitative constraints (e.g., before, during)
- delays (min / max)
- periodicity constraints on repeated actions
Temporal Constraints in Clinical Guidelines repetitions

The therapy for multiple myeloma is made by six cycles of 5-day treatment, each one followed by a delay of 23 days (for a total time of 24 weeks). Within each cycle of 5 days, 2 inner cycles can be distinguished: the melphalan treatment, to be provided twice a day, for each of the 5 days, and the prednisone treatment, to be provided once a day, for each of the 5 days.
WHEN Temporal Reasoning is useful in Guidelines?

ACQUISITION
- to check consistency

EXECUTION
- to compare the duration of paths, in hypothetical reasoning (simulation) facilities
- to schedule next actions
- to check that the time of execution of actions on patients is consistent with the constraints in the guideline
GLARE: Model Checking

- Temporal Reasoning Module
- Contextualization Module
- Update Module
- Decision-Making Module
- Model-Checking Module
- GLARE KERNEL
- SPIN
GLARE: Model Checking

After the acquisition of a GL, it is important to verify its properties (e.g., correctness, patient class eligibility, patient applicability)

GLARE is loosely coupled with the model-checker SPIN

General-purpose solution! Given any GLARE GL, any property that can be expressed in LTL can be checked!

EXAMPLE:
inconsistencies in a guideline

• If a recovery treatment has been excluded, later on the guideline cannot prescribe it

• Given the LTL formula:

\[ \Box (\text{conclusion }\Rightarrow\neg \lozenge \text{proc_recovery_treatment }\Rightarrow\text{started}) \]

SPIN produces a counterexample to this property.
GLARE: Decision-making

Temporal Reasoning Module

Contextualization Module

Update Module

Decision-Making Module

Model-Checking Module

SPIN

GLARE KERNEL
GLARE: Decision-making

Decision making is a core issue in the clinical practice. In particular, therapy selection is a critical issue.

Different parameters (cost, effectiveness, expected utility) must be taken into account.

In GLARE: a semi-automatic decision support system based on
-simulation capabilities
-Decision Theory


GLARE: Decision-making

“local information”: considering just the decision criteria associated with the specific decision at hand

“global information”: information stemming from relevant alternative pathways in the guideline
Local information associated with treatment choice
(in the symptomless gallbladder stones guideline)

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“Global” information: “What if” facility

Facility for gathering the chosen parameter (e.g., resources, costs, times) from the “relevant” alternative paths on the guideline.

It provides an idea of what could happen in the rest of the guideline if the physician selects a given alternative for the patient, and supports for comparisons of the alternatives.
Syntomless gallbladder stones treatment choice: “global information”

- Treatment choice
  - Surgical treatment
    - Choice of surgical appr.
      - Laparoscopy
      - Laparotomy
  - Expectant management
  - Litholitic therapy
  - Litholitic treatment
  - Laparotomy
  - Laparotomy
Syntomless gallbladder stones

treatment choice: “global information”

Duration: min:2 days  Max:3 days
Syntomless gallbladder stones
treatment choice: “global information”

- **Treatment choice**
  - Surgical treatment
  - Expectant management
  - Litholitic therapy
  - Litholitic treatment

- **Choice of surgical appr.**
  - Laparoscopy
  - Laparotomy

**Duration**
- min: 6 days
- Max: 8 days
Syntomless gallbladder stones

treatment choice: “global information”

Treatment choice

Surgical treatment

Choice of surgical appr.

Laparoscopy

Laparotomy

Expectant management

Litholitic therapy

Litholitic treatment

Duration

min: 1 day

Max: all life long
Syntomless gallbladder stones
treatment choice: “global information”

- Treatment choice
  - Surgical treatment
    - Choice of surgical appr.
      - Laparoscopy
      - Laparotomy
  - Expectant management
  - Litholitic therapy
    - Litholitic treatment

Duration: min: 2 months, Max: 1 year
Enhancing Decision Making through Decision Theory

- **State**: parameters that describe the patient’s clinical condition
  - Query action: means for observing the state
- **State transition**: changes in the patient’s state variables
  - State transition produced by the set of actions between two therapeutic decisions
- **Utility**: life expectancy corrected by QALYs
  - Information provided by the medical literature or by physician interviews
- **Cost**: not only monetary expenses
  - Resources
  - Time
GLARE: latest evolutions

Dealing with exceptions (e.g., “non-typical” patients).

Dealing with comorbid patients (i.e., patients affected by more than one disease)
Guidelines and Comorbidities

Clinical Guidelines and CIGs are developed for the treatment of **single diseases**.

Unfortunately, two or more guidelines cannot be executed “blindly” on a **comorbid** patient.

Dangerous **interactions**. E.g., warfarin (anticoagulant for venous thrombosis) and amoxicillin (prescribed in case of pulmonary tract infections) may increase the risk of dangerous bleedings.

Though some CIGs covering frequently occurring comorbidities might be devised, the approach of considering all the possible combinations of pathologies does not scale up.

Thus, there is a need for **formal methodologies** to support physicians in the detection and resolution of interactions between guidelines, and, ultimately, in the process of merging two or more guidelines.
GLARE approach: Desiderata

Real problem

- **Dimensional Complexity**: CIGs can contain dozens/hundreds of actions. In principle, each combination of actions has to be considered.
- **Temporal complexity**: time has to be considered, causing a combinatorial growth of the space of cases.
- Defining a priori a set of all the possible interactions and their managements is practically infeasible, and not useful for physicians.

Usefulness of the application

- The application should help physicians, not substitute them.
- **Black-box** tools are not useful.
- User friendly interaction is needed in both interaction detection and management.

Usefulness of the result

- Clinical guidelines (and consequently CIGs) are evidence-based decision support documents.
- Changes should be limited and approved by physicians.
GLARE methodology: three subtasks

Knowledge-Based Detection of relevant interactions

Management of interactions

CIG Conciliation
Extended Architecture

- Protégé
- Nontemporal Detection
- OWL Reasoner
- Ontological Model / Knowledge Base
- GLARE CIG system
- Patients DB
- GLARE GUI
- CIG Conciliation
- Constraint Propagation
- TO CSP
- Facilities Manager
- Temporal Reasoner
- GUI
- User Physician + Knowledge Engineer
- Snomed / ATC
- Knowledge Manager
GLARE: current status

A Java prototype implements the kernel of the system

- The prototype interacts with the (current) patient records (stored in Cache) during execution

- All software developed by students: no “fully engineered” and “supported” software available yet

Different extensions of the prototype to demonstrate the feasibility of contextualization, decision making, model-checking, and temporal reasoning facilities

The development of a new version of the software (META-GLARE) is ongoing

Alessio Bottrighi, Paolo Terenziani:
Concluding remarks

GL can provide crucial advantages for
- Organizations
  (service optimization, standardization, quality → reduce errors)
- Physicians (decision support, quality → reduce errors)
- Patients (quality & standardization of the treatment, error reduction)

Computer-based approaches can help

A strict and long-term cooperation of Physicians and Computer Scientists has lead to the development of GLARE

GLARE is domain-independent & supports GL acquisition and execution

GLARE is unique in that it provides physicians with ADVANCED support facilities, obtained by adopting\extending advanced Artificial Intelligence methodologies
Some Publications about GLARE (since 2010)


• Luca Piovesan, Paolo Terenziani: A Constraint-Based Approach for the Conciliation of Clinical Guidelines. Proc. of the 15th *Ibero-American Conference on AI* (IBERAMIA’16), San José, Costa Rica, November 2016, 77-88, *Best Paper Award*


