
EXHIBIT 2005

Estimating Respiratory and Heart Rates from the Correntropy Spectral Density of the Photoplethysmogram

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Abstract

The photoplethysmogram (PPG) obtained from pulse oximetry measures local variations of blood volume in tissues, reflecting the peripheral pulse modulated by heart activity, respiration and other physiological effects. We propose an algorithm based on the correntropy spectral density (CSD) as a novel way to estimate respiratory rate (RR) and heart rate (HR) from the PPG. Time-varying CSD, a technique particularly well-suited for modulated signal patterns, is applied to the PPG. The respiratory and cardiac frequency peaks detected at extended respiratory (8 to 60 breaths/min) and cardiac (30 to 180 beats/min) frequency bands provide RR and HR estimations. The CSD-based algorithm was tested against the Capnabase benchmark dataset, a dataset from 42 subjects containing PPG and capnometric signals and expert labeled reference RR and HR. The RR and HR estimation accuracy was assessed using the unnormalized root mean square (RMS) error. We investigated two window sizes (60 and 120 s) on the Capnabase calibration dataset to explore the time resolution of the CSD-based algorithm. A longer window decreases the RR error, for 120-s windows, the median RMS error (quartiles) obtained for RR was 0.95 (0.27, 6.20) breaths/min and for HR was 0.76 (0.34, 1.45) beats/min. Our experiments show that in addition to a high degree of accuracy and robustness, the CSD facilitates simultaneous and efficient estimation of RR and HR. Providing RR every minute, expands the functionality of pulse oximeters and provides additional diagnostic power to this non-invasive monitoring tool.

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Introduction

The ability to track multiple vital signs from a simple, low cost, and easy to use non-invasive sensor is desirable to facilitate physiological tele-monitoring. There is a clear need for reliable and simple methods for tracking cardio-respiratory activity over time to monitor patients in the intensive care environment or patients at home with long-term disease with associated instability in respiratory or cardiovascular function. Therefore, the remote and automated monitoring of heart rate (HR) and respiratory rate (RR) is an important field of research [1].

An abnormal RR is often an early sign of critical illness. For example, an essential criterion integrated in guidelines for the diagnosis of pneumonia in children (age 1–5 years) is the assessment of an elevated RR (>40 breaths/min) [2]. However, clinical measurement of RR has been shown to have poor reliability and repeatability [3]. A reliable estimate of RR assessed in an automated way is therefore crucial in the application of remote tele-monitoring, where persons with no specialized training are conducting the assessment. This would enable early support for timely recognition and management of physiological deterioration of high-risk patient groups [4].

Pulse oximetry is widely used in health facilities to monitor physiological vital signs. It is based on the principle of photoplethysmography (PPG), an optical technique to measure local variations of blood volume in tissues. Two light-emitting diodes (LEDs) illuminate the tissue and a photo detector detects the light reflected by the tissue. The intensity of the light detected varies with each heart beat as the blood volume changes over time [5]. Blood oxygen saturation (SpO₂) is calculated by measuring the difference in absorption of oxygenated and deoxygenated hemoglobin at two distinct wavelengths, red (660 nm) and infrared (940 nm). Oxygenated blood preferably absorbs infrared light and transmits red light and deoxygenated blood has the inverted absorption characteristics [4].

The PPG is a complex signal composed of different but related components. The most recognized PPG waveform component is the peripheral pulse synchronized to each heart beat (AC component). This AC component is superimposed and modulated by a quasi DC component that varies slowly due to respiration, vasomotor activity and vasoconstrictor waves [4]. In addition, an autonomic response to respiration causes a variation of HR synchronized with RR, referred to as respiratory sinus arrhythmia. The PPG signal is also influenced by other mechanisms that are not completely understood. However, it is generally accepted that

it has potential to provide clinically useful information about the cardio-vascular and respiratory system [6] and its SpO₂ pattern characterization has successfully applied to detect sleep apnea [7].

Well-established methods have been described for the estimation of SpO₂ and HR from the PPG [8], [9]. In addition, several methods based on characterization of the PPG cycles morphology in the time domain, using time-frequency analysis [10], [11], [12], [13], [14], [15], [16] digital filtering [5], [17] and smart fusion [6] have been proposed to estimate RR. However, this estimation of RR in pulse oximetry is not yet commercially established. The simultaneous estimation of HR and RR from the PPG signal would provide a low processing overhead that is desirable for simple and low cost physiological monitor. This would reduce vital sign monitoring hardware to one peripheral sensor and one signal-processing step.

Correntropy-based spectral density (CSD) has been found to be particularly well suited for the characterization of modulated signals. This method provides an improved spectral resolution compared to conventional techniques like power spectral density (PSD) and shows promise in the detection of modulated patterns [18]. Correntropy is a generalized correlation function that provides information on higher-order statistics. It is able to detect nonlinearities that conventional techniques (based on second-order statistics), may be unable to detect. Another attractive property of the correntropy function is its robustness against impulsive noise [19], [20].

In this paper we propose a novel algorithm based on CSD to estimate both RR and HR simultaneously from the PPG signal obtained from pulse oximetry. The initial application will be to develop an easy-to-use portable device that measures multiple vital signs. This algorithm is ideally suited to be implemented on the *Phone Oximeter*[®], a mobile device that integrates a commercially available and federal drug administration (FDA) approved pulse oximeter (Xpod) with a mobile phone. The *Phone Oximeter*[®] enables the analysis of vital signs and intuitive display of information to health care providers [21]. In addition, *Phone Oximeter*'s SpO₂ characterization has been successfully applied to detect sleep apnea [7].

This paper is organized as follows; the Materials and Methods section describes the dataset used for the development and testing of the newly developed algorithm to estimate RR and HR based on CSD, and explains the algorithm with brief description of CSD and PSD methods. The accuracy of the CSD-based algorithm is presented in the Results section, which is followed by the Discussion, Limitations and Conclusion sections.

Materials and Methods

CSD-based Algorithm

Conventional spectral analysis assumes a stationary signal and is therefore unable to identify HR and RR changes over time. An approach to account for such changes is to implement a time-varying spectral analysis. Firstly, a sliding time window of 60 s or 120 s with 50% overlap is used to segment PPG signal into segments assumed to be stationary and suitable for spectral analysis. Secondly, the CSD is applied to the signal segments. Thirdly, the HR is estimated by detecting the maximum frequency peak within the cardiac frequency band and filtered from the signal, and lastly the RR is estimated by detecting the maximum frequency peak within the respiratory frequency band (see Figure 1).

Correntropy spectral density. The CSD is a generalization of the conventional power spectral density. It is based on the Fourier transform of the centered correntropy function [18],

$$P_v(\omega) = \sum_{m=-(N-1)}^{N-1} V_c(m) \cdot e^{-j\omega m}, \quad (1)$$

where $V_c(m)$ is the centered correntropy function, in which the mean of the transformed data is subtracted so as to reduce the effect of output DC bias. It is estimated by $V_c(m) = V(m) - \bar{V}$ where $V_c(m)$ is the correntropy function and \bar{V} the correntropy mean, defined as:

$$V(m) = \frac{1}{N-m+1} \sum_{n=m}^N \kappa(x(n) - x(n-m)), \quad (2)$$

$$\bar{V} = \frac{1}{N^2} \sum_{m=1}^N \sum_{n=m}^N \kappa(x(n) - x(n-m)). \quad (3)$$

The sigmoidal, Gaussian, polynomial, and spline kernels are the most commonly used symmetric positive definite kernels, applied to machine learning, function approximation, density estimation, and support vector machine classification [22], [23]. The Gaussian kernel function, applied in the present study, is given by

$$\kappa(x(n) - x(n-m)) = \frac{1}{\sqrt{2\pi}\sigma} e^{-\left[\frac{(x(n) - x(n-m))^2}{2\sigma^2}\right]}, \quad (4)$$

where σ is the kernel parameter, here set using Silverman's rule of density estimation [19].

Correntropy, introduced by Santamaria et al. [19], is a similarity measure defined in terms of inner products of vectors in a kernel parameter space. It provides information on both the time structure and the statistical distribution. In addition, the use of kernel methods makes the correntropy computationally efficient since it can be computed directly from the data.

Autoregressive (AR) spectral analysis based on the Yule-Walker method was applied to improve spectral resolution compared to conventional techniques [18]. The autoregressive coefficients were estimated from the correntropy function, using the Yule-Walker equations [24]. The selection of model order is a trade-off between the frequency resolution and the spurious peaks. The optimal model order between 5 and 15 was selected using the minimal description length criteria defined by Rissanen [25].

HR and RR estimation. The CSD over time shows both respiratory and cardiac frequency peaks reflecting the RR and HR respectively (Figure 2). These peaks can be tracked in the region of the respiratory and cardiac frequency bands. Reference HR and RR ranges were extracted from a review of observational studies that used HR data from 143,346 children and RR data from 3,881 children (from 6 months to 18 years old) [26]. Based on 99th and 1st centiles for children and young adults, the HR could range from 30 to 180 beats/min (0.5 to 3 Hz, respectively) and RR from 8 to 60 breaths/min (0.14 to 1 Hz, respectively) [26]. The range in adults is much more restricted but would be included in this range. An extreme range may occur in critical illness, such as an elevated HR in the presence of an arrhythmia or an elevated RR (> 40 breaths/min in children with pneumonia [2]) as an early indicator of critical illness. However, those pathological or abnormal RR and HR values will also be included in this extended HR and RR ranges extracted from the review. Therefore, the maximum value

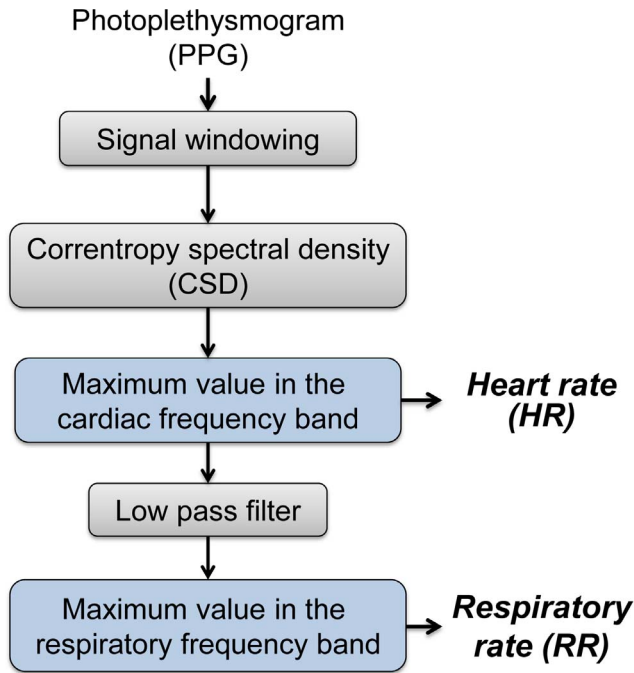


Figure 1. Overview of the CSD-based algorithm. Initially the PPG signal is segmented into windows (60 s or 120 s) with 50% of overlap. In the subsequent step the CSD is applied to calculate the spectrum of the windowed signals. The HR is estimated by detecting the maximum frequency peak within the cardiac frequency band. The signal is then low pass filtered and the RR is estimated by detecting the maximum frequency peak within the respiratory frequency band.
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peak frequencies in the cardiac frequency band (0.5 to 3 Hz) and in the respiratory frequency band (0.14 to 1 Hz) were automatically extracted, reflecting HR and RR, respectively.

For improved resolution around the respiratory frequency peak, the HR was filtered using a zero-phase 5th order low pass filter with a cutoff frequency of 0.1 Hz below the cardiac frequency. In addition, frequency peaks close to the secondary harmonics around HR were excluded when an elevated RR (> 45 breaths/min) were detected. An example of the RR and HR extracted from the time varying CSD (Figure 2) is illustrated in Figure 3.

Power spectral density. Following the same concept a PSD-based algorithm was implemented. For a parametric PSD, the signal $x(n)$ was modeled through an AR model by

$$x(n) = -\sum_{k=1}^p a[k]x(n-k) + e(n), \quad (5)$$

where $e(n)$ denotes zero-mean white noise with variance σ_e^2 , $a[k]$ the AR coefficients and p the model order. Once the autoregressive coefficients and the variance σ_e^2 have been estimated, the PSD of an autoregressive process is computed by means of

$$P_x(\omega) = \frac{\sigma_e^2}{|1 + \sum_{k=1}^p a[k] \cdot e^{-j\omega k T}|^2}, \quad (6)$$

being T the sampling period. As for the CSD, the optimal model

order between 5 and 15 was selected using the minimal description length criteria defined by Rissanen [25].

Simulation Database

To show certain performance properties of the algorithm a simulated PPG signal was first produced. Respiration has three different effects on the PPG waveform. The first and more predominant effect is a shift in the baseline during each breath. The second is a change of the amplitude of the pulse beats with each breath which implies that the PPG signal is subject to amplitude modulation (AM) [15]. The third effect is a variation of HR due to an autonomic response to respiration and usually decreases with age. Based on the first 2 effects for sake of simplicity, the PPG signal was simulated using AM and a baseline shift as follows:

$$x(n) = [(1 + \mu \cos(\omega_r n)) \cos(\omega_c n)] + b(n), \quad (7)$$

where $f_c = \omega_c/2\pi$ is the cardiac frequency, $f_r = \omega_r/2\pi$ is the respiratory frequency, $\mu \in [0,1]$ is the modulation index and $b(n)$ is the baseline shift synchronized with f_r . One hundred outliers with values between mean ± 5 standard deviation of $x(n)$ were randomly added to the signal to simulate noise.

Capnabase Database

Ethics statement. All subjects were studied according to a protocol approved by the University of British Columbia and Children's and Women's Health Centre of British Columbia Research Ethics Board. Informed and written consent to be part of the research database was obtained for all subjects. For subjects under 16 years of age, parental/guardian written consent was obtained. Written assent was obtained for all subjects over the age of 11 years.

Database. Capnabase is an on-line database that contains physiological signals collected during simultaneously elective surgery and routine anesthesia for the purpose of development of improved monitoring algorithms in adults and children [27]. The signals were recorded from 59 children (median age: 8.7, range 0.8–16.5 years) and 35 adults (median age: 52.4, range 26.2–75.6 years) receiving general anesthesia at the British Columbia Children's Hospital and St. Paul's Hospital, Vancouver BC, respectively. The recordings included ECG with a sampling frequency of 300 Hz, capnometry with a sampling frequency of 25 Hz, and PPG with a sample frequency of 100 Hz. All signals were recorded with S/5 Collect software (Datex-Ohmeda, Finland) using a sampling frequency of 300 Hz (PPG and capnometry with lower sampling rates were automatically up-sampled).

Capnabase contains a benchmark dataset with forty-two 8-min segments from 29 pediatric and 13 adults cases containing reliable recordings of spontaneous or controlled breathing. The capnometric waveform was used as the reference gold standard recording for RR. A research assistant manually labeled each breath in the capnogram and pulse peak in the PPG and validated the derived instantaneous reference RR and HR. The beginning and end of all artifacts in the PPG waveforms were also manually labeled and almost 50% of the cases contained artifacts due to movements or similar noise. Capnabase also contains a calibration dataset with one hundred twenty-four 2-min segments randomly selected from the remaining 52 cases. This dataset is particularly challenging because it includes other disturbances such as cardiac oscillations etc., which influence the respiratory induced parameters and it also contains substantially more movement artifacts than the benchmark dataset. Signals with significant apnea have

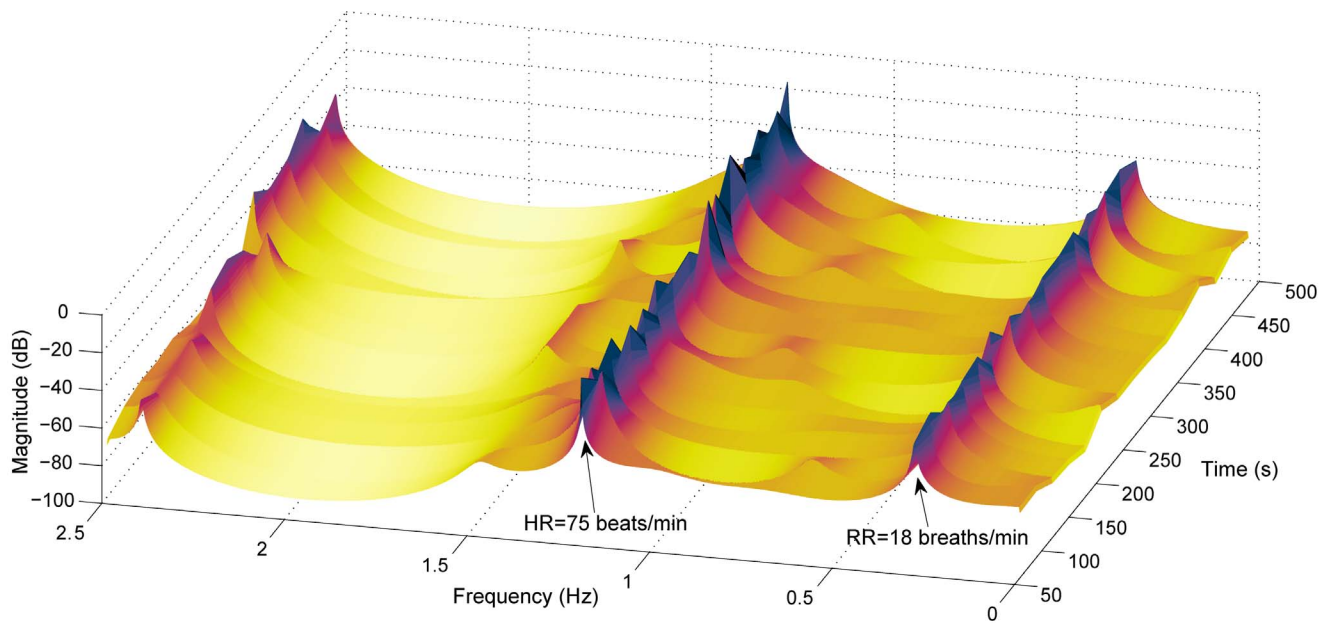


Figure 2. Time-varying CSD of 8-min PPG signal. Both respiratory and cardiac frequency peaks reflect RR and HR, respectively. Respiratory frequency peak is around 0.3 Hz (18 breaths/min) and cardiac frequency peak around 1.25 Hz (75 beats/min). doi:10.1371/journal.pone.0086427.g002

been excluded from the analysis. Datasets can be downloaded from the on-line database, CapnoBase.org [27]. CSD-based algorithm was optimized using the calibration dataset and then validated using the benchmark dataset. Both, the calibration and benchmark datasets with reference RR and HR have been previously used to test RR estimation from PPG [6].

Algorithm Evaluation

The accuracy of the CSD-based algorithm was evaluated and compared to other methods, using the un-normalized root mean square (RMS) error. The RMS error was calculated for each subject, considering all estimations over time:

$$\text{RMS error} = \sqrt{\frac{1}{n} \sum_{i=1}^n (x_i^{\text{ref}} - x_i^{\text{est}})^2}, \quad (8)$$

where n is the number of observations and x_i^{ref} and x_i^{est} are the reference and the estimated values, respectively. The median of the instantaneous reference RR and HR were compared to the estimations for each time window.

Calibration. The spectral resolution increases with longer time-windows with a concomitant reduction in real-time performance (clinicians are required to wait longer for each estimation). To investigate the trade-off in window size, the accuracy of the algorithm was evaluated with the calibration dataset, using time windows of 60 s and 120 s with an overlap of 50%. The statistical significance of the error with the different windows was evaluated using Wilcoxon signed-rank test to compare related samples.

The choice of the kernel parameter (σ) is trade-off between the power of the respiratory peak and the spurious peaks. The power of the respiratory peak and spurious harmonics decreases as σ increases [18]. The CSD-based algorithm's sensitivity to σ was evaluated using the calibration dataset. The σ calculated according to Silverman's rule ($\sigma_{\text{Silverman}}$) was used as a reference.

Validation. The calibrated algorithm was then validated using the Capnobase benchmark dataset. All subjects and all signal segments with mechanical or spontaneous breathing, including those with artifacts, were analyzed. The median error and 1st and 3rd quartiles were calculated to account for a non-normal RMS distribution. A Bland-Altman plot was also performed to compare the estimated HR and RR to the reference rates.

In addition, the performance of our algorithm was compared to previously proposed methods based on PPG cycles morphology [6], time-frequency analysis [15], [7] and digital filtering [17], using the Capnobase benchmark dataset. These methods have been implemented according to the description included on these papers.

A Wilcoxon signed-rank test for related samples using Bonferroni correction for multiple comparisons was also applied to evaluate the statistical significance of our algorithm's improvement. The normality of all distributions was tested using One-Sample Kolmogorov-Smirnov test.

Results

CSD Output

The median RR error obtained with the CSD-based algorithm applied to the calibration dataset was 4.2 breaths/min when using 60-s windows and 1.9 breaths/min when using 120-s windows. The RMS error significantly ($p < 0.05$) decreased with longer windows. A kernel size of ($10\sigma_{\text{Silverman}}$) reduced the spurious harmonics and provided more accurate RR estimates (see Figure 4) [19]. Therefore, a $10\sigma_{\text{Silverman}}$ was applied to the Capnobase Benchmark dataset.

CSD shows two clear frequency peaks at HR and RR locations, for both simulated and in-vivo signals (Figure 5 and 6). As reported in our previous work [18], the AM effect is reflected in CSD through a frequency peak at its true position. In comparison, the AM in PSD is manifested as secondary harmonics surrounding the cardiac frequency peak. Further, CSD is more robust to impulsive

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