A Markov model to describe daily changes in organ failure for patients at the ICU

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Abstract. As the support and stabilization of organ function is a major goal of treatment in the Intensive Care Unit (ICU), changes in the function of organ systems are an important indicator of the progression of the disease and recovery. This paper presents how to construct a model that describes changes in organ failure of ICU patients on a day-to-day basis. The model is based on the daily Sequential Organ Failure Assessment (SOFA) scores for six organ systems and predicts, for each of these organ systems, whether failure or recovery is due on the next day, using six logistic regression equations. The joint set of equations, extended with equations for predicting ICU discharge and death, constitutes a first-order multivariate Markov model. We applied the procedure on a dataset and found that most types of organ failure are highly persistent.

Keywords: Decision-support; Intensive Care; Prognosis; SOFA score; Multivariate Markov Model

1. Introduction

A major goal of treatment in the Intensive Care Unit (ICU) is to stabilize organ function and if necessary to temporarily take over the vital functions by machinery or medication. Changes in the functioning of the organ systems are an important indicator of the progression of the disease and the probable outcome: the more organ systems with problems, the higher the probability that the patient will not survive the stay at the ICU. In contrast, if the function of organ systems is stabilized or improved, the probability of ICU survival increases. For this reason it is important to monitor the organ systems concisely and to have an estimate of future changes in organ function.

Recently, state transition (Markov) models have been used to analyze progression of chronic diseases [1, 2]. In analogy with this research, in this paper we analyze the changes in organ failure in ICU patients using a Markov model. In the ICU organ failure can be described on a day-to-day basis using the Sequential Organ Failure Assessment (SOFA) scoring system [3]. In this scoring system the degree of organ failure is expressed by six scores that indicate the function of six major organ systems: circulation, respiration, kidney function, central nervous system, liver and coagulation.

The model that is presented in this paper captures changes in organ failure in terms of changing SOFA scores. A rudimentary modeling approach is employed, where

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logistic regression equations are developed to predict organ failure of individual organ systems on the next day and a first-order multivariate Markov model is constructed by combining these regression equations.

The paper is structured as follows: Section 2 provides more detail on the use of the SOFA score. Section 3 describes the procedure to develop the regression equations and to combine them into a multivariate Markov model. Section 4 presents the results of applying these methods on a dataset from the ICU of the Onze Lieve Vrouwe Gasthuis (OLVG) in Amsterdam. In Section 5 we elaborate on the use of the model in practice and discuss our work.

2. The SOFA score for measuring organ failure at the ICU

The SOFA scoring system was developed in the late 1990s to describe organ failure of patients at the ICU. Although the score was developed to describe organ failure and not to estimate the prognosis of a patient, research has shown that the SOFA score and changes in the SOFA score are related to mortality (see e.g., [4]).

The scoring system consists of six subscores and one aggregate score, each calculated on a daily basis [3]. This proceeds as follows: for each organ system the degree of organ failure is quantified by an integer value between 0 and 4 (with 0 indicating normal organ function and 4 referring to complete failure). These scores are based on the values of one or two (mostly physiological) variables related to the particular organ system. For example, the score for the hepatic system is determined by the level of bilirubin in the blood. The total (aggregate) SOFA score is calculated as the sum of the six subscores and has a maximum value of 24. The total SOFA score gives a global impression of the patient’s condition, but the subscores provide more information on the state of the organ systems and therefore may be more relevant from a clinical point of view. In our models we will therefore only use the subscores.

Table 1 Series of SOFA scores and ICU status for an example patient

<table>
<thead>
<tr>
<th>Variable</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SOFA subscores</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>4</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Coagulation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Circulatory</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Neurological</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Hepatic</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td><strong>Total SOFA score</strong></td>
<td>8</td>
<td>9</td>
<td>9</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td><strong>ICU status</strong></td>
<td>At the ICU</td>
<td>At the ICU</td>
<td>At the ICU</td>
<td>At the ICU</td>
<td>Died at the ICU</td>
</tr>
</tbody>
</table>

As the scores are measured on a daily basis, we obtain a series of SOFA scores for each patient. Table 1 depicts the series of SOFA scores for an example patient. In the first two days this patient mainly has respiratory and circulatory failure. After day 2 the kidneys start failing and subsequently coagulation and hepatic dysfunction occurs. After four days the patient dies at the ICU. This example also shows the limitations of the use of the total SOFA score: the total SOFA score of 9 on both days 2 and 3 suggests that the condition of the patient remains the same, whereas the subscores reveal that renal failure develops on day 3 (as the renal subscore equals 3).
3. Modeling organ failure at the ICU

In this section we present how the SOFA scores were used to construct a Markov model that describes changes in organ failure. Section 3.1 introduces the data that we have used for the analyses. Section 3.2 describes how models were developed which predict failure for the six organ systems. In Section 3.3 we explain how these models for the individual organ systems were combined into a multivariate Markov model.

3.1 Data for the experiments

The model we present in this paper is based on data collected in the ICU of the Onze Lieve Vrouwe Gasthuis (OLVG), an 18 bed mixed medical-surgical closed-format ICU in a teaching hospital in Amsterdam. We used data from patients admitted between January 1st, 2002 and December 31st, 2004. We excluded patients admitted after cardiac surgery as in these patients the changes in organ failure are known to be very different from patients admitted for other reasons. For patients who were readmitted to the ICU during the same hospital stay we only used information on the first ICU admission.

Our dataset contained information on 1508 patients of which 248 (16.4%) died in the ICU. The median length of stay was 2 days, 587 patients (39%) were discharged or died after 1 day of ICU stay. In total 6845 records on SOFA scores were available. The total SOFA score ranged from 2 to 20 (median value 8). Almost all patients had respiratory failure during their entire ICU stay. Hepatic and neurological failure were seen less frequent (subscore > 0 in 15.8% and 18.9% of the records, respectively).

3.2 Prognostic models for failing organ systems

To create a model that describes the changes in the functioning of an organ system, we need to estimate the conditional probability that a particular organ system will fail on a specific day, given the states of that organ system, and all other organ systems, on the preceding day. Formally, such a conditional probability is written as:

\[ P(\text{system}_{t+1} | \text{renal}_t, \text{respiratory}_t, \text{coagulation}_t, \text{neurological}_t, \text{hepatic}_t, \text{circulatory}_t), \]  

where \( t \) refers to the day within the period of ICU admission (\( 1 \leq t \leq \text{length of stay (LOS)} - 1 \)), \( \text{system} \) gives the state of a particular organ system at time \( t \), and \( \text{system} \in \{\text{renal, respiratory, coagulation, neurological, hepatic, circulatory}\} \). As the SOFA score per organ system has five possible values, and we use the state of six organ systems at day \( t \) and one at day \( t + 1 \) (see Eq 1), we need to estimate 5^6 of these conditional probabilities per day. Even with a very large dataset we could not estimate all of these probabilities directly from the data, especially because some types of organ failure occur very rarely.

We therefore decided to reduce the number of probabilities that is to be estimated in three steps: (i) assuming the process of changes in organ functioning to be stationary, (ii) dichotomization of the SOFA scores, and (iii) use of a parametric approach to estimate the conditional probabilities. We will now briefly explain these steps:

(i) For the current analyses we assumed the probabilities in (1) to be stationary, i.e., we assumed that they are independent from the value of \( t \). This implies that we have to estimate 5^5 probabilities in total. We restructured the dataset such that each record contained the SOFA scores on day \( t \) and the SOFA scores and the ICU status on day \( t+1 \). The number of records per patient in this restructured dataset equals \( \text{LOS} - 1 \).

(ii) To further reduce the number of probabilities the SOFA scores were dichotomized, with \( \text{system}_{t} = 1 \) indicating failure at time \( t \) and \( \text{system}_{t} = 0 \) indicating that there is no failure. The thresholds for dichotomization were chosen based on the
distribution of the data, such that the two classes were as balanced as possible. By this step the number of probabilities to be estimated was reduced to $2^7$.

(iii) To estimate the conditional probabilities in (1) logistic regression equations were developed for each of the organ systems. First, a full model was constructed using the states of all organ systems on day $t$ as covariates. Subsequently, a backward stepwise regression analysis was applied to obtain the model that minimized the Akaike Information Criterion (AIC). To prevent patients with a long length of ICU stay from largely influencing the parameters of the model, the observations in the analyses were weighted by $1/\text{LOS}$.

This procedure resulted in six logistic regression equations, one per organ system, to estimate the probabilities given in Eq. 1.

3.3 Multivariate Markov model

In the procedure described above we have considered the influence of organ failure on the functioning of each of the organ systems separately. However, it is also the combination of these findings that we are interested in. In fact, on a given day the patient can be in three possible states that are mutually exclusive: (i) the patient is at the ICU and his/her condition is characterized by the functioning of the six organ systems, (ii) the patient has died, and (iii) the patient has been discharged from the ICU.

For the first type of state we have $2^6 = 64$ possible states in our model; for both the second and third type of state we have only one possible state that patient can either be in or not. These latter two states can be described by the variables ICUdeath and ICUdischarge, respectively. The conditional probabilities for these two variables at $t+1$, given the state of the organ systems at day $t$, were derived using the procedure presented in Section 3.2, resulting in two additional logistic regression equations.

Thus, the state of the patient can be described by the combination of the six dichotomized variables that represent the functioning of the organ systems, together with ICUdeath and ICUdischarge. The changes in the condition of the patient can be seen as a Markov process: at one day the patient is in a particular state described by the eight variables mentioned above and the next day the patient is either in the same state or has moved to another state. The transition probabilities for the changes from one state to another can be derived from the eight logistic regression equations.

Once we know the state of the patient on day $t$, we can predict the distribution over the possible states on the next day. Note that the states in which ICUdeath $= 1$ or ICUdischarge $= 1$ are absorbing states: once the patient is in such a state, the probability of transition to another state equals zero.

4. Results

Figure 1 presents the results from the analyses based on the data from the OLVG. The left side of the figure provides the odds ratios obtained from the eight logistic regression equations. For all organ systems we observe that patients with failure in a particular organ system on day $t$ have a high probability of organ failure in the same organ system on the next day. This phenomenon is called persistence. Furthermore, we observe differences between the extents to which organ systems are involved in the failure in other organ systems. E.g., circulatory failure on day $t$ influences respiratory and circulatory organ failure on day $t + 1$, ICU discharge, and ICU death. In contrast, hepatic failure only influences hepatic and coagulation failure on the next day.
The right part of the figure displays a graphical representation of the multivariate Markov model obtained from combining these equations. The absorbing states “ICU death” and “ICU discharge” are indicated by a double ellipse. Arcs indicate which organ systems influence the state at day $t+1$. It is seen that not all organ systems are equally important for prediction of the state of the patient on the next day. The maximum possible number of arcs is 48, whereas only 20 arcs are present in the current model.

5. Discussion

We have developed a Markov model to describe progression of disease in a situation where the condition is acute and state changes occur rapidly. Markov models have been applied in health care for various purposes since the 1970s [5], most prominently in cost-effectiveness analyses [6] and clinical decision analyses [7]. Recently, Markov models have been used to describe progression of disease. Salazar et al. [1] have used multi-state Markov models to analyze the progression of dementia. Saint-Pierre et al. [2] described the progression of disease in overweight asthmatic patients. The relation between organ failure and ICU survival has been modeled before using logistic regression (e.g., [4]), and dynamic Bayesian networks [8], but not using a Markov model in combination with regression equations.

The model we developed can be used for several purposes. First, the odds ratios derived from the regression equations provide us directly with information on the relationships between the organ systems, and between organ failure and ICU outcome on the next day. Second, the model can be used in daily patient care to estimate which organ systems are likely to fail in the next day, given the information from the current state of the patient. For example, in our model a patient with renal and hepatic failure on day $t$ has a probability of 15% on coagulation failure on the next day. These estimates can be used to determine the treatment strategy for the patient, and also for
planning of beds and technical equipment at the ICU. A third use of the model lies at the population level. For some patient groups the changes in organ failure that occur frequently are well-known, but for other patient groups this knowledge is lacking. The model can be used for simulations, to discover frequently occurring patterns and combinations of organ failure for a specific patient group.

The current model constitutes a first approach and has two types of limitations. First, we have made a set of four assumptions. We assumed that the underlying process of organ failure is a first-order Markov process, i.e., the state at day $t+1$ is completely determined by the state at day $t$. We also assumed stationarity, i.e., that the state transition probabilities do not change over time. For ICU care this is questionable, as the changes in the first few days of ICU stay are generally considered to be different from changes that occur later on in the ICU admission. In the future we will investigate whether it is beneficial to relax this assumption of stationarity. Further assumptions that need to be investigated are the dichotomization of the SOFA subscores and the assumption that logistic regression equations without all possible interactions between variables are appropriate to estimate the state transition probabilities.

A second limitation is the fact that we have focused on organ failure only, whereas other patient characteristics (e.g. diagnosis, admission type) may also influence the changes in organ failure. These factors can be included into the model by adding an interaction with such type of variables to the logistic regression equations. In future work we will investigate the influence of the aforementioned assumptions and develop a model that incorporates the influence of other patient characteristics. At the conference we aim to present a model which includes the improvements mentioned above, developed and validated on a dataset from a large number of ICUs.

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References