

Adverse Drug Events prevention Rules: multi-site Evaluation of Rules from various Sources

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Abstract. Adverse drug events are a public health issue (98,000 deaths in the USA every year). Some computerized physician order entry (CPOEs) coupled with clinical decision support systems (CDSS) allow to prevent ADEs thanks to decision rules. Those rules can come from many sources: academic knowledge, record reviews, and data mining. Whatever their origin, the rules may induce too numerous alerts of poor accuracy when identically applied in different places. In this work we formalized rules from various sources in XML and enforced their execution on several medical departments to evaluate their local confidence. The article details the process and shows examples of evaluated rules from various sources. Several needs are enlightened to improve confidences: segmentation, contextualization, and evaluation of the rules over time.

Keywords. Adverse drug events, data mining, decision rules, XML, CPOE, CDSS.

1. Introduction

Adverse drug events (ADEs) are a public health issue: every year they are considered responsible for 10,000 deaths in France and 98,000 deaths in the USA [1] in both ambulatory care and hospitalization. During hospitalizations some ADEs can be prevented when a computerized provider order entry (CPOE) is the frame of the medication use process and is coupled with a clinical decision support system (CDSS). In those CDSS it is possible to implement some alert rules, e.g. when some drugs are prescribed despite a drug-drug or a drug-diagnosis contraindication. Many different methods allow generating alert rules, each method having some qualities and drawbacks in regard to formalism, confidence, segmentation, and generation hardness:

- Academic knowledge (e.g. summaries of products characteristics, pharmacology teaching, ADE declarations, clinical trials)
- Staff operated reviews (e.g. records reviews, charts reviews, expert reviews)
- Automated data mining (e.g. decision trees, association rules)

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Each method has advantages and drawbacks. Three drawbacks seem to be often underestimated:

- **the lack of segmentation** (subgroups variations of the confidence):

A rule such as “drug_A => effect” might be always true, but its confidence depends on several other variables. Some conditions such as “age>70” or “renal insufficiency” could improve the confidence of the rule and then the interest of alerting the physicians:

$$\begin{array}{ccccc} P(effect) & < & P(effect | drug_A) & < & P(effect | drug_A \cap age>70) \\ prevalence & < & confidence\ of\ the\ rule & < & confidence\ of\ the\ rule\ with\ segmentation \end{array}$$

- **the lack of contextualization** (transversal changes):

Whatever their origin, rules are applied as they are in every medical department assuming that the same causes necessary lead to the same effects with a constant probability. But in fact the alerts are too numerous and their accuracy seems to strongly depend on the place. Though, depending on the medical department the patients could differ (gender, age, associated diseases), the indication of the same drug could vary, as well as the physicians’ knowledge about drugs and their risk aversion.

- **the lack of over time evaluation** (longitudinal changes):

We hope that good rules implemented into a CDSS coupled with a CPOE will improve the physicians’ knowledge about drugs and their practices. Therefore the confidences of the rules will decrease and there will be an over-alerting risk. Only an iterative evaluation of the confidences could answer that problem.

The aim of the present work is to formalize different rules from various sources in a uniform way in order to feed a rules repository, and to be able for each rule to compute its confidence on the fly in different medical departments.

2. Material

2.1. Datasets for rules evaluation

Electronic Health Records (EHRs) seems to be the best data source in the field of ADEs [2, 3]. A data model has been designed in the context of PSIP. It contains 8 tables and 92 fields (Figure 1) and is used in a central repository.

Data extractions were performed to feed the repository. An important point is that no data has to be specifically recorded for the project: only widely available data are used. As a consequence, data extraction generalization and follow-up is much easier. These data include:

- medical and administrative information
- diagnoses encoded using ICD10 [4]
- medical procedures encoded using national classifications
- drug prescriptions encoded using the ATC classification [5]
- laboratory results encoded using the C-NPU classification (IUPAC) [6]

Data extraction is still being continued. The present work is realized on 10,500 complete hospital stays of year 2007 from Denmark and France, mostly from cardiologic or geriatric units:

- Capital Region of Denmark hospitals (Dk): 2,700 hospital stays

- Denain hospital (Fr): 7,000 hospital stays
- Rouen university hospital (Fr): 800 hospital stays. This hospital doesn't have any CPOE: that's the reason why its data cannot be used to generate rules. However, as discharge letters could be semantically-mined, ATC codes found in the text can be used to replace data from CPOE. It is sufficient to allow for rules evaluation on the Rouen hospital stays.

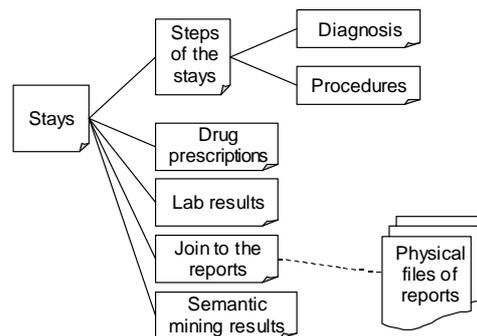


Figure 1. Simple view of the 8 tables of the data model.

2.2. Rules from academic knowledge

Vidal S.A. [7] is a French company that provides information about drugs and therapeutics. Vidal contents are used by almost all French physicians and also in different languages in others countries. Vidal's knowledge comes from official summaries of product characteristics, recent studies, official recommendations, literature, and experts' advice. Vidal contents and services include drug information, therapeutic guidelines and decision support modules. Being a partner of the PSIP project, the Vidal Company gives us access to formalized associations rules.

Their association rules provide four alert levels: absolute contra-indication, relative contra-indication, use caution, notice. The rules are built as follows: two causes brought together might induce one effect. The effect is expressed according to a proprietary thesaurus. The two causes can be of several kinds (but at least one of the conditions is a drug of a class of drug):

- drugs or classes of drugs
- classes of diagnoses
- creatinine clearance lower than a given threshold
- age, gender, pregnancy, allergies, breast feeding...

Advantages:

- That source provides all the "official" information.
- Even rare effects are mentioned.
- Even conditions that might never occur together appear (exhaustive list of absolute contra-indications).

Drawbacks:

- The number of rules is very high.

- Support and confidence (positive predictive values) of the rules are not provided (academic knowledge relies on clinical trials and spontaneous declarations that do not reflect the prevalence of ADEs [8, 9]).
- Many effects described by the rules are available in the EHRs (e.g. clinical events). Only some of the effects are usable in this work in view of which a mapping has to be realized.
- There are only and always two conditions per rule, no segmentation.
- There is no contextualization: the knowledge applies on a whole country

Integration of this knowledge in the repository:

- The rules are first restricted to absolute contra-indications.
- The rules are then limited to those where the effect can be traced in the database. Some approximations are done to trace some effects, e.g. “*drug_A => rhabdomyolysis*” is transformed into “*drug_A => hyperkaliemia & elevation of muscle enzymes & renal insufficiency*”.

2.3. Rules from expert reviews

In a recent paper [10], Jah et al. published a list of 30 alerts from the VigiLanz commercial application. Those alerts are rules composed by a drug as the cause, and a lab alert. 10 of those alerts are validated as ADEs or potential ADEs.

Advantages:

- The rules are easy-to-implement, the effect is traceable.
- Rules have been validated by a staff operated record review.
- Confidence (positive predictive value) and support have been computed.

Drawbacks:

- The number of events is low.
- There is only and always one condition per rule, there is no segmentation.
- The rules are not contextualized.

Integration of this knowledge in the repository:

- The rules are implemented without any change in the rules repository.

2.4. Rules from data mining: decision trees

In the frame of the PSIP project [11] we analyzed 10,500 hospital stays. We computed decision trees [12-18] with the CART method thanks to the RPART package [19] of R [20]. The rules were computed separately on each medical department. The rules we obtained associate a variable number of conditions to a traceable effect and take chronology into account. The conditions can have various natures: a drug prescription, the presence of a group of ICD10 diagnoses, an acute or chronic lab abnormality, data about the patient (e.g. gender, age), data about the organizational conditions of the hospital stay (e.g. admission by emergency, with a too high INR, on Saturday, etc.)

Advantages:

- The rules can be automatically implemented: the same structured database is used for rules generation and for rules evaluation.

- Confidence (positive predictive value) and support have been computed.
- Each rule can consider a variable number of causes, from various natures (lab, drugs, diagnoses, patient, organizational causes).
- The population is segmented in order to optimize the confidence of the rules and to decrease over-alerting.
- The rules are contextualized: their confidence have been computed separately on each medical department

Drawbacks:

- Only events that are not too rare can be observed because a strong statistical link is required
- Only conditions that occur together can appear: absolute contra-indications should never appear although their implementation is mandatory
- Trees are known for their instability and the risk of omitting interesting rules

Integration of this knowledge in the repository:

- The rules are implemented without change in the rules repository. Only the rules that can be validated according to drug-related web information portals [21-23] and Pubmed [24] are used.

In the frame of the PSIP project we are now completing the data mining by using association rules [25, 26]. The aim is to discover some rules that could not appear using decision trees. Association rules produce a more exhaustive set of rules than decision trees. Those rules have to be filtered.

2.5. Rules description and storage in the central repository

The central rules repository is fed by several sources (Figure 4a):

- Automatic rules production from the Denain hospital (F) and the RegionH hospital (Dk), using data mining (decision trees and association rules) [11]
- Manual transformation of rules coming from foreign sources: academic knowledge (presently Vidal) and scientific articles (presently Jah et al.)

An XML [27] scheme has been conceived to represent the rules. XML is chosen because of the following characteristics:

- XML allows building semi-structured database: a complex data scheme with much cardinality can be defined much simpler than using relational databases. Any update of the scheme is easy too.
- XML can be easily produced by many programs. Our R scripts were modified to automatically generate XML in addition to standard output (Figure 2). During the test phase we were able to edit the data with only a simple text editor and to get preliminary results.
- XSL and XSL-FO transformation allows to quickly designing many kinds of outputs (e.g. text files, HTML, PDF, and XML). All the programming languages are able to load XML data to compute treatments that would be too complex for XSLT.
- A unique central repository can then be used to store all our knowledge about ADEs, including free text comments and bibliographic references

The XML data scheme contains two main parts: (1) the rules description (2) last available data about rules occurrences on every place (Figure 3).

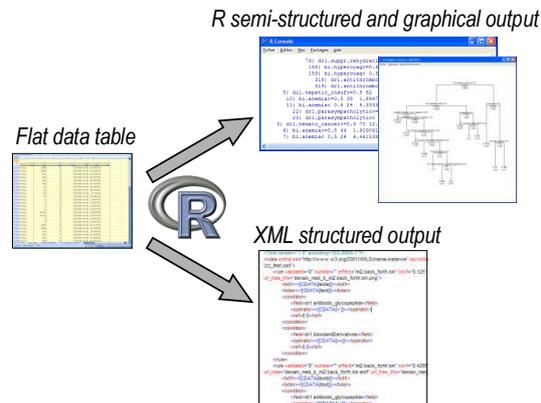


Figure 2. Automatic XML output of R scripts

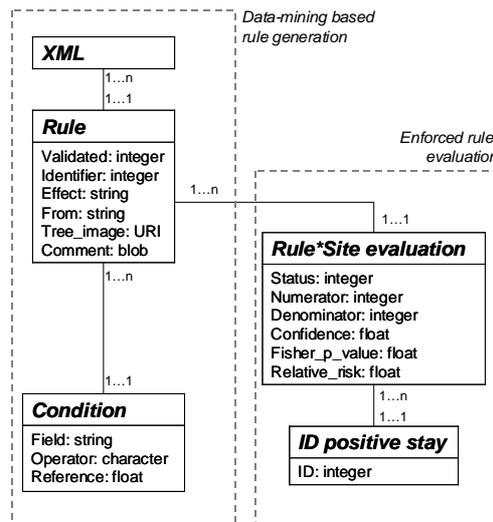


Figure 3. XML data scheme

2.6. Rules evaluation

A rule is a set of causes leading to an effect, such as $C_1 \& C_2 \& C_3 \Rightarrow E$

In a few seconds, all the validated rules can be automatically evaluated on every medical department. The evaluation uses the 10,500 hospital stays from Denain (F), RegionH (Dk) and also Rouen (F) (Figure 4b). Rules enforced evaluation allows to add another knowledge into the database: rules occurrences. Then it is possible to answer several questions for each rule, separately in each medical department:

- Do some hospital stays match the conditions?
 $number\ of\ stays = \#(C_1 \cap C_2 \cap C_3)$

- Among those stays, do some hospital stays encounter the expected effect?
 $number\ of\ stays = \#(E \cap C_1 \cap C_2 \cap C_3)$
 $support = P(E \cap C_1 \cap C_2 \cap C_3)$
 $confidence = P(E | C_1 \cap C_2 \cap C_3)$
- What are the identifiers of the hospital stays that match the complete rule?
- Is it possible to quantify the strength of the association?
 $relative\ risk = confidence / prevalence = P(E | C_1 \cap C_2 \cap C_3) / P(E)$
 $p\ value\ of\ the\ Fisher\ test\ comparing\ P(E | C_1 \cap C_2 \cap C_3)\ and\ P(E)$
- Are those patients similar to others? (Descriptive statistics only)
 $on\ the\ subset\ E \cap C_1 \cap C_2 \cap C_3, compute\ mean(gender), mean(age), etc.$
- What happens to those patients? (Descriptive statistics only)
 $on\ the\ subset\ E \cap C_1 \cap C_2 \cap C_3, compute\ mean(death), mean(duration), etc.$

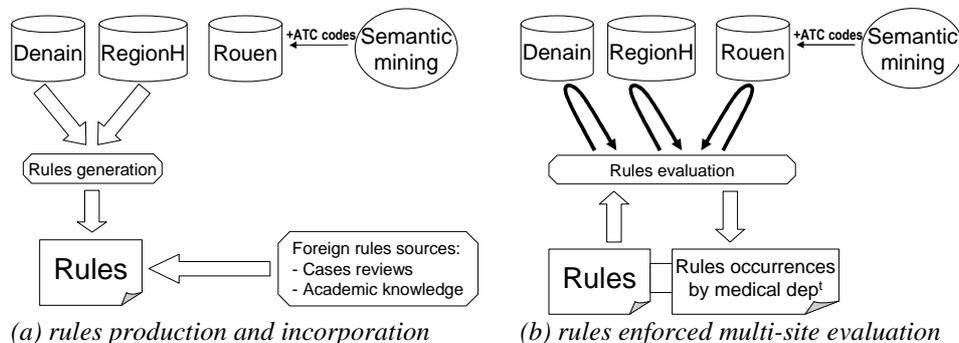


Figure 4. Rules centralization and enforced multi-site evaluation

3. Results

The mechanism properly works and the present task has to be carried on. Till now, rules centralization and evaluation use:

- 75 rules from data mining (rules were obtained from decision trees. Association rules exploitation has just began)
- about 100 rules from Vidal
- 30 rules from Jah et al.

Table 1 presents nine rules that are interesting.

Rules Nr 1 & 2 are single condition rules that come from a staff operated review. It is interesting to notice that their confidences are low and vary from a medical department to another.

Rule Nr 3 comes from the same source and was also found as is by our decision trees. Decision trees are able to find that rule because the confidence is 33% in two departments. That confidence also varies according to the medical department.

Rules Nr 4, 5 & 6 help to understand what can happen when the confidence of academic rules is low. Rule Nr 4 & 5 come from the staff operated review, their confidence is low because the denominator is a too high number (their use would induce an over-alerting). Decision trees also allow finding rule Nr 6: that rules

combines rules Nr 4 & 5 with other conditions so that the confidence is increased. Rule Nr 6 would have less false positives than rules Nr 4 or 5.

Rules Nr 7, 8 & 9 are generated by the data mining process. They are an interesting example of thinking about a prospective use of retrospective rules. Rules Nr 7 & 9 look the same except the third condition of each one: in rule Nr 7 there is a hypoalbuminemia and in rule Nr 9 there is no hypoalbuminemia. This third condition leads to different confidences in the departments, it is a segmentation condition. But in a prospective way it might be possible that this lab setting is still not available. However, we are able to answer the question “what is the probability of too low INR if we don’t know the albumin blood rate”. The answer is provided by rule Nr 8 where hypoalbuminemia=NA (not available), assuming that the lab result is missing at random.

Table 1. Example of rules and enforced evaluation results

Effect	id	Condition(s)	REGION H	Denain Medicine A	Denain Medicine B	Denain Surgery	Rouen
Appearance of a renal insufficiency [Lab]	1	Histamine h2 antagonist	0/3=0%	2/15=13%	0/13=0%	0/4=0%	0/3=0%
	2	Non-steroidal anti-inflammatory agent	20/686=3%	15/393=4%	19/319=6%	3/217=1%	5/234=2%
	3	Antiviral agent	0/12=0%	1/3=33%	4/12=33%	0/1=0%	0/6=0%
	4	Heparin	17/445=4%	26/478=5%	34/473=7%	7/798=1%	1/50=2%
	5	Potassium lowering diuretic	46/841=5%	39/467=8%	25/297=8%	9/218=4%	5/260=2%
	6	Diuretic & Heparin & Age>75	3/32=9%	14/19=73%	9/19=47%	2/18=11%	0/0
Appearance of a too low inr [Lab]	7	Previous too high INR & Age>75 & Hypoalbuminemia	7/12=58%	2/2=100%	2/3=66%	2/7=29%	6/8=75%
	8	Previous too high INR & Age>75 & Unknown blood albumin level	8/20=40%	20/53=38%	15/26=58%	7/13=54%	8/11=73%
	9	Previous too high INR & Age>75 & NO hypoalbuminemia	1/8=12%	18/51=35%	13/23=56%	5/6=83%	2/3=66%

4. Discussion and conclusion

Each of the various sources of ADE rules has its own characteristics. A comparison is provided in Table 2. Our conclusion is that an efficient rules repository should incorporate rules from various sources because of the advantages and drawbacks of each method.

This work enabled the uniform representation and storage of ADE detection rules into a common repository. Those rules can be then evaluated in a few seconds in several medical departments. This work has to be followed up in order to get more rules and more rules evaluations. However it already enlightens three major points that are often underestimated in ADE prevention rules:

- **the need for segmentation** in order to get more precise estimators of probabilities and to reduce over-alerting. Some of those segmentation

conditions can also be “non medical” conditions such as organizational causes and human factors [11]

- **the need for contextualization:** whatever their origin, the rules do not have the same confidence everywhere
- **the need for an evaluation over time** of the rules over time: the existence of alert rules could quickly change the practices and then the confidences of the rules.

Table 2. General considerations about various sources of rules

Question	Academic knowledge	Staff operated record review	Data mining
Number of rules	Very high	Low	Medium
Need for validation	No, commonly accepted	Yes, already done in the process	Yes, must be performed, but sometimes difficult
Confidences of the rules	Not available	Computed by experts	Automatically computed
Number of the conditions	Few (1 or 2)	Depends on the review, often few	Variable, potentially high
Population segmentation, confidences optimization	No	No	Yes
Ability to propose rules when conditions never occur (e.g. absolute contra-indications)	Yes	No	No
Ability to describe very rare events	Yes	Sometimes possible	No
Ability to find all the interesting rules of a dataset	Yes	Yes but limited by the size of the review	Yes depending on the methods (association rules better than decision trees)
Time needed to find rules	Already available	Very time-consuming	Quite fast
Time needed to update confidences over space and times	Not possible	Very time-consuming	Very fast

5. Acknowledgements

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