Synthesis of Elementary Single-Disease Recommendations to Support Guideline-Based Therapeutic Decision for Complex Polypathological Patients

Gersende Georg, Brigitte Séroussi, Jacques Bouaud

STIM, DPA / DSI / AP-HP, Paris, France &
INSERM ERM 202, UFR Broussais – Hôtel-Dieu, Université Paris 6, France

Abstract

Situations managed by clinical practice guidelines (CPGs) usually correspond to general descriptions of theoretical patients that suffer from only one disease. The lack of decision support for complex multiple-disease patients is thus transferred to computer-based systems. Starting from the GEM-encoded instance of CPGs, we developed a module that automatically generated IF-THEN-WITH decision rules. We propose a two-stage unification process. All the rules which IF-part is in partial matching with a patient clinical profile are triggered. A synthesis of triggered rules is then performed to eliminate redundancies and incoherences. All remaining, eventually contradictory, recommendations are displayed to physicians leaving them the responsibility of handling the controversy and thus the opportunity to control the therapeutic decision.

Keywords: *clinical practice guidelines, decision support systems, GEM-encoding, decision rules.*

Introduction

Clinical practice guidelines (CPGs) are originally textual documents. Usually structured as a set of clinical situations, they provide, for each case, evidence-based therapeutic recommendations. However, these clinical situations usually correspond to general descriptions of theoretical patients that suffer from only one disease in addition to the specific pathology CPGs focus on. For instance, in the case of the Canadian guidelines on the management of hypertension (HT) [1], recommended therapies are provided for patients with HT and diabetes, with HT and ischemic heart disease, with HT and systolic dysfunction, etc. However there is no explicit therapeutic decision support for patients suffering from HT *and* diabetes *and* ischemic heart disease *and* systolic dysfunction.
This is not a difficulty for the clinician who looks for the best treatment for this kind of complex polypathological patient while *reading* textual guidelines: he can indeed interpret the guidelines and either rank eventually contradictory evidence-based recommendations resulting from the different diseases associated to HT to choose the best suitable therapy, or combine these different recommendations and propose the corresponding association of drugs. But, the simple dissemination of textual guidelines has no impact on physician compliance with clinical recommendations: reading documents takes time and is not appropriate to the physician-patient interaction that occurs during clinical encounters.
Guideline knowledge is thus currently embedded within knowledge bases of decision support systems (DSSs) which, when integrated into the clinical workflow, automatically provide, at the point-of-care, at the very moment of the medical decision, the best recommended patient-specific therapy. However, incompleteness and ambiguities of original guideline documents are transferred to DSSs' knowledge bases during the formalization step [2]. As a direct consequence, such DSSs do not provide any support for the therapeutic decision of complex clinical cases, where patients suffer from numerous diseases.
Starting with the textual document of the Canadian recommendations for the management of hypertension [1], we used the Guideline Elements Model (GEM) [3], proposed as a document-based model, to structure and organize the guideline content. In a previous work [4], we presented an interpretative framework to disambiguate the narrative guideline and build the corresponding GEM-encoded instance. In this paper, we propose a solution to deal with the incompleteness of the set of clinical situations managed by the guideline. We first developed a module of derivation that automatically built a rule base from the GEM-encoded instance. Then, we developed an inference engine implementing a forward chaining mechanism to exploit the derived decision rules. For any complex patient suffering from numerous disorders, a treatment is recommended. Though not always evidence-based, this treatment is elaborated from the synthesis of multiple disease-specific but evidence-based recommendations triggered from the partial matching of patient data and rule preconditions.

Background

Establishing the best therapeutic decision for any given patient can be formalized as a classification problem. Although numerous paradigms have been proposed to support classification processes, there is no satisfactory solution in the medical domain. If classes are clearly identified and correspond to theoretical clinical situations, descriptors used in the classification process are the parameters classically stored in medical records that describe patient clinical profiles. However such data is often incomplete and imprecise.

The management of imprecision and uncertainty has often been modeled using fuzzy logic [5]. In a fuzzy set, an element has a partial membership, rather than an all-or-none membership as in a conventional set. The degree of membership is described by a membership function. With fuzzy inferencing [6], fuzzy sets can be combined to create multiple conclusions, each of them with varying degrees of truth. Such an approach has been implemented by Liu *et al.* [7] for the computerization of CPGs related to lumbar puncture. For instance, it allowed to "weight" the different qualitative values that characterize the strength of recommendations like "not routinely warranted", "considered", "strongly considered", or "recommended".

We propose in this paper an alternative approach to support the decision of the best therapy for any given patient suffering from hypertension. Although this problem is similar to the one addressed by PROforma, a major difference is that emphasis is on dynamic interaction between potentially conflicting rules coming from different unrelated protocols, rather than consistency of a single integrated representation [8]. In the case of complex polypathological patients, each elementary disease associated to hypertension triggers the corresponding therapeutic recommendations. Then, a synthesis of therapeutic recommendations, that may be redundant or even contradictory, is performed on the basis of a patient clinical profile. If more than one recommendation remains, the physician is free to adopt the best therapy in the ordered set of recommendations, or to combine recommendations and prescribe the corresponding association of drugs. Following a documentary approach of medical decision making, similar to the one developed with OncoDoc [9], the aim is to propose patient-specific recommendations to the physician while leaving her the responsibility of a contextual interpretation of guideline knowledge to determine the best suitable therapy.

Materials

The GEM DTD

GEM is a document model based on an XML DTD [3] that organizes the heterogeneous knowledge contained in CPGs. It is a multi-level hierarchy of more than 100 discrete elements structured in nine major branches. The *knowledge components* section represents the recommendation's logic and constitutes "the essence of practice guidelines". We only used conditional recommendations that apply under specific circumstances. They are composed of different sub-elements among which only few are actually used: *(i) decision.variable* stores tests and observations that determine the appropriateness of related action elements*, (ii) action* represents the actions to be carried out given the specific circumstances defined by the *values* of decision variables*, (iii) recommendation.strength* stores the information specified by guideline authors to represent the grade of evidence of recommendations.

The 1999 Canadian recommendations for the management of hypertension

Like the ASTI project [10], we worked on the 1999 Canadian recommendations for the management of hypertension [1]. As compared to other guidelines (ANAES, WHO, etc.), this guideline document is well structured in chapters that correspond to specific clinical situations. Within each chapter, an ordered sequence of therapeutic recommendations is proposed. The case of ischemic heart disease as a complicating factor of hypertension is presented in figure 1.

VIII Ischemic heart disease

1. For patients with stable angina and hypertension, ß-adrenergic antagonists are preferred as initial therapy (grade D).
2. Alternative therapies would include long-acting calcium-channel blockers (grade B). Short-acting calcium-channel blockers should not be used (grade C).
3. Patients with hypertension and a recent myocardial infarction should be treated with either ß-adrenergic antagonists, ACE inhibitors or both. Both classes of drug protect against reinfarction and death (grade A).
4. Alternative therapies would include verapamil (grade A) and diltiazem (grade C), but only in the setting of normal left ventricular function.

Figure 1- Therapeutic recommendations for hypertensive patients with ischemic heart disease.

Method

One of the aims of our work was to automatically derive IF-THEN rules from the GEM-encoded instance of the Canadian recommendations for the management of hypertension. So, we first slightly extended the original GEM DTD to standardize the process of IF- and THEN- parts generation. Then, under the syntactic constraints of the new GEM DTD, *(i)* we created a normalized instance of the Canadian CPGs, *(ii)* we developed a module able to automatically derive a rule base from the instance, *(iii)* we elaborated a classic forward chaining inference engine to exploit the rule base and *(iv)* we proposed an algebra to resolve conflicts and to synthesize eventually contradictory therapeutic recommendations proposed by the system for any given patient.

Creation of the GEM-encoded instance

Extension of the GEM DTD

To standardize the process allowing the automatic extraction of executable rules from the GEM-encoded instance, we extended the GEM DTD by adding the *value* sub-element to the *action* element, so that, *decision.variable* and *action* have the same XML structure (figure 2).

```
< !ELEMENT decision.variable (#PCDATA | value | decision.variable.description | test.parameter | decision.variable.cost | %block;)*>
< !ELEMENT action (#PCDATA | value | action.benefit | action.risk.harm | action.description | action.cost | %block;)*>
```

Figure 2- Extended GEM DTD with the value sub-element for the action element.

Modeling clinical situations and strengths of evidence

A clinical situation is described in CPGs as a set of clinical criteria, denoted $C=\{C_i\}$, and a set of therapeutic history elements, denoted $T=\{T_j\}$.

We have organized clinical criteria in three classes of parameters *i.e.* age, risk factors, and associated diseases. Therapeutic history elements consist in the characterization of the ongoing treatment as well as the patient's response to this

treatment. To resolve guideline semantic ambiguities in the representation of the chronological steps of therapy, we have proposed a framework that "temporalizes" the therapeutic strategy. We represented the therapeutic strategy as an ordered sequence of therapeutic lines, each therapeutic line being made of a set of treatments ordered according to therapeutic levels of intention. When instanciating the CPGs, these informations have been marked-up as attribute *ids* of corresponding *value* of *decision.variable* elements.

For a given clinical situation [C ∩ T], described in the guidelines, a set of recommended therapies {$Reco_k$} is provided. For each one, the proposed treatment is either among the following levels of intention within the same therapeutic line or the first level of intention of the following therapeutic line. These proposed treatments have been marked-up as attribute *ids* of corresponding *value* of *actions* elements.

The grade of each recommendation $Reco_k$ is labeled as the *recommendation.strength* according to the guideline information (A, B, C, D).

Automatic rule base derivation

Preliminary steps

Decision rules have been formalized, as IF-THEN-WITH statements. For a given GEM-encoded recommendation, the IF-part corresponds to the set of *decision.variable* elements, the THEN-part corresponds to the set of *action* elements, and the WITH-part corresponds to the *id* of the *recommendation.strength* element.

When studying the Canadian CPGs, it appears that recommendations have been implicitly ordered by priority. As a consequence, we defined an additional attribute, the "*character*", to make the difference between:

(i) "dominant" recommendations, denoted D_Reco, established for hypertensive patients suffering from a specific disease (diabetes, etc.), and that have priority upon other therapeutic options;

(ii) "neutral" recommendations, denoted N_Reco, that follow the recommendations established for uncomplicated hypertension (peripheral vascular disease, etc.);

(iii) "recessive" recommendations, denoted R_Reco, that follow the recommendations established for concurrent diseases or risk factors (cerebrovascular disease, etc.).

We defined a second additional attribute, the "*sign*", to distinguish positive recommendations (sign = "+"), which advocate to recommend a given therapeutic class, from negative recommendations (sign = "-"), which advocate, on the contrary, to avoid a therapeutic class. Rules are thus formalized as follows:

$\mathbf{R_i}$: **IF** $[C \cap T]_{Ri}$ **THEN** $Reco_i$
WITH [strength ∩ *character* ∩ *sign*]$_i$

Parsing the GEM-encoded instance

The construction of the rule base relies on the identification of *decision.variable, action*, and *recommendation.strength* elements from the GEM-encoded instance. The aim is to locate and extract the contents of these different elements to generate rules. We used SAX (Simple API for XML) [11] to parse the instance. As opposed to DOM (Document Object Model) [12] based on a tree structure that builds a in-memory tree representation of the XML document, SAX is based on an event approach and uses calls in order to report parsing events to the current application. In addition, SAX was more appropriate because only few elements had to be extracted from the GEM-encoded instance. The 3rd item of recommendations for ischemic heart disease (Figure 1) of the Canadian CPGs is represented by the following rule:

IF

Clinical criteria {C_i}:
- state_patient.pathology = HT
- ∩ state_patient.pathology = ISC HEA DIS
- ∩ state_patient.pathology = REC_MYO_INF

Therapautic history elements {T_j}:
- ∩ treatment.line = L1 *// first line therapy*
- ∩ treatment.intention = INT1 *// first level of intention*
- ∩ treatment.type = MONO *// monotherapy*
- ∩ treatment.nature = ACE_IN *// ACE inhibitor*
- ∩ treatment.reaction = INT *// intolerance*

THEN

Recommended action:
- treatment.line = L1
- ∩ treatment.intention = INT2 *// second level // of intention*
- ∩ treatment.type = MONO *// monotherapy*
- ∩ treatment.nature = BB *// ß-adrenergic // antagonists*

WITH

- recommendation.strength = A
- ∩ *character* = D_Reco
- ∩ *sign* = +

Inference engine

We have developed a simple inference engine implementing a forward chaining mechanism to handle the previously built rule base. In fact, there is no actual inference-based reasoning but a two-stage unification process. For any given patient, the engine searches the knowledge base and selects any rule R_i which IF-part, denoted $[C \cap T]_{Ri}$, matches the patient's description $[C \cap T]_{patient}$.

Because real patients are usually more complicated than the theoretical clinical situations taken into account in guidelines, clinical descriptors found in IF-parts of decision rules C_{Ri} are usually less specific than the clinical set of patient parameters $C_{patient}$: $C_{Ri} \cap C_{patient} \neq \varnothing \Rightarrow C_{Ri} \cap C_{patient}$.

On the contrary, as information concerning therapeutic history is usually missing in patient medical records [13], the set of patient parameters concerning therapy-based information $T_{patient}$ is included in IF-parts of decision rules T_{Ri}: ∩ R_i / $C_{Ri} \cap C_{patient} \Rightarrow T_{patient} \cap T_{Ri}$.

As a consequence, the two-stage unification process operates as follows:

a) A strict unification stage is first processed. When there is at least one rule R_i whose IF-part strictly matches patient parameters, *i.e.* ∩ R_i / $[C \cap T]_{patient} = [C \cap T]_{Ri}$, then R_i is triggered leading to the recommendation of drug therapies. When no rule is triggered, the set of recommended drug therapies is empty.

b) A relaxed unification stage is then processed that triggers rules R_i which IF-part includes diseases present in the set $C_{patient}$ of patient clinical parameters and considered by the guidelines as relevant to recommend specific therapies (diabetes, ischemic heart disease, etc.), *i.e.* ∩ R_i / $C_{patient} \cap C_{Ri} \cap \{\text{associated diseases}\} \neq \varnothing$.

Synthesis of recommendations

Preliminary filter

A module has been developed to summarize the set of therapeutic recommendations provided when numerous rules have been activated. Two modalities have been considered on the basis of both character and sign of competing recommendations.

(i) Fusion of recommendations to eliminate redundancies: when two or more rules R_1 and R_2 leading to the same recommendations having identical character and sign are triggered, the two recommendations are merged. For instance, in the case of a patient suffering from HT, diabetes, and systolic dysfunction, the following two rules are triggered: R_1: "IF HT and diabetes THEN ACE-inhibitor WITH A □ D_Reco □ +", and R_2: "IF HT and systolic dysfunction THEN ACE-inhibitor WITH A □ D_Reco □ +". Both recommendations are then merged in a unique recommendation of ACE inhibitor, with *character* = D_Reco.

(ii) Deletion of recommendations to eliminate incoherences: when two or more rules R_1 and R_2 leading to the same recommendations having identical character, but opposite signs, are triggered, the two contradictory recommendations are eliminated. For instance, in the case of a patient suffering from HT and stable angina and reversible airway disease, the following two rules are triggered: R_1: "IF HT and stable angina THEN beta-adrenergic antagonists WITH D □ D_Reco □ +", and R_2: "IF HT and reversible airway disease THEN beta-adrenergic antagonists WITH A □ D_Reco □ -". Both recommendations are then cancelled and beta-adrenergic antagonists are eliminated from the final therapeutic recommendation.

Final display

Once the fusion and deletion steps are performed, there may still be more than one recommendation to be considered. The last filter to be applied is based on the character of the different recommended therapies. A simple intuitive algebra has been defined: recessive recommendations are absorbed by neutral recommendations, and neutral recommendations are absorbed by dominant recommendations.

- N_Reco + R_Reco = N_Reco
- D_Reco + R_Reco = D_Reco
- D_Reco + N_Reco = D_Reco

As a conclusion, (i) if there is at least one dominant recommendation in the set of selected recommendations, neutral and recessive recommendations are eliminated and *all the remaining dominant recommendations are finally displayed* allowing the user to choose how to handle the controversy; (ii) if there is no dominant recommendation, the neutral recommendation is applied.

Example

We consider the case of a patient older than 60 years, suffering of hypertension with a history of chronic nephropathy (NEPH), systolic dysfunction (SYS_DYS), ischemic heart disease (ISC_HEA_DIS), and a recent myocardial infarction. The aim is to propose the best initial therapy, *e.g.* the first level of intention of the first therapeutic line. Six elementary rules presented in table 1 are triggered by the different diseases associated to hypertension.

The chronic nephropathy is included in the patient clinical description and leads to recommend ACE inhibitors (ACE_IN) with grade A, the systolic dysfunction also leads to recommend ACE inhibitors with grade A. The ischemic heart disease leads to 4 recommendations (cf. Figure 1), ACE inhibitors, ß-adrenergic antagonists (BB), verapamil (VER) with grade A, and diltiazem (DIL) with grade C.

Table 1 – First level of intention of the first line of therapy for each associated pathology.

	NEPH	SYS_DYS	ISC_HEA_DIS			
Recommendations	ACE_IN	ACE_IN	ACE_ IN	BB	VER	DIL
Grade	A	A	A	A	A	C

The three recommendations leading to the same therapeutic class with the same grade of evidence are merged in a unique recommendation of ACE inhibitors with grade A. As the remaining recommendations have identical sign, *e.g.* positive, there is no deletion. Among the 4 final recommendations, characters are identical (D_Reco). They are then displayed as such with their associated grade (table 2).

Table 2 – Final recommendations with their associated grade.

Recommendations	ACE_IN	BB	VER	DIL
Grade	A	A	A	C

After 6 months of ACE inhibitors therapy, the ischemic heart disease is stable for this patient, but nephropathy and systolic dysfunction increased. The ongoing therapy is thus inadequate and has to be modified. When the system is processed, 4 different therapies are provided for the 2nd level of intention of the 1st therapeutic line (table 3), *i.e.* ACE inhibitors and loop diuretics (LD), hydralazine and isosorbide dinitrate, ACE inhibitors and thiazide diuretics (TD), ACE inhibitors and ß-adrenergic antagonists.

Table 3 – New recommendations when the 1st level of intention of the 1st therapeutic line is inadequate.

	NEPH	SYS_DYS		ISC_HEA_DIS
Recommendations	ACE_IN + LD	Hydralazine + isosorbide dinitrate	ACE_IN + TD	ACE_IN + BB
Grade	D	A	A	A

In this case, recommendations proposed by triggered rules are all different, thus fusion cannot be performed. All recommendations are positive, thus deletion cannot be activated. Recommendations correspond to specific pathologies with identical character, *e.g.* dominant. The synthesis of triggered recommendations cannot go further, and the 4 recommendations are finally displayed to the physician, leaving her the responsibility of choosing the best treatment (probably ACE_IN + LD as the renal function is highly degraded).

Discussion

Our work addresses the problem of proposing guideline therapeutic recommendations given a patient condition characterized by clinical parameters and a therapeutic history. CPGs are organized as a set of simple theoretical clinical situations for

which evidence-based therapies are recommended. Usually, the principle adopted in guideline structuration is to "cut" the patient according to the diseases that may be associated to the specific pathology described by the CPGs. As a consequence, theoretical clinical situations concern only one-disease patients.

Finding the best therapy for multiple-disease patients could be formalized as the classification of an element having a partial membership in different sets. However we think that fuzzy logic is not a good way to model the problem because memberships functions and classes used to describe fuzzy sets are arbitrary.

On the contrary, we proposed a partial matching to select candidate recommendations. A synthesis of triggered recommendations is then performed to eliminate redundancies and incoherences. The aim is to identify the recommendations that apply to the relevant pieces of the patient clinical description, *i.e.* the additional disease, and to provide these recommendations to physicians, leaving them the responsibility of a contextual interpretation and allowing them some flexibility in the evaluation of recommendations. As there is no known algebra on grade of evidence, it is the choice of physicians to choose between ordering recommendations and adopting the therapy recommended by the "best one", or combining recommendations and adopting the corresponding association of drugs.

In this way, we keep the advantages of textual understanding with the display of a global picture of what CPGs recommend for the different diseases of a given patient, without the drawback of textual reading, *i.e.* time loss.

In order to issue recommendations for patients suffering for multiple diseases, we aggregate decision rules produced from the various CGPs corresponding to each of these diseases. This is equivalent to "cut" the patient into virtual individual patients each afflicted by a single disease. Further work will be dedicated of extending our approach to the case of multiple-diseases patient using multiple therapeutic guidelines, like it has been done with prevention guidelines in the EsPeR Project [14].

Conclusion

From the GEM-encoded instance of CPGs, we automatically generated a rule base that has been exploited by an inference engine. As the CPGs have been developed according to a single-disease approach, the problems of conflicting and incomplete knowledge are not related to the GEM encoding but are inherent to the guidelines themselves. To deal with the incompleteness of the set of clinical situations originally in the CPGs and transferred to the rule base, we propose a mechanism that triggers all the rules which IF-part matches the different pathologies a patient may suffer from. A synthesis is then performed to eliminate redundancies and incoherences. We have left the user the responsibility of handling eventually contradictory recommendations leaving her the freedom of weighting patient parameters or levels of evidence.

References

[1] Feldman RD, Campbell N, Larochelle P, Bolli P, Burgess ED, Carruthers SG, *et al*. 1999 Canadian recommendations for the management of hypertension. CMAJ 1999;161(12):S1-22. URL: http : // www.cmaj.ca / cgi / content / full / 161 / 12_suppl / S1

[2] Patel VL, Allen VG, Arocha JF, Shortliffe EH. Representing clinical guidelines in GLIF: individual and collaborative expertise. *J Am Med Inform Assoc* 1998;5(5):467-83.

[3] Shiffman RN, Karras BT, Agrawal A, Chen R, Marenco L, Nath S. GEM: a proposal for a more comprehensive guideline document model using XML. *J Am Med Inform Assoc* 2000;7(5):488-98.

[4] Georg G, Séroussi B, Bouaud J. Interpretative framework of chronic disease management to guide textual guideline GEM-encoding. In: Baud R, Fieschi M, Le Beux P, Ruch P (eds). *Proceedings of MIE 2003*. IOS Press 2003: pp. 531-6.

[5] Zadeh LA. Fuzzy sets. *Information and Control* 1965;8(3):338-353.

[6] Zadeh LA. Outline of a new approach to the analysis of complex systems and decision processes. *IEEE Transactions on Systems, Man, and Cybernetics* 1973;3(1):28-44.

[7] Liu JCS, Shiffman RN. Operationalization of clinical practice guidelines using fuzzy logic. *J Am Med Inform Assoc* 1997;4(4):283-87.

[8] Fox J. and McBurney P. Decision making by intelligent agents: logical argument, probabilistic inference and the maintenance of beliefs and acts. In: NMR'2002, Toulouse, France, April 2002.

[9] Séroussi B, Bouaud J, Antoine EC. OncoDoc: a successful experiment of computer-supported guideline development and implementation in the treatment of breast cancer. *Artif Intell Med* 2001;22(1):43-64.

[10] Séroussi B, Bouaud J, Dréau H, Falcoff H, Riou C, Joubert M, Simon C, Simon G, Venot A. ASTI: A guideline-based drug-ordering system for primary care. In: Patel VL, Rogers R, Haux R (eds). *Medinfo* 2001;84(1):528-32.

[11] URL: http://www.saxproject.org

[12] URL: http://www.w3.org

[13] O'Connor MJ, Tu SW, Musen MA. Representation of temporal indeterminacy in clinical databases. *J Am Med Inform Assoc* 2000;7(5):615-9.

[14] Colombet I, Dart T, Leneveut L, Zunino S, Menard J, Chatellier G. A computer decision aid for medical prevention: a pilot qualitative study of the personalized estimate of risks (EsPeR) system. *BMC Med Inform Decis Mak* 2003 Nov 27;3(1):13.

Address for correspondence

Gersende Georg
STIM
91 Boulevard de l'Hôpital
75634 Paris Cedex 13, France.
gge@biomath.jussieu.fr