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Epileptic Seizure Monitoring by Using Multivariate Statistical Process Control

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Abstract: Although refractory epileptic patients suffer from uncontrolled seizures, their quality of life (QoL) may be improved if the seizure can be predicted in advance. In the preictal period, the excessive neuronal activity of epilepsy affects the autonomic nervous system. Since the fluctuation of the R-R interval (RRI) of an electrocardiogram (ECG), called heart rate variability (HRV), reflects the autonomic nervous function, an epileptic seizure may be predicted through monitoring RRI data. The present work proposes an HRV-based epileptic seizure monitoring method by utilizing multivariate statistical process control (MSPC) technology. Various HRV features are derived from the RRI data in both the interictal period and the preictal period recorded from epileptic patients, and an MSPC-based seizure prediction model is built from the interictal HRV features. The result of applying the proposed monitoring method to a clinical data demonstrates that seizures can be detected at least one minutes prior to the seizure onset. The possibility of realizing an HRV-based seizure monitoring system is shown.

Keywords: Epilepsy, Seizure prediction, Heart rate variability analysis, Process monitoring, Multivariate statistical process control

1. INTRODUCTION

Epilepsy is a diverse set of chronic neurological disorders characterized by seizures, that can be usually controlled with appropriate medications. However, about 30% of epileptic patients do not have seizure control even if they use the best available medications (Chang and Lowenstein (2003)).

Accidents by convulsions or loss of consciousness associated with uncontrolled seizures may cause serious injuries not only to patients themselves but also people around them. If patients can predict seizures a few minutes prior to the seizure onset, their quality of life (QoL) may be improved because they can ensure safety. A wearable epileptic seizure monitoring system that can predict and alert seizures before its onset should be developed.

Although seizure prediction based on the electroencephalogram (EEG) has been studied (Iasemidis (2003)), the use of EEG in daily living is not realistic because EEG strongly restricts a body and is intolerant to artifacts.

On the other hand, the heart rate pattern changes prior to a clinical seizure, because excessive neuronal activities affect the autonomic nervous system (Lotufo et al. (2012)). Actually, Gennaro et al. (2004) reported that the heart rate of epileptic patients increased prior to the seizure onset.

The R-R interval (RRI) fluctuation of an electrocardiogram (ECG), called heart rate variability (HRV), is a well-known phenomenon which reflects the autonomic nervous function (Pagani et al. (1986)), and many HRV features have been proposed for HRV analysis (Camm and Malik (1996)). Recently, the seizure prediction by using RRI data in the preictal period has been attempted (Kerem and Geva (2005)). Although the Holter monitor has been used to measure long-term RRI, it is also difficult to use at home because the Holter monitor is expensive and requires

skills of operation. A new methodology for monitoring an epileptic seizure that can be used in daily life needs to be developed.

Yamakawa et al. (2012) developed a wearable HRV sensor, which could measure RRI without any special skills and be manufactured for less than 100 dollars. If an HRV-based seizure monitoring method is implemented in such a device, a wearable epileptic seizure monitoring system becomes available.

In the present work, a new HRV-based seizure monitoring method is proposed. The proposed method consists of two parts: HRV feature extraction from RRI data of epileptic patients, and epileptic seizure monitoring by using a seizure prediction model whose inputs are the extracted HRV features. Multivariate statistical process control (MSPC), which is a well-known process monitoring method in the field of process control (Nomikos and MacGregor (1994); Kano et al. (2001)), is applied to seizure prediction model construction.

This paper is organized as follows. In Secs. 2 and 3, the HRV features used in this work and the seizure monitoring method based on the MSPC framework are introduced. Section 4 reports an application result of the proposed monitoring method to a clinical data collected from five epileptic patients. Finally, the conclusion and the future work are described in Sec 5.

2. HEART RATE VARIABILITY ANALYSIS

Since HRV reflects autonomic nervous activity, HRV analysis has been used for stress or sleepiness estimation as well as cardiovascular disease monitoring, and various HRV features have been already proposed (Kleiger et al. (1987); Camm and Malik (1996); Malliani (1991)). In this section, the HRV features used for seizure monitoring are explained briefly.

2.1 RR Interval

A typical ECG trace of the cardiac cycle consists of some peaks as shown in Fig 1, and the highest peak is called the R wave. The R-R interval (RRI) [ms] is defined as the interval between an R wave and the next R wave.

A part of the raw RRI data collected from a healthy person is shown in Fig. 2 (a). Since the raw RRI data are not sampled at equal intervals, it is difficult to analyze them directly. The raw RRI data are interpolated by using spline, and the interpolated RRI data are resampled at equal intervals. Figure 2 (b) shows the resampled RRI data whose sampling interval is one sec.

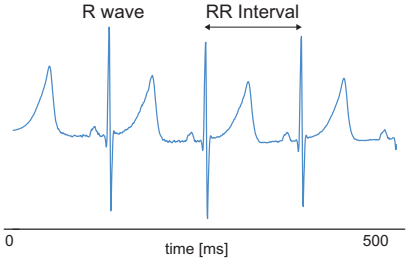

Fig. 1. An example of a typical ECG

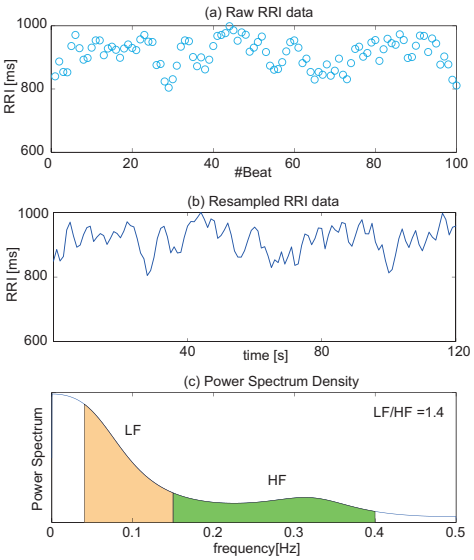

Fig. 2. An example of RRI data analysis: (a) raw RRI data, (b) resampled RRI data and (c) PSD and its LF/HF

2.2 Time Domain Features

The time domain features can be directly calculated from the resampled RRI data.

- **meanNN**: Mean of RRI.
- **SDNN**: Standard deviation of RRI.
- **RMSSD**: The root mean square of difference of adjacent RRI.
- **Total power**: Variance of RRI.
- **NN50**: The number of pairs of adjacent RRI whose difference is more than 50 msec.
- **pNN50**: The number of pairs of adjacent RRI, whose difference is more than 50 msec, divided by the total number of RRI.
- **HRV triangular index**: The number of RRI divided by the height of the histogram of all RRI measured on a discrete scale with bins of 1/128 sec.

2.3 Frequency Domain Features

The frequency domain features can be obtained through the power spectrum density (PSD) of the resampled RRI data, and it can be calculated by using Fourier analysis or an autoregressive (AR) model.

- **LF**: The power of the low frequency band (0.04Hz - 0.15Hz) in PSD. LF reflects sympathetic nervous system activity.
- **HF**: The power of the high frequency band (0.15Hz - 0.4Hz) in PSD. HF reflects parasympathetic nervous system activity.
- **LF/HF**: Ratio of LF to HL. LF/HF expresses the balance of the sympathetic nervous system activity with the parasympathetic nervous system activity.

Figure 2 (c) shows a PSD and its LF/HF of the resampled RRI data shown in Fig. 2 (b).

According to the HRV analysis guideline, the RRI data should be measured for at least three minutes for precise frequency analysis (Camm and Malik (1996)).

3. SEIZURE MONITORING METHOD

An HRV-based epileptic seizure monitoring method is proposed to predict and alert of a seizure a few minutes before its onset. In this work, the MSPC framework is used for seizure monitoring.

3.1 Multivariate Statistical Process Control (MSPC)

MSPC is a useful technique for process monitoring, that has been widely used in many processes (Nomikos and MacGregor (1994); Kano et al. (2001)).

In MSPC, the changes in correlation among variables are monitored because the correlation changes when a fault occurs in a process. To detect such changes, two indexes, the T^2 and Q statistics, are monitored simultaneously. They are derived from principal component analysis (PCA), which is a tool for data compression and information extraction (Jackson and Mudholkar (1973)). PCA finds linear combinations of variables that describe major trends in a data set.

Given a data matrix $\boldsymbol{X} \in \Re^{N\times M}$ whose ith row is the ith sample $\boldsymbol{x}_i$, the singular value decomposition of $\boldsymbol{X}$ is as follows:

$$\begin{aligned}\boldsymbol{X} &= \boldsymbol{U}\boldsymbol{\Sigma}\boldsymbol{V}^T \\ &= [\,\boldsymbol{U}_R\ \boldsymbol{U}_0\,] \begin{bmatrix} \boldsymbol{\Sigma}_R & \boldsymbol{0} \\ \boldsymbol{0} & \boldsymbol{\Sigma}_0 \end{bmatrix} [\,\boldsymbol{V}_R\ \boldsymbol{V}_0\,] \end{aligned} \tag{1}$$

where $\boldsymbol{U}$ is the left singular matrix, $\boldsymbol{\Sigma}$ is the matrix whose diagonal elements are singular values and $\boldsymbol{V}$ is the right singular matrix. In PCA, the loading matrix $\boldsymbol{V}_R \in \Re^{M\times R}$ is derived as the right singular matrix of $\boldsymbol{X}$ and the column space of $\boldsymbol{V}_R$ is the subspace spanned by principal components. Here, M, N, and $R(\leq M)$ denote the number of variables, samples, and principal components retained in the PCA model, respectively. All variables are mean-centered and appropriately scaled. The score is a projection of $\boldsymbol{X}$ onto the subspace spanned by principal components. The score matrix $\boldsymbol{T}_R \in \Re^{N\times R}$ is given by

$$\boldsymbol{T}_R = \boldsymbol{X}\boldsymbol{V}_R. \tag{2}$$

$\boldsymbol{X}$ can be reconstructed or estimated from $\boldsymbol{T}_R$ with linear transformation $\boldsymbol{V}_R$.

$$\hat{\boldsymbol{X}} = \boldsymbol{T}_R\boldsymbol{V}_R^{\mathrm{T}} = \boldsymbol{X}\boldsymbol{V}_R\boldsymbol{V}_R^{\mathrm{T}} \tag{3}$$

The information lost by the dimensional compression, that is, errors, is written as

$$\boldsymbol{E} = \boldsymbol{X} - \hat{\boldsymbol{X}} = \boldsymbol{X}(\boldsymbol{I} - \boldsymbol{V}_R\boldsymbol{V}_R^{\mathrm{T}}). \tag{4}$$

Using the errors, the Q statistic is defined as

$$\begin{aligned} Q &= \sum_{m=1}^{M} (x_m - \hat{x}_m)^2 \\ &= \boldsymbol{x}^T(\boldsymbol{I} - \boldsymbol{V}_R\boldsymbol{V}_R^T)\boldsymbol{x} \end{aligned} \tag{5}$$

where $\boldsymbol{x}$ is a newly measured sample. The Q statistic is the distance between the sample and the subspace spanned by principal components. In other words, the Q statistic is a measure of dissimilarity between the sample and the modeling data from the viewpoint of the correlation among variables.

In addition, to guaranteeing that the sample is located in modeling data and to avoid extrapolation, Hotelling's T^2 statistic is used. The T^2 statistic is defined as

$$\begin{aligned} T^2 &= \sum_{r=1}^{R} \frac{t_r^2}{\sigma_{t_r}^2} \\ &= \boldsymbol{x}^T\boldsymbol{V}_R\boldsymbol{\Sigma}_R^{-2}\boldsymbol{V}_R^T\boldsymbol{x} \end{aligned} \tag{6}$$

where σ_{t_r} denotes the standard deviation of the rth score t_r. The T^2 statistic expresses the normalized distance from the origin in the subspace spanned by principal components. When the T^2 statistic is small, the sample is close to the mean of the modeling data. In MSPC, a fault is detected when each the T^2 or Q statistic exceeds the predefined control limit.

Although, in general, both normal and anomalous data are needed when a classification model is constructed, the MSPC framework requires only normal data for model construction. In addition, since MSPC is a linear method, the number of required modeling samples in MSPC is smaller than that of nonlinear methods. These points can be advantages of MSPC when the seizure prediction model is constructed. In seizure monitoring, the normal and anomalous data are the interictal and preictal data, respectively. It is difficult to collect a sufficient number of preictal RRI data from epileptic patients, and collecting the interictal RRI data and the RRI data of healthy people is much easier than preictal RRI data collection.

3.2 Epileptic Patient Monitoring

To monitor epileptic seizures, the seizure prediction model is used in the proposed method, and a pair of Eqs. (5) and (6) is called the seizure prediction model. The following procedure is adopted for model construction.

(i) Acquire interictal RRI data of epileptic patients, and extract the HRV features described in Sec. 2.
(ii) Normalize each HRV feature, that is, adjust it to zero mean and unit variance.
(iii) Generate data sets from the normarized HRV features by moving the time window.
(iv) Constract the seizure prediction model Eqs. (5) and (6), and determine the control limits of the T^2 and Q statistics.

Using the constructed seizure prediction model, seizures can be monitored according to the following procedure.

(1) Measure the RRI data representing the current autonomic nervous function from an epileptic patient.
(2) Extract the HRV features from the measured RRI data.
(3) Normalize the HRV features with the mean and the variance obtained at the model construction procedure (ii).
(4) Calculate the T^2 and Q statistics from the normalized HRV features by using Eqs. (5) and (6).
(5) Judge that a seizure will occur in a few minutes, if either statistic is outside their control limits.

Table 1. Patients demographic and clinical characteristics

Patient	Sex	Age	Seizure type	Epilepsy syndromes	Medication* [mg/day]
A	male	27	generalized	atypical Lennox-Gastaut syndrome	VPA 1200, LEV 2000, CZP 2
B	male	46	partial	left frontal lobe epilepsy	VPA 1600, CBZ 800, ZNS 400, TPM300
C	male	25	partial	right frontal lobe epilepsy	CBZ 800
D	male	30	partial	left temporal lobe epilepsy	CBZ 400, CLB 10
E	male	14	partial	localization-related epilepsy	TPM 550, PHT 250, CLB 20, LTG 400

*VPA: Valproic acid, LEV: Levetiracetam, CZP: Clonazepam, CBZ: Carbamazepine, ZNS: Zonisamide, TPM: Topiramate, CLB: Clobazam, PHT: phenytoin, LTG: lamotrigine

(6) Return to step (1).

In the model construction procedure (iv), the control limits of the T^2 and Q statistics should be determined.

4. APPLICATION TO CLINICAL DATA

In this section, an actual application result of the proposed seizure monitoring method to a clinical data is reported.

4.1 Data Collection

The interictal and preictal RRI data of patients with intractable epilepsy were collected for pre-surgical tests at the department of neurosurgery of Tokyo Medical and Dental University (TMDU) hospital. This retrospective evaluation of clinically acquired data was considered by Medical Research Ethics Committee of TMDU and individual patient consent was not required.

The video, electrocardiogram (ECG) and EEG data of patients were simultaneously recorded for about 24 - 72 h by using the long-term video-EEG monitoring system (Neuro Fax EEG-1200, NIHON KOHDEN). These pre-surgical tests took place in the shield room for EEG recording.

Two clinical epilepsy specialists, certified by Japan Epilepsy Society, defined the clinical seizure onset by consulting the EEG data and the seizure video. The ECG data 15 minutes before and 5 minutes after the seizure onset were stored as the preictal ECG dataset. On the other hand, the ECG data recorded in the interictal period were organized as some interictal ECG datasets for seizure prediction model construction, and their length was 20 min.

4.2 Patients

The interictal and preictal ECG datasets were collected from five epileptic patients with generalized epilepsy or localization-related epilepsy. Tables 1 and 2 show the patient profile and their collected datasets, respectively. In Table 1, Medication means the anticonvulsant dosage [mg/day] on the inspection day. The total numbers of collected preictal ECG dataset and interictal ECG dataset are six and thirteen, respectively. The patients were all male unintentionally, and the preictal ECG data of patients D and E could not be recorded.

Table 2. Collected dataset

Patient	Preictal	Interictal
A	A1 - A3	A'1-A'2
B	B1	B'1 - B'4
C	C1, C2	-
D	-	D'1 - D'4
E	-	E'1 - E'3

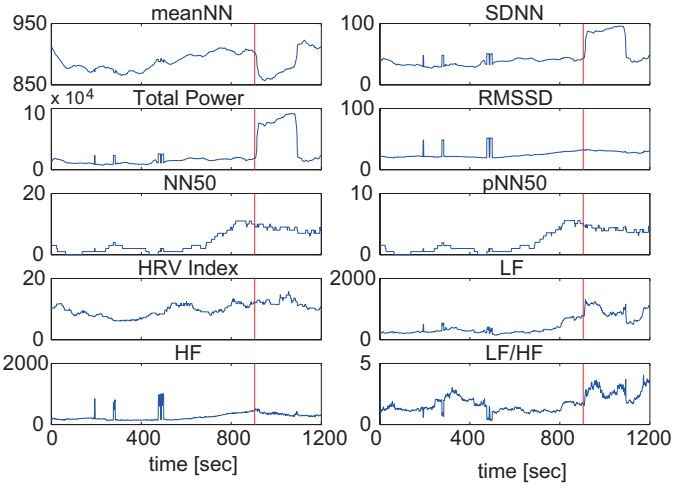

Fig. 3. HRV features of episode A1

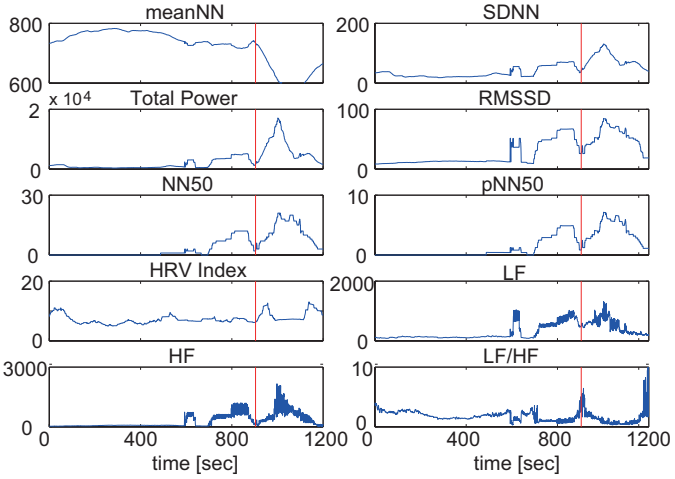

Fig. 4. HRV features of episode B2

4.3 HRV Features

The R waves in the collected ECG data were detected and each RRI was calculated. The obtained raw RRI data was resampled so that its sampling points were arranged at equal intervals to calculate the frequency domain features. In this work, the third-order spline was used for RRI interpolation, and the sampling interval of the interpolated RRI was one sec.

A rectangular sliding window was applied to the original and resampled RRI data, and ten HRV features described in Sec. 2 were calculated within each window. The window size was three min, as determined by trial and error. An AR model was used to calculate frequency domain

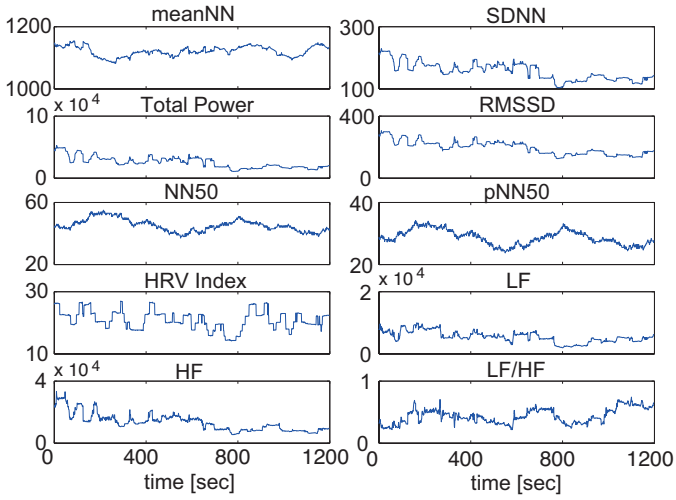

Fig. 5. HRV features of episode B'2

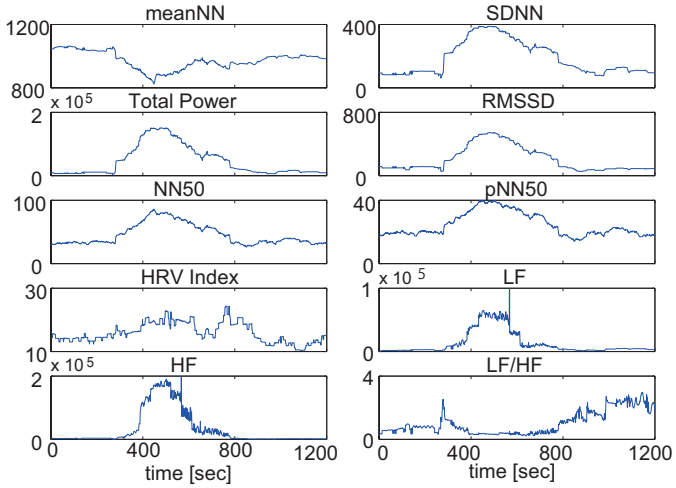

Fig. 6. HRV features of episode D'2

features, and its order was determined on the basis of Akaike information criterion (AIC) (Akaike (1973)).

The obtained HRV features of two ictal episodes A1 and B2 and two interictal episodes B'2 and D'2 are shown in Figs. 3-6. Red vertical lines in Figs. 3 and 4 show the seizure onset.

These figures show that the RRI dramatically changes shortly after the seizure onset in all episodes, and it indicates that the seizure certainly affects the autonomic nervous function. The HRV features of episode A1 and B2 show that almost all features changed about five minutes before its seizure onset. On the other hand, Fig. 6 shows the HRV features suddenly changed nevertheless this episode does not contain the seizure onset.

These results indicate that it is difficult to predict the epileptic seizure by monitoring respective HRV features and multiple features should be monitored together.

4.4 Seizure Monitoring

The performance of the proposed seizure monitoring method was validated through an application to the clinical data. First, the seizure prediction model Eqs. (5) and

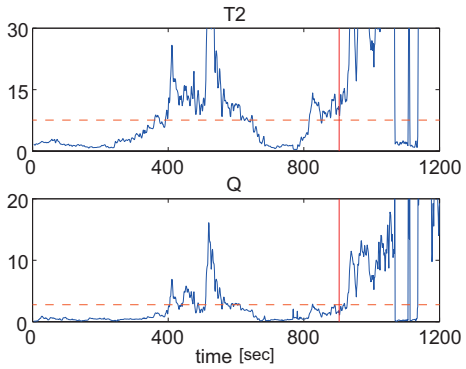

Fig. 7. Monitoring result of episode A2

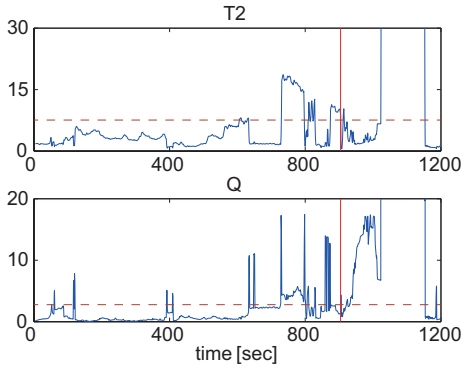

Fig. 8. Monitoring result of episode C3

(6) was constructed by using seven interictal datasets A'1, B'1-3, D'1 and E'1-2.

In this model, all HRV features calculated in Sec. 4.3 were used as inputs. However, as shown in meanNN of Figs. 3-6, an instantaneous heart rate of each episode differed from each other, and it affects the magnitudes of other features. To take these differences into account, four HRV features, such as meanNN, NN50, pNN50 and HRV triangular index, were standardized by Total power. In addition, to take into account changes in the HRV features, the input data consist of the present features and the features derived from the RRI data measured one and two beats before. In MSPC, the number of retained principal components was four. These were determined by trial and error.

In addition, the control limits of the T^2 and Q statistics were determined by using operation data so that they represent 90% confidence limits. In other words, the control limits were set so that 90% of samples representing the interictal condition were inside the control limits and the other 10% were outside. Although this criterion may be rather restrict, the control limits should be restrict in the seizure monitoring because seizures do not have to be missed even if some false-positives occur.

The constructed model was applied to all seizure episodes and six interictal datasets A'2, B'4, D'2-4 and E'2. Although all seizure episodes were tested, only two results of episodes A3 and B2 are shown in Figs. 7 and 8 here. In addition, Figs. 9 and 10 show the monitoring results of the interictal datasets D'3 and E'2. In these figures, the

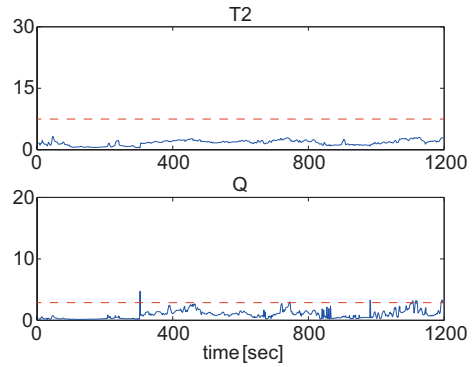

Fig. 9. Monitoring result of interictal episode D'3

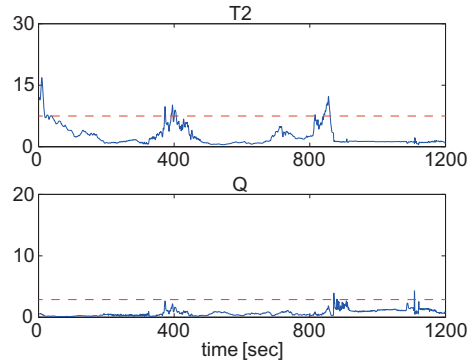

Fig. 10. Monitoring result of interictal episode E'2

horizontal dash lines express the control limits of the T^2 and Q statistics.

In Figs. 7 and 8, both the T^2 and Q statistics exceeded their control limits substantially at least three minutes before the seizure onset. On the other hands, both the T^2 and Q statistics of interictal episodes rarely exceed their control limits. Another episodes showed almost the same tendency although they are not shown here. These results indicate that the proposed method can predict a seizure before its onset although there are a few false-positives, and the control limits of the T^2 and Q statistics have to be determined carefully.

5. CONCLUSION

A new HRV-based epileptic seizure monitoring method is proposed, by which the RRI data recorded from epileptic patients are translated into the HRV features, and the seizure is monitored by using the MSPC framework.

In future work, various time series analysis methods for the RRI data and classification methods will be evaluated to improve the seizure monitoring performance. In addition, the constructed seizure monitoring method will be implemented in a wearable HRV sensor.

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