TEMPORAL PATIENT STATE CHARACTERIZATION USING ITERATIVE ORDER AND NOISE (ION) ESTIMATION: APPLICATIONS TO ANESTHESIA PATIENT MONITORING

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ABSTRACT. Objective. As more sensors are added to increasingly technology-dependent operating rooms (OR), physicians such as anesthesiologists must sift through an ever-increasing number of patient parameters every few seconds as part of their OR duties. To the extent these many parameters are correlated and redundant, manually monitoring all of them may not be an optimal physician strategy for assessing patient state or predicting future changes to guide their actions. **Methods.** The method is illustrated by application to seventy-six anesthetized patients for which thirty-two fundamental and derived variables were recorded at 20-second intervals. The Iterative Order and Noise estimation algorithm (ION) estimated the noise on each parameter. The performance of principal components analysis (PCA) was improved by normalizing the noise estimated by ION to unity. A linear regression of the resulting seven high signal-to-noise ratio principal components (PC's) predicted tachycardia 140 seconds in advance. **Results.** ION estimated the noise on each parameter with sufficient accuracy to increase the number of significant PC's from two to seven, all of which had identifiable physiological correlates. The resulting receiver operating characteristic (ROC) suggested that a 70 percent prediction rate with 5 percent false alarms could be achieved. **Conclusions.** This paper illustrates the use of ION to improve significantly the performance of PCA in the efficient representation of patient state and in improving the performance of linear predictors of clinically significant parameters.

KEY WORDS. Anaesthesiology, multivariate signals, biomedical signal analysis, biomedical monitoring, multivariate noise reduction, principal components.

INTRODUCTION

When time is critical, the ability to consolidate information into an effective patient model to support apt decisions is crucial to patient care. Assimilating information has become increasingly harder as the number and frequency of patient sensor data available to physicians continues to grow with more computer technology and monitoring tools entering the operating room. Previous studies have examined the optimization of monitoring tools and variables employed for anesthesia [1]. This paper illustrates the use of an efficient new tool, the Iterative Order and Noise estimation algorithm (ION), for addressing this problem of efficient, dynamic patient state characterization and analysis. It does so in the context of tachycardia prediction in patients anesthetized with desflurane and undergoing surgery.

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Clinical Background

Many drugs affect the central nervous system and produce general anesthesia – comprised of sleep, hypnosis, analgesia, muscle relaxation, and loss of reflexes. One drug in this class, desflurane, is commonly used during surgery in the operating room.

One method for administering anesthetics, such as desflurane, involves inhalation of the agent as a vapor. In the case of desflurane, one specific protocol is the following [2]: 1) intravenous administration of an initial anesthetic as well as muscle relaxant, propofol and succinylcholine, 2) tracheal intubation (i.e., placement of the breathing tube through the vocal cords via the mouth), 3) setting of the desflurane vaporizer (which transforms desflurane to the gaseous phase) to 18 percent, 4) setting of the rate of super-oxygenated air to 1 L/min, 5) observing the concentration of desflurane in the inspired and expired gas increases with each breath, and 6) setting of the vaporizer to 9 percent once the desired inspired and expired concentrations are achieved (i.e., 8 percent and 6 percent, respectively).

Although desflurane is expensive to administer in an open circuit where the patient breathes only fresh gas, in a semi-closed or partial-rebreathing circuit (where the patient re-breathes exhaled gases supplemented with oxygen and new anesthetic), desflurane administration is cost efficient, effective, and fast (due to its low blood/gas solubility) [3]. Yet desflurane does present a few issues related to tachycardia [4], which generally occur during the period when inspired and expired concentrations rise. This initial period generally lasts less than 15 minutes.

This paper explores a method of characterizing patient state in terms of seven numbers based on thirty-two direct and indirectly measured parameters, and the use of these seven in tachycardia prediction. For purposes of this paper, tachycardia is defined using the classical definition of a heart rate above 100 beats per minute (BPM). Such a prediction, even 140 seconds in advance, would usefully alert the clinician to the impending tachycardia and facilitate its prevention, control, and correction.

Developing a model

Since tachycardia is a variable derived directly from heart rate, a black-box predictor of heart rate has greater clinical utility than a Boolean (yes/no) predictor because it would quantify when the tachycardia threshold is being approached or dangerously exceeded. By monitoring this prediction as well as the subsidiary variables, the clinician can take steps (e.g., reducing inspired concentration or administering other drugs) in order to minimize the duration of tachycardia or even prevent its onset.

METHODS

Strategy

The data used to test the proposed strategy for modeling patient state was collected at the Brigham and Women's Hospital at the Harvard Medical School in Boston, Massachusetts. For the patients in this study, the anesthesiologist adjusted the drug vaporizer setting based on sensors that record and display patient state via twenty-five fundamental variables sampled every 20 seconds. Although such data recording is uncommon, it can be performed using standard anesthesia monitoring systems and was done during the routine course of anesthesia administration (e.g., via Modulus 2 Anesthesia Delivery System with Central Display, Ohmeda, Madison WI). The twenty-two fundamental (three of the twenty-five were not recorded) and ten derived parameters used for this research are listed in Table 1. These parameters generally focus on cardiovascular, pulmonary, and anesthetic performance. Derived parameters include the presence of tachycardia or hypertension (i.e., systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg). Also, the rates of change and historical information of the fundamental variables are captured via their time derivatives, integrals, and means (see Table 1).

Although one might reduce these original and derived parameters to an optimal, condensed ensemble of variables for clinical use, no validated physiological model or reduced data set has gained wide acceptance. In lieu of such models, linear regression can be used to develop predictors for physiological parameters of interest. The inputs to such a regression might include the values of all the available variables, sampled at several times in the past. If it is important to account for nonlinearities, neural networks can be trained in similar fashion. Unfortunately both of these techniques are handicapped by the requirement for an adequate training set from which the statistics can be deduced. In practice, trustworthy systematic medical data sets are seldom available for cohorts of more than tens or hundreds of patients. Moreover, economics and practical considerations often preclude collection of all the relevant variables. For example, patients of substantially different ages, medical conditions, and state of health may be combined, and it may be uneconomic to tran-

Table 1. Fundamental and derived parameters

No.	Parameter	Units	Description
1	SYS	mmHg	Systolic blood pressure
2	DIA	mmHg	Diastolic blood pressure
3	MAP	mmHg	Mean arterial blood pressure
4	PR	BPM	Heart/pulse rate
5	SpO2	%	Oxygen saturation
6	CO2 I	mmHg	Inspired CO_2
7	CO2 E	mmHg	Expired CO_2
8	RR	BPM	Respiration rate
9	VE	L	Ventilation expired
10	VT	mL	Tidal volume
11	Pmax	cmH_2O	Pressure max.
12	Pmin	cmH_2O	Pressure min.
13	PPlat	cmH_2O	Pressure plateau
14	I:E	N/A	Inspired: expired ratio
15	O2 I	%	O_2 inspired
16	N2O	%	N_2O concentration
17	Agt I	%	Agent inspired
18	Agt E	%	Agent expired
19	VT-sp	N/A	Tidal vol. #2
20	Vent-st	N/A	Ventilation state (mechanical vs. non-mechanical)
21	iT-st	N/A	Monitor state (logging vs. normal)
22	NIBPint	N/A	Non invasive blood pressure interval
23	PR_shift_7	BPM	HR 7 samples (2 min. 20 sec.) in the future
24	DERIV_AGT	% / sample	Derivative of agent expired
25	INT_AGT	% × sample	Integral of agent expired
26	AVG_AGT	%	Average of agent expired all samples
27	HI_HR	N/A	Tachycardia present
28	HI_BP	N/A	Hypertension present
29	HI_HR_BP	N/A	Tachycardia or hypertension present
30	DERIV_SYS	N/A	Slope of systolic BP
31	DERIV_DIA	N/A	Slope of diastolic BP
32	DERIV_HR	N/A	Slope of HR

scribe certain elements of patient treatment into the database being analyzed. As a result, the effective noise on each variable is often not just the sensor noise, but also the relevance of that parameter to the problem at hand; this relevance is seldom known accurately in advance. Thus, when using such data sets to develop predictors, it is important to estimate and ameliorate the total noise on each parameter to the extent practical.

The method presented here involves five steps: 1) the ION algorithm [5] is applied to the time history of training data vectors to estimate the additive noise present in each variable, 2) the resulting noise estimates are used to normalize each variable so that the noise variances of each are equal, 3) PCA is used to derive the principal components of the normalized data set, 4) the number of degrees of freedom in the data set deduced by ION is the number of principal components that survive; the remainder are discarded, and 5) the surviving principal components, possibly supplemented by a few parameters believed to be singularly important, are used in a traditional linear regression to produce the desired predicted output. The final operator outlined above (i.e. linear regression) can be replaced by a neural network if the data set is sufficiently robust, and the problem sufficiently nonlinear, to warrant it.

Due to the critical role of ION in this process, it is useful to examine its operation. The ION algorithm operates on $m \times n$ matrices $\mathbf{X}$ comprising m unordered vectors X of dimension n. Each vector X is presumed to be the sum of a linearly transformed stochastic signal vector P of order p, and an independent noise vector, $\mathbf{G}^{1/2}\omega$, of order $n > p$, as specified by Equation (1):

$$X = \mathbf{A}P + \mathbf{G}^{1/2}\,\omega \tag{1}$$

where $\mathbf{A}$ is the unknown mixing matrix, and P is assumed to be a zero-mean Gaussian signal vector having unity variance for all p non-zero variables. $\mathbf{G}$ is the unknown diagonal noise covariance matrix. The noise vector ω is Gaussian with zero mean and its covariance matrix is the identity matrix of order n. The algorithm estimates p, $\mathbf{G}$, and the set of ω's based on a single training matrix $\mathbf{X}$. It does so by iteratively: 1) normalizing the noise variances to unity, 2) estimating p using a scree plot such as that in Figure 1, 3) normalizing the vectors X so that the estimated noise has unity variance: $X' = X\mathbf{G}^{-1/2}$, 4) estimating $\mathbf{G}$ and $\mathbf{A}$ using p and the Expectation-Maximization (EM) algorithm [6], and 5) testing for convergence sufficient to terminate the algorithm.

DESIGN

To demonstrate and test the proposed patient-state characterization protocol, OR data for ninety patients at the Brigham and Women's Hospital were randomly selected from all those who received desflurane during

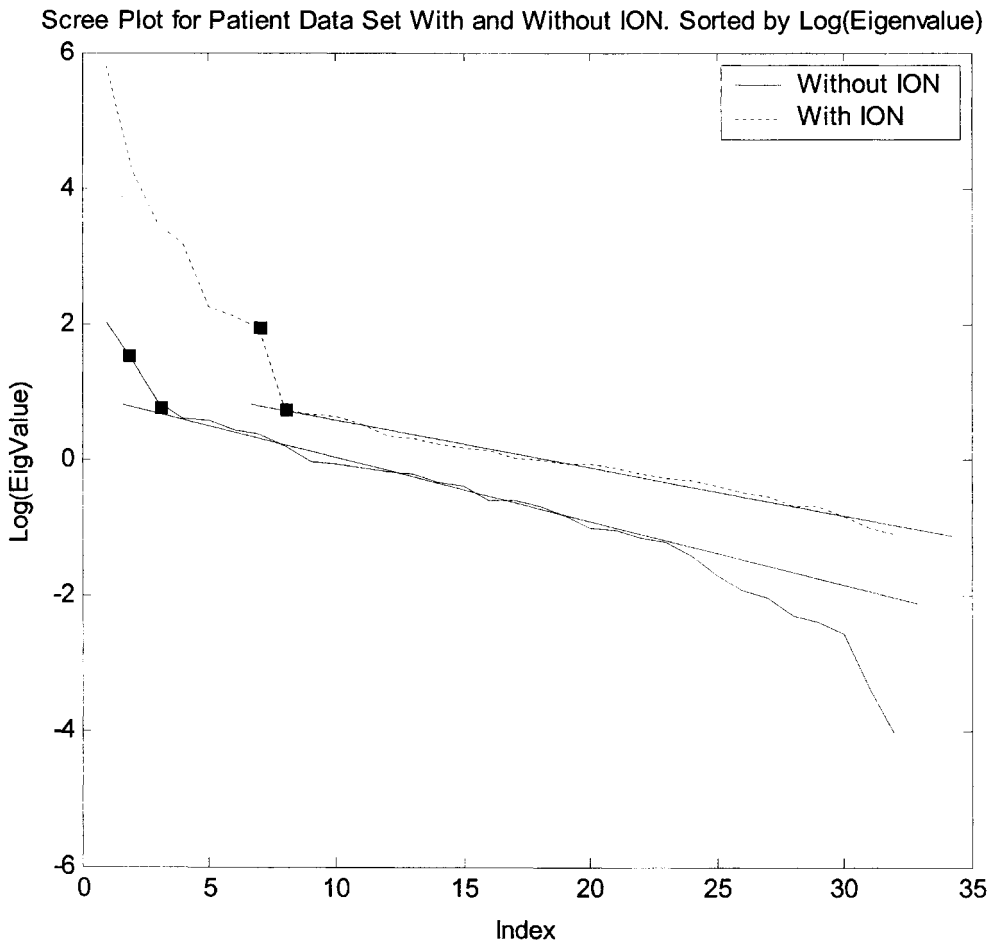

Fig. 1. Scree plot of patient data set. Solid line refers to scree plot of data set processed without ION. Dashed line refers to scree plot of data set processed with ION.

the period July 1997 to July 2000 using the aforementioned induction protocol and anesthesia monitoring equipment. For each patient, the parameters listed in Table 1 were recorded every 20 seconds. Each patient record was defined to begin at that first time sample when all sensors were connected and functioning. Next, the time of initiation of induction by inhaled desflurane was located, and samples were taken for the following 15 minutes (45 samples at 3 per minute). This initiation point was determined based on inspired agent concentration values above zero. For less frequently sampled data (which included non-invasive blood pressure - NIBP), linear interpolation was used. If too many consecutive points were missed for a given parameter, the patient file was rejected.

The target prediction interval, 140 seconds, was chosen based on an anesthetic physiological model which included response times for the breathing circuit, uptake into the lungs, uptake into blood, and transfer of the drug to the vessel rich group (which includes the brain and other effect sites where a change in heart rate is observed). This process has been described in previous works [7, 8, 9]. There are several consequences of this process to the control design criteria. If this change is predicted 140 seconds in advance, then it can be mitigated by aggressive control of inspired concentration. The normal circuit time constant is otherwise Volume/Flow = (6 L)/(1 L/min.) = 6 minutes, plus the alveolar time constant of 0.5 minutes. Aggressive control can be achieved by rapidly changing inspired concentration using high fresh gas flow to overcome the time delay introduced by the breathing circuit in combination with the low fresh gas flow (normally used to conserve anesthetic agent and cost during induction of anesthesia). Another approach to averting the change in heart rate involves administering other drugs.

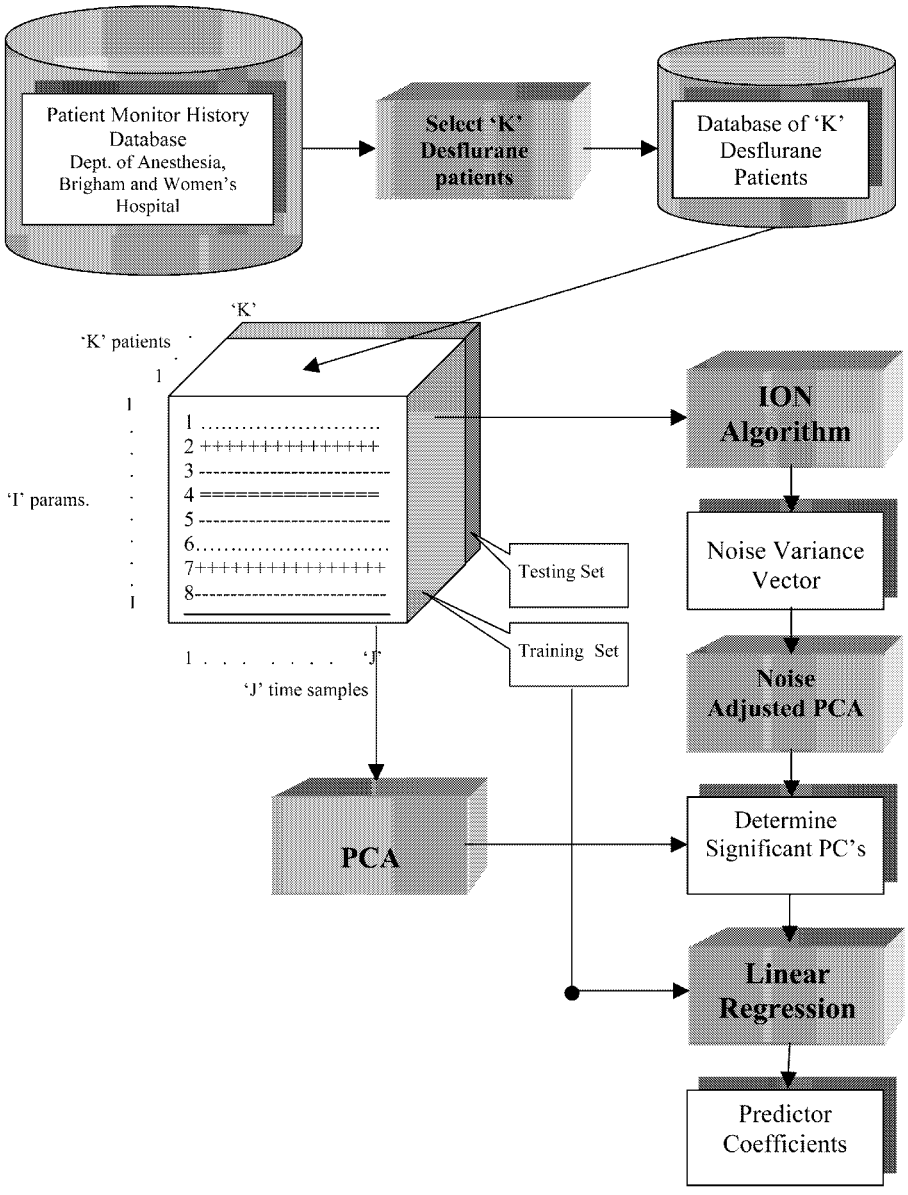

Fig. 2. ION-based predictor setup.

RESULTS

Patient State Characterization

Of the 90 patients selected, 76 had sufficiently complete data records for analysis. The approach outlined in Figure 2 was implemented. That is, the noise was estimated using ION and PCA was then performed on the noise-normalized data set. Figure 1 illustrates the impact of using ION before performing PCA, where the eigenvalues of the principal components are plotted sequentially with and without ION-based noise normalization. This presentation, often called a scree plot, is a useful way to estimate the number of meaningful degrees of freedom in a multivariate data set. Such plots typically exhibit a sloped plateau that corresponds to noise. If the data set is large and the noise is perfectly normalized, this plateau becomes less sloped and more nearly flat. Eigenvalues significantly above this plateau

generally correspond to meaningful signal-to-noise ratios. The scree plot in Figure 1 illustrates how use of ION increased the number of degrees of freedom with useful signal-to-noise ratios from two, for PCA performed on a multivariate data set with uniform variance and zero mean across all parameters, to seven when the variables are noise-normalized using ION noise estimates. Not only did ION permit seven meaningful principal components to be extracted, but their signal-to-noise ratios are substantially larger. For example, the leading principal component with ION has an eigenvalue more than four orders of magnitude above the noise floor, whereas this ratio is scarcely one order of magnitude without ION.

In order to reveal the contributions of the original 32 parameters to each principal component, the top three parameter coefficients for each PC were calculated. To facilitate comparison, the weights were normalized to yield unity variance for each parameter. The result is presented in Table 2. The physiological significance of these principal components can be discerned. The first PC combines various blood pressure (BP) measurements. Certain of these BP parameters are expected to be grouped since the mean arterial BP is approximately two-thirds of the diastolic BP plus one-third of systolic BP. The second PC helps quantify the gas being administered and absorbed by the patient. Respiratory and cardiovascular variables predominate in the third and forth PC's. Specifically, the third PC contains respiratory and heart variables synchronized. That is, a higher PC-based value results if respiration and heart rate both decrease. A different situation is represented within the forth PC; a higher PC-based value results when heart rate decreases and respiration rate increases. Ventilation of the patient is nicely quantified by the fifth PC through tidal and expired volumes. The sixth PC includes interaction of ventilation variables and pulse rate via the weighted coefficients shown in Table 2. The seventh PC reflects a history of the change and total drug absorbed by the patient through various recordings (integral, average, and derivative) of the expired drug vapor.

These seven significant PC's were plotted against time (i.e. as PC-based time values) and compared with heart rate to determine if tachycardia could be traced by inspection to fluctuations in one or more of these PC's. In this case, the threshold "HR==100," defined as tachycardia. It was visually evident that the fourth PC was particularly relevant.

Table 2. Principal components of patient data set

Parameter number	Name	Value
PC #1: BP quantification		
3	MAP	0.054095
2	DIA	0.052442
1	SYS	0.051436
PC #2: Gas quantification		
17	Agt I	0.107807
18	Agt E	0.101020
20	Vent-st	–0.069209
PC #3: Respiratory-cardio synced		
8	RR	–0.153017
9	VE	–0.095526
27	Tachycardia	–0.074475
PC #4: Respiratory-cardio unsynchronized		
27	Tachycardia	–0.116201
29	Tachy or hypertension	–0.115300
8	RR	0.095465
PC #5: Ventilation quantification		
10	VT	0.221765
9	VE	0.167392
19	VT-sp	0.160948
PC #6: Pulse rate – vent. volume interaction		
4	PR	–0.168363
10	VT	0.121817
9	VE	0.114756
PC #7: Agent history quantification		
25	Integral agt E	0.213944
26	Current avg of agt E	0.193742
24	Derivative agt E	–0.119401

Tachycardia prediction

Two tachycardia predictors were developed. The first used a linear predictor based on the seven dominant principal components deduced from PCA of 32 parameters that had been noise-adjusted using ION. The weights of any derived components with future information (e.g. predicted heart rate) were eliminated to prevent non-causal behavior. The second predictor was based on heart rate history. The predictors were trained on the first 80% of the 76 patient database (i.e., 61 patients), and these predictors were then tested on the remaining 20% of the patient database. The history-

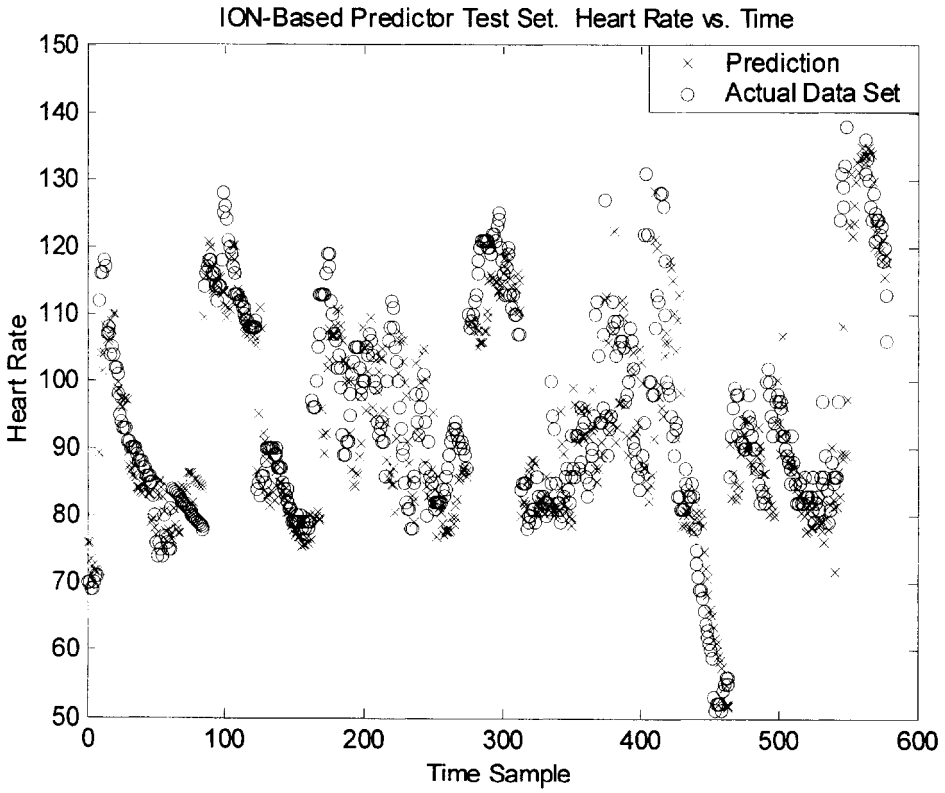

Fig. 3. ION-based predictor output for test data set. The heart rate (BPM) for the ION-Based Predictor Model is shown with ×'s. The actual data set heart rates are shown with ○'s.

based predictor computes a running average of heart rate samples to make a prediction. The ION-based predictor uses the aforementioned seven significant PC's. The addition of time shifted versions of these PC's was also implemented, but did not significantly improve performance. Using the predictor on the test data set yielded the results shown in Figure 3. The largest residues occur when the heart rate is changing rapidly. The root mean square discrepancies between the predicted and observed heart rates were 11.5 and 15.6 BPM for the ION-based and the heart rate history-based predictors, respectively. For PCA-only (i.e. without using ION), it was 14.1.

Perhaps of greater clinical utility is an assessment of how often tachycardia is predicted correctly. To characterize this performance, Receiver Operating Characteristic (ROC) curves were developed for the ION and history-based predictors, as illustrated in Figure 4. Each ROC relates the probability of tachycardia detection to the probability of false alarm. Figure 4 shows how the number of missed detections is reduced by roughly 10–25% through use of the ION-based method. For example, the curve suggests that the probability of tachycardia detection is 70 percent with as few as 5 percent false alarms. The probability of detection can be boosted above 80 percent if one is willing to tolerate 15 percent false alarms.

These results are dependent in part on the heart rate threshold used in defining a tachycardia episode. Figure 5 illustrates several ROC curves for different definitions of tachycardia. Perhaps the best performance is achieved for thresholds in the vicinity of 100 BPM (the classical tachycardia definition), although dropping the threshold to 70 BPM permits seemingly perfect prediction. Care must be taken, however, in interpreting these curves. For example, predicting 70 BPM is easy since almost all predictions are above this point, and forecasting tachycardia continuously will yield a high detection rate and few false alarms. Also, the 130 BPM case had limited data for training.

As part of this study, the general incidence of tachycardia and hypertension was explored. While it was possible that some patients would exhibit one or the other of these conditions based on the work by Muzi referred to earlier (especially considering that little or no opioid was administered during the course of surgery),

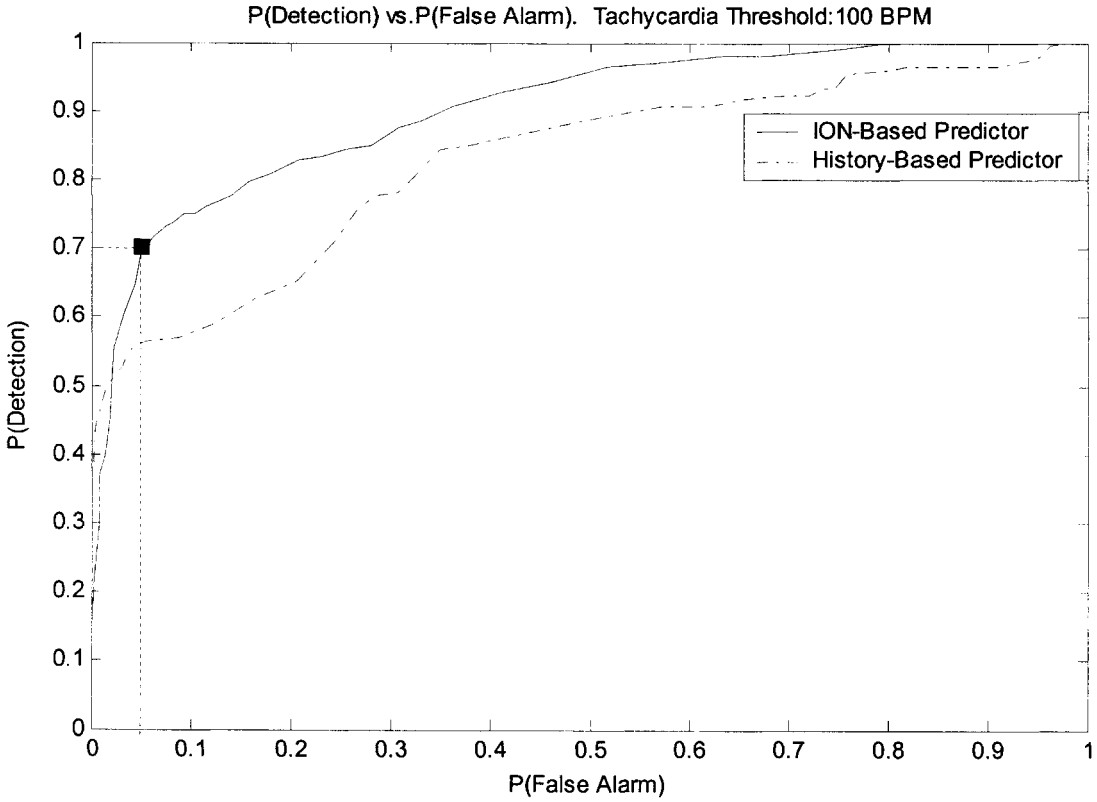

Fig. 4. ION-based heart rate predictor output for test data set- with operating point marked. The solid line refers to the ION-based predictor. The dashed line refers to the history-based predictor.

it was surprising to find that nearly all the patients (97.4%) surveyed here exhibited either tachycardia, hypertension, or both at some point during the first hour of the operation. This high incidence rate suggests that the ability to predict onset of tachycardia (as well as hypertension) could be a useful clinical tool for patient evaluation if one wanted to avert such episodes. It should be noted that the patient population studied here was a group of healthy patients undergoing general or gynecologic surgery which was expected to result in no postoperative pain because of the nature of the procedure and the administration of local anesthesia. No patient had a measurable adverse outcome of any kind. Additionally, approximately 80 percent, 78 percent, and 58 percent of the patients exhibited tachycardia alone, hypertension alone, or both, respectively (see Table 3).

Table 3. Tachycardia and hypertension incidence during first hour of operation

Patient condition	Percent affected
Tachycardia (HR > 100 BPM)	80.3%
Hypertension (systolic > 140 or diastolic > 90 mmHg)	77.6%
Tachycardia or hypertension	97.4%
Both tachycardia and hypertension	57.9%

DISCUSSION AND CONCLUSIONS

ION-based PCA analysis of high-order multivariate clinical data based on limited numbers of patients can facilitate efficient characterization and prediction of patient state. This approach was illustrated in the context of tachycardia prediction in anesthetized patients inhaling desflurane. It is conjectured that incorporation of such software in multivariate patient monitoring systems could provide clinically useful support to physicians in the operating room or in other contexts. Applying these methods to other medical databases and applications would be a useful next step in developing this approach to improving clinical practice in an increasingly automated multivariate medical environment.

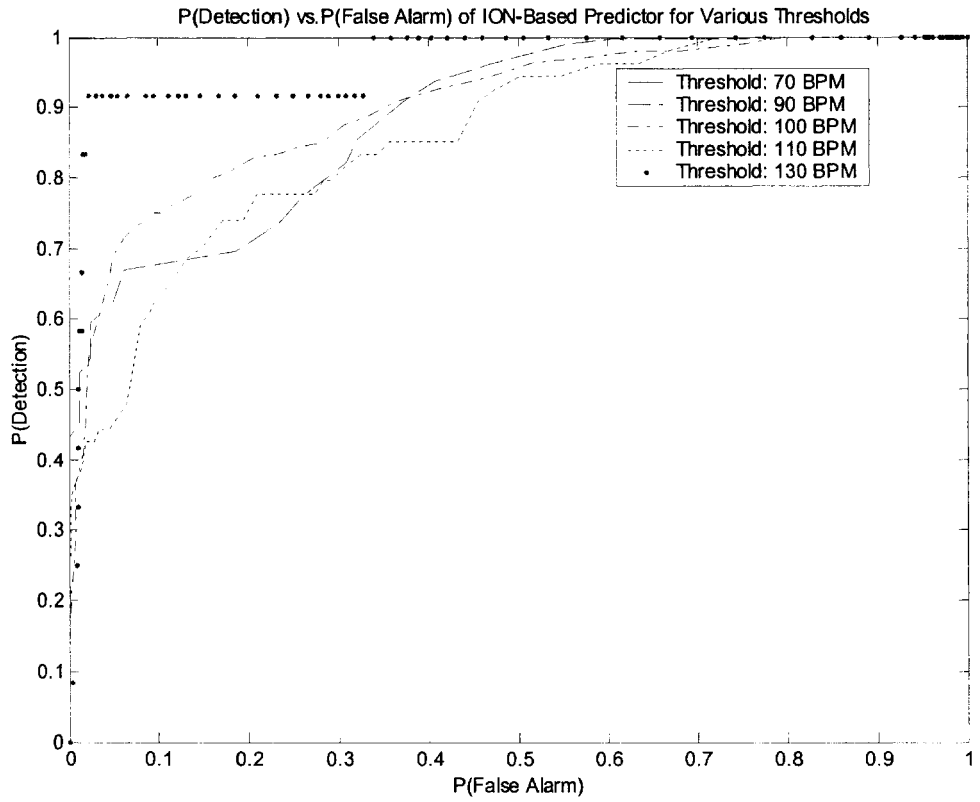

Fig. 5. Receiver operating characteristic (ROC) for ION-based predictor for various thresholds.

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