KRAMERS–MOYAL EXPANSION OF HEART RATE VARIABILITY*

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(Received April 2, 2009)

The first six Kramers–Moyal coefficients were extracted from human heart rate variability recordings. The method requires the determination of the Markov time and of the proper conditional probability densities. We analyzed heart rate data recorded in a group of ten young, healthy subjects. We obtained non-negligible higher order Kramers–Moyal (K–M) terms in 6 h nighttime parts of the 24 h recordings. This indicates that the data is a non-Gaussian process and probably a correlated signal. The analysis yielded important new insights into the character and distribution of the stochastic processes measured in healthy group. In the night hours, the dominant oscillation in the heart rate is the so called respiratory sinus arrhythmia (RSA) — a physiological phenomenon in which respiration acts as a drive for the heart rate. Certain kinds of pathology may disrupt RSA. We compared nighttime recordings of the healthy group with those recorded in six patients with hypertrophic cardiomyopathy (HCM). HCM is generally a pathology of heart cells but abnormalities in autonomic regulation are also observed. Using the higher order Kramers–Moyal coefficients, we analyzed the skewness and kurtosis in the nighttime recordings for the normal subjects.

PACS numbers: 02.50.Fz, 02.50.Ga, 05.10.Gg, 05.45.Tp

1. Introduction

Recently, the extraction of the Kramers–Moyal coefficients was performed for human heart variability (RR interval time series) [1,2]. The Markov time was determined from the Chapman–Kolmogorov equation. The analysis of

* Presented at the XXI Marian Smoluchowski Symposium on Statistical Physics Zakopane, Poland, September 13–18, 2008.

just the first two K–M coefficients (the drift and diffusion terms) showed differences between healthy and congestive heart failure subjects [1,2]. In previous research, other groups [2] selected such heart rate variability data for which only the drift and diffusion terms were non-negligible allowing the use of the Langevin equation for data reconstruction. However, the description of heart rate variability using this method is not complete and the stochastic properties have not been fully understood. In this paper, we extend the analysis by looking at higher order K–M coefficients also. We show that the method may be used to enhance medical diagnostics by adding new insight into properties of heart rate variability.

2. The extraction of Kramers–Moyal coefficients

Extraction of the Kramers–Moyal terms requires the calculation of conditional density probabilities [3] directly computed from experimental data:

$$D^{(n)}(X,t) = \frac{1}{n!} \lim_{\tau \to 0} \frac{1}{\tau} \int \left(X'(t+\tau) - X(t)\right)^{(n)} P\left(X'(t+\tau)|X(t)\right) dX' . \quad (1)$$

The conditional density probability distribution $P(X'(t+\tau)|X(t))$ is the probability of the system to be found in state X' at $t+\tau$ time, when the previous X state at time t was given. The parameter τ is determined from the Chapman–Kolmogorov (CK) equation with the time $t_2 < t_3 < t_1$ [4]:

$$P(X_2, t+\tau|X_1, t-\tau) = \int P(X_2, t+\tau|X_3, t)\, P(X_3, t|X_1, t-\tau) dX_3 . \quad (2)$$

The parameter $\tau = t_2 - t_3 = t_3 - t_1$, which fulfills the condition (2), is the Markov time. In Eq. (2) the time intervals between all three time series elements X_1, X_3, X_2 are equal, which means that our process is assumed to be stationary [4].

3. Medical data

Heart rate variability data was extracted from 24-hour Holter ECG recordings using the 563 Strata Scan Del Mar Avionics system at the Institute of Cardiology (Warszawa, Poland). The data was in the form of time series of the time intervals between heartbeats (RR intervals of the ECG trace). All data were checked by a qualified cardiologist: normal beats were detected, artifacts were deleted and arrhythmias were recognized. The data was sampled at 128 Hz.

Ten young (age $26-4+3$ y) healthy males were analyzed. Six data sets for hypertrophic cardiomyopathy (HCM — a disease of the heart muscle) were analyzed (2 men and 4 women $26.5+4-6$ y). From the 24 hour

recordings for the normal and HCM subjects, we extracted 6 h nighttime (between 10.30 p.m. and 6 a.m.) fragments.

For better comparison, all recordings were rescaled taking into account the mean value $\langle \mathrm{RR} \rangle$ and the standard deviation σ of the 24 hours signal: $X_i = (\mathrm{RR}_i - \langle \mathrm{RR} \rangle)/\sigma$. In Fig. 1, we depict the rescaled nighttime RR intervals series for a healthy male. After rescaling, RR intervals are dimensionless.

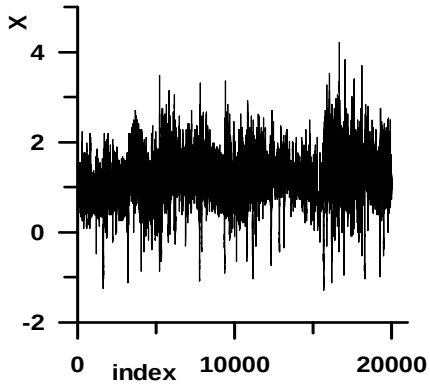

Fig. 1. Example of a 6 hour RR interval time series for a healthy subject (CHM).

4. Higher order expansion coefficients

The Markov time τ was estimated for each 6 h fragment from the CK equation (2). The time τ, expressed in units of the data index, varied between 1 and 4. After estimating the Markov time, we calculated the first six Kramers–Moyal expansion terms Eq. (1). For computational analysis, equation (1) and (2) were discretized by dividing the range of X into a constant number of 45 bins.

The errors of the Kramers–Moyal terms for extreme values of the argument X can be large due to the poor statistics in that range. We found the recognition of this effect crucial for the proper measurement of the expansion coefficients. Therefore, we limit the range of X to what we call the *significance range i.e.,* such range of X in which the number of data points in a given bin exceeded 10^2. The extent of the significance range is marked in the figures by vertical gray lines.

Within a certain range of X, the higher order terms for the nighttime series (especially of $D^{(3)}$ and $D^{(4)}$) were comparable in magnitude to $D^{(1)}$ and $D^{(2)}$ (Fig. 2 and Fig. 3) for 9 cases of the 10 recordings of cardiological norm. Within the significance range of X, $D^{(3)}$ and $D^{(4)}$ exceed well over 10% of $D^{(1)}$ and $D^{(2)}$, respectively, so that the higher order terms are not negligible.

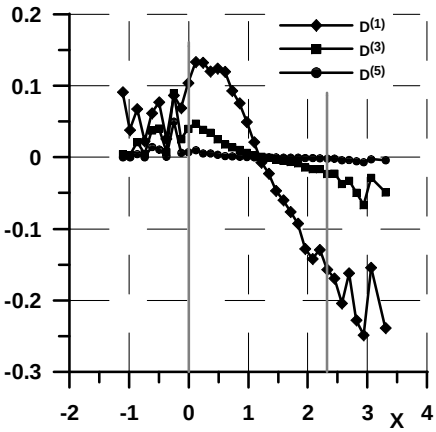

Fig. 2. Odd higher order Kramers–Moyal coefficients for the nighttime signal (single patient, CHM).

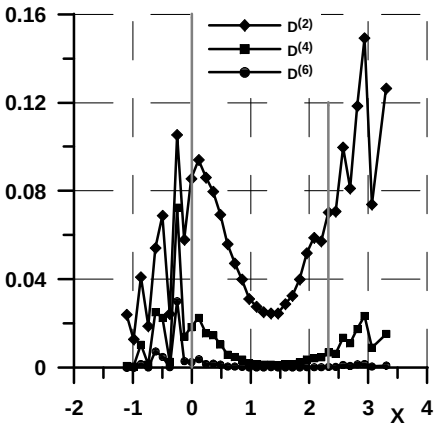

Fig. 3. Even higher order Kramers–Moyal coefficients for the nighttime signal (single patient, CHM).

If a process obeys the Pawula theorem ($D^{(n)}(X,t) = 0$, for $n \geq 3$) [3], its dynamics can be described by the Langevin equation [5]:

$$\frac{dX}{dt} = D^{(1)}(X,t) + \sqrt{2D^{(2)}(X,t)}\Gamma(t) \ , \tag{3}$$

where $\Gamma(t)$ is Gaussian noise with $\langle\Gamma(t)\rangle = 0$ and $\langle\Gamma(t)\Gamma(t')\rangle = \delta(t-t')$. Because of the occurrence of higher order terms for the nighttime data, the dynamics of heart rate variability in the nighttime recordings analyzed here cannot be reconstructed using Eq. (3).

5. Detrending nighttime signals

To check whether the occurrence of the higher order terms in the Kramers –Moyal expansion of the nighttime data are not due to non stationarity, we applied a detrending method to our data [6]. The signal was smoothed by a one hundred data point sliding window. The extrema of the smoothed signal were determined, a linear trend was found between successive extrema and removed from the data. Finally, the resultant signal was rescaled to regain the original range of the data. An example of the original and of the detrended nighttime signal is shown in Fig. 4(a) and 4(b). It can be seen that the linear trends were successfully removed but isolated extremely short and long RR intervals remain.

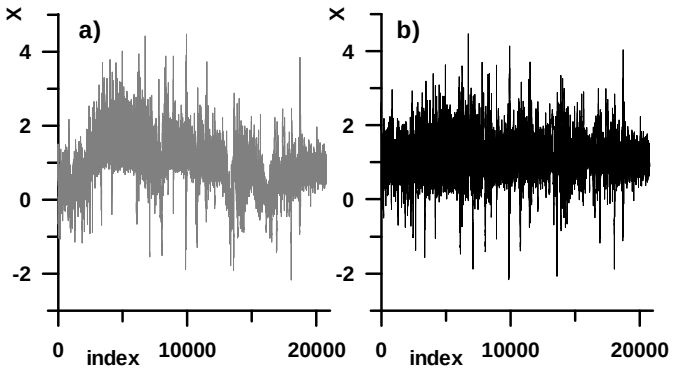

Fig. 4. The original (a) and detrended (b) nighttime series for the healthy subject CHB.

In Fig. 5(a) and 5(b) we show the effect of trend removal from the signal on the drift $D^{(1)}$ and diffusion $D^{(2)}$ terms. The gray curves in both figures mark the same results as shown in Fig. 2 and Fig. 3, respectively, before the trend was removed. The black curves depict the results obtained for the detrended data. The gray vertical straight lines marked the significance range for the detrended data.

The drift $D^{(1)}$ after detrending exhibits an extended linear dependence within the significance range. Such a linear dependence is characteristic for an oscillating process [7]. A physiological oscillatory process which is dominant during the night is respiratory sinus arrhythmia (RSA) [8]. It is one of the reasons for heart rate variability: the RR interval shortens during inspiration and it is lengthened during expiration.

An asymmetry of the diffusion term (Fig. 5(b)) calculated for the detrended signal within the significance range of X was obtained. The $D^{(2)}(X)$ dependence has a characteristic parabolic shape with usually a single minimum. Within the significance range, the curve to the left of the minimum

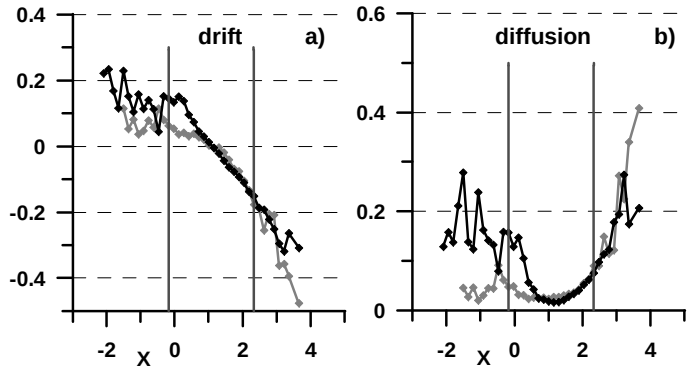

Fig. 5. Drift (a) and diffusion term (b) for the original CHB (gray curve) and detrended CHB (black curve) nighttime signal.

increases faster than to the right. $D^{(2)}$ was an asymmetrical function for 9 of the 10 detrended recordings for the normals. We can interpret the asymmetry as a result of RSA which leads to a preference for short RR intervals. The asymmetry described may be related to the well known different time scales of the acceleration and the deceleration of heart rate [9]. $D^{(2)}$ as a function of X obtained for 3 of the 6 nighttime detrended recordings of HCM analyzed in this work is depicted in Fig. 6(a) (only for the significance range). Fig. 6(b) depicts 3 examples of the functional dependence of $D^{(2)}$ for the healthy subjects. It can be seen that asymmetry in diffusion coefficient in the case of HCM is disrupted or not present. Note that the minima of $D^{(2)}$ do not coincide because the 24 h average and standard deviation of the heart rate is different for each case.

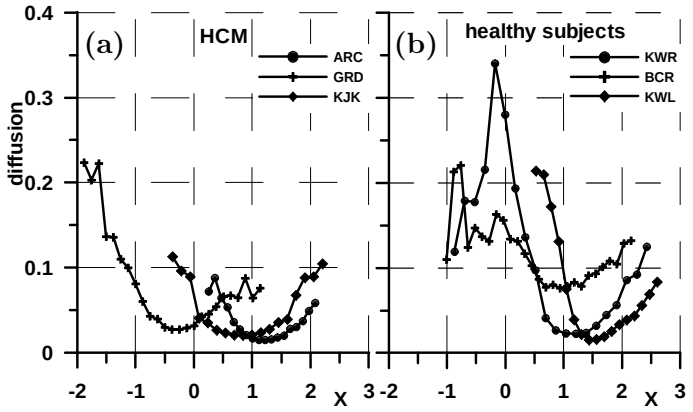

Fig. 6. Diffusion terms of the nighttime data for 3 HCM patients (part a) and 3 healthy subjects (part b) calculated within the significance range. The signals were detrended and rescaled.

6. The analysis of higher order terms

Using the higher order terms, we analyzed the skewness:

$$\gamma_1 = \frac{D^{(3)}}{\left(D^{(2)}\right)^{3/2}}\,, \tag{4}$$

and kurtosis:

$$\gamma_2 = \frac{D^{(4)}}{\left(D^{(2)}\right)^{2}} - 3\,, \tag{5}$$

of the *conditional probability distributions* for the nighttime data for each nighttime signal as functions of the argument X. In Fig. 7 and Fig. 8 we depict the curves only within the significance range of X. Because the functional dependences overlap, for clarity, we show skewness and kurtosis only for 6 subjects of the 10 subjects we analyzed and in two separate panels (the acronyms in the legend denote the individual recordings). It can be seen that, for each case, we obtained a skewness coefficient decreasing with X and not symmetric with respect to zero.

The dominance of the positive sign of the skewness (Fig. 7) is in accordance with the asymmetry of the functional dependence of the diffusion term described above.

In Fig. 8 we present the functional dependence of the kurtosis on X calculated for each of the six cases analyzed here. For the most part, the kurtosis obtained at different X is negative. However, in all cases there was

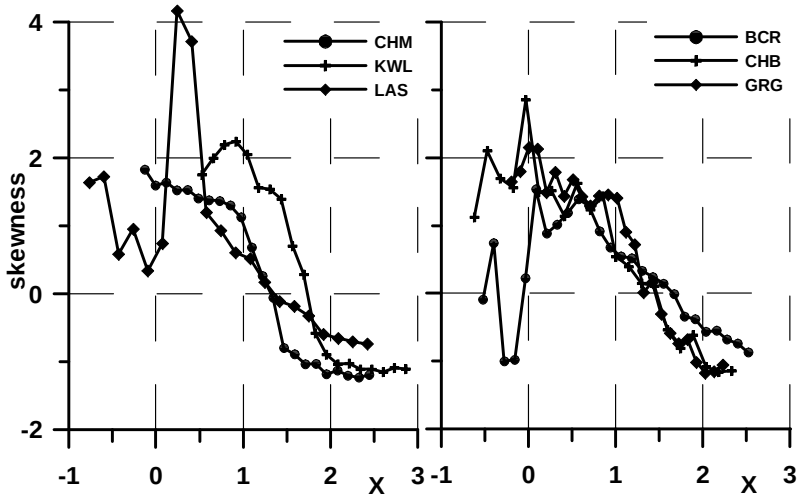

Fig. 7. Skewness of the nighttime recordings for the conditional distributions (6 subjects).

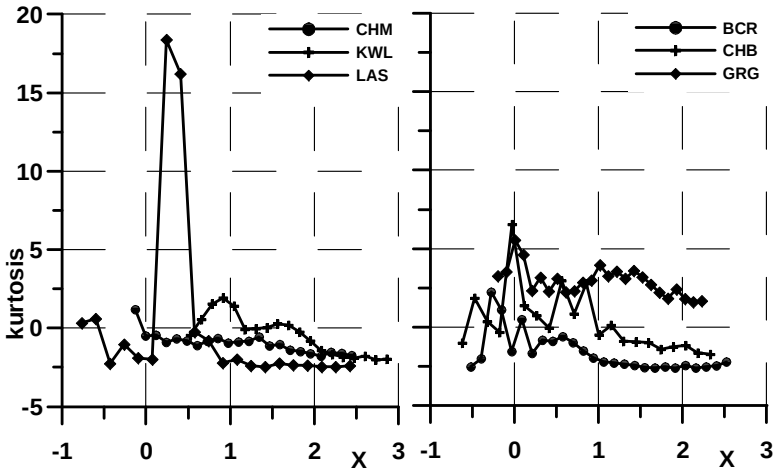

Fig. 8. Kurtosis of the nighttime recordings for the conditional distributions (6 subjects).

a range of X for which the kurtosis was positive. For one case all values of the kurtosis were positive. A large positive kurtosis suggests a strong concentration around the expectation value of the conditional distribution and is characteristic for heavy tailed distributions [10]. When kurtosis is negative and small a Gaussian-like distribution of the conditional probability density is indicated. Note that the time series analyzed here may be too short to accurately analyse the rare events which form the tails of the conditional distributions.

7. Conclusions

The Kramers–Moyal expansion was applied to nighttime recordings of the heart rate variability of ten healthy males. Because of the occurrence of higher order coefficients in Kramers–Moyal expansion it was impossible to reconstruct the nighttime data using the Langevin equation. The properties of the skewness and kurtosis of conditional probabilities calculated using the third and the fourth order expansion terms suggests that nighttime heart rate variability is a non-Gaussian process.

The linear dependence of the drift term $D^{(1)}$ on the rescaled heart rate X may be due to an oscillation in the heart rate. In the night hours, the dominant oscillation is RSA. We observed an asymmetry in the diffusion term $D^{(2)}$ for the detrended night signals for the normals and interpret it as caused by RSA. We did not obtain this effect in the heart rate variability of hypertrophic cardiomyopathy patients for which the asymmetry in diffusion coefficient is disrupted or not present. This result may be useful for medical diagnosis.

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