Clinical decision support: distance-based, and subgroup-discovery methods in intensive care
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Citation for published version (APA):

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Chapter 1. GENERAL INTRODUCTION
1.1. Problem domain and objectives

Healthcare is constantly changing and becoming more complex. We live in an era of growing concern with regards to the quality and costs of healthcare. The rapid technology advances since the 1990s have made it possible for (computerized) Clinical Decision Support Systems to play an important role in healthcare improvement, and such improvements have already been shown in many occasions [1]. Most clinical decision support systems described in the literature interact with the healthcare provider (usually a physician) about a specific patient and concern computer applications running at the same location where decision support is provided.

This thesis has two parts, each addressing a form of decision support that deviates from this mainstream scenario and which has been less investigated. In the first form, decision support is aimed at health care managers, aiding them in scrutinizing and improving healthcare practice by finding “interesting” patient subgroups. These are patients whose behavior deviates markedly from the rest. In the second form, decision support is embedded within a larger telemedicine system. We dub such systems with the term “Decision Support Telemedicine Systems” (DSTS). Below we describe each of these two forms and state the respective objectives and research questions.

1.1.1 Part 1: Subgroup discovery

Clinical decision support systems operate on a knowledge base. Knowledge can be elicited from experts or extracted from the literature. Knowledge can also be derived from large databases. In this case we speak of knowledge discovery. CDSSs that use knowledge obtained by knowledge discovery are often referred to as intelligent decision support systems. However, communicating the discovered knowledge itself to the user (without using it for further reasoning) can often be very useful, for example by focusing the user’s attention to interesting phenomena thereby aiding them in generating hypotheses or taking actions for improving health care practice.

Many methods of knowledge discovery exist. Most of them aim at obtaining knowledge in the form of a global predictive model where an outcome of interest (e.g. survival status) or its probability can be predicted for any subject in the population. For certain applications, however, one searches for interesting subgroups that stand out in a certain sense, think for example of a subgroup of patients with an extremely high probability of dying, or a subgroup of patients with a very high or very low blood glucose level. Instead of fitting a global model to the whole population, one may directly investigate which characteristics of subjects are responsible for this behavior.

There are various subgroup discovery methods discussed in the literature. Of particular interest in this thesis is the Patient Rule Induction Method (PRIM) [2]. In contrast to other methods, PRIM is patient (in the sense that it is not greedy) with using the observations in the provided sample: to find a subgroup the algorithm removes a very small proportion of the observations in each step. This allows PRIM, which is in essence a hill climbing algorithm, to have sufficient data in subsequent steps to correct possible suboptimal earlier choices. PRIM was introduced in 1999 and is gaining popularity as a tool in
applied research, although its use in clinical medicine is still minimal. The objective of the first part of this thesis is to investigate the merits and limitations of applying PRIM to medical data. Specifically the following research objectives were pursued:

- To assess the value of PRIM and compare it to the logistic regression model in the ability to discover subgroups of old intensive care patients with very high in-hospital mortality (Chapter 2). Mortality is represented as a binary variable.
- To identify and assess PRIM subgroups of intensive-care patients with very high values of blood glucose, in spite of being on an intensive insulin therapy (Chapter 3). The blood glucose measurements are continuous and are ordered in time.
- To compare the capabilities of PRIM with the established Classification and Regression Trees (CART) algorithm in subgroup discovery (Chapter 4).

These three studies together are the most comprehensive attempt in medical informatics to shed light on the applicability of PRIM to clinical medical applications in static and temporal domains.

1.1.2 Part 2: Decision Support Telemedicine Systems

In Decision Support Telemedicine Systems (DSTS), which is the topic of the second part of the thesis, one may leave the clinical decision support system (CDSS) at the site where it was developed and provide the services of the system at a distance e.g. via the web. This not only eases the maintenance problem of the system, but the decision support services can also be provided to a wide range of users, most notably patients.

We investigated the literature to understand what kinds of systems have already been described. Of specific interest were recurrent properties of such systems such as the type of communication used (e.g. store-and-forward such as email, or continuous such as teleconferencing), the type of decision support, and the types of medical processes that were relevant in a DSTS (e.g. monitoring, diagnosis or treatment).

We assumed that the combination of telemedicine systems and decision support systems would also lead to a number of emerging properties that are not present in these systems separately. The value of one property often has implications for other properties. For example, when a low frequency store-and-forward form of communication is used (communication is carried out e.g. only 1 time every day), it will be impossible to provide decision support related to monitoring of data where rapid intervention is required in case of an abnormal measurement. An example in practice is an intensive care unit in a remote/rural area, with only minimal expert staff available at all times [3]. In this case a DSTS could be of assistance by relaying data of the remote Intensive Care Unit (ICU) to an ICU that does have enough resources available. The decision support task in such a system, would be to alert the staff of the assisting ICU of abnormal values observed in the monitored ICU and presenting the data in a way that facilitates the staff of the assisting ICU in making decisions and taking action. The types of available data may also have implications for its communication and what input data is available for the decision support system part of a DSTS.
It is probable, due to such relationships among properties, that we may find certain recurring structures in the DSTSs described in the literature. In the second part of this thesis we seek to conceptualize these recurring structures in a conceptual framework for DSTSs.

Although conceptualizations are available for clinical decision support systems and telemedicine separately, the main advantage of using a single conceptualization for DSTSs is that it will focus on DSTS-related properties while leaving out information that may be relevant for only telemedicine systems or only clinical decision support systems. Such a conceptualization has many potential benefits. By focusing on a conceptualization unique for DSTSs, its elements will be relevant for stakeholders involved in DSTSs. Essentially these stakeholders include 1) clinicians looking for opportunities for DSTSs. Clinicians may be relatively unaware of telecommunication technology and clinical decision support technology. A unifying conceptualization can help clinicians to fill in blanks in their knowledge and may make them aware of certain important things when they consider a DSTS to support a medical process that they are knowledgeable about; 2) information communication technology (ICT) specialists (project managers, developers) responsible for implementing a DSTS. They are not necessarily knowledgeable about medical care processes and clinical decision support systems, and a unifying conceptualization will assist them in understanding these topics. Of course ICT specialists are generally very knowledgeable about telecommunication technology and integration of systems; 3) decision support system developers who seek to embed their system within a telemedicine environment. A unifying conceptualization may assist them in understanding important relevant elements involved in extending the (geographical) reach of their systems.

A unifying conceptualization also has other advantages. Investigation of the DSTS literature made clear that in many cases descriptions of DSTSs were lacking some essential properties, and thus made it impossible to really understand what type of DSTS was being described. A unifying conceptualization can serve as a checklist of important properties that require description. Furthermore, a unifying conceptualization can also be used as a way of categorizing and comparing DSTSs.

Our aims in obtaining DSTS conceptualization are:
- To formulate a set of characterizing DSTS properties based on the literature that are important to describe and categorize a DSTS (Chapter 5).
- To provide, aside from a general conceptual DSTS model and a definition of the term DSTS, a number of specific DSTS types (Chapter 6).

1.2. Preliminaries

The following paragraphs provide some background information on important topics related to the research in this thesis.
1.2.1 Intensive Care

All chapters of the first part of this thesis are concerned with research within the medical domain of intensive care. This is not a coincidence as this environment is data and information intensive and there is a need to make sense of these data.

Intensive care has been defined as “a service for patients with potentially recoverable conditions who can benefit from more detailed observation and invasive treatment than can safely be provided in general wards or high dependency areas” [4]. Detailed observation of the patients often involves a plethora of monitoring devices at the patient’s bedside. These devices produce large amounts of data being continuously generated over time, which are often stored in Patient Data Management Systems (PDMS).

In many cases these data overwhelm clinicians and nurses responsible for interpreting and acting upon them. In addition there is evidence that doctors have difficulty to deal with temporal information [5]. Hence knowledge discovered from the data could potentially help intensive care physicians to get insight in the phenomena generating these data. This insight can support decisions about the management of health care, such as about withholding treatment or revising clinical guidelines.

In the first part of this thesis we focus on two kinds of subgroups: patients with a high risk of mortality and patients with hyperglycemia (very high blood glucose levels). Below we describe the current approaches for mortality prediction and for blood glucose regulation in intensive care.

Mortality prediction models in Intensive Care

An important application of prognostic models of mortality in intensive care is to compare quality of care among different intensive care units. Survival status is easy to determine, it is linked to the effectiveness of an Intensive Care Unit (ICU), and mortality in the ICU has a relatively high frequency. However, when comparing ICUs one needs to adjust their mortality to the severity of illness in each ICU: some ICUs may have more severely ill patients than others. Prognostic models are used to correct for these case-mix differences as they provide a statement of the probability of death for each patient given their characteristics that together determine the severity of illness.

A valid prognostic comparison is conducted as follows: for a given ICU the prognostic model is applied to predict mortality of each patient. The predicted number of deaths is the average of these probabilities multiplied by the number of patients. This predicted number is compared to the actual number of deaths in the ICU by calculating the Standard Mortality Ratio (SMR). SMR is the ratio of the actual observed number of deaths and the predicted mortality by the model. The SMR can be calculated for a given probability range (e.g. between .1 and .2). When an ICU’s SMR = 1, the ICU is performing as predicted (in the given probability range); when SMR > 1, the ICU is performing worse than predicted; and when SMR < 1, the ICU is performing better than predicted.
Examples of well-known prognostic models are APACHE [6], SOFA [7] and SAPS [8]. These are logistic regression models that provide a probability of mortality for an individual patient based on a severity of illness score. A severity of illness score is calculated as the sum of “penalty points” assigned to some variables (such as age) and for deviations from normality for other variables (e.g. too high or too low blood pressure).

Another important emerging type of prediction does not concern the prediction of mortality of every patient and it is not directly concerned with comparison between ICUs. This type concerns the discovery of subgroups with very high mortality. The rationale behind this approach is that for these patients answers to a set of clinical management questions is particularly important. The first question is whether such patients will still benefit from intensive care treatment; a clinician may share this information (about the elevated risk of dying) with the patient or his family to consider whether to pursue treatment. A second question is whether this information can be used to avoid admission to the ICU in the first place (e.g. to decide whether to perform surgery or not). Although the conventional (logistic regression) models are not specifically meant for subgroup discovery, they have been used to identify high-risk patients and it is natural to investigate their ability to perform this task and to compare them to a subgroup discovery algorithm.

**Hyperglycemia in Intensive Care**

Critically ill patients, even those without diabetes, often develop hyperglycemia (high blood glucose levels) in the ICU. Normally, when blood glucose is high the body produces insulin to decrease its concentration in the blood. However, trauma effects resulting from surgery often disturb the glucose homeostasis and can cause insulin resistance. Until recently, it was common practice to treat only marked hyperglycemia in these patients, since hyperglycemia was considered to be an adaptive response to critical illness. The landmark study of van den Berghe, however, showed that so-called “intensive insulin therapy” (IIT) aiming at normoglycemia (i.e., blood glucose level (BGL) between 4.4 – 6.1 mmol/l [80–110 mg/dl]) decreases mortality and morbidity of intensive care unit patients [9,10].

Since then, various variants of the IIT guidelines have been developed and implemented around the world, especially in Europe. Interestingly, although the mean blood glucose values for all patients has indeed decreased (as intended), it was still often the case that many patients suffered from hyperglycemia. It is true that hypoglycemia is more life-threatening than hyperglycemia as the brain cannot last long without glucose, but hyperglycemia is harmful in the longer run. Research described in [10] suggests a significant difference in mortality of patients in the intensive care unit with normal glucose values compared to those with hyperglycemia. The question that the ICU we worked with has posed was: which patients do not seem to respond to therapy, that is, which patient characteristics can predict an elevated risk for hyperglycemia even when IIT is applied?
This is again a subgroup discovery problem. It is more complex than the problem of finding subgroups with very high mortality because the glucose measurements are time-ordered (with no fixed sampling time) requiring design choices for representing these data and performing a sensitivity analysis of the performance of the discovered groups over time.

1.2.2 Clinical Decision Support Systems

When asked to describe the concept of Clinical Decision Support Systems, many will describe computers playing the role of a doctor in determining a diagnosis, or robots performing surgery. But in practice various types of CDSSs are used in many different medical domains supporting a wide range of medical processes.

Short history of CDSSs

In the early days (the early 1970s) researchers developed Bayesian and rule-based CDSSs that would support the process of diagnosis. Famous CDSSs from this period are the AAPHelp diagnostic system for acute abdominal pain [11], Internist-1, a diagnostic program for internal medicine [12] and MYCIN, a system for diagnosing and treating severe infections such as bacteremia and meningitis [13]. Although sometimes the clinical accuracy of these systems was reported to be better than that of (human) medical experts, most of these systems with a few exceptions, did not find successful implementation for several reasons and were approached with skepticism [14].

Over time this skepticism has declined, as described by Musen et al. [14] because of:

- Increased pressure on cost-effectiveness.
- The practice of evidence based medicine in a world of increased information availability.
- Technology becoming cheaper, more efficient, more effective and user-friendly.
- The availability of more physicians educated in the use of technology.

There has been a shift in focus in CDSSs from diagnosis to reminder systems, guideline implementation, and knowledge discovery approaches. Finally, there is heightened awareness that such systems must be well integrated into clinical workflow processes (an important reason for not accepting these systems in the past).

Classification of different types of CDSSs

A CDSS can be characterized by the level of support, the consultation mode, and the communication style. The level of support ranges from general to patient specific, and includes:

- Tools for information management: tools that provide an environment in which relevant information can easily be found and stored. Although these systems support healthcare, they are not directly involved in the actual decision making process, which is left to its users. An example is a system that merely displays protocol charts on the screen.
• Tools for focusing attention: systems that, based on some patient data (e.g. which medications they are using, or a lab value), alert healthcare professionals when ‘abnormal’ circumstances are detected or may occur. These systems are generally used to alert the user of potential problems that may be overlooked. A typical example of this kind of system is a pharmacy system alerting for drug interactions. In this example the knowledge in the system is primarily about drugs.

• Tools for providing patient specific recommendations, which provide advice based on the data of a specific patient. Examples of the type of advice these systems provide are suggestions for diagnosis, or lab tests that need to be performed to narrow the differential diagnosis, or systems that suggest therapy (e.g. the exact amount of antibiotics for a female patient with renal failure).

The boundaries between these levels are not crisp but existing systems tend to fall in one of them. Aside from the level of support, systems differ in their consultation mode: some systems are passive providing advice only on demand, while others are active, providing feedback to the healthcare worker without being asked for it. Finally, regardless of the level of support and the consultation mode, a CDSS may operate in two communication styles: in the critiquing mode the system provides advice which is dependent on the adherence of clinical practice to a standard or a protocol (e.g. notifying the nurse that a BGL measurement was expected but not performed), whereas in the non-critiquing mode it provides advice regardless of whether a protocol is followed or not.

The research presented in the first part of this thesis, related to subgroup discovery in intensive care, does not concern decision support systems in the classical sense. It is not a bedside system providing advice about a specific patient to a clinician. However, subgroup discovery can be perceived as decision support for the management of care. The user is typically a clinician responsible for improving the quality of care in the ICU. The level of support belongs to the “focusing attention” type. In particular, the system focuses attention on patient subgroups that behave “differently” from the rest. The “alert” is not triggered by a specific value of a lab result or a drug-drug interaction for a specific patient, but is rather a description of a group responding markedly differently than the rest. The user must decide on the subsequent steps to take (e.g. revise policy of admissions or refine a guideline).

In terms of consultation mode, our “system” is passive: subgroup discovery is performed on demand. In contrast to mainstream CDSSs this demand may be very infrequent. However, it is conceivable to use the system in an active mode by allowing it to run regularly and to alert the user about changes in the subgroup definitions over time. Finally, our systems (as we apply them) have a non-critiquing mode in the strict sense at the process level: they do not compare what physicians do with a guideline. However, at the outcome level, the subgroup discovery approach for seeking hyperglycemia patients can be perceived as a critiquing system: in spite of implementing a protocol meant to
maintain blood glucose within a narrow range for any patient, some are not responding well to therapy. In this specific sense it is a critiquing system providing alerts on patients not conforming to the intention of the guideline.

1.2.3 Telemedicine

Telemedicine can simply be described as medicine at a distance. A more extensive definition (from Chapter 5) is that telemedicine is a process involving the remote communication of medical information by healthcare professionals and/or patients, using any electronic medium to facilitate clinical care.

Telemedicine is often confused with telehealth, which is similar to telemedicine but also incorporates non-clinical care provision such as education of patients. There is also the term e-health, which is generally used as an umbrella term to encompass telemedicine, telehealth, electronic patient records, mobile health and consumer health informatics.

The main advantage of telemedicine is that the care provider and receivers do not have to be at the same location. This can be useful when either of the communicating parties is in a hard to reach location, e.g. rural areas, war territory, sub-marines, or outer space. Telemedicine may also have other advantages in that it can lift certain social barriers, and in some cases can reduce costs of healthcare.

Examples of common forms of telemedicine are teledermatology: sending of dermatologic images across a distance, and teleradiology: sending radiographic images across a distance.

1.2.4 Telemedicine and decision support

With the growing need for decision support and the need to have clinical data available at all times and places, the future will likely see more integration of telemedicine initiatives and decision support systems. To make this integration successful there is a need for standards. At OSI Layer 6 (the presentation layer), a good example of a valuable standard is XML. SOAP (XML over http/https) is a common way of exchanging information nowadays, e.g. in web service oriented architectures. If SOAP is used, the only thing that is necessary to get data from one system into another is to convert the data to be communicated to XML format. Of course we still require mappings between the shared XML data to a form that is acceptable for the data source and the receiving system.

If OSI Layer 7 (the application layer) standards are used across many systems, information exchange is facilitated even more. An example of an OSI level 7 standard is Health Level 7 (HL7) [15]. If both the data source and decision support system represent their data using HL7, information exchange becomes trivial (assuming they use a standard or shared terminology). Our framework presented in this thesis does not focus on these standards and on integration, these issues are covered in other frameworks such SANDS [16], which focuses on interfaces between decision support systems and data sources (at a distance).
1.3. References


