Verification of Medical Guidelines by Model Checking - A Case Study.

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Abstract. This paper presents a case study on how to apply formal modeling and verification in the context of quality improvement in medical healthcare. The aim is to verify quality requirements of medical guidelines and clinical treatment protocols that are used to standardize patient care both for general practitioners and hospitals. This research is supported by the European Commission's IST program and brings to-gether experts from computer science, artificial intelligence in medicine, hospitals, and the Dutch Institute for Healthcare Improvement (CBO). We present the process of formal modeling and verification of guidelines using the modeling language Asbru, temporal logic for expressing the quality requirements, and model checking for proof and error detection. The approach is illustrated with a case study on a guideline from the American Association for Pediatrics on "Jaundice in healthy Newborns" 1

Key words: model checking, verification, formal methods, Asbru, abstraction, medical guidelines

1 Introduction

Over the last decade, the approach of evidence-based medicine has increased the application of clinical guidelines in medical practice. Medical guidelines provide clinicians with healthcare recommendations based on valid and up-to-date empirical evidence. Usually they consist of "systematically developed statements to assist hospital staff with appropriate healthcare decisions" [FL92]. Application of guidelines improves the quality of medical treatment and it has been proven that adherence to guidelines and protocols may reduce healthcare costs up to 25%.

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Many practical guidelines and protocols still contain ambiguous, incomplete or even inconsistent elements. Recent efforts have tried to address quality improvement of guidelines [TMB04]. Our general approach to verification of guidelines is based on the observation that guidelines can be viewed as parallel programs. Therefore the classical formal methods for the quality assurance of software can be applied for the case of medical guidelines, especially because guidelines are highly-structured, systematic documents that are amenable for formal verification.

Because most parts of a guideline consists of informal plain text an appropriate representation language, with clear and well-defined semantics is required. To this purpose we use Asbru [Mik98]. Asbru is a temporal, skeletal plan-representation language which was especially designed for the medical domain. The most important advantage of using Asbru as a modelling language is its formal semantics [Bal02]. Figure 1 shows the overall documents flow in the verification process. The original guideline depicted in the upper left corner is modeled as Asbru plan using the knowledge-representation language Asbru.

The Asbru model is the basis for further tasks, e.g. to build decision support systems. For these tasks it is necessary to ensure the quality of the model. Thus, we are interested in tools to efficiently debug the model, e.g. to ensure its consistency. [Duf99] defines a number of structural properties which should be fulfilled by a good quality Asbru model. Some of these properties can be checked by syntactic analysis. Other properties require formal analysis. Furthermore, we are interested in the formal verification of more complex medical properties such as medical indicators. Complex, infinite state properties in general require interactive theorem proving. For structural and simple medical properties we aim for efficient techniques which can be automatically applied. For this, we automatically translate the model into a formal representation for an interactive theorem prover KIV [BRS00]. In order to apply model checking, we further translate the model into the input language of SMV model checker. In this paper, we focus on model checking of properties.

Simultaneously to the above transformation, in Figure 1, a number of interesting properties have been identified while analyzing both the original protocol and its Asbru model. We distinguish between *Medical Properties* and *Structural Properties* (see 3.2).

To evaluate our approach we have considered the medical guideline for "Jaundice in healthy newborns", a medical guideline from the American Association of Pediatrics, that covers different features of Asbru. We will use the jaundice protocol in the following sections as running example for our paper.

The identified properties do not depend on timing constraints. Therefore, it has been possible to abstract from time which reduces the complexity of the model. For the verification of these properties, we have chosen SMV as a model checker, because to our knowledge this is one of the most efficient tools to verify large models without complex timing constraints. For real-time properties, the use of timed model checkers, e.g. UPPAL[LPW97], will be of interest.



Fig. 1. Formalization and verification of protocols in the Protocure project.

We have used Cadence SMV version 10-11-02 with default settings on a computer with a 3 GHz Pentium processor and 2 GB of RAM.

Our main contributions are: (i) a validated formal model of a concrete medical guideline where the quality has been assured by automatic techniques, (ii) tool support for automatic verification of all of the properties of [Duf99], (iii) case study to assess the possibilities of light-weight model checking techniques to verify structural or simple medical properties of medical guidelines; this case study could serve as a reference case study for other model checkers and other automatic techniques in the field of medical guidelines. We do not present new strategies for model checking SMV models in general.

The paper is organized as follows. Section 2 gives a short overview of the Jaundice guideline and the Asbru language with its formal semantics. Section 3 gives a description of a concrete infinite state model of the jaundice protocol and describes its reduction to a finite state model using an abstraction. In section 4 we summarize our experiences from this case study and describe possible improvements of the current process planned for future work.

2 Asbru: a knowledge representation language for protocols

We describe Asbru and its use by a simple example. Details on Asbru can be found in [Mik98].

2.1 The jaundice protocol

Jaundice, or hyperbilirubinemia, is a common disease in newborns which is caused by increased bilirubin levels in blood. Under certain circumstances, high bilirubin levels may have destructive neurological effects and thus must be accurately treated. Often jaundice disappears without treatment, but sometimes a phototherapy is needed to reduce the level of total serum bilirubin(TSB). In a few cases, however, jaundice is a sign of a severe disease, which must be treated appropriately.

The jaundice reference guideline [AAP94] is a 10 pages document which contains various notations: the main text; a list of factors to be considered when assessing a jaundiced newborn; two tables - one for the management of the healthy term newborns² and another for the treatment options for jaundiced breast-fed ones; and a flowchart describing the steps in the protocol. The Protocol consists of two parts performed sequentially: diagnosis and treatment. Treatment is performed if disease symptoms are detected. During the application of the protocol, as soon as the possibility of a more serious disease is uncovered, the recommendation is to exit without any further action. The further treatment is not considered in the guideline.

2.2 Modeling the jaundice protocol in Asbru

Medical guidelines are represented as hierarchical skeletal **plans**, i.e. plans with subplans. Figure 2 shows the hierarchy of plans representing the Asbru model of jaundice protocol. It is made up of about 40 plans. Two phases in the protocol control flow clearly emerge: diagnostics and treatment parts which are executed sequentially. Three "Check-for-..." plans model two check-ups at specific time intervals and a continuous monitoring of the TSB level. We focus here on the diagnostic and treatment phase, which is more interesting from the verification point of view. It consists of two parallel plans, namely the actual treatment and a cyclical plan asking for the input of new TSB and age values every 12 to 24 hours. Depending on the current bilirubin level, either the regular-treatments or an exchange-transfusion can take place. The plan-body of regular-treatments plan contains two subplans which are executed in parallel without any ordering. The regular-treatments* subplan (which is abbreviated with * in Figure 2) represents a group of therapies, which are executed sequentially without any order. All of the therapy plans are optional with the exception of the *observation* plan which completion is obligatory for the successful completion of the parent plan. Any of these therapies can be restarted, in case if it is eventually aborted.

Figure 3 shows an example of two Asbru plans from the jaundice guideline. An Asbru model of a plan contains the definitions of different descriptive elements like intentions, conditions, plan body and control structures. In the following we describe these main elements.

The **intentions** are the high-level goals of a plan. Intentions can be expressed in terms of achieving, maintaining or avoiding certain states or actions. The states or actions to which intentions refer can be intermediate or final. Thus, the intention label "maintain-intermediate-state" means that always during the execution of the plan a certain condition must be satisfied. Generally

 $^{^{2}}$ Defined as 37 completed weeks of gestation.



Fig. 2. Asbru plans modeling jaundice protocol.

there are twelve possible forms of intention: [achieve/maintain/avoid] [intermediate/overall] [state/action]. Most of the properties we use in the verification are gained from the intentions (see Sec. 3.2). For example, one of the intentions of the phototherapy-intensive plan (Fig. 3) is to maintain a certain intermediate state, i.e. there is a bilirubin decrease in 4 to 6 hours after the activation of the plan. As all intentions of the jaundice guideline this is an universal property.

Every **plan-body** contains the actions to be performed by the plan and/or subplans to be executed as part of the plan. A wide variety of **control** structures can be used to specify the execution order of the actions in the plan-body. There are the following types of plan-bodies in Asbru:

- user-performed: an action to be performed by the user, which requires user interaction and thus is not modeled further
- single step: an action which can be either an activation of a subplan, an assignment of a variable, or request for an input value
- subplans: a set of steps to be performed in a given order. The possible execution orders are: sequential, parallel, in any possible sequential order(anyorder) and in parallel without any restrictions on the synchronization (unordered)
- cyclical plan: a repetition of actions over time periods

When a plan-body contains subplans it is possible to define the completion of some (or all) subplans as a necessary precondition for the successful completion

```
plan regular-treatments
intentions ...
conditions ...
plan-body type=unordered, wait-for all
    feeding-alternatives
    /* implicit subplan regular-treatments*: */
    do type=any-order, retry-aborted-subplans=yes, wait-for observation
         phototherapy-intensive
         photottherapy-normal-prescription
         photottherapy-normal-recommendation
         observation
plan phototherapy-intensive
intentions
    achieve-overall-state: (bilirubin=observation)
    maintain-intermediate-state:
            (and(TSB-decrease=yes in [[4h,-],[-,6h],[-,-]] SELF)
                (TSB-change>1 in [[4h,-],[-,6h],[-,-]] SELF))
conditions
    setup-condition: (or(bilirubin=phototherapy-intensive in NOW)
                        (normal-phototherapy-failure))
    abort-condition: (or(and(bilirubin!=phototherapy-intensive)
                            (not normal-phototherapy-failure))
                        (intensive-phototherapy-failure))
    intensive-phototherapy-failure:
            (and(bilirubin=phototherapy-intensive in NOW)
                (or(and(TSB-decrease=yes in [[4h,-],[-,6h],[-,-]] SELF)
                      (TSB-change<1 in [[4h,-],[-,6h],[-,-]] SELF))
                   (TSB-decrease=no in [[4h,-],[-,6h],[-,-]] SELF)))
plan-body
```

prescribe-intensive-phototherapy

Fig. 3. Regular-treatments and Phototherapy-intensive plans

of parent-plan. For example **wait-for all** type of plan-body means, that the parent plan can only complete if all of the subplans are completed. Similarly **wait-for one** or **wait-for someplan** can be defined.

The regular-treatments plan (Fig. 3) is a good example for a more complicated structure of the plan-body. It has an unordered plan-body with wait-for-all option and two subplans: feedings-alternatives and regular-treatments^{*}. The implicit plan regular-treatments^{*} consists of several different therapies executed in any order (see Fig. 2 and Fig. 3). Its subplan phototherapy-intensive (Fig. 3), for instance, describes one of the therapies. Its plan-body simply contains the activation of the subplan prescribe-intensive-phototherapy.

A variety of **conditions** can be associated with a plan, which influence control of an execution of the plan. The most important types of conditions are the following: filter-, setup-, activate-, abort-, and complete-condition. The meaning of these conditions is described more closely in the section 2.3. Conditions can not only specify a set of satisfying current states³ but also they can be monitored over the time, if they are formulated using time annotations, e.g. in 4 to 6 hours after the activation of plan the bilirubin level change decrease is greater then 1.

Time annotations can occur in conditions. They specify the time period where a parameter condition used in the time annotation is monitored. A time annotation is defined by the following eight entities: reference point (*REF*), earliest starting shift (*ESS*), latest starting shift (*LSS*), earliest finishing shift (*EFS*), latest finishing shift (*LFS*), minimum duration (*MinDu*), maximum duration (*MaxDu*) and parameter proposition *ParamProp*. These components are combined in the data structure:

(ParamProp in [[ESS,LSS], [EFS,LFS], [MinDu, MaxDu]] REF)

Reference points like NOW (current time) and SELF (time of activation of this plan) are commonly used. Consequently a time annotations defines a set of time intervals (also called set of possible occurrences). A time annotation is TRUE if and only if there exist a time interval in the set of possible occurrences where the condition *ParamProp* is evaluated to TRUE in all time points within this interval.

As example consider the following time annotation from the phototherapyintensive plan:

$$(TSB-decrease = yes in [[4h,-], [-,6h], [-,-]] SELF)$$

This time annotation monitors the bilirubin level on the time interval between 4 to 6 hours after the plan start. It is evaluated to TRUE if there is a new bilirubin measurement with a value smaller than the latest value before the plan started. It has the following meaning: there exist time interval (or point as special case of interval) with earliest starting at 4h after the plan activation and latest finishing at 6h after activation where TSB-decrease=yes is true. The predicate TSB-decrease=yes is evaluated to TRUE on the given interval if and only if for all time point t_0 on this interval the bilirubin value is smaller than bilirubin value at the time of plan activation.

2.3 Formal semantics of Asbru

As formal semantics for Asbru we use [Bal02]. The semantics follows two goals: first it should document Asbru and be understandable for users; on the other hand it should be formal enough. We use the example of *regular-treatments** plan to explain the semantics here.

³ An Asbru state is composed of the state of execution of all plans and the state of the patient. Further we have the Asbru history which is defined as a mapping from the Asbru clock (ticker) to an Asbru state and allows to specify time annotated conditions.



 ${\bf Fig.~4.~State charts~modeling~regular-treatments^*~plan.}$

The operational semantics of Asbru is defined using statecharts. We use the statecharts semantics defined in [DJH98]. Asbru plans are modeled as statecharts which run in parallel and communicate via shared variables and signals. Asbru conditions are monitored over time. The evaluated conditions trigger transitions of the statecharts. The evaluation of conditions depends on the data inputs from the environment usually describing dynamics of patient. Shared variables like patient parameters or state of other plans can also influence the evaluation of Asbru conditions. For example the abort-condition of phototherapy-intensive plan (see Fig. 3) triggers the abort of the plan as soon as it fails to reduce bilirubin level in 4 to 6 hours after the plan activation.

The regular-treatments^{*} plan is an implicit subplan of the regular-treatments plan (see Fig. 2 and Fig. 3). The behavior of the regular-treatments^{*} plan is defined by the statechart in Figure 4. This statechart is divided into a Selection phase and an Execution phase. Initial state of the plan is Inactive. An external signal consider triggers the selection phase (transition SC). In the state Considered the condition filter_tp is checked. In case this condition is satisfied, the plan changes to the state Possible and so on. In the state Activated the subplans are executed. The execution of subplans is controlled by the regular_treatments^{*}_Control statechart (Fig. 4), which models an anyorder control of subplans. It is responsible for the generation of the consider-, activate- or retry-signals, which control the execution of subplans. All subplans are selected in parallel (transition c) and executed such that at most one subplan is active at the same time (transitions *i.a*). If the activated plan terminates(transitions i.T) another one can be activated. If several subplans reach state Selected simultaneously, one of them is activated nondeterministic. If parameter flag "retry-aborted" is set, then the transition *i.r* initiates a restart.

The concrete infinite state model of the system is composition of statecharts running in parallel and reacting on environment inputs. Interaction with environment happens in micro- and macro-steps. One macro-step consists of many micro-steps which describe reaction of system on certain environment input. As a system achieves a stable state the corresponding macro-step is completed and in the first micro-step of the next macro-step new input from the environment is read. This model corresponds to the assumption that the system, which models the guideline, always reacts quick enough to changes of the environment. It is also intuitively the proper modeling for medical plans, i.e. control of plans does not take time to activate or cancel some plans. The notion of time is defined using macro-steps. Time passes only with the begin of every macro-step.

In Asbru we have no explicit model of the patient, i.e. we does not model specific patient behavior. We assume that the patient has chaotic behavior, i.e. parameter values blood pressure, bilirubin level in blood etc. changes arbitrary over time. This allows us to investigate whether medical protocol reacts adequately in all possible cases. Consequently the infinite state concrete model is composition of statecharts modeling medical plans, environment and Asbru clock modeling current time, see Figure 5. This model resembles somehow the model of parallel processes communicating over shared variables.

3 Model checking process

The crucial point in model checking and verification in general is computing an optimal abstraction of the examined system. Recently, much research has concentrated on tackling the state explosion problem. A variety of abstraction techniques have been developed, for example [Gru01], [GS97], [CGL94], [GHJ01] and [DGG97]. An important observation is basis for these investigations: there are different aspects in the concrete model that have no impact on the checked property and can be abstracted in such a way that the size of the model is drastically reduced, but the property is still safely verified, i.e. the satisfaction of a property over an abstract model implies satisfaction over the concrete model. Methods that derive an abstract model directly from some high-level description of the system are needed.

3.1 Abstract finite state model

Generally, it is a hard task to construct a correct abstract finite state model for the generic Asbru model completely automatically, since Asbru is a very expressive language.

The infinite parameters describing the patient (or environment) can be abstracted to finite state variables using data abstraction [CGL94], [Lon93]. The more problematic issue is time, which usually requires some kind of history



Fig. 5. Infinite state concrete model of medical guideline.

variable. All plans, in order to proceed, must know whether their setup-, filter-, abort- or complete-condition is satisfied or not. Some of these conditions contain time annotations, as for example the abort-condition of *phototherapy-intensive* plan does (see Fig. 3). In order to evaluate some time annotated conditions a plan must access the history.

Our goal is an abstraction which can be constructed automatically for the given Asbru model. In order to construct a finite state model an appropriate abstraction which eliminates time and history is needed. We use a simple abstraction that maps all time annotations to atomic propositions which logical value is randomly assigned in every macro step. Those random inputs can eventually generate behavior in the abstract model that is not present in the concrete model. This abstraction preserves only ACTL⁴ properties, as it is an over-approximation, which adds extra behavior to the abstract model. Nevertheless, this is not a problem for us, because most interesting properties we aim to verify are intentions, which are ACTL properties.

The main weakness of this abstraction is the generation of false negatives during the verification of properties. On the other hand the important advantage is its automatic generation. By this abstraction we shift the complexity of time and history to the environment. According to the statechart semantics inputs from the environment happen in the first micro-step of every macro-step and provide the required information about the patient needed for the controls of plans, e.g. up-to-date value of blood pressure or information about change of the bilirubin level in blood over the period of 6 hours after the start of the plan.

For the generation of the SMV model we translate the statecharts from the Asbru semantics into an equivalent flat state transition system, which can be be encoded directly in the SMV language. This part models the control flow of the guideline. On the other hand, the data flow and time is modeled using the abstraction techniques described above.

⁴ The logic ACTL is the set of all well-formed state formulas from CTL[Eme90] containing no existential operators (EX and EU)

Fig. 6. SMV specification of structural properties for Phototherapy-intensive plan

3.2 Properties

The results from the verification of properties should help to improve the quality of medical guideline. Structural properties specify the general correctness requirements, which must be satisfied by every Asbru protocol, regardless of its contents. For example, every plan should eventually terminate, every plan must have a chance to execute or be able to complete. Our experiences from jaundice case study has shown that verification of structural properties helps to discover errors produced during the translation of informal medical guideline into the formal Asbru model. Following structural properties have been considered: termination (Asbru plans should always terminate), every plan can eventually be activated (completed), there are no redundant conditions (i.e. every condition can eventually have influence on the control flow of plans) and all wait states are eventually quitted. These properties have been formalized as CTL formulas and are automatically generated for every Asbru plan as SMV specifications. Most of them are originally not ACTL properties, but their verification can be indirectly accomplished by the verification of the corresponding ACTL properties, as described in Section 3.3. For example, the corresponding ACTL properties (in SMV syntax) for the plan phototherapy intensive(pti) are depicted in Figure 6. The property term_pti_plan formulates termination property, i.e. every plan that was previously selected always terminates in the future. By the satisf_abort_pti_plan property we try to verify whether the abortcondition of the phototherapy-intensive plan is redundant or not. In case we found a non-spurious counter-example for satisf_abort_pti_plan we know that abort-condition is not redundant, i.e. it has an influence on the plan execution. Similar properties can be formulated for all other Asbru conditions. Reachability of important states is tested by properties like reach_activated_pti_plan. The property wait_possible_pti_plan tests whether wait state possible is eventually guitted.

Medical property address high level aspects of medical protocol, such as relevant clinical parameters or general safety requirements concerning actions of physicians or overall intentions of the guideline. As an example, when treating jaundice, it is required that 6 hours after application of phototherapy the biliru-

Fig. 7. SMV specification of medical properties for Phototherapy-intensive plan



Fig. 8. Verification scheme.

bin level must drop significantly. In jaundice case study we considered only plan intentions as conceptual properties. For instance, plan *phototherapy-intensive* has two intentions, which can be specified as ACTL properties, as Figure 7 shows. With the *intermediate state* in the second property we mean only stable states, i.e. states in which the reaction of the plan on the environment inputs is completed. Therefore, the variable *tick* is used to describe the *activated* state of the *pti* plan where it is *stable*, i.e. no transitions of the corresponding statechart are activated.

3.3 Verification process

The abstraction we use is described in 3.1. It allows us to generate the SMV model fully automatically. On the other hand it can introduce unrealistic behavior, which has an impact on the verification process. Figure 8 illustrates the general scheme of verification. Due to property preservation considerations we examine only ACTL properties although it is also indirectly possible to verify ECTL properties. The medical properties we considered are the intentions of the plans, which are formulated as ACTL formulas.

If ACTL property is proved to be false the corresponding counter example is generated. In the next step we have to analyze this trace to find out whether



Fig. 9. Counter example visualization.

it is a real bug in the concrete model or just some unrealistic trace added by the over-approximation. We have also to verify ECTL properties since most implementation level (structural) properties are existential properties, e.g. satisfiability of Asbru conditions or non-redundancy of plans. If, for instance, a ECTL formula $EF\phi$ must be verified, we verify first the ACTL formula $AG\neg\phi$. If it is true then original formula is false. On the other hand, if a counter example is found then we analyze whether it is realistic one. If the found counter example trace is realistic then the original formula is true and generated counter example is the trace that satisfies the original formula.

3.4 Results and experiences from verification of jaundice

The abstracted model of the jaundice guideline was constructed in the SMV language and model checking was used to verify different properties. Especially we verified structural and medical properties of approximately 30 Asbru plans from the jaundice hierarchy of plans. Automatic generation of 3000 lines of SMV model including 360 properties has accelerated the whole process. Checking of one property has taken about 2 minutes whereby 2000000 BDD-nodes were allocated. Complete verification of circa 400 properties lasted 3.5 hours and 4000000 BDD-nodes were allocated.

In the whole verification process the manual effort of analyzing the counter examples and refining the abstract model was rather small and acceptable. The verification of structural properties helped immensely to gain confidence in the formal Asbru model.

During the process of formalization and verification of the medical properties, a number of errors and ambiguities were discovered. We have found special cases of treatment that violate plan intentions. These special cases have been overseen by the Asbru modelers and consequently not appropriately considered in Asbru model. Figure 3.4 illustrates the possible execution sequence that violates the intention of phototherapy-intensive plan, see Figure 3. The intention postulates that in 4 to 6 hours after plan start the bilirubin level must decrease in the other case plan must abort. As we see on Figure 3.4 bilirubin level does not decrease in the corresponding time interval and plan does not aborts. The reason for violation of plan intention is too weak abort-conditions that does not consider all possible cases. Using model checking verification method we have discovered many other similar "forgotten" cases in the overall plan hierarchy containing 30 plans.

4 Summary and Outlook

In this paper we have described the automated verification of medical guidelines using jaundice case study as an example. The simple abstraction we applied yielded surprisingly good results in jaundice case study. In fact only few refinements and fine tuning were needed while verifying properties. This simple abstraction allows us to construct the SMV model fully automatically, which is an important advantage as we plan to apply this method on further case studies. Nonetheless the approach as whole is not completely automatic but partly an interactive one (see Fig. 8) because our abstraction is over-approximation. Due to high expressiveness of Asbru modeling language it is practically not possible to construct correct abstraction for the general case of Asbru-model automatically without any user interaction. But this process can be highly automated.

First errors we have found were consequence of too coarse abstraction. In some cases our first verification experiments have shown that used abstraction is too coarse. Therefore, to avoid the interactive component ANALYZE in the process, see Figure 8, we plan to construct the correct abstraction. We see this as promising direction for further work on verification of Asbru. Further we plan to use the KIV theorem prover to show the correctness of the constructed abstraction by proving the corresponding bisimulation equivalence. Another profitable improvement were visualization of model checking results. The graphical interpretation of counter examples can make verification more efficient as it makes the interpretation of traces easier.

Our approach to verify simple properties of medical guidelines by model checking were surprisingly successful. Therefore, it is promising to also apply other automatic techniques to the verification of more complex properties, e.g. real-time properties, and larger guidelines.

Currently, we are applying our method on a second guideline, which describes the treatment of breast cancer. This guideline is considerably larger but our first experiences with it were very promising.

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