Statistical Methods in Intensive Care Online Monitoring

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Abstract: Intelligent alarm systems are needed for adequate bedside decision support in critical care. Clinical information systems acquire physiological variables online in short time intervals. To identify complications as well as therapeutic effects procedures for rapid classification of the current state of the patient have to be developed. Detection of characteristic patterns in the data can be accomplished by statistical time series analysis. In view of the high dimension of the data statistical methods for dimension reduction should be used in advance. We discuss the potential of statistical techniques for online monitoring.

1 Introduction

In intensive care, today clinical information systems (CIS) acquire and store all physiological and device parameters online every minute. Currently a physician can be confronted with more than 200 variables of the critically ill patient during a typical morning round. However, even an experienced physician is not able to develop a systematic response to any problem involving more than seven variables (Miller, 1956) nor is he able to judge the degree of relatedness between more than two variables (Jennings et al., 1982). Thus electronic bedside decision support offers huge potential benefit. On the other hand, the technological progress achieved in the electronic patient record during the last ten years (Imhoff, 1993) bears new challenges for statistical methodology. Techniques of statistical data analysis have to be automated and adapted to the online-monitoring context.

Existing alarm systems based on fixed thresholds produce a large number of false alarms due to measurement artefacts or patient movements (O'Carrol, 1986). Usually changes of a variable with time are more important than a single pathological value at the time of observation. Hence, the online detection of qualitative patterns such as outliers, level changes or trends in physiological variables is important for assessing the patient's state. Qualitative data abstraction has been developed using deviations of the measurements from the target range (Miksch et al., 1996), so-called trend templates (Haimowitz and Kohane, 1996), or robust adaptive control charts (Daumer, 2000). However, they do not consider temporal correlations or they demand predefinition of expected behaviour, which is hard to specify in advance because of the irregular patterns found in critical care.

Statistical time series modelling has been proven useful for retrospective analysis of physiologic variables. It leads to interpretable descriptions of complex underlying dynamics, provides forecasts, gives confidence bounds and allows the assessment of the clinical effects of therapeutic interventions (Hill and Endresen, 1978, Gordon and Smith, 1990, Hepworth et al., 1994, Imhoff et al., 1997). For pattern detection in single variables, techniques such as multiprocess models, dynamic linear models, ARIMA-models, and phase space models have already been applied.

Pattern detection in multivariate time series of several physiologic variables is much more difficult than in univariate series. Furthermore, in high dimensions the computational effort can exceed any available computational power (Huber, 1999). This problem becomes even more severe in the online monitoring context where fast and robust algorithms are needed. The demand for robustness against disturbances like sequences of patchy outliers arises because of their negative effects on correct pattern classification. In consequence, reliable procedures for analysing multivariate physiologic time series have to be developed and validated with real data. Statistical methods like graphical models, sliced inverse regression, principal component analysis and factor analysis can be applied for dimension reduction.

In the following we discuss statistical methods for time series analysis and for dimension reduction. We explore how they can be combined for achieving suitable bedside decision support and report our experiences w.r.t. analysing the hemodynamic system, i.e. variables such as blood pressures, heart rate, pulse, blood temperature and pulsoximetry.

2 Statistical Time Series Analysis

Subsequent measurements of the same variable typically show autocorrelated behaviour, i.e., subsequent observations are often positively related. Statistical methods for time series allow to consider such autocorrelations in the data analysis. Particularly we aim at the online detection of patterns such as level changes, artefacts and trends in physiologic time series. The reliable distinction between these patterns is difficult since often combinations of several patterns occur (see Figure 1).

2.1 Dynamic Linear Models

In one of the first attempts to apply statistical time series analysis to online monitoring data, Smith and West (1983) used a multiprocess dynamic linear model to monitor patients after renal transplantation. In dynamic linear models (DLMs) (West and Harrison, 1989) the observation X_t at time t is considered as a linear transformation of an unobservable vector of state parameters. These states are assumed to change dynamically in time according to a simple regression model. The linear growth model

$$\begin{aligned} X_t &= \mu_t + \epsilon_t \\ \mu_t &= \mu_{t-1} + \beta_{t-1} + \delta_{t,1} \end{aligned}$$

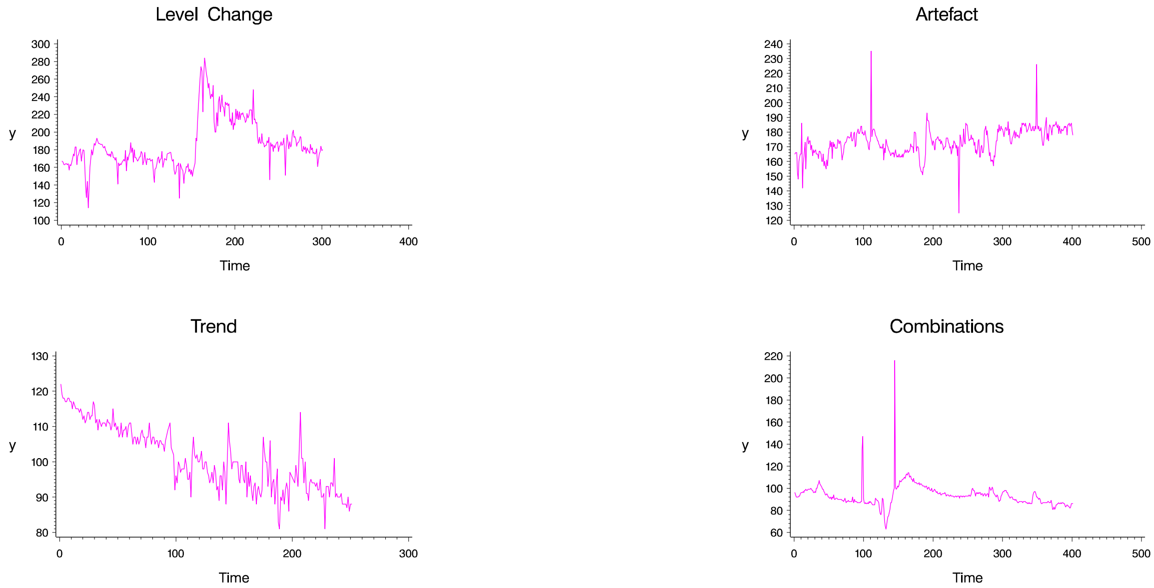


Figure 1: Patterns of change in univariate physiologic time series. Combinations of several patterns, which usually occur in practice, may cause problems for any identification rule

$$\beta_t \quad = \quad \beta_{t-1} + \delta_{t,2}$$

is very appealing for describing hemodynamic variables. Here, μ_t is the unknown process level and β_t is the unknown slope at time t. In the multiprocess version used by Smith and West different variances of the random observation error ϵ_t and the random change in evolution $\delta_{t,j}$ at time t are assumed for describing the steady state, outliers, level changes and trends. For pattern classification they calculated the posterior probabilities of these states in a Bayesian framework using a multiprocess Kalman filter. In related work time series from anaesthesia were analysed (Daumer and Falk, 1998).

Routine application of these models has not been practiced yet because of their very strong sensitivity against misspezification of the hyperparameters and their insensitivity against moderate level shifts.

The computational effort can significantly be reduced by using a single-process model. Pattern detection can be accomplished by assessing the influence of recent observations on the parameter estimates. This can be done via influence statistics (Cook, 1977) which compare estimates of the state parameters calculated with and without the most recent observations. When an outlier occurs the current level is supposed to be far from the current observation, while for a level change and a trend the recent observations should have a large influence on the estimate of the level and slope parameter respectively.

While this technique was successfully applied for retrospective analysis (Peña, 1990, De Jong and Penzer, 1998), online detection of patterns by influence statistics has difficulties with little variability during the estimation period, with level changes occuring stepwise and with patterns of outliers in short time lags. Little variability during the estimation period causes the detection of outliers and level changes to be too sensitive subsequently. Stepwise level changes are hard to detect since the smoothed level parameter adjusts step by step, so that the influence statistics do not have significant values at any time. Several close outliers may either mask each other or be mistaken for a level change. Nevertheless, all kind of patterns in hemodynamic time series could correctly be identified in most cases (Gather et al., 2000a).

2.2 ARMA Models

An autoregressive moving average (ARMA(p, q)) model (Box et al., 1994) for a time series formally resembles a multiple regression, where the observation X_t is assumed to be a linear transform of p past observations $X_{t-1}, \ldots, X_{t-p}$ and q unobserved past shocks $\epsilon_{t-1}, \ldots, \epsilon_{t-q}$

$$X_t = \phi_1 X_{t-1} + \ldots + \phi_p X_{t-p} + \theta_1 \epsilon_{t-1} + \cdots \theta_q \epsilon_{t-q} + \epsilon_t, t \in \mathbb{Z},$$

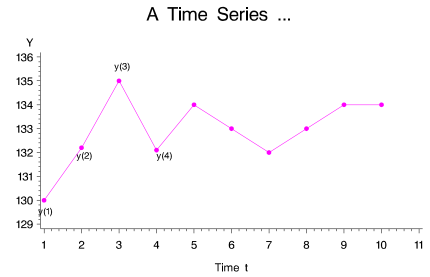
where $\phi_1, \ldots, \phi_p, \theta_1, \ldots, \theta_q$ are unknown weights. The unobserved shocks ϵ_t are assumed to form a sequence of uncorrelated variables from a fixed distribution with mean zero and time invariant variance. This model describes the autocorrelations within a time series in a tractable way and results in simple computational formulas for parameter estimation, prediction and confidence intervals for predictions.

Pattern detection can be accomplished by comparing the incoming observations to confidence intervals for the predictions (PI). Time series segments can be classified into the several patterns according to the number of values outside the PI. Following medical reasoning we can classify observations as outliers if less than 5 consecutive observations are outside the PI, while a level change can be identified by 5 or more consecutive observations outside the PI (Imhoff et al., 2000).

In practice, a suitable model order has to be determined first. This can be done by analysing a preliminary estimation period of, say, 60 minutes. Either one could use the autocorrelation and partial autocorrelation function of these observations, or model selection criteria such as the Akaike information criterion (De Gooijer et al., 1985) could be used to specify a suitable model order for this estimation period. However, this is time-consuming and needs some statistical experience. Moreover, in practice sampling variation makes this task difficult, particularly in the online monitoring context where estimation intervals have to be rather short. Hence, an extensive model selection process is not possible in online monitoring and has to be avoided.

Online application of ARMA models can be simplified significantly by using the same model order for all patients. Analysis of hemodynamic time series provided evidence that autoregressive models (AR(p), i.e. ARMA(p,q)-models with $q = 0$) of order two may be suitable to describe the autocorrelations within the data in most cases (Lambert et al., 1995, Imhoff et al., 1996, 1997), while choosing higher model orders results in minor differences only (Imhoff et al., 2000). Therefore, choosing an overparameterized autoregressive model could be suitable.

Adaptive control limits corresponding to the current state of the patient can be achieved by moving a time window through the data for estimation. Prediction intervals for the incoming observations are calculated using the parameter estimates from the observations measured within the last hour for instance. If the incoming observation



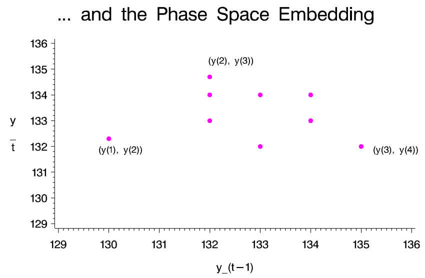


Figure 2: Two-dimensional phase space vectors from a time series

lies within the prediction interval, then the time window is moved one step ahead, otherwise the incoming observation is replaced by its prediction.

Trend detection cannot appropriately be achieved in an online manner by AR-models, while both outliers and level shifts can be detected reliably. The level chosen for the PI has to be adjusted in case of very high or low variability during the estimation period.

2.3 Phase Space Models

In phase space models the dynamical information of a time series $x_1, \ldots, x_N$ is transformed into a geometric information in an m-dimensional Euclidean space. For this purpose the phase space vectors

$$\vec{x}_t := (x_t, x_{t+1}, \ldots, x_{t+(m-1)})' \in \mathbb{R}^m$$

are constructed, where m can be chosen similarly to the order of an AR-model (Bauer et al., 1999a). Figure 2 visualizes the transformation of a time series into a 2-dimensional space.

In the steady state the phase space vectors arising from a linear Gaussian process form an m-dimensional elliptic cloud. A control ellipsoid can be estimated using classical or robust estimators of the mean and the autocovariances of a time series. The position of the phase space vectors w.r.t. this control ellipsoid gives information about their deviation from the steady state. If all observations are inside the estimated ellipsoid, it can be said that the patient is in a steady state. Disturbances can be detected by the movement of the affected vectors in the phase space outside the control ellipsoid (Bauer et al., 1999b).

In this way, outliers and level shifts can reliably be detected. A trend, however, can only be detected by looking at the shape of the vector ellipsoid, which is a relatively insensitive method for the detection of slight trends. For achieving adaptive control limits corresponding to the current state moving window techniques can be applied as described above.

3 Dimension Reduction

In critical care a multitude of variables is measured in the course of time. Figure 3 shows a nine-dimensional time series consisting of the heart rate, the pulse, the central

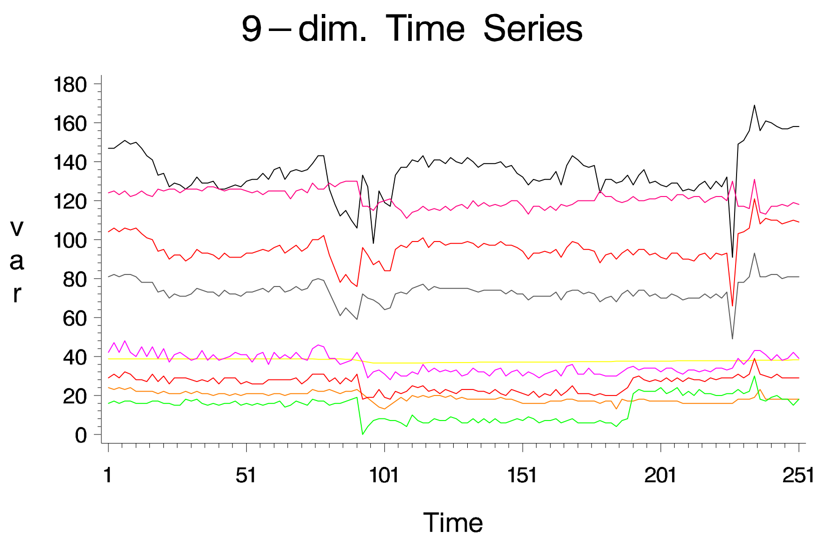


Figure 3: Multivariate time series representing the hemodynamic system of a patient measured during about four hours. Some patterns of change occur simultaneously in several variables, while others seem to occur in distinct variables in short time lags or in a single variable only

venous, the arterial, and the pulmonary arterial pressures of a patient measured during about four hours.

For the reason of interpretability we should reduce the dimension of the data on which decisions are based. This can be achieved either by selecting a subset of the most important variables or by searching for combinations of the observed variables which contain as much information as possible.

3.1 Graphical Models

In clinical practice physicians first select a subset of the monitored variables to get a manageable number of variables. For instance, they neglect the arterial diastolic pressure and the arterial systolic pressure and restrict attention to arterial mean pressure since it is closely related to the other arterial pressures.

Graphical models (Cox and Wermuth, 1996) allow to investigate the associations in multivariate data by statistical analysis. Dahlhaus (2000) extended this concept recently to multivariate time series by means of correlation analysis in the frequency domain, where time series are considered as combinations of waves with different harmonic periodicities. This allows to assess the linear, possibly time-lagged relationships between the variables.

The practical value of this new technique for medical data analysis could already be appraised in a clinical study (Gather et al., 2000). Known associations within the hemodynamic system could reliably be reidentified by graphical models calculated for critically ill patients. Separate analysis of different clinical states even resulted in characterisations of the states by distinct association structures.

3.2 Sliced Inverse Regression

Sliced inverse regression (SIR) (Li, 1991) is a powerful statistical instrument for dimension reduction in linear regression. Starting from a regression problem with d covariables a subspace of dimension $k < d$ is calculated which is sufficient to describe the relationships between the dependent variable and the covariables.

SIR can be applied to multivariate time series from intensive care regressing each variable on the others. This allows to calculate the minimal number k of linear combinations of the other variables which is needed to substitute the dependent variable. If k is large a variable has to be considered as important.

When SIR is applied to multivariate time series one should take the dynamical structure of the data into account. This can be done rather easily when we augment the observation space with time lagged measurements.

In most cases the inclusion of lagged observations allowed a large dimension reduction. Furthermore, we obtained different values of k for different clinical states. These findings confirm the results derived with graphical models.

3.3 Principal Component Analysis

While graphical models and SIR analyse the associations between a single variable and the remaining ones, principal component analysis aims at finding a parsimonious joint description for all variables. Those directions (principal components) within the data space are searched for, which contribute most to the variability in the data. Principal component analysis consists of a stepwise search for the direction which explains most of the variability among all directions which are uncorrelated to the previous ones.

First applications of principal component analysis to the hemodynamic system showed, that the first three principal components capture almost all variability. Patterns found in the hemodynamic variables were also visible in the principal components. Thus, the number of variables and the computational effort could significantly be reduced by concentrating on the principal components.

The series of the first principal components corresponding to the nine-dimensional time series shown in Figure 3 are provided in Figure 4. The series has been differenced since our phase space procedure for pattern detection is based on the differenced series. The important structural changes in the original series are still obvious in the series of the differenced principal components.

3.4 Factor Analysis

Factor analysis aims just like principal component analysis at the reduction of the dimension of multivariate data by searching suitable linear combinations of the variables. However, factor analysis assumes that there are a few, say q, latent variables (factors) which actually drive the series and cause the correlations between the observable variables. For achieving good interpretability the factors found in the analysis can be rotated in the q-dimensional space.

In view of the good results obtained for three principal components, one can try to describe the hemodynamic system with three latent factors. When the factors are

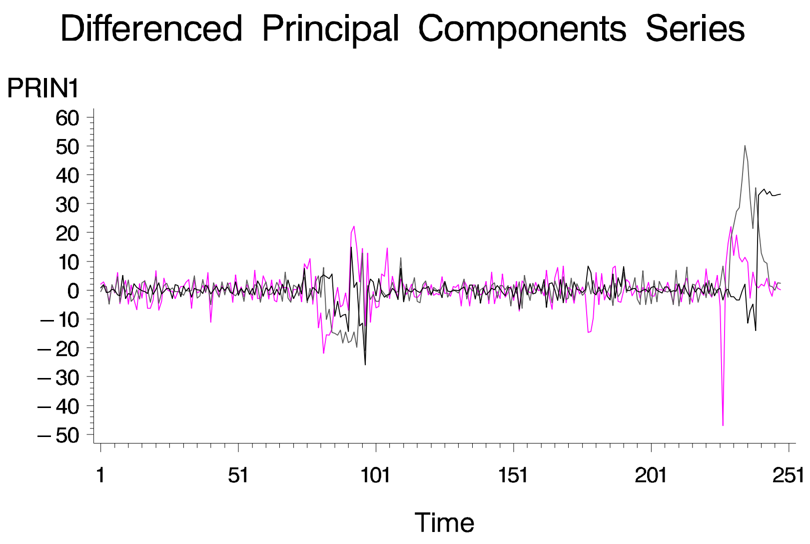


Figure 4: Time series of the three principal components of a nine-dimensional time series representing the hemodynamic system. The important patterns of change in the original series are also obvious in the series of the principal components

calculated for the whole series they are interpretable by pathophysiologic knowledge. Moreover, we found factors not to vary considerably between patients. However, when factors are determined from short estimation periods, the factors may vary markedly. This would present a serious problem for any automatic analysis based on the time series of extracted factors.

4 Conclusion

Patterns in univariate physiological time series can be identified using models from statistical time series analysis with corresponding detection rules. AR-models and phase space models reliably detect outliers and level changes, but both approaches have problems with trend patterns. For AR-models sometimes manual adjustment of the confidence level is necessary. DLMs allow online trend detection, but they are not as reliable as the other approaches. Hence, a combination of the procedures might give the best results.

All approaches to monitoring of univariate series were found to be more sensitive than clinically relevant. This could be overcome by using an automatically adjusted level. This has already been included into the phase space procedure and has lead to significant improvements. For DLMs robust Kalman filter procedures, which are less sensitive against outliers, might improve the classification.

Statistical methods for dimension reduction offer large potential for the joint monitoring of several variables. Graphical models and SIR explore the associations between the variables and facilitate the choice of a suitable subset of the variables. Principal component and factor analysis result in a set of linear combinations of the variables which could be monitored. Factor analysis could be more suitable than principal component analysis for online monitoring since the results are better interpretable for physicians. However, both approaches suffer from the problem that in any dynamic system both the factors and the principal components may vary over time.

Methods for automatic online analysis of physiological variables give an option for a more reliable evaluation of the individual treatment. Statistical methods could be employed to construct intelligent alarm systems, which are more reliable than simple threshold alarms. Adequate bedside decision support could be achieved by combining the statistical techniques proposed here with methods of artificial intelligence (Morik et al., 2000).

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