DYNAMIC AUTOREGRESSIVE MODELLING OF CRITICAL CARE PATIENTS AS A BASIS FOR HEALTH MONITORING

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Abstract: Real-time modelling techniques could be valuable to continuously evaluate individual critically ill patients and to help the medical staff with estimation of prognosis. This preliminary study examines the possibilities to distinguish survivors from non-survivors on the basis of instabilities in the dynamics of daily measured variables. A data set, containing 140 patients, was generated in the intensive care unit (ICU) of the university hospital of Leuven. First and second order dynamic auto-regression (DAR) models were used to quantify the stability of time series of three physiological variables as a criterion to distinguish survivors from non-survivors. The best results were found for blood urea concentration with true negative fractions of 45/72 (63%) and true positive fractions of 43/68 (62%). The results indicate that the dynamics of time series of laboratory parameters from critically ill patients are indicative for their clinical condition and outcome.

1 INTRODUCTION

Physicians have for long recognized the importance of considering the temporal dimension of illness for arriving at a diagnosis and deriving treatment strategies (Belair et al., 1995). The study of disease dynamics, or how disease states change with respect to time, is providing a key to understanding abnormalities in underlying physiologic control mechanisms (Goldstein et al., 2003). For monitoring purposes, especially changes in dynamic characteristics seem to be relevant in distinguishing health from disease (Glass, 2001; Buchman, 2004; Van Loon et al., 2010). This indicates the potential of approaches that aim at quantifying dynamic characteristics of individual patients on-line during their stay in the intensive care unit (ICU). Several attempts to take the time-varying aspect of the health status of critically ill patients into account have been reported (e.g. Chang et al., 1988; Clermont et al., 2004; Toma et al., 2007, 2008).

In most of these studies, the available information at a certain instance in time was summarised in one score and the calculation of this score was repeated in time. Afterwards, a classification or prediction model was built using these summary variables. Instead of using repeated scores, it is also possible to extract dynamically relevant features from the commonly measured physiological data itself. A large number of variables are continuously monitored and stored in the ICU environment.

A candidate approach for monitoring individual patients in the ICU is time series analysis. A few investigations have employed the use of time series analysis in the field of intensive care medicine (e.g. Lambert et al., 1995). It has been shown that time series analysis techniques are suitable for retrospective analysis of physiological variables. A computationally similar, but more challenging task is the on-line analysis of intensive care monitoring data (Imhoff et al., 1999).

The objective of the reported research was to explore whether recursive time series analysis can be used to monitor individual patients in the ICU. More specifically, the aim was to test if the occurrence of temporal instabilities in the dynamics of time series of continuously measured physiological data contains valuable information for distinguishing between survivors and non-survivors.

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2 MATERIALS AND METHODS

2.1 Patient Database

The database was derived from a larger database (1200 patients) created for a clinical study with a similar setup and purpose in a group of critically ill patients from a medical ICU (Van den Berghe et al., 2006). In order to have enough data points for time series analysis we had to select patients with a length of stay of at least 20 days because in the existing data sets, most of the stored data were available only once daily. A second selection criterion was that we only accepted patient data with no missing measurement values. A set of 140 patients fulfilled both criteria.

An overview of the used data set is depicted in Table 1. The protocol of this trial was approved by the ethical commission of our hospital.

Table 1: Characteristics of the database.

Number of patients	140
Age (mean ± std)	62 ± 14
Sex	M: 95, F: 46
BMI	25 ± 5

We used daily measurements of three variables, namely: maximum body temperature (Tmax, °C), white blood cell count (WBC, 10^9/L) and urea concentration (Uconc, mg/dl).

2.2 Recursive Modelling

Since the physiological patient responses are time variant, most of the measured physiological variables are non-stationary, in the sense that the statistical properties of the signal are changing slowly over time in relation to the rates of change of the stochastic state variables in the system under study. When the system is non-stationary, models with time varying parameters should be used for the analysis (Pedregal et al., 2007). In this study we used a Dynamic Auto-Regression (DAR) model which can be formulated as:

$$y_t = \frac{1}{A(z^{-1},t)} e_t \quad (1)$$

in which $A(z^{-1},t) = 1 + a_{1t}z^{-1} + a_{2t}z^{-2} + \cdots + a_{pt}z^{-p}$ is a time variable parameter polynomial in the backward shift operator z^{-1}; y_t is the considered physiological variable; e_t is zero mean white noise.

Here, the adjective 'dynamic' means the model has time variable parameters and not that the DAR model is dynamic in a systems sense. A random walk model was specified and a time domain maximum likelihood estimation was applied to find the optimal parameter estimates.

By multiplying equation (1) throughout by $A(z^{-1},t)$ the DAR model in the time series formulation is obtained:

$$y_t = -a_{1t}y_{t-1} - \cdots - a_{pt}y_{t-p} + e_t \quad (2)$$

From this equation it can be seen that y_t is calculated from previous samples of itself plus a random component in the form of the white noise e_t. For more details, reference can be made to Taylor et al. (2006) and Pedregal et al. (2007).

In a first step, first and second order DAR models were computed for the three variables of the development data set, since in preliminary analysis these model orders led to the best results in terms of the Akaike's Information criterion (AIC). The first and second order model structures were as follows:

$$y_t = -a_{1t}y_{t-1} + e_t \quad (3a)$$

$$y_t = -a_{1t}y_{t-1} - a_{2t}y_{t-2} + e_t \quad (3b)$$

On the basis of the correlation coefficients between the measured variables and the one-step-ahead predictions, the best performing variables were selected for further analysis in the second step. Average correlation coefficients < 0.70 were considered as not sufficient in order to have an accurate model.

A further selection in the variables and model orders was made considering the uncertainty of the parameters in the calculated models. The average standard error (SE) on the parameters was calculated and used as a measure for the reliability of the model. In the recursive algorithm, for all consecutive estimations of the model parameters, the relative standard error (RSE) of the parameters was calculated using following equation:

$$RSE = \frac{SE}{|parameter\ value|} \times 100\ (\%) \quad (4)$$

The average of the relative standard errors was taken from day 15 until the end of the data set for each patient. The recursive algorithm needed about 14 data points to result in a reliable model, so the 14 first values were not considered.

2.3 Model-based Classification of Survivors vs. Non-survivors

The hypothesis of this work was that a patient that becomes unstable at least once during his/her stay in the ICU, will not survive. When measured variables

become unstable, this does not imply an increase in the variability or the irregularity of the signal. A higher variability often even corresponds to more healthy conditions (Lipsitz, 2002).

To have a stable system, in this case the patient, it is required that all poles of the transfer function lie inside the unit circle. For a first order system, this means that the following criterion should be met for the a_1-parameter in equation (3a) (Box et al., 1994):

$$-1 < a_1 < 1 \quad (5)$$

The time course of the measured urea concentration values (as an example) and the calculated stability criterion (equation 5) for two example patients are shown in Figure 1 for a survivor and a non-survivor.

For a second order model, the criteria for stability can be expressed in terms of the two model parameters in the following way (Box et al., 1994):

$$\begin{aligned} a_1 + a_2 &> -1 \\ a_2 - a_1 &> -1 \\ -1 &< a_2 < 1 \end{aligned} \quad (6)$$

where a_1 and a_2 are the model parameters as described in equation (3b). When one of these criteria is not met, the system is unstable.

On the basis of the stability criteria, the classification between survivors and non-survivors was made and quantified in terms of true positive fractions (sensitivity) and true negative fractions (specificity). The true positive fraction (TP) was defined as the fraction of patients that becomes unstable at least once during the stay in the ICU and died. The true negative fraction (TN) was defined as the fraction of patients that did not become unstable and survived. Because the recursive parameter algorithm needed about 14 data points (days) of past data to produce reliable parameter estimates, the stability test was performed from day 15 on. This is a drawback of the used methodology, but the aim of this preliminary study was to investigate whether the stability of measured physiological variables of the patients gives valuable information about the patients' survival when they have a long ICU stay and not to predict the outcome as soon as possible after arrival in the ICU.

3 RESULTS AND DISCUSSION

In the first step, first and second order models were calculated for the three variables and the correlation coefficients between the measured variables and the one-step-ahead predictions were analysed. Table 2 gives an overview of the average correlation coefficients for each variable for the first as well as for the second order models. The results indicate that the variable Tmax could not be modelled accurately (average correlation coefficients < 0.70). Consequently, only the variables Uconc and WBC were selected for further analysis.

Table 2: The correlation coefficients between the measured variables and the one-step-ahead predictions of the first and second order dar models calculated on the variables tmax, uconc and wbc.

	Tmax	Uconc	WBC
1st order	0.51	0.86	0.73
2nd order	0.54	0.85	0.77

Secondly, the reliability of the parameters was examined in terms of their relative standard errors. The average errors are given in Table 3 for the first and second order models of the two remaining variables. From this table it can be seen that the errors on the parameters of the second order models were always larger than those of the first order models. Therefore it was decided to disregard the second order models from this step on.

Table 3: The mean relative standard errors (MRSE) on the parameters of the first and second order DAR models calculated on the variables Uconc and WBC of the development data set (%).

Model	Parameters	MRSE Uconc (%)	MRSE WBC (%)
1st order	a_1	43.15	39.16
2nd order	a_1	486.24	386.72
	a_2	1036.58	909.44

The recursively calculated parameter estimates were tested against the stability criteria (equation (5)) in a third step. Table 4 summarizes the calculated true positive fractions and the true negative fractions for the first order models of the two remaining variables.

Table 4: The TN and TP values for Uconc and WBC.

	Uconc	WBC
TN	45/72 (63%)	61/72 (85%)
TP	43/68 (62%)	22/68 (32%)

If we were to base clinical decisions upon a model, it would be clinically more acceptable to classify a non-survivor erroneously as a survivor than to classify a survivor as a non-survivor. So, preferably the TN is at least as big as the TP and both the TP

and TN should be as close to 100% as possible. Considering this, the best result was obtained for Uconc with a TN of 45/72 (63%) and a TP of 43/68 (62%). This signal was consequently considered as the most indicative variable for outcome prediction, although these results are not good enough to be useful in clinical practice.

Uconc turned out to be the best choice for the classification of survivors versus non-survivors. The TN for WBC was better than in the case of Uconc, but the TP was a lot worse. When looking at the reliability of the parameters, the relative standard errors on the parameters of the models WBC were lower than the errors for Uconc, but the former have a very low TP. Consequently, Uconc is the best option for the given study purpose.

All selected variables are used in the clinical setting as markers of inflammation or organ function and therefore it is not surprising that they are predictive for mortality in this subset of patients with a prolonged stay in the ICU. The blood urea concentration was found to be a prognostic marker in several types of patients (Beier et al., 2011). In the study of Jackson et al. (2008) it is shown that an elevated urea concentration is more powerful than the estimated glomerular filtration rate at predicting an increased risk of early mortality following admission with heart failure. In this study a Cox-proportional hazard model of log[urea] (per unit change) resulted in a hazard ratio for risk of death of 1.79 (± 95% CI 1.08-2.97, P = 0.003). An increased postoperative serum urea concentration is also associated with an increase in 30-day mortality in patients undergoing emergency abdominal surgery (odds ratio 4.79, ± 95% CI 2.37-9.70, P = 0.003; Harten et al., 2006). The relevance of blood urea nitrogen (BUN) as a marker for length of stay and mortality at the intensive care unit for patients with acute necrotizing pancreatitis was investigated by Faisst et al. (2010). In their study, these authors used thresholds on absolute values of BUN as a predictive value. When using a threshold (cutoff) value of 33 mg/dl, high BUN levels correctly predicted a prolonged length of stay in 89% of the cases (positive predictive value, PPV) and the negative predictive values (NPV) for BUN on admission and in the course of the disease was 62% and 77%. With the same threshold, mortality could be correctly ruled out in 82% of the cases on admission and in 92% of the cases in the course of the disease (NPV). The PPVs were lower with 67% on admission and 56% in the course of the disease. In addition to these studies, our results indicated that not only the absolute steady state levels of Uconc, but also its dynamics, can be predictive for survival in the ICU. To the authors' knowledge no studies have been performed using time series dynamics of urea concentration in critically ill patients at the ICU in relation with mortality.

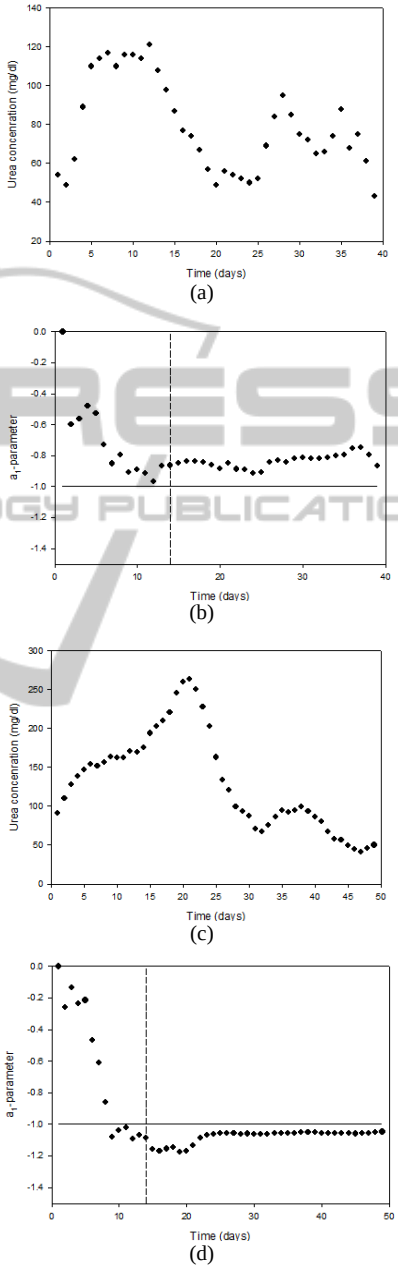

Figure 1: Time courses of the daily measured urea concentration values for a survivor (a) and non-survivor (c) as well as the corresponding time-varying a_1-parameter values for a survivor (b) and non-survivor (d). The vertical dashed line in (b) and (d) indicate the end of the period of the first 14 data points (days) that are needed for reliable parameter estimation. The horizontal line indicates the threshold of $a_1 = -1$.

The occurrence of instabilities in the measured biological signals of (most) non-survivors might be explained by the fact that, in critical care patients before dying, the complex closed-loop responses that operate to keep the organism in equilibrium may not be evolved to produce a healthy response to stress, and thus respond in a maladaptive way. This fits with the work of Lipsitz (2002) who connects the proper working of physiological systems with the stability of its dynamic response. However, it can be expected at one hand that some patients become dynamically unstable but recover from this situation or on the other hand that some patients can die due to very acute problems (e.g. brain haemorrhage) which are not preceded by periods of instability in the measured dynamics. Therefore, the findings in our study need to be validated and confirmed in a larger sample of patients to evaluate the concept thoroughly.

In ICU's worldwide, attempts to improve data processing have centered on computerized systems and several patient data management (PDMS) systems have been developed (Toma et al., 2007). This is software where virtually all patient and therapy related information is stored on a high resolution basis. Consequently, there is a great need for integrating the data and automating the recognition of several diagnoses, since the quality of health care systems depends on making the right decisions at the right time and place (Fonseca et al., 2009). Without automated systems, clinicians have to manually extract the necessary information, which is a time-consuming work that distracts them from critical tasks and increases the risk of making mistakes (Spencer et al., 1997). In combination with recursive modelling techniques, such systems might allow to model the patients' dynamic responses in real-time as a basis for improving personal health status monitoring.

4 CONCLUSIONS

We found that the patients' dynamics contains interesting information when distinguishing between survivors and non-survivors. A data set of 140 patients was used for the analyses. On the basis of stability measurements calculated from the parameters of recursive time series models on physiological data, we were able to separate survivors form non-survivors. The best results were obtained when using blood urea concentration which gave a true negative fraction of 45/72 (63%). The true positive fraction was 43/68 (62%). The results of this study need to be validated and afterwards confirmed in larger trials, before the described methodology could be considered in the future in combination with patient data management systems to support the physician in on-line monitoring and decision taking for individual patients.

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