An Expert System for Microbiological Data Validation and Surveillance

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In this work, we describe a system for microbiological laboratory data validation and bacteria infections monitoring. In the following sections we report about the first results we have obtained with a prototype that adopts a knowledge-base approach for identifying critical situations and correspondingly issuing alarms. The knowledge base has been obtained from international standard guidelines for microbiological laboratory practice and from expert suggestions.

1 Introduction

The main goal of this work is to describe the design and the implementation of an Expert System for Microbiological Data Validation and Surveillance. For bacterial infections, stored data usually includes: information about the patient (sex, age, hospital unit where the patient has been admitted), the kind of material (specimen) to be analysed (e.g., blood, urine, saliva, pus, etc.) and its origin (the body part where the specimen was collected), the date when the specimen was collected (often substituted with the analysis request date) and, for every different bacterium identified, its species and its antibiogram. For each isolated bacterium, the antibiogram represents its resistance to a series of antibiotics [1] and it is usually represented by a vector of couples (antibiotics, resistance), where four types of resistance to antibiotics are possibly recorded: R when resistant, I when intermediate, S when susceptible, and null when unknown. The set of antibiotics to be tested can be defined by the user.

About microbiological data validation, the quality of antibiogram results is a critical point because clinicians use directly these results for therapy definition. Some instruments execute intelligent controls on performed antibiotic test results but these controls are limited because they do not have information about specimen, patient characteristics and infection history. A system, capable of using all available information, may be a better support for laboratory personnel in the validation task. This system should also control the application of standard antibiotic testing guidelines: these guidelines, used by almost all microbiological laboratories, indicate

antibiotic test execution methods and result interpretations. Examples of problems that this system should manage are: automatic correction of antibiotic results for particular species that present in vitro susceptibility but in vivo resistance, controls on the list of tested antibiotics, predictions of test results for a group of antibiotics using some representative antibiotics (ex. Tetracycline is representative for all tetracyclines), intelligent reporting.

The expert system presented in this work is able to provide automatic data validation performing a series of controls. Regarding bacteria infection monitoring, the system identifies critical situations for a single patient (e.g., unexpected antibiotic resistance of a bacterium) or for a hospital unit (e.g., contagion events) and alarms the microbiologist. The prototype adopts a knowledge-base approach to identify critical situations and correspondingly generate alarms. The knowledge base has been obtained from international standard guidelines for microbiological laboratory practice and from expert suggestions. Rules have been validated by laboratory experts and also by an automatic system that uses Data Mining techniques for automatic knowledge extraction [2].

In following sections, we describe the first results we have obtained in a testing trial on two-year real microbiological data.

2 Microbiological Surveillance Expert System

A Surveillance system may be realized using an Expert System programming approach. This Artificial Intelligence programming technique has been applied to the medical field since 1980. In an Expert System [3], also called Knowledge Based System (KBS), knowledge about the problem is translated into special data structures and rules. An inference engine applies these rules to the available data to perform some specific tasks.

Specifications and Features

Given a newly isolated bacterium and the related antibiogram, the system performs five main tasks: validates the culture results, reports the most suitable antibiotics list, issues alarms regarding the newly isolated bacterium, issues alarms regarding patient clinical situation and identifies potential epidemic events inside the hospital.

In the validation of culture results, the system finds antibiotics not tested but necessary, identifies impossible antibiotic results for particular species and tests common relations between antibiotic results.

In the intelligent reporting of antibiotics results, the system associates to each antibiotics a suitability, obtained considering some antibiotic characteristics: costs, infection site, bacteria specie and hospital ward.

In single analysis alarms, the system provides information regarding the bacteria (dangerous resistance, multiresistant bacteria, etc.).

In single patients alarms the system issues alarms considering the infection history of the patient. For example:

- **Polimicrobic population:** if two or more bacteria species where found in two different (consecutive) time points in the same sample material;

– **Resistance Acquisition:** if the newly identified bacteria has more antibiotic resistances than the last previous one of the same specie.

The system will also provide ***information regarding the hospital ward*** (contagion) and ***epidemic breakout alarm***: the system architecture is ready but these controls are not implemented yet.

Knowledge elicitation

For knowledge elicitation we selected NCCLS [4], the international standard organization recognized by almost all laboratories as the reference in routinely work. NCCLS writes an annual compendium [5] containing testing guidelines for microbiological laboratories. NCCLS guidelines are basically composed, for each species, of: a table that specifies antibiotics to be tested, a table that specifies antibiotic test interpretation and a list of exceptions regarding particular antibiotic test results.

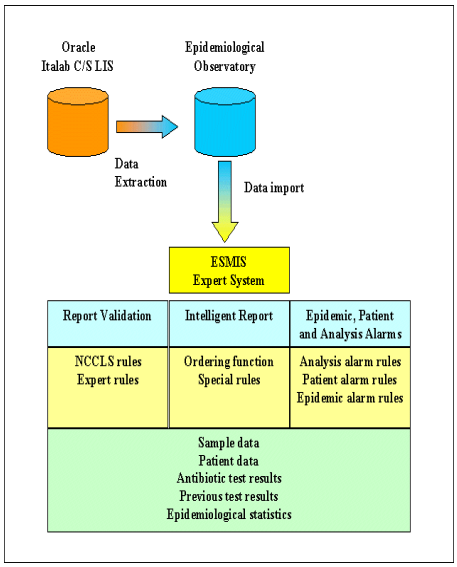

Fig.1 – Databases and Data types

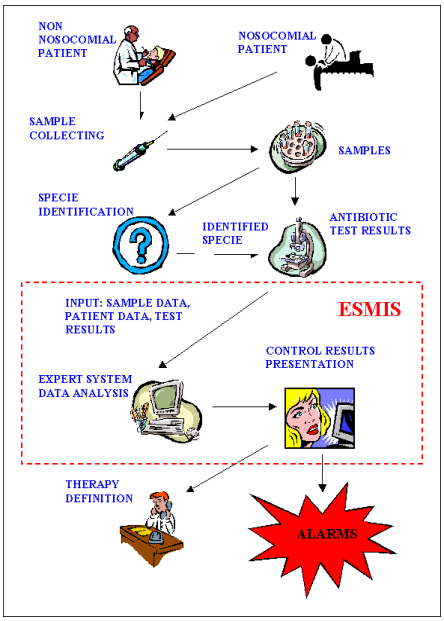

Fig.2 – Control flow of the overall system

System Architecture

A laboratory information system called Italab C/S (developed by Dianoema S.p.A. an information technology company operating in the health care market) manages and stores all the information concerning patients, analysis requests and analysis results in an Oracle database and transfers in real-time microbiological data to a dedicated database called Epidemiological Observatory. Description of databases and data types are shown in figure 1. ESMIS will became part of the routinely laboratory result production process as described in figure 2. ESMIS introduces in the process the automatic validation step: in this step ESMIS presents the results of its controls to

laboratory personnel that will decide to agree or disagree with them and to make, if necessary, changes on antibiotic test results. ESMIS also produces the final report and issues alarms regarding the patient clinical situation.

3 Implementation and first prototype description

We developed an ESMIS prototype using the Expert System Tool Kappa-PC 2.4 by Intellicorp [6] which offered a good cost/features degree and a simple and powerful programming language. Moreover, it works in interpreted and compiled mode and can perform both forward and backward chaining reasoning.

Knowledge Base
Since NCCLS compendium guidelines can change each year, ESMIS rules are designed as templates: rules are general and are dynamically instantiated referring to NCCLS table entries, so they can be updated with the last guidelines version by simply updating the table. Thus the problem of continuous knowledge update by qualified people is avoided since it is sufficient to update NCCLS table entries which are stored in an Oracle database. We have implemented also exception rules, representing particular cases not considered in NCCLS tables. Of course these exception rules need to be changed if the specific cases changes. Template rules work on a NCCLS table that specifies antibiotics to be tested on a specific species subdivided in: Main reporting antibiotic groups (basic, advanced, specific and for urinary tract infections), Antibiotic subgroups (antibiotics with similar characteristics) and Antibiotic equivalencies (antibiotics with the same bacteria test result). Examples of template and exception rules used in ESMIS knowledge base are the following:

- There are two types of Rack test rules: template rule and exception rules.
  - **Template rules** verify if at last one antibiotic from each subgroup was tested.
  - **Exception rules** are used to represent exceptions in rack test specified in NCCLS table notes. One example is:
    IF **InfectionSite** = "Urinary Tract" AND **Tested**(Erythromycin)
    THEN DisplayComment("Erythromycin was tested but it isn't relevant")
- Single analysis alarms
  - For implementing the Resistance Acquisition control we use the following rule:
    Considering the patient infection history
    IF **SpeciesOfLastBacteria** = **BacteriaSpecies**(*IdentifiedBacteria*) **AND ResistanceNumOfLastBacteria > ResistanceNumOfNewBacteria**
    THEN **IssueAlarm**("Therapy is failed! Bacteria has increased the number of antibiotic resistances")

Graphical User Interface
In every medical software application, the system GUI is very important and needs particular attention. Laboratory personnel use ESMIS as a decision support system so the information provided must be simple, direct and self-explaining in order not to introduce a delay in the results production process. These objectives are obtained tuning the knowledge base and organizing the main window in a suitable manner.

4 Results of first ESMIS testing trial

Actually we have realized a prototype of ESMIS that contains knowledge regarding the *Staphylococcus* species and the *Enterobacteriaceae* species. The KB is composed of: 9 culture result validation template rules, 24 culture result validation exception rules for the *Staphylococcus* species, 29 culture result validation exception rules for the *Enterobacteriaceae* species, 8 single patient alarm rules and 6 single analysis alarms rules.

This prototype has been tested off-line on two-year culture results collected from the Clinical, Specialist and Experimental medicine department, Microbiology section of the University of Bologna (Italy). During these two years, another microbiological expert system was used for microbiological data validation. This system presents some problems: the knowledge base is "closed" and no change can be made on it, some controls were not implemented and must be manually executed by laboratory personnel and finally there are no clear descriptions about generated alarms.

ESMIS analysis results were compared with the previously adopted expert system. Even if data have been already validated, ESMIS was able to discover inconsistencies over data. Figure 3 shows ESMIS evaluation process results regarding a *Staffilococcus Aureus* bacterium:

REP.GRP.	ANTIBIOTIC	STRUM. RES.	ESMIS RES.	DER.	TO REPORT	RACK NOTE	VALID. NOTE	REPORT NOTE
C41	RIFAMPIN	S	S	no	no	--	--	N_REP1
B41	VACOMYCIN	S	S	no	*	--	--	--
B21	CLINDAMYCIN	R	R	no	*	--	--	--
B11	CLARITHROMYCIN	R	R	no	*	--	--	--
---	NETILMYCIN	S	>R<	no	*	N_RACK1	N_VALI1	--
A11	OXACILLIN	R	R	no	*	--	--	--
A21	PENICILLIN	R	R	no	*	--	--	--
B31	SULFA/TRIMETH	R	R	no	*	--	--	--
---	CLOXACILLIN	-	>R<	*	no	--	--	N_REP2
---	DICLOXACILLIN	-	>R<	*	no	--	--	N_REP3

Fig.3 – Antibiogram results after ESMIS evaluation

For each alarm there is an associated note explaining the name of the rule applied and its description. Please notice that in Figure 3, an inconsistency arises between NETILMYCIN (belonging to the AMINOGLYCOSIDE antibiotic group) and OXACILLIN. The validation note about this inconsistency is N_VALI1:

```
VALIDATION NOTE: N_VALI1 -->  1: ( Vali_Stafi_23_5)
    If OXACILLIN test result is Resistance (R) then test results for
AMINOGLYCOSIDE should be Resistance too. The expected test result is R.
```

Beside data validation, further objectives achieved by ESMIS are:

1. **Flexibility:** ESMIS knowledge base is mainly composed by rules obtained by NCCLS international guidelines. These rules are not always recognized as correct and sometimes personalization are needed to adapt the control to the local environment. The expert has easily applied his personalization and has made ESMIS better tailored to the local situation.

2. **Clarity:** Now, only the description of issued alarms (customizable by the laboratory expert) is showed, allowing a simpler problem identification. For every validation step, the evolution of reasoning is also shown.
3. **Intelligent reporting:** the intelligent reporting features of ESMIS was recognized by experts as one of the most important innovation. For each bacteria, only the antibiotic results of less dangerous antibiotics (to which the bacterium is susceptible) must be presented in the final report. The expert may customize the final report and guide therapy definition by creating appropriate reporting rules. The reporting note for RIFAMPIN antibiotic, presented in Fig.3, is N_REP1:

```
REPORTING NOTE:  N_REP1 -->  1: ( Ref_Stafi_29)
 Antibiotics belonging to Group C and U should be presented in the
final report only if the infection location is Urinary tract.
```

4. **Contagion alarms:** ESMIS has found some possible contagion events by analyzing the culture results of some patients. The laboratory expert has analyzed these alarms and recognized that these events need further investigation.
5. **Patient infection surveillance:** for each patient, culture results are compared with the previous ones on the same patient and alarms regarding possible dangerous bacteria mutations and infection evolutions are issued. Experts recognize that these alarms may be useful for supporting therapy control.
6. **Performance:** In real-time analysis simulation the first ESMIS prototype has evaluated each antibiogram in 33 second and this performance is compatible with the normal production process of analysis results.

5 Related work

During the last few years, many surveillance systems have been developed in order to monitor microbiological analysis results and to early identify infection and epidemiological events. All these systems have peculiar features that make them not suitable for efficient and correct analysis of Italian data. Significant examples of these systems are WHONET 5 [7], GermWatcher [8] and TheraTrac 2 [9]. WHONET 5 is a database software for the management of microbiology laboratory test results. GermWatcher is an expert system, which applies both local and international culture-based criteria for detecting potential nosocomial infections. TheraTrac 2 is a system for microbiological data validation and real-time alarming. It directly interacts with Vitek [10] an expert system for test results validation, that is integrated in particular analytical instruments. All systems use international standard guidelines in order to defining controls to be executed on laboratory test results. WHONET is an off-line tool useful for medium and long term data analysis but it is not suitable for real-time monitoring and alarm generation. GermWatcher works on-line but in order to work correctly needs a lot of data not available in Italy. TheraTrac 2 works on-line but is designed for USA hospital organization (focused on pharmacists) that is different from Italian hospital organization.

In the past, DEIS University of Bologna and Dianoema S.p.A. have designed and implemented an expert system for the validation of biochemical analysis [11].

6 Conclusions and Future work

In this paper we have described a system for microbiological laboratory data validation and bacteria infections monitoring. We also described the first results we have obtained with a prototype that adopts a knowledge-base approach to identify critical situations and to correspondingly issue alarms. Expert system technology gives the following advantages to our system: knowledge base easy update (thanks to template rules), quality of service, clarity and flexibility. In [2] we have also experimented automatic knowledge validation and extraction of ESMIS rules by using Data Mining techniques.

In the future we plan to further develop our system by identifying the final tool for ESMIS implementation, by extending ESMIS knowledge base and by integrating the system with datamining techniques and time series analysis.

7 Acknowledgements

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8 References

1. A.Balows, W.J.Hauser,Jr, K.L.Herrmann, H.D.Isenberg, H.J.Shadomy, *Manual of Clinical Microbiology*, 5°Ed, American Society for Microbiology, Washington, 1991
2. E.Lamma, M.Manservigi, P.Mello, A.Nanetti, F.Riguzzi, S.Storari, *The Automatic Discovery of Alarm Rules for the Validation of Microbiological Data*, IDAMAP2001, London, UK
3. M. Stefik, *Introduction to knowledge systems*, Morgan Kaufmann, 1995
4. National Committee for Clinical Laboratory Standards (NCCLS), www.nccls.org, Accessed 10 July 2001
5. NCCLS, *Performance Standards for Antimicrobial Susceptibility Testing; Ninth Informational Supplement*, M100-S9 Vol. 19 No. 1, January 1999
6. Intellicorp, Inc., Http://www.intellicorp.com, Accessed 10 July 2001
7. World Health Organization, *WHONET 5 – Microbiology Laboratory Database Software*, WHO/CDS/CSR/DRS/99.1
8. M.G.Kahn, S.A.Steib, V.J.Fraser, W.C.Dunghan, *An Expert System for Culture-Based Infection control Surveillance*, Washington University, 1992
9. Theratrac, Biomerieux, http://www.theratrac.com, Accessed 10 July 2001
10. Vitek, Biomerieux, http://www.biomerieux.com, Accessed 10 July 2001
11. M.Boari, E.Lamma, P.Mello, S.Storari, S.Monesi, *An Expert System Approach for Clinical Analysis Result Validation*, ICAI 2000,Las Vegas, Nevada, USA
12. Ministero dell'università e della ricerca scientifica e tecnologica, www.murst.it, Accessed 30 June 2001