J. Biomed. Eng. Res.
Vol. 24, No. 2, 151-158, 2003

심혈관 신호에 있어서 단기간 beat-to-beat 변이의 비선형 역할에 관한 연구

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(2002년 12월 15일 접수, 2003년 4월 23일 채택)

Study on Nonlinearites of Short Term, Beat-to-beat Variability in Cardiovascular Signals

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(Received December 15, 2002. Accepted April 23, 2003)

요 약 : 심장혈관 신호에 있어서 단기간의 beat-to-beat 변이(variability)에 대한 여러 연구에서 선형 분석기법들이 사용되었다. 그러나 단기간 beat-to-beat 변이에 대해 선형기법 사용의 타당성에 대한 연구나 선형과 비선형 특성을 비교한 연구는 수행되지 않았다. 본 논문의 목적은 단기간 beat-to-beat 변이의 비선형성 특성을 조사함으로써 선형기법 사용의 적절함을 증명하고자 한다. 이를 위해 선형 ARMA와 비선형 신경망(NN) 모델을 사용하여 예측을 수행하였는데, 과거의 순시 심박(HR)과 평균 혈압(BP)으로부터 현재의 심박과 혈압 예측을 상호 비교하였다. 이러한 예측모델을 평가하기 위해 MIMIC 데이터베이스로부터 HR와 BP 시계열을 사용하였다. 실험결과에 의하면 신경망에 의한 비선형성은 단기간 beat-to-beat 변이를 생성하는 시스템 동특성을 나타내는데 의미있는 역할을 하지 못하였으며, 이 사실은 ARMA 선형 분석기법이 이러한 시스템 동특성을 나타내는데 적절함을 보여주고 있다

Abstract : Numerous studies of short-term, beat-to-beat *variability in cardiovascular signals* have used *linear analysis* techniques. However, no study has been done about the appropriateness of linear techniques or the comparison between linearities and nonlinearities in short-term, beat-to-beat variability. This paper aims to verify the appropriateness of linear techniques by investigating nonlinearities in short-term, beat-to-beat variability. We compared linear autoregressive moving average(ARMA) with nonlinear neural network(NN) models for predicting current instantaneous heart rate(HR) and mean arterial blood pressure(BP) from past HRs and BPs. To evaluate these models, we used HR and BP time series from the MIMIC database. Experimental results indicate that NN-based nonlinearities do not play a significant role and suggest that l0 technique provides adequate characterization of the system dynamics responsible for generating short-term, beat-to-beat variability.

Key words : Beat-to-beat variability, ECG signal, Neural networks, Autoregressive moving average, Signal prediction

Introduction

Numerous analyses of hemodynamic signals have been performed to understand cardiovascular regulatory mechanisms. Most studies of heart rate variability in cardiovascular signals have relied mainly on linear analysis methods such as spectral methods or linear parametric approaches[1,2]. Although linear methods provide a comprehensive view of characterizing fluctuations in hemodynamic signals, these techniques cannot identify the presence of nonlinear coupling. It is also reported that there are nonlinear interactions between the parasympathetic and the sympathetic nervous systems with respect to heart rate control. Previous studies in analysis of cardiovascular signals hypothesize linear relationships among heart rate, blood pressure, and respiration. These papers

본 연구는 금오공과대학교 학술연구비에 의해서 연구된 논문임.
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assume that linear method should be adequate in signal analysis. However, there are no comprehensive studies on the appropriateness of linear methods in the analysis of cardiovascular signals or comparison between linearities and nonlinearities in the role of short-term, beat-to-beat variability.

Despite numerous studies involving the analysis of beat-to-beat variability in cardiovascular signals, there continues to be a debate about the completeness of linear analysis techniques. At least one previous study has attempted to settle this debate[3]. However, this study only attributed the importance of the nonlinear analysis to the description of the effect of instantaneous lung volume and arterial blood pressure on heart rate fluctuations. It only considered the significance of second-order nonlinearities. Thus, so far the role of nonlinear contributions in hemodynamic variables has not been fully explored. In this paper, we aim to evaluate thoroughly the role of nonlinearities on short-term, beat-to-beat variability in a clinical patient population using neural networks that can account for higher-order nonlinearities, and also verify that the linear analysis technique is appropriate in representing adequate characterization of the system dynamics responsible for generating short-term, beat-to-beat variability.

To investigate the nonlinear characteristic on short-term, beat-to-beat variability such as heart rate and blood pressure, an appropriate nonlinear model should be used. However, the database in this paper is collected from human patients which can be considered as nonlinear systems, and there also exists inter-patients or intra-patient variability. Thus, the nonlinear characteristic of the database is inherently not known. These facts make difficulties in determining the best suitable nonlinear model for representing their variability. The approach instead is to choose widely used linear and nonlinear models to analyze linear and nonlinear characteristic. Thus, ARMA model as a linear model and neural networks, lately applied to fields requiring temporal signal processing such as system identification and nonlinear prediction, as a nonlinear model are used respectively.

Multilayer neural networks(NN), an important class of neural networks, have been used in diverse areas ranging from communication[4] to biomedical engineering[5,6]. These networks, commonly referred to as multilayer perceptrons, may be viewed as a practical vehicle for performing a nonlinear input-output mapping. According to the universal approximation theorem for multilayer perceptrons[7,8], a single hidden layer is sufficient for a multilayer perceptron to uniformly approximate any continuous function. In terms of system identification[9], a multilayer NN can realize linear and nonlinear systems. These papers provide the theoretical background that the multilayer NN approximating higher-order continuous functions can evaluate the role of nonlinearities in short-term, beat-to-beat variability of cardiovascular signals.

In the past few years, a growing interest has been devoted to methods, which allow introduction of temporal dynamics into the multilayer network model. There are two methods to provide static neural networks with dynamic behavior. One method is to insert buffers somewhere in the network to implement an explicit memory of the past inputs such as buffered multilayer perceptron and time-delay neural networks. The other method is to use feedbacks such as Elman and Jordan recurrent neural networks(RNN). It is known recently that neural networks with feedbacks(or recurrent elements) have useful dynamic modeling behavior, comparing with buffered neural networks. Thus, Elman RNN is used as a nonlinear model in this paper. As the training method, the modified gradient descent algorithm is applied to improve the convergence speed. This learning algorithm updates the connecting weights between neurons as well as the parameters of the activtion function at each iteration.

In order to evaluate that Elman RNN is able to approximate higher-order polynomials, we tested the prediction of time series generated from linear($y(n)=0.7x(n)-0.4x(n-1)-0.1x(n-2)+0.25y(n-1)-0.1y(n-1)+0.4y(n-3)$) and nonlinear systems($y(n)=0.3x(n)-0.13x(n-2)+0.2y(n-1)-0.11y(n-3)-0.11x^2(n-1)+0.13y^2(n-2)-0.18x(n-1)y(n-1)+0.06x^3(n-2)-0.08y^3(n-1)+0.1x(n-1)y^2(n-2)+0.01x^4(n-1)+0.01y^4(n-2)-0.01x^2(n-2)y^2(n-1)$). It showed that the normalized root mean square errors were almost zero(4.95×10^{-4} for a linear system, 4.2×10^{-3}, 1.13×10^{-4}, and 1.5×10^{-3} for the second, third, and fourth order nonlinear systems). Recently a paper[10] compared RNN prediction with ARMA prediction on nonlinear and nonstationary signals such as Mackey-Glass time series and speech signals, in which RNN-based prediction is superior to the ARMA prediction. Thus, it can be said that the RNN is capable of predicting higher order nonlinear polynomials including linear signals.

This paper describes RNN-based nonlinear prediction and compares its performance with that of a linear model in order to evaluate the role of nonlinearities of short-term, beat-to-beat variability in cardiovascular signals.

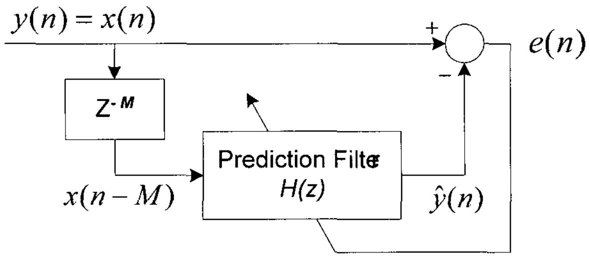


Fig. 1. Block diagram of a prediction system

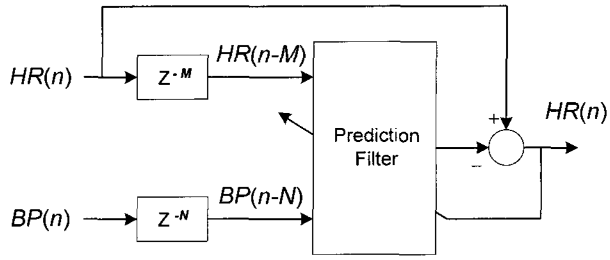
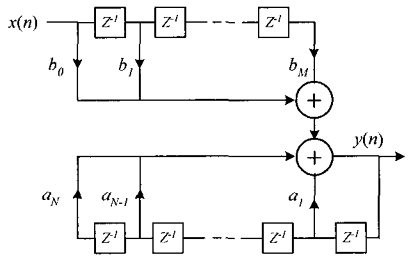
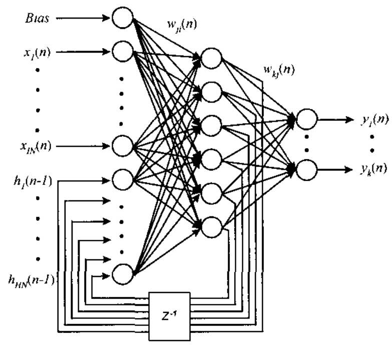


Fig. 3. Structure for HR prediction

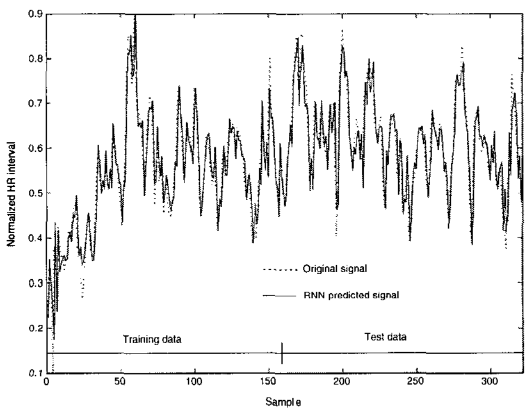


(a) ARMA

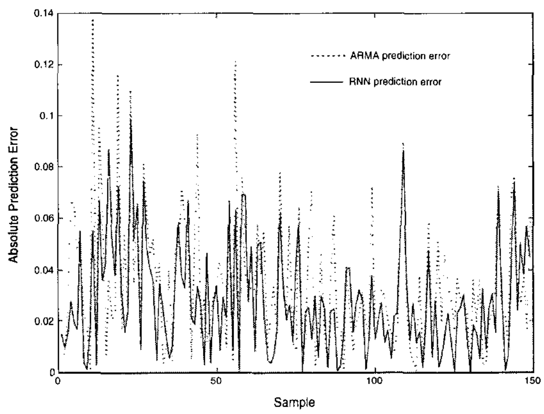


(b) Recurrent neural networks

Fig. 2. Structure of prediction filters



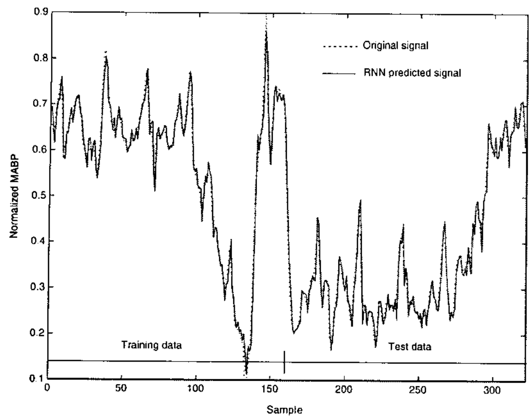
(a) HR prediction



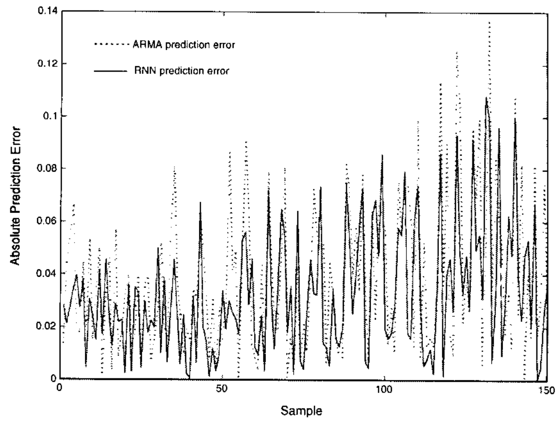
(b) Absolute prediction error

Fig. 4. Example of RNN-based HR prediction (Record: 411, N=M=9)

We constructed and compared linear and nonlinear models for predicting current heart rate(HR) and mean arterial blood pressure(BP) from past values of HRs and single-beat BPs. The former is the ARMA model, and the latter is based on Elman type RNN. For the evaluation of these models, we compared their mean-squared HR and BP prediction errors using the MIMIC(Multi-parameter Intelligent Monitoring for Intensive Care) database[11]. Based on experimental results, it is verified that there is no significant difference between RNN and ARMA models in prediction of short term beat-to-beat variability, indicating that linear techniques are appropriate to analyze the cardiovascular signal analysis although weak nonlinearities exist.

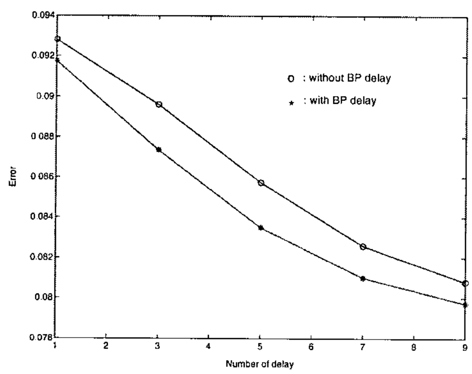


(a) BP prediction

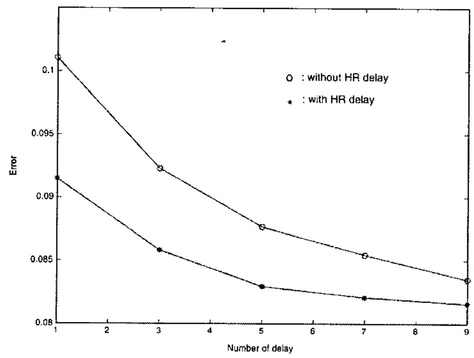


(b) Absolute prediction error

Fig. 5. Example of RNN-based BP prediction (Record: 240, N=M=9)

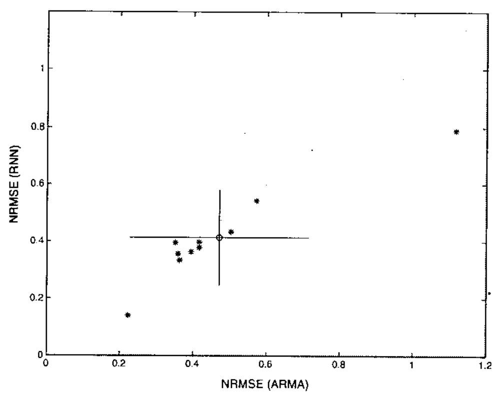


(a) HR prediction

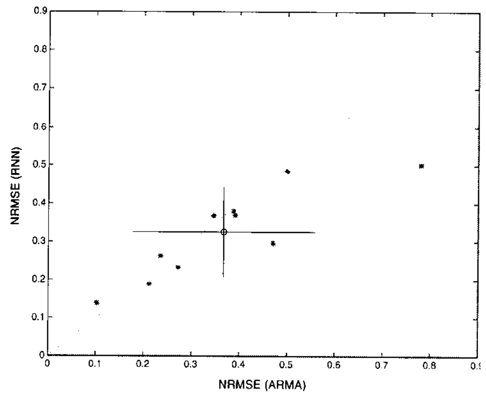


(b) BP prediction

Fig. 6. RNN-based prediction error versus number of delays



(a) HR prediction



(b) BP prediction

Fig. 7. Graphical representation of NRMSE in HR and BP predictions

Neural network based prediction

Signal prediction means to estimate future signals using past signals. Fig. 1 shows the block diagram of a single-step prediction system.

The prediction $\hat{y}(n)$ of the future $y(n)$ is estimated using only the delayed inputs x(n-M). Most linear prediction systems, which estimate the future value using a linear combination of input values, use the ARMA model for finding all zeros and poles of the system transfer function H(z) of the prediction filter, which is described by the following equation.

$$H(z) = \frac{\sum_k b_k z^{-k}}{\sum_k a_k z^{-k}} \tag{1}$$

The impulse response of the prediction filter is determined by the error signal $e(n) = y(n) - \hat{y}(n)$. The coefficients a_k and b_k of the IIR(Infinite Impulse Response) filter are computed by minimizing error $\sum_n |e(n)|^2$. Fig. 2(a) shows the structure of linear ARMA prediction filter.

The linear model works well for signals generated by linear systems. However, it is not appropriate for the prediction of nonlinear and nonstationary signals. The cardiovascular signals can be considered as nonliear and nonstationary signals since the human is the pure nonlinear system. For the higher order nonlinear signal processing using multilayer neural networks, dynamic neural networks such as time-delay neural networks and recurrent neural networks are adequate models. They use feedback loops or delay elements as memories in order to process temporal information, and can perform more complex signal processing well. Thus, our approach for dealing with the inherent nonlinearity of cardiovascular signals is to replace the linear prediction filter with the neural network based nonlinear adaptive filter. The neural network used as a nonlinear filter in this paper is the Elman type RNN shown in Fig. 2(b). It consists of three layers. All the units in a layer are fully connected to all the units in the following layers, i.e. they are one-to-many variable connecting weights. The input layer has external inputs $x(n)$ and additional inputs $h(n)$ that are fed from the outputs of all neurons of the hidden layer with one-to-one weight connections. These recurrent connections improve the dynamics of the network.

The learning method of the network is an extension of the gradient descent algorithm. It is modified to enhance the convergence speed. The connecting weights between neurons as well as the parameters of the node activation function are updated at the same time using the error backpropagation algorithm. The conventional learning algorithm in the RNN updates only connecting weights, not parameters of the activation function. All neurons in the hidden and output layers use sigmoid transfer functions[12]. The output of a node l is as follows.

$$y_l(n) = f(v_l(n)) = \frac{g(n)}{1 + e^{-s(n)\{v_l(n) - v'(n)\}}} \tag{2}$$

where $v_l(n)$ is the internal state of a neuron l and g(n), s(n), v'(n) represent the gain, slope, and delay of the activation function, respectively. The parameters of the activation function are assumed to be time-varying variables.

The cost function, the sum of squard error of the neural networks, is defined as

$$E(n) = \frac{1}{2}\sum_k e_k^2(n) = \frac{1}{2}\sum_k \{d_k(n) - y_k(n)\}^2 \tag{3}$$

The $d_k(n)$ and $y_k(n)$ are desired output and actual output of the networks. The purpose of the adaptive learning algorithm is to minimize the cost funtion E(n) by adaptively adjusting weights w(n) and parameters p(n). The p(n) represents g(n), s(n), and v'(n) of the activation function. The incremental weights $\Delta w(n)$ and incremental function parameters $\Delta p(n)$ of the network are defined as

$$\Delta w(n) = -\eta_w \frac{\partial E(n)}{\partial w(n)} + \alpha \Delta w(n-1) \tag{4}$$

$$\Delta p(n) = -\eta_p \frac{\partial E(n)}{\partial p(n)} \tag{5}$$

The η_w and η_p represent the update rates for weights and function parameters, and the α represents the momentum rate. The momentum term $\alpha\Delta w(n-1)$ is added to only the incremental weights to speed up the learning. Eqs. (6-10) show changes of weights $\Delta w_{kj}(n)$ and parameters $\Delta p_k(n)$ for the output layer.

$$\Delta w_{kj}(n) = -\eta_w \delta_k(n) y_j(n) + \alpha \Delta w_{kj}(n-1) \tag{6}$$

$$\delta_k(n) = \frac{\partial E(n)}{\partial v_k(n)} = -e_k(n)\frac{\partial y_k(n)}{\partial v_k(n)} \tag{7}$$

$$\Delta p_k(n) = -\eta_p \frac{\partial E(n)}{\partial p_k(n)} = \eta_p e_k(n)\frac{\partial y_k(n)}{\partial p_k(n)} \tag{8}$$

The $\delta_k(n)$ is the local gradient of a neuron of the output layer, $y_j(n)$ and $y_k(n)$ are neuron outputs of the hidden and output layers, respectively. The $\eta_p(=\eta_g$ for gain, η_s for slope, and $\eta_{v'}$ for delay of the activation function) represents the update rate for each parameter. The $\Delta p_k(n)(=\Delta g_k(n)$ for gain, $\Delta s_k(n)$ for slope, and $\Delta v'_k(n)$ for delay of the function) represents the incremental parameter of the activatin function in the output layer.

The incremental weights $\Delta w_{ji}(n)$ and parameters $\Delta p_j(n)$ of the hidden layer can be derived same way as those of the output layer and are defined as follows.

$$\Delta w_{ji}(n) = -\eta_w \delta_j(n) y_i(n) + \alpha \Delta w_{ji}(n-1) \tag{9}$$

$$\begin{aligned}\delta_j(n) &= \frac{\partial E(n)}{\partial v_j(n)} = -\sum_k e_k(n)\frac{\partial y_k(n)}{\partial v_k(n)} w_{kj}(n) \\ &= \sum_k \delta_k(n) w_{kj}(n)\end{aligned} \tag{10}$$

$$\begin{aligned}\Delta p_j(n) &= -\eta_p \frac{\partial E(n)}{\partial p_j(n)} \\ &= \eta_p \sum_k e_k(n)\frac{\partial y_k(n)}{\partial v_k(n)} w_{kj}(n)\frac{\partial y_j(n)}{\partial p_j(n)} \\ &= -\eta_p \sum_k \delta_k(n) w_{kj}(n)\frac{\partial y_j(n)}{\partial p_j(n)}\end{aligned} \tag{11}$$

The $\delta_j(n)$ is the local gradient of a neuron of the hidden layer. The $\Delta p_j(n)$ represents an incremental parameter of the activatin function in the hidden layer. An adaptively tuned multilayer neural network updated with above equations at every iteration is used to predict time-varying heart rate and blood pressure.

Experimental results

To investigate the nonlinearities, we used HR and BP time series from patients without diagnosed autonomic dysfunction from the MIMIC database(http://www.physionet.org[13]). To get time series of heart rate, QRS waves from ECG signals are firstly detected to recognize every beat, and then HR time series is obtained by computing time differences between beats. The BP time series is also collected by computing the mean of blood pressure between beats. These HR and BP time series are used as test signals to evaluate the prediction filters. The data sets in the database were originally sampled at 125[Hz]. A study[14] has shown that the choice of sampling rate may affect accurate detection of QRS complexes, especially if a low sampling rate is chosen. However, the sampling rate of 125[Hz] used in this study is high enough to allow for accurate detection of QRS complexes. Several studies have shown that dynamics of HR fluctuations are located at frequencies below 0.5[Hz]. Thus, instantaneous HR and BP signals are downsampled by 3, resulting in a sampling rate of 125/3[Hz] and then these decimated signals are used for prediction.

In this paper, the single-step prediction is performed in two ways. First, the current HR is predicted based on several past HRs and BPs. Next, the current BP is also predicted using several past BPs and HRs.

$$\begin{aligned}\mathrm{HR}(n) = &\sum_{k=1}^{M} a(k)\,\mathrm{HR}(n-k) \\ &+ \sum_{k=0}^{N} b(k)\,\mathrm{BP}(n-k) + e(n)\end{aligned} \tag{12}$$

$$\begin{aligned}\mathrm{BP}(n) = &\sum_{k=1}^{N} c(k)\,\mathrm{BP}(n-k) \\ &+ \sum_{k=0}^{M} d(k)\,\mathrm{HR}(n-k) + e(n)\end{aligned} \tag{13}$$

The M and N represent the delays of HR and BP. The $e(n)$ is the residue error after prediction. Fig. 3 shows the structure for predicting HR(or BP). We used the ARMA structure as a linear model and the RNN as a nonlinear model in the prediction filter. The $a(k)$, $b(k)$, $c(k)$, and $d(k)$ are coefficients of IIR filter in ARMA model. In RNN model, these coefficients are distributed into connecting weights of the networks. Their prediction results are compared each other to evaluate relative performance of the linear and nonlinear models.

We tested the prediction on 10 different records from the MIMIC database. Average segment length of all records is about 13 minutes. Each segment was divided into two equal parts. The first half of the segment was used to train the prediction filter, and the second half was used to test the predictive quality of both models. The structure of the NN consists of the input layer with neurons of external inputs(delayed M HRs and N BPs) and with additional feedbacks from the hidden layer, the hidden layer with 10 neurons, and the output layer with one neuron. The update rates of weights and parameters of the network as well as the network structure are determined empirically, thus they are slightly different for each record. Typical values are as follows: learning rate of 0.02, momentum rate of 0.0015, update rate of 0.01 for both gain and slope, and 0.001 for delay in the activation function of a neuron.

The network is trained for 10,000 iterations to reach a stable error level, beyond that iteration the error does not reduce much as iteration continues. The prediction should be tested for all combinations of delays. However, it is not proper since there are too many cases and it takes so long time to experiment. Instead, the delays (M, N) of the HR and BP in the input of the network are set equal and tested for N=M=1, 3, 5, 7, and 9. The best delay for each record is determined when the rate of error change does not reduce significantly. The final prediction error is the average of five experiments with different initial values of the neural networks. For the linear ARMA model, the model order, i.e., the order of poles and zeros of $H(z)$, for each data record is determined by use of the Akaike information criterion[15].

Fig. 4(a) and 5(a) show representative examples of RNN-based HR and BP predictions for both training and test data. In these figures, the dotted and solid lines represent the original and predicted signals for both training and test data. Fig. 4(b) and 5(b) show examples of prediction errors for both RNN-based(solid line) and ARMA-based(dotted line) predictions. The errors are absolute difference between the original signal and the predicted signal. In the figures, we can identify that the nonlinear neural network model can predict satisfactorily HR and BP variations, and RNN prediction is better than ARMA prediction since ARMA prediction error is larger than RNN prediction error.

For the quantitative evaluation of the prediction error only on the test data, we define the normalized root mean square error(NRMSE) as follows.

$$NRMSE = \sqrt{\frac{\sum_{n=1}^{N}[e(n)-\overline{E}]^2}{\sum_{n=1}^{N}[y(n)-\overline{Y}]^2}} \tag{14}$$

where, $e(n) = y(n) - \hat{y}(n)$, $y(n)$ and $\hat{y}(n)$ are the sample values of the original and the predicted signals, $\overline{E}$ and $\overline{Y}$ are averages of $e(n)$ and $y(n)$, N is the number of samples to be evaluated. This NRMSE represents fractional error with respect to what is predicted. Table 1 compares the prediction error of HR and BP for all records. The value in the table is the best prediction result for given delays and function parameters in the test data set. The AVG and STD in the table represent average and standard deviation of the prediction error for all records.

From the table, it can be stated that the linear ARMA model is able to represent 52.89% +/- 24.47% of the HR variations, but the nonlinear RNN model accounts for 58.74% +/- 16.57%. For the BP variations, the linear and nonlinear models can represent 63.26% +/- 19.09% and 67.57% +/- 11.78%, respectively. These results show that the RNN-based model is about 6% and 4% better in representing the nonlinearities of HR and BP variations than the linear ARMA model in terms of NRMSE. Based on paired T-tests, however, there is no significant difference between linear and nonlinear predictions(p=0.098 for HR prediction and p=0.2156 for BP prediction). In other words, there are not much nonlinearities in short- term, beat-to-beat variability from a statistical point of view.

From the experimentation in the RNN-based prediction, we found that the more delays the better the prediction for HR and BP in both training data and test data sets. It was also found that the HR(or BP) prediction using past BPs(or HRs) is better than the prediction without using past BPs(or HRs). Fig. 6 shows an example of the RNN-based prediction error versus delays of HR or BP for test data set. The error in the figure is computed based on Eq. (14) assuming $\overline{Y}=0$. The number of x-axis indicates the number of delay, i.e., $N=M\neq0$ for with HR or BP delay, $N=0$ for without BP delay, and

Table 1. Summary of NRMSE in HR and BP predictions

Record	HR		BP	
	ARMA	RNN	ARMA	RNN
411	0.5025	0.4332	0.7795	0.5020
408	0.4160	0.3965	0.4996	0.4854
401	0.3585	0.3558	0.2354	0.2625
224	0.3508	0.3953	0.1022	0.1378
240	0.3626	0.3336	0.3910	0.3687
055	0.4165	0.3776	0.3883	0.3792
211	0.3940	0.3629	0.3462	0.3674
041	0.2228	0.1401	0.2719	0.2317
417	1.1156	0.7896	0.4707	0.2963
218	0.5716	0.5416	0.1891	0.2119
AVG	0.4711	0.4126	0.3674	0.3243
STD	0.2447	0.1657	0.1909	0.1178

$M=0$ for without HR delay. For example, in the HR prediction of Fig. 6(a) the number 3 for with BP delay means $N=M=3$ and the number 3 for without BP delay means $M=3$ and $N=0$ in Eq. 12. We found similar results in the BP prediction(refer to Fig. 6(b)).

Fig. 7 shows graphical representation of Table 1, i.e., NRMSE of RNN model versus NRMSE of ARMA model. The "*" symbol means a coordinate point of NRMSE of RNN and ARMA for each record, the "o" symbol means mean of all records, and the solid lines represent standard deviations. From these figures, all "*" symbols except one are distributed near the diagoanl line, which means that there are no meaningful difference between these two models in predicting HR and BP variations.

Conclusions

The aim of this study is to evaluate nonlinearities in short-term, beat-to-beat variability in cardiovascular signals by performing signal prediction. We compared the linear ARMA and nonlinear neural network models in predicting instantaneous heart rate and mean arterial blood pressure. Experimental results indicate that the neural network based nonlinearities do not play a significant role in short-term, beat-to-beat variability in the MIMIC patient population. This means that linear analysis techniques provide adequate characterization of the system dynamics responsible for generating short-term, beat-to-beat variability. Thus, we conclude that the linear techniques are appropriate to analyze cardiovascular signals for these patients even though there exist weak nonlinearities. Further investigations on the appropriateness of linear analysis techniques should be carried out in other patient populations and with other nonlinear techniques.

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