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Transferability modelling in the TREAT decision support system

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Abstract: One of the key-components for success of a decision support system is in its flexibility and applicability to different clinical locations. The present study is devoted to a system which is capable of successful transfer to a distant environment. We have developed a decision support system for antibiotic treatment (TREAT), which was adapted to four different hospitals in Europe. The system is based on a causal probabilistic network (CPN). The purpose of this paper is to present the models for transferability used in TREAT. The problem of transferability is addressed in the context of CPNs, emphasising the advantages of use of CPNs for solving the problem. The process of adapting TREAT is relatively easy; that is due to the modularity of the system. The system has been built using a modular architecture that allows rapid transfer of the system to different clinical environments. Such modularity can be archived by simple means which include the universal and modular structure of the CPN, the establishment of a large group of conditional probabilities in the CPN that are assumed to be independent of time and place, and the use of hierarchical Dirichlet methods for learning of data. Due to the universal structure of the CPN, the problem of transferability in TREAT concerns only the medical domain factors, not the topology of the system.

1. INTRODUCTION

A medical decision support system (MDSS) is constructed to assist clinicians in making decisions relating to diagnosis, treatment or prognosis. To achieve clinical and commercial success, such a system must possess transferability, i.e. it must be applicable to environments, different from the environment, where it has been developed. Most systems have to be adapted to a new location, because the factors their advice relies on can be widely different from one location to another (Spiegelhalter and Knill-Jones, 1984).

Transferability is a key issue in the development and implementation of MDSSs. The term 'transferability' has been defined as 'the degree to which the system retains its credibility and therefore reliability and usefulness, when applied in another organisational environment' (Nolan *et al*., 1991). In general, transferability is a complex property encompassing many basic properties related to the structure and function of MDSSs. The transfer of the system may affect the quantitative attributes of the system, as well as the topology of the models used in the system. The factors relevant for adaptation (or transferability) can be organized under two main headings: factors concerning the medical domain and factors concerning the information technology domain. Domain factors, such as epidemiology, methodology, terminology and resources belong to the medical domain addressed by the MDSS. Information technology factors, such as knowledge acquisition, knowledge representation, system functionality and design, are independent of clinical medicine and belong instead to the discipline of knowledge engineering (Nolan *et al*., 1991; Schioler *et al*., 1994). Transferability is not only relevant for transfer in space (different geographical locations), but also for transfer in time. For example, in the case of application to the domain of infections diseases, it should be remembered that some epidemiological factors, the output of a MDSS relies on (e.g., the susceptibility of pathogens to antibiotics), may change over time, requiring periodical adaptation of the system even at the same hospital.

The process of adaptation to new conditions depends on the techniques used to construct a system. The examples of experiments with transferability of MDDSs in the literature include studies about the systems based on Bayesian classification (Zagoria and Reggia, 1983), CPN (Jensen and Andreassen, 2007), neural networks (Ellenius and Groth, 2000), rules (Boon-Falleur *et al*., 1995), diagnostic scores (Lindberg *et al*., 1987), case-base reasoning (Gierl *et al*., 2003).

The actuality of the transferability problem is supported by many examples of MDDSs, which did not perform well after being transferred to a distant environment (Zagoria and Reggia, 1983; Lindberg *et al*., 1987; Leibovici *et al*., 1997). One such system is a MDDS for empirical antibiotic treatment of severe infections built at Rabin Medical Center (Beilinson Campus, Petah-Tiqva, Israel) (Leibovici *et al*., 1997). This logistic regression based-system was tested in a prospective, non-interventional, comparative cohort study at the original site and at another hospital. It outperformed physician at the original site, but its performance deteriorated

when transferred to another site. The authors of the system believe that the reason for this failure was due to underestimating the necessity of adapting the system to the settings of another hospital. First of all, it concerns the epidemiological factors related to infectious diseases. For example, the prevalence of different pathogens and their associated susceptibility to antibiotics may differ from region to region and from hospital to hospital and even different departments at the same hospital may have distinct patterns of susceptibility (Leibovici *et al*., 2000).

A system called TREAT for treatment of severe infections has been applied in four hospitals in Denmark, Germany, Italy, and Israel. In these countries many epidemiological factors are different, the most important being that pathogens have substantially different susceptibility to antibiotics. Therefore, an antibiotic treatment which is appropriate in one country may be considered inappropriate or overkill in the other countries. TREAT is based on a CPN (Andreassen *et al*., 2005) and the aims of the system are to improve the rate of appropriate antibiotic treatment, thereby reducing mortality, and to shift antibiotic use towards economical antibiotics, both in terms of direct cost, side effects and ecological cost, ascribed to the reduction of susceptibility due to use of antibiotics. Retrospective and prospective controlled clinical trials in four countries showed that despite differences between these countries, TREAT improved the rate of appropriate antibiotic treatment while reducing hospital stay and antibiotic costs, mainly the ecological costs (Kristensen *et al*., 2001; Paul *et al*., 2006). TREAT thus presents an example of a system that can be successfully transferred to a distant environment.

We believe the ease with which the transfer has been accomplished is due to the strategy chosen. In essence, the adaptation has been achieved by calibration, where we use the word calibration to indicate that it has only been necessary to make quantitative changes, without making qualitative changes, i.e. the parameters of the CPN have been modified, while it has been possible to leave the structure of the CPN unchanged. In this paper it is outlined, what data are needed for modelling and how the transferability is technically achieved. The problem of transferability will be addressed in the context of CPNs**,** emphasising the advantages of use of CPNs for solving the problem. We will show that the process of calibrating TREAT is relatively simple, affecting only the medical domain factors, not information technology factors. The system has been built using a modular architecture that allows rapid transfer of the system to other clinical environments. The paper describes the means used to achieve such modularity.

2. STRUCTURE OF TREAT

The main components of the TREAT system are the following (see also Fig. 1):

User interface. The user interface is designed for entering the patient data and displaying the results of TREAT's advice. It is implemented as a web page, thus enabling easy access to the system from different computers on the wards.

Patient database. All patient data are stored in a SQL database. The data ranges from general patient and admission information to signs and symptoms observed by the clinician as well as microbiological results from blood and other types of cultures.

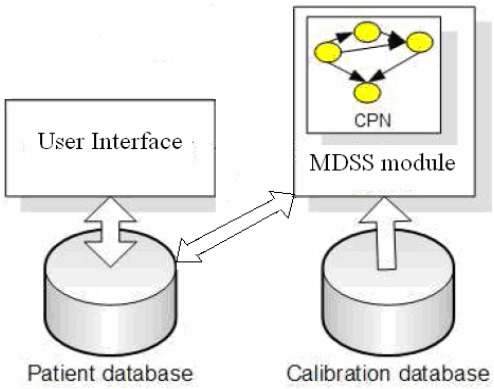

Fig. 1. Structure of the TREAT system

Calibration database. This SQL database contains information, which is specific for each hospital (distributions of pathogens, pathogens susceptibilities to antibiotics, therapy costs, etc.).

MDSS module. This module plays the main role in the system. It can predict the diagnosis and recommend an appropriate antibiotic therapy based on data entered by the clinician. The module has two components: a CPN representing different infectious diseases, pathogens, treatments and treatments coverage; and an algorithm for finding the optimal antibiotic therapy. The CPN has been built using the Hugin tool (Hugin, 2004). The algorithm has been written in C++ using Hugin's API for handling the CPNs.

The TREAT's advice is based on the probabilities read from the CPN on diagnosis, infections severity, and the coverage of different single and combination antibiotic treatments. The algorithm chooses the most appropriate treatment using a cost-benefit analysis, where the main benefit components are the increase in the survival rate of the patient and reduction in bed days; the main cost components are the cost of administering the antibiotic therapy, the potential cost of adverse effects associated with antibiotics, and the cost of ecological impact on susceptibility associated with each antibiotic.

2.1. TREAT CPN

CPNs make it possible to build highly structured stochastic models. They can be used to express prior knowledge both of a qualitative and quantitative nature about the behaviour of biological systems. In general, a CPN (or a Bayesian network, or a belief network) is a probabilistic graphical model that represents a set of variables and conditional probabilities linking them. For example, a CPN can be used to calculate the probability of a patient having a specific

disease, given the absence or presence of certain symptoms, if the conditional probabilities between symptoms and disease are assumed to be known. Formally, CPNs are directed acyclic graphs whose nodes represent variables, and whose arcs encode conditional dependencies between the variables. A node that receives a link from another is called a *child*, and a node from which the link originates is called a *parent*. Each node has an associated table of conditional probabilities: the probability of the states in the node. A generalization of CPNs that can represent and solve decision problems under uncertainty are called Influence diagram. More about the theories behind a CPN (Pearl, 1988) and their introduction into the medical domain by (Heckerman, 1989; Andreassen *et al*., 1987) can be found elsewhere.

The CPN in TREAT was built from distinct modules, each module representing one site of infection (e.g., urinary tract infections site (UTI)). Each site includes a set of specific pathogens that may cause an infection in the site (e.g., there are 13 different pathogens in UTI) and the state of infection by each pathogen before and after the treatment. The sites are connected to a stochastic variable *sepsis*. (The word "sepsis" refers to the fact that, in this condition, sites in the body that are normally sterile may contain pathogens.) Sepsis is assumed to have several states, among them "moderate sepsis", "severe sepsis", etc. Sepsis may cause several signs and symptoms, e.g. fever, which is represented by 5 states: <36, 36-36.5, 36.6-37.9, 38-38.6, >38.6. Each pathogen at each site of infection is also connected to the variables representing microbiological findings in blood culture.

One of the virtues of the CPNs, is that decision theory can easily be applied (by means of the influence diagrams formalism). In TREAT, the advice on the most appropriate treatment is based a cost-benefit analysis. But it should be noted, that the decision theory module in TREAT is placed outside the CPN, in the algorithm. The CPN does not include any influence diagrams due to a computational limit caused by the complexity of the CPN.

The topology of the TREAT CPN was chosen to reflect the most universal scenario for an infection episode. By other words, the CPN is larger than otherwise needed to be built for use at a single location. For example, the set of pathogens belonging to a site of infection is chosen to be larger than could be observed at a specific hospital. Pathogens in TREAT represent a more or less full collection of pathogens observed all over the world. Another example concerns the routine of blood sampling for culture. The current CPN for blood-culture bottles has space for 2 samples, each including 3 sets. One set consists of maximum 3 bottles: 2 aerobic and 1 anaerobic. This is presumably sufficient to cover all possible combinations of samples/sets/bottles taken in the hospitals worldwide. In more details the structure of the CPN is described elsewhere (Andreassen *et al*., 2000; Leibovici *et al*., 2000).

3. MODELLING FOR TRANSFERABILITY IN TREAT

Establishment of the universal attributes and the factors for calibration formed the main decision concerning modelling for transferability in TREAT.

3.1. The universal attributes in TREAT

Due to the universal nature of the CPN (for example concerning pathogens and blood samples) we allowed ourselves to fix the CPNs structure. Only the quantitative parameters of the TREAT model were adapted to changes in locations and in time. Thus the problems of transferability in TREAT do not concern the factors belonging to the information technology domain.

The next point of dealing with transferability was the discussion about the conditional probability tables belonging to the stochastic variables used in the CPN. The discussion has revealed that they can be divided into two groups. The first group, which is far the largest, consists of conditional probabilities that we assume to be independent of time and place. Typically, these conditional probabilities are hard-wired into the CPN, among them the probabilities required for the assessment of the state of sepsis. For example, the conditional probabilities of the states of fever given various states of sepsis are assumed to be the same for all hospitals. Other examples of universal factors include signs and symptoms of sites of infection. For instance, the conditional probability for flank pain (a sign of UTI) given various diagnosis in UTI is independent on location.

Conditional probabilities in the other group are assumed to be specific for each participating hospital and they may change over time. The factors they correspond to are discussed in the next section.

3.2. The factors for calibration in TREAT

The factors for calibration in TREAT belong only to the medical domain. They can roughly be divided into the two groups: epidemiological and administrative. For practical convenience, both epidemiological and administrative factors are kept in the calibration database.

The epidemiological factors for calibration in TREAT are included in Table 1. The data can be collected based on the local databases and the literature, or other sources of knowledge. These calibrations are the most important, as they are involved into the basic reasoning of the system. Conditional probabilities corresponding to these factors have to be compiled into the CPN.

Due to the explicit nature of the CPN, where the data can be found for both the parent and child nodes, the learning of data related to the epidemiological factors can be archived by simple counting.

Table 1. Epidemiological factors for calibration in TREAT

1. Prevalence of risk factors
2. Prevalence of pathogens
3. Distribution of contaminants in blood- culture bottles
4. Pathogens susceptibility to antibiotics

The problem of transferability of administrative factors was encountered mostly at the level of workflow of the system and user interaction. These factors are included in Table 2. The factors marked as "Other information" include the names of the hospital departments, the names of the local-culture samples, the units for laboratory values, and other text strings and information that at least partially allow the text available in the system to be more specific for the hospital or adapted to the local language, and that allow measurements to be converted between different unit systems. These administrative factors are compiled into the CPN and the user interface.

Table 2. Administrative factors for calibration in TREAT

1. Treatments available at the hospital and corresponding costs
2. Basic hospital costs (e.g., the cost of a bed-day)
3. Antibiotics available at the hospital pharmacy
4. Antibiotics used for testing of susceptibilities
5. Routine of blood sampling for culture
6. Other information

In the following we give some examples of calibration of the factors given in Tables 1 and 2.

3.2.1. Prevalence of pathogens

Based on the distribution of pathogens, the CPN calculates probability for diagnosis. The prevalence of a pathogen may vary from place to place, either due to genuine geographical variation or to different reasons for referral to the clinical centre. In TREAT we specify the prevalence of the sites of infection in the population at large and in the hospital; and the prevalence of pathogens by site of infection, place of acquisition (community/hospital) and various risk factors.

The prevalences of pathogens in the CPN are represented by the conditional probabilities for pathogens given specific risk factors. For calibrating pathogens at a hospital, we ask a local clinician to fill a table with prevalences of pathogens within site of infection with specific risk factors, given place of acquisition.

3.2.2. Pathogens susceptibility to antibiotics

The knowledge about pathogens susceptibility to an antibiotic forms the basis for the decision-theoretical calculation of advice by TREAT. The knowledge required takes the form of a matrix that contains the susceptibilities of each of the 156 pathogens considered in TREAT. The *susceptibility* of a pathogen to an antibiotic is the probability that the activity of a pathogen can be eliminated by the given antibiotic. The susceptibility also depends on the place of acquisition of the infection. Hospital-acquired infections tend to be less susceptible to antibiotics than infections acquired in the community; therefore the place of acquisition is also an entry in the matrix of susceptibilities.

The susceptibilities differ from region to region and from hospital to hospital. At a given hospital, at a given point in time, we need to provide estimates of susceptibilities to allow the CPN to calculate the probability that a given treatment will cover.

In the process of calibration the hospital is asked to compile a database of *in vitro* susceptibilities of most of the relevant pathogens for a number of antibiotics. The size of local databases is limited as susceptibilities change over time. Even though the databases may contain several thousand cases, complications may arise. Some of the pathogens are not frequently occurring, and some pathogens may only be tested for their susceptibility to a small number of antibiotics. As a consequence, a matrix of susceptibilities can contain a minority of entries with high counts; for example, several hundred cases where the pathogen *Escherichia coli* had its susceptibility tested for antibiotic ampicillin. Most of the entries have very few observations, and the susceptibility must be decided on the bases of a few, or even zero, observed cases.

To generate susceptibilities even when the counts that can be acquired from the local databases are very low, we have chosen a Bayesian approach, where a prior distribution is specified for the susceptibility. It is practical to use beta distributions as the priors and to update the posterior using hierarchical Dirichlet learning (Andreassen *et al*., 2003). These prior distributions may be based on observations from the literature; on databases from other clinical sites; or from the same database, but without distinguishing between different places of acquisition of infection; on databases from another period of time; on the knowledge, that some antibiotics will always be ineffective against pathogens; on the knowledge about similar properties of some pathogens (Andreassen *et al*., 2007).

3.2.3. Treatments available at the hospital and corresponding costs

Different hospitals have different politics regarding antibiotic therapy. For instance, the hospitals in the Northern Europe are known as being conservative in the choice of antibiotic treatment and penicillins are still widely used in these countries, while clinicians in the Southern Europe are prone to prescribe drugs of newer generations, e.g., cephalosporins and carbapenems.

Each location can define which antibiotic drugs or combinations will be allowed to be tested and thus recommended by TREAT. Treatments in TREAT are calibrated, as well as their costs of administration, which include the cost of purchasing a drug, with addition of the cost of disposables and the labour costs. The cost of ecological impact on resistance associated with each antibiotic depends on pathogens susceptibility to this antibiotic at a hospital and has also to be calibrated. We note,

that the side-effects cost (the potential cost of adverse effects associated with the drug) is assumed to be the same for all the sites given similar modes and doses of administration.

3.4 Practical applications

TREAT has been calibrated to four different sites: 1) Aalborg Hospital in Denmark; 2) Rabin Medical Centre, Beilinson Campus, in Petah-Tiqva, Israel; 3) The University Hospital in Freiburg, Germany; 4) Gemelli Hospital, Universitá Cattolica del Sacro Cuore School of Medicine, in Rome, Italy.

Aalborg Hospital participated in a retrospective, non-interventional trial (Kristensen *et al*., 2001). Data collection here was based on the local databases and the literature. The results of the trial shows, that TREAT suggested antibiotics which would provide coverage in 89% compared to 61% for which empirical therapy actually provided coverage. Other three hospitals participated in a prospective randomised controlled trial of the system (Paul *et al*., 2006), designed as a cluster-randomised trial. The first round of calibration connected to the cluster randomised trial was performed for Rabin Medical Centre in Israel. The data for calibration were found in the local databases and the literature. The next two participants of the trial, University Hospital in Freiburg and Gemelli Hospital in Rome, used not only their local databases and literature, but they also had access to the data collected at the Rabin Centre. The calibration tables for Freiburg and Rome were pre-filled by the default data based on the Rabin collection. That simplified the task of calibration, as in some cases the clinicians in Freiburg and Rome observed the similarity between their and the Rabin's data. The aim of the cluster randomised trial was to compare performance of wards which used TREAT (intervention) to those without TREAT (control). The rate of appropriate empirical antibiotic treatment was higher in intervention wards using the TREAT system versus control wards that had no access to the MDDS, but were openly monitored (73% versus 64%). Length of hospital stay, costs related to the ecological impact on resistance and total antibiotic costs were lower in intervention versus control wards.

4. DISCUSSION

Based on the promising results of the clinical trials of a MDSS based on a CPN (TREAT), it was concluded that modelling for transferability in the system gave good results, and that successful transfer to a different environment can be achieved. The aim of the paper was to present modelling for transferability of TREAT and to analyse the means which lead to success in transferability.

The system has been built using a modular architecture that allows rapid transfer of the system to different clinical environments. Such modularity can be archived by several relatively simple means. First of all, the core of the TREAT system is a CPN having a modular structure. For purpose of transferability a CPN offers a collection of advantages, that is unique to this platform for decision support systems: a clear differentiation between qualitative and quantitative knowledge; a way to draw strong knowledge into the system, without the need to repeat the statistical analysis and collection of large databases at each site; an explicit differentiation between local and universal factors; a way to combine data derived from the literature with data derived from local databases.

A clear differentiation between qualitative and quantitative knowledge is an important feature of CPNs. The universal and fixed structure of the CPN in TREAT lead to a relatively simple process of calibration affecting only the medical domain factors, not information technology factors. In the case of other platforms it would require revising the knowledge base with complete development from scratch (for example, a rule-based approach would require revision of the set of rules).

Based on the explicit differentiation between local and universal factors in CPNs, we established a large group of conditional probabilities in the TREAT CPN that are assumed to be independent of time and place, thus reducing the group of factors needed to be calibrated.

We have shown, that due to the universal topology of the CPN, the calibration of TREAT is only of quantitative nature, without changes in the CPN's structure. We do not foresee a situation in which there will be need to modify the structure of the CPN. The design reflects the pathogenesis of infections as it is currently understood. However, if new biological markers of infections emerge, that change our understanding of the relations between pathogens, sepsis and the manifestations of sepsis, these will probably have to be incorporated into the model.

Future efforts should be invested in optimising the process for calibrating distribution of pathogens. The collection of data for calibrating pathogens is a complex and time consuming process. The full data for prevalences of pathogens given risk factors are available only in an environment in which a full patient electronic file is kept, and the diagnoses of sites of infection must be linked to bacteriological results. But even in such an environment data might be biased by missing data (e.g., of hospital acquired infections), and the result of data collection may be sparse and poor. Application of machine learning methods is one of possible solutions for minimising the problem. Another solution may probably be found in revising the current structure of the CPN for pathogens and reducing the state space of conditional probabilities for pathogens.

To conclude, we have built a CPN-based MDSS, which is capable of successful transfer to a different environment. The modularity of the system makes it easier to add or revise the knowledge base without necessitating complete development from scratch. Modularity was archived by simple means, including the universal and modular nature of the CPN, the establishment of a large group of conditional probabilities in the CPN that are assumed to be independent of time and place, and the use of hierarchical Dirichlet methods for learning of conditional probabilities.

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