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A Methodology for Modular Representation of Guidelines

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Abstract

Computer-based clinical practice guidelines often need to be modified when medical knowledge evolves or when guidelines are implemented in a local setting with specific constraints and preferences. To enable easy modifications to guidelines and maintain their integrity, we have developed a methodology for modular representation of guidelines. Using this approach, we create guidelines in a hierarchical and modular manner. We use the Axiomatic Design methodology to facilitate the development of independent modules. Design matrices capture the interactions among modules. The design matrices can be used during guideline modification to create a change process and to enable identification of other modules that are affected by a change to a module. We implemented this modular knowledge representation approach by incorporating it into the Guideline Interchange Format (GLIF) language. We applied this approach to encode parts of three outdated guidelines released during 2000-2001, and we revised these designs to model updated releases of the guideline. Qualitative and quantitative metrics were developed to assess the types of changes made to the encoded guidelines.

Keywords:

clinical practice guidelines, knowledge representation, local adaptation

Introduction

Computer-interpretable guidelines have been shown to be an effective way to increase the acceptance [1] of clinical practice guidelines. Since great effort must be expended to develop high-quality guidelines and to make them computer-interpretable, it is highly desirable to be able to share computer-interpretable guidelines among institutions. Several new representation formalisms have been developed to facilitate the sharing of guideline knowledge [2] in a form executable by decision support. Modification of text-based setting-independent guidelines for adaptation to local clinical contexts or to include new medical knowledge is not well-supported by these knowledge representation approaches [3]. One study found that guidelines become outdated every 6 years [4]. Hence, the ability to easily revise setting-independent computer-interpretable guidelines while maintaining their integrity is important.

Guideline modifications place the following requirements on the representation schema and authoring tools of computer-interpretable guidelines: 1) a change to one part of the guideline should have minimal impact on other parts; 2) when a change to one part does have wider impact, the tools should direct the user to review those parts of the guideline affected; and 3) the tools must assist with the integration of *revised* setting-independent guidelines into locally adapted guidelines.

To enable easy modification of guidelines while maintaining guideline integrity, we developed a method for modular representation of guidelines. We use the **Axiomatic Design** methodology to facilitate the development of modules in a hierarchical tree structure. We applied this approach to encode parts of three outdated national guidelines released during 2000-2001, and we revised these designs to model the most recently updated 2002-2003 release of the guidelines. Qualitative and quantitative measures were developed to assess the types of changes made to the structure of the encoded guidelines.

Background

Axiomatic Design

Axiomatic Design (AD) theory was developed in the field of mechanical engineering as a principled approach to product design [5]. AD methodology allows designers to be more creative and minimizes the iterative trial-and-error process traditionally used in design. The use of two axioms results in product designs that are flexible and easily modified. The Independence Axiom states that the independence of intentions or ***functional requirements*** should be maintained throughout the design. The Information Axiom states that the best design contains the least information. This latter axiom is important in comparing designs and is beyond the scope of this paper.

AD involves the interaction between "what we want to achieve" and "how we achieve it" or "how to satisfy the needs." In AD, four domains create demarcation lines between various design activities: customer, functional, physical, and process. The functional and physical domains are the most relevant to guideline modeling and will be our focus.

Axiomatic Design applied to guideline modeling

AD guideline modeling constructs two design trees: a functional requirement (FR) tree and a design parameter (DP) tree. The designer may begin by specifying an overall guideline intention or FR1 and placing it at the highest level of the FR tree. (Actually guideline modeling may begin with one or many FRs at the topmost level). At the top of the DP tree is placed an action or DP1

that is used to carry out FR1. The second level of FRs is built by the decomposition of FR1 based on the constraint of DP1. In our example, DP1 decomposes FR1 into the sibling group: FR11, FR12, and FR13. Ideally, a sibling group should be composed of mutually exclusive and exhaustive components of its parent. Second-level DPs -- DP11, DP12, and DP13 -- are specified to carry out the intention of each of the second-level FRs. Continuing with our example, DP11 decomposes FR11 into the mutually independent FRs, FR111 and FR112. Each of the other second-level DPs will decompose its own FR and in this way contribute to the building of the third level of the FR tree, and so forth.

To summarize, guideline modeling creates an FR and a DP tree. Designing begins by specifying one FR or a sibling group of more than one FR at level one of the FR tree. A DP is chosen for each FR. DPs are used to decompose their own FRs. FR decomposition should optimally result in independent FRs in a sibling group or a single child at the next lower-level. Leaf FRs are not further decomposed because their corresponding DPs are concrete and detailed enough to be deployed. This building method is called "zigzagging".

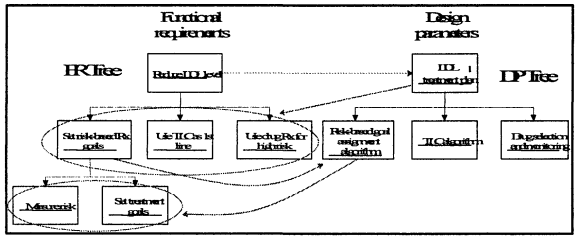

Figure 1 - Zigzagging" process of building Axiomatic Design trees

The Design Matrix

The relationship or interaction among FRs and DPs within a sibling group is specified by the design equation: {FRs}=[A] {DPs}. [A] is the design matrix. Thus, for three FRs:

$$\begin{Bmatrix} FR1 \\ FR2 \\ FR3 \end{Bmatrix} = \begin{bmatrix} A11 & A12 & A13 \\ A21 & A22 & A23 \\ A31 & A32 & A33 \end{bmatrix} \begin{Bmatrix} DP1 \\ DP2 \\ DP3 \end{Bmatrix}$$

Linear algebra equations for three FRs can be written:

FR1 = A11 DP1 + A12 DP2 + A13 DP3
FR2 = A21 DP1 + A22 DP2 + A23 DP3
FR3 = A31 DP1 + A32 DP2 + A33 DP3

We see that a functional requirement can be expressed as a linear combination of each of the design parameters in its sibling group. This linear combination is called a module. Submodules specifically refer to modules that are not at the highest level of the guideline. In designing guidelines, the numerals 1 and 0 are the most appropriate entries for DPs within the design matrix because it is important only to know that a DP either interacts with an FR or not. Three types of design matrices are important in guideline modeling:

1. A *diagonal* matrix represents an ***uncoupled design***, in which each FR is *independently* satisfied by only its own DP.:

$$\begin{bmatrix} FR1 \\ FR2 \\ FR3 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} DP1 \\ DP2 \\ DP3 \end{bmatrix}$$

   This is the optimal design because altering one functional requirement only requires the altering of its own design parameter. Thus, the FRs fully satisfy the independence axiom.
2. A ***triangular*** matrix represents a ***decoupled design***. The matrix here is an off-diagonal lower triangular matrix; the elements of the lower triangle are A21=A31=A32=1; an upper triangular matrix would have the same effect. Since decoupled designs with upper triangular matrices can be converted to decoupled designs with lower triangular matrices, we used the lower triangular matrix as our standard. In this sibling group, FR3 is dependent on DP3, DP2 and DP1; FR2 is dependent on DP2 and DP1, and FR1 is dependent only on DP1. This sibling group of three FRs has three out of a possible three ***off-diagonal lower triangle dependencies or dependencies.***:

$$\begin{bmatrix} FR1 \\ FR2 \\ FR3 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 0 \\ 1 & 1 & 0 \\ 1 & 1 & 1 \end{bmatrix} \cdot \begin{bmatrix} DP1 \\ DP2 \\ DP3 \end{bmatrix}$$

   In this case, we can satisfy the functional requirements by specifying the DPs in a ***particular order***. For example, let's define high-level FRs for hormone replacement therapy guidelines for a perimenopausal woman complaining of hot flushes and decreased libido:

FR1: Obtain clinical assessment
FR2: Hormone replacement therapy?

We would first specify **DP1: History, physical, etc** to satisfy FR1 since it alone determines FR1. The FR1 module is then completely decomposed by DP1 to leaf submodules before DP2 can be specified. Then, based on the information derived from the clinical assessment module, we can specify DP2, which might be **DP2: Collaborative decision making and management with patient** to satisfy FR2. The 2x2 design matrix for this example would have one out of a possible one dependency because FR2 is dependent on DP2 *and* DP1.

When an uncoupled design is impossible, it becomes incumbent upon the designer to construct a decoupled design. This process involves creating a design matrix and then ordering the FRs in such a way that the matrix becomes triangular.

3. 3. Any other kind of matrix represents a coupled design.:

$$\begin{bmatrix} FR1 \\ FR2 \\ FR3 \end{bmatrix} = \begin{bmatrix} 1 & 0 & 1 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{bmatrix} \cdot \begin{bmatrix} DP1 \\ DP2 \\ DP3 \end{bmatrix}$$

In the above **coupled** design, where A21=A31=A32=A13=1, the procedures used in the decoupled design for specifying DPs and FRs are not possible. There is no one algorithm that can be used to satisfy any DP without reversing and changing the other DPs. We did not use coupled guideline designs.

HieroGLIF

The Guideline Interchange Format (GLIF) is a language for structured algorithmic representation of guidelines [6]. HieroGLIF is an extension of GLIF that supports the representation of hierarchical modular guidelines [7]. HieroGLIF extends the GLIF ontology by explicitly supporting representation of FRs.

A software tool known as SIGTool was developed to support authoring of guidelines in HieroGLIF. The software tool was implemented in Java by extending libraries developed for the GLIF project [8]. During guideline creation the tool facilitates the creation of the hierarchical structure and allows the user to specify the design matrix. In the guideline modification mode, when a guideline module is changed, the tool uses the design matrix to identify other steps affected by the change.

Study Objectives

Our study objective was to demonstrate that modular knowledge representation of clinical practice guidelines using Axiomatic Design facilitates easy guideline revision. These endpoints were used to test our hypothesis:

1. Most FRs will maintain the independence axiom.
2. Most non-independent FRs will occur at higher-levels of the design tree.
3. Revisions to encoded guidelines are more likely to occur at the lower more detailed levels of the design tree.

Material and Methods

Choice of guidelines

With SIGTool, three text-based guidelines were encoded and revised in HieroGLIF:

1. Lipid Screening in Adults, developed by the Institute for Clinical Systems Improvement (ICSI), Bloomington, MN, released Jan. 2000. Revised and re-released Dec. 2002,
2. Hormone Replacement Therapy: Collaborative Decision Making and Management, developed by ICSI released in Jul. 2001. Revised and re-released Oct. 2002, and
3. Indications for Initiation of Antiretroviral Therapy in the Chronically HIV-1-Infected Patient (HIVRX), developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services and the Henry J. Kaiser Family Foundation released Aug. 2001. Revised and re-released Feb. 2002.

These guidelines were chosen because they each addressed clinically important problems. The guidelines were modeled and revised by one informatics fellow who is board certified in both internal medicine and preventive medicine and public health. The author is involved in the development of HieroGLIF and is experienced in using SIGTool. The author consulted with other physicians in the study group and with a practicing internist-endocrinologist outside of the study group. Consultants agreed that the encoded guidelines maintained the integrity of the recommendations in the text-based guidelines.

Defining types of revisions to encoded guidelines

We gave the name "*Primary Change*" to any change made to an encoded guideline as a direct consequence of a revision in the text-based guideline. Every revision to an encoded guideline involved adding/deleting module(s), changing the information detailed in a module, or a combination of these revisions.

Primary Insertion (Deletion): A new module is added (deleted) because of changes specified in the most recently published guideline.

Inspection: A module (let us call it FRx) must be inspected for a possible change when it is dependent on at least one other module's design parameter and the design parameter(s) upon which FRx is dependent underwent a change. Also, changing FRx requires inspection of FRx's children.

Secondary Deletion: A module is removed from the guideline because of a change or deletion elsewhere in the design. For example, a sibling group was deleted if its parent was deleted.

Secondary Change: A module is changed because a change elsewhere indicated that the author inspect the module -- and upon inspection, it is determined that changes are required.

Defining design dependencies

For decoupled guideline designs, the numerals 1 and 0 are the most appropriate entries for DPs within the design matrix *because it is important to know only that a DP either interacts with an FR or does not.* For any sibling group, we defined off-diagonal dependencies as the number of numeral 1s in the lower triangle of the design matrix. To compute the total number of possible dependencies per sibling group of n FRs with an nxn design matrix, we used this equation:

Possible dependencies per sibling group of n FRs= $n(n-1)/2$

Endpoints

Our study objective, that modular knowledge representation of guidelines with AD facilitates easy guideline revision, was tested using these three endpoints on each design's FR tree:

Most functional requirements will maintain the independence axiom. This was determined by finding the ratio of actual lower triangular dependencies per total number of possible lower triangular dependencies.

Most non-independent functional requirements will occur at higher-levels of the design tree. This was determined by com-

paring the number of dependencies in the *higher-level* versus (vs.) the *lower-level* of the design tree. For an even number of levels in an FR tree, we considered higher-level dependencies to be those in the top half of the tree; the rest of the tree was the lower-level. For an FR tree with an odd number of levels, the higher-level included the extra level. For dependency counts only, a single top-level FR was not counted as a level.

Revisions to encoded guidelines are more likely to occur at the lower, more detailed levels of the design tree. This was determined by comparing the actual number of changes and inspections in the higher vs. the lower level of the design tree.

Statistical analyses

We calculated relative risk (RR) at a 95% confidence interval (CI) using Fisher's exact test one-tailed p-value. EpiInfo version 6 Statcalc was used for all calculations.

Results

Lipid Screening in Adults (LSA) guideline

The FR design tree of the original LSA guideline had 45 modules in a six-level hierarchy; the design had a single top-level FR. Most modules were independent -- 77%. The design matrices contained 15 dependencies of 64 total possible dependencies. All 15 of these dependencies were in the higher-level of the hierarchy (15 higher-level dependencies of 23 possible higher-level dependencies). There were no dependencies in the lower-level (0 lower-level dependencies of 41 possible lower-level dependencies). We calculated the relative risk for higher-level versus lower-level dependencies to be [RR 2.54, CI 1.80, 3.57, p<.003]. This represents significantly more higher-level than lower-level dependencies.

The revision of the LSA guideline included the elimination of initial non-fasting screening blood tests for both total and HDL cholesterol. Also removed were risk factor assessments that were part of the decision criteria to perform fasting cholesterol fractionation. LDL, HDL, and triglyceride threshold values, all used for decision criteria for lipid management referral, were removed and replaced with only elevated total cholesterol. These revisions required:

1. A primary deletion of the "initial blood test" module at level 4 with secondary deletions of both its children (assessment of HDL and total cholesterol results)

2. A primary deletion of the "assess risk factors" module with secondary deletions of all its children (the specific risk factors) at levels 4 and 5, respectively

3. Six primary changes to threshold values at level 6

4. One primary addition at level 5 and two at level 6. These were needed to include "results of total cholesterol blood test" as a criterion for lipid management.

The design matrices identified the need for seven inspections (four at level 4 and three at level 5); one of these inspections led to twelve module deletions (modules that categorized patients after initial blood testing and modules that assessed the number of risk factors).

Table 1: Frequency of primary and secondary changes made in the LSA guideline according to the level of the design tree

	Level (numbered from root)				
	1-3	4	5	6	Total
Primary Add	0	0	1	2	3
Primary Delete	0	2	0	0	2
Primary Change	0	0	0	6	6
Secondary Delete	0	3	11	6	20
Secondary Change	0	1	0	0	1
Inspect	0	7	0	0	7
Total	0	13	12	14	39

A total of 39 changes and inspections were performed to revise the guideline -- 11 primary and 21 secondary changes and 7 inspections. All 39 changes were made among the 40 modules of the lower-level (Table 1) of the hierarchy. There were significantly more changes made to lower-level modules than higher-level modules [RR 1.13, 95% CI 1.01 - 1.25, p<.04].

Hormone Replacement Therapy (HRT) guideline

The design tree of the original HRT guideline had 32 modules on five levels. Most modules were independent -- 58%.There were significantly more higher-level dependencies: 81% (13 of 16 possible higher-level dependencies) in the top 3 levels versus 10% (2 of 20) in the lower-level [Risk Ratio 4.93, 95% CI 1.24 - 19.63, p<.02].

This guideline was revised to remove cardiovascular indications for initiation of HRT therapy and to recommend discontinuation of HRT for women on HRT solely for cardiovascular indications. The revised guideline also included the possible addition of androgen therapy for women with decreased libido not improved on estrogen/progesterone therapy if both the patient and provider agreed this was appropriate.

A primary deletion of the cardiovascular indications module was performed with no ensuing secondary changes. The patient education module underwent a primary change without secondary changes to include the new medical knowledge responsible for the guideline revisions. Under the module entitled "management of women on HRT", the "drug adjustment" sub-module underwent primary changes for two distinct reasons: (1) An addition of a sub-module to discontinue HRT for women on HRT for cardiovascular reasons alone and (2) Changing the drug adjustment algorithm to include consideration of androgen therapy for reasons previously noted. Four other inspections were required due to these changes, but no secondary changes were necessary. In total, to revise this guideline, eight changes including inspections were made all at higher-levels (six at level 5 and two at level 4) and all occurring on leaf nodes. There were three primary changes, no secondary changes, and five inspections. Statistical analyses were not performed because of a small sample size.

Initiation of Antiretroviral Therapy (HIVRX) guideline

The design tree of the original HIVRX guideline (Figure 2) had 16 modules on four levels. Most modules were independent -- 77%. The design matrices identified dependencies on level 1 of the guideline structure only. There were 3 dependencies from a total of 13 possible dependencies. This guideline was revised to

replace threshold values obtained from the bDNA assay of HIV RNA v. 2.0 with threshold values for the newer v. 3.0 of the assay. Only primary changes to the detail of the two children of the bDNA module were required. No inspections were indicated. Statistical analyses were not possible due to a very small sample size.

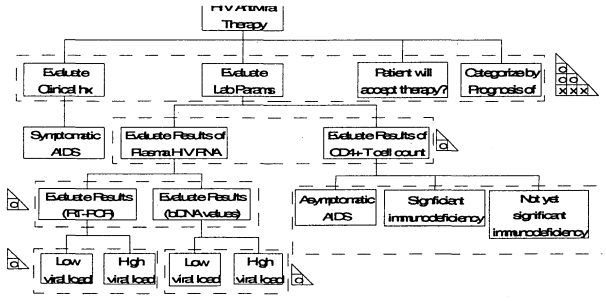

Figure 2 - DP design tree for guideline entitled HIV Antiretroviral Therapy showing lower triangular dependencies of sibling groups (dashed areas) by level. Upper-level intentions corresponding to upper-level DPs are: FR1: Assess for AIDS defining illness or history of, FR2: Assess laboratory parameters, FR3: Will patient accept therapy? FR4: Categorize chronically infected HIV-1 patient into groups initiation of therapy or not

Discussion

The results of this study suggest that modular knowledge representation of guidelines using AD facilitates easy guideline revision. Although each of our designs was a decoupled design, *most modules maintained the Independence Axiom*. A change to an independent FR only required changing its DP and inspecting its children; thus, revisions to one part of our encoded guidelines had minimal impact on more distant parts.

In our FR trees, *most non-independent modules occurred at upper-levels*. Upper-level modules contained general intentions and less directed actions and required decomposition to more concrete and detailed lower-level components before actions could actually be deployed. Our designs had significantly fewer dependencies at the lower levels and *revisions to our guidelines occurred significantly more often at these more detailed lower-levels of the design tree*. Although decoupled designs are less than optimal designs, AD was still able to facilitate easy revision of our guidelines because the designer was able to minimize dependencies at lower tree levels where changes were most likely to occur and thus minimize the impact of primary changes on other modules. Using SIGTool, the author created design matrices that supported the revision process.

Our results appear promising. However, we only designed parts of three guidelines because of the tremendous effort required for structured modeling of the guidelines. As more study group members become experienced in guideline modeling, AD's Information Axiom will facilitate comparing designs from diverse design approaches to derive the "best" design. Guideline authors will need to structure modules to reduce upper level dependencies. We are currently modeling other guidelines: hypertension management, child in-clinic algorithm for determining which immunization(s) are due, asthma management, and acute low back pain management.

Our future work will include conducting a controlled clinical trial to assess physician acceptance of locally adapted guidelines; HieroGLIF and SIGTool will be more extensively assessed during this trial.

Acknowledgments

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References

[1] Johnston ME, Langton KB, Haynes RB, et al. Effects of computer-based clinical decision support systems on clinician performance and patient outcome. A critical appraisal of research. *Ann Intern Med* 1994;120(2):135-42.

[2] Peleg M, Tu S, Bury J, et al. Comparing computer-interpretable guideline models: a case-study approach. *J Am Med Inform Assoc* 2003;10(1):52-68.

[3] Boxwala AA, Tu S, Peleg M, et al. Toward a representation format for sharable clinical guidelines. *J Biomed Inform* 2001;34(3):157-69.

[4] Shekelle PG, Ortiz E, Rhodes S, et al. Validity of the Agency for Healthcare Research and Quality clinical practice guidelines: how quickly do guidelines become outdated? *JAMA* 2001;286(12):1461-7.

[5] Suh NP. *The principles of design.* New York: Oxford University Press; 1990.

[6] Peleg M, Boxwala AA, Ogunyemi O, et al. GLIF3: The evolution of a guideline representation format. *Proc AMIA Annu Fall Symp* 2000:645-9.

[7] Boxwala AA, Zeng Q, Tate D, et al. Applying axiomatic design methodology to creating guidelines that are locally adaptable. In: Kohane I, editor. *AMIA Fall Symp*; 2002; San Antonio, TX: Hanley & Belfus, Inc.; 2002. p. 980.

[8] Boxwala AA, Zeng Q, Vuong J, et al. GLIF software components and tools: Programmer's manual and reference documentation. Technical Report. Boston, MA: Decision Systems Group; 2001. Report No.: TR-2001-10.

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