An Application of The Lomb-Scargle Periodogram To Investigate Heart Rate Variability During Haemodialysis

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Abstract

Objective: Short-term cardiovascular compensatory responses to perturbations in the circulatory system caused by haemodialysis can be investigated by spectral analysis of heart rate variability. This could provide an important variable for categorising individual patients response to haemodialysis leading to a more personalised treatment. However, data obtained over a four-hour haemodialysis treatment is significant in volume and subject to artefacts that can compromise its analysis.

Methods: The Lomb-Scargle Periodogram can provide a robust method of generating power spectral density estimates for large, irregularly sampled and noisy data sets obtained in clinical settings, provided that careful attention is given to frequency limits. The effect of different pre-processing methods on the resulting power spectrum is explored with simulated and real heart rate variability data.

Results: Common pre-processing methods for correcting individual artefacts in heart rate records, such as interpolation, are unreliable as they act as non-linear low-pass filters and distort the resulting spectral analysis. These distortions are present, but less apparent within patient data and can mislead clinical interpretations.

Conclusion: It is more appropriate to exclude suspect data points than to edit them prior to spectral analysis via the Lomb-Scargle periodogram, and where required, de-noise the entire heart rate signal by empirical mode decomposition. The use of a False Alarm Probability metric can help establish whether spectral estimates are valid

Significance: Methods established to pre-process time-invariant data prior to power spectral density estimation fail when used in conjunction with the Lomb-Scargle method.

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***Index Terms*—Biomedical engineering, biomedical signal processing, hemodialysis, time-variant systems, spectral analysis, heart rate variability.**

I. Introduction

Patients receiving chronic haemodialysis (HD) as a result of End-Stage Kidney Disease (ESKD) are at a much higher risk of morbidity and mortality, which is in part due to the prevalence of cardiac complications in this population [1]. In part, this is because HD causes circulatory stress leading to abnormal haemodynamic and cardiovascular function [2]. While not fully explored, it appears that cardiovascular regulatory mechanisms are unable to adequately compensate for fluid removal from the vascular compartment during HD[2]. These mechanisms can be investigated via the analysis of heart-rate variability (HRV) in order to provide valuable insight into physiological and pathological conditions, and to enhance risk stratification [3][4].

Cardiac activity is controlled by the sympathetic (accelerating) and parasympathetic (decelerating) arms of the autonomic nervous system (ANS) which induce oscillations between successive sinus beats at different rhythms. These can be quantified on the electrocardiograph (ECG) as the interval between the peak of one 'QRS' complex to the peak of the next, referred to as the 'RR' interval. Analysis of HRV rests upon different mathematical (time-domain) and spectral (frequency-domain) measures that have identified significant physiological rhythms hidden in RR interval fluctuations, oscillating at specific frequencies [3]. These rhythms can be characterised by the signal energy (power) found in a low frequency (LF) band ($0.04<LF<0.15$Hz) and a high frequency (HF) band ($0.15<HF<0.4$Hz). The power component in the HF band is correlated with parasympathetic activity [5] and corresponds to the HR variations related to the respiratory cycle. Power in the LF band involves contributions from both sympathetic and parasympathetic activity, and it has been suggested that a better approach to understanding sympathetic activity relies on analysing the LF/HF ratio [3][5].

The iTrend (Intelligent Technologies for Renal Dialysis) programme is a long-term collaborative project conducted by a multidisciplinary research team from the Universities of Derby and Nottingham, and the Royal Derby Hospital Renal Unit in the UK. The primary goal of the programme is to develop supporting technologies to enable personalised treatment in ESKD [6]. Adult participants were recruited from the Renal

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Unit's prevalent dialysis population and received continuous non-invasive monitoring of haemodynamic parameters using pulse wave analysis (Finapres NOVA) and heart rate via ECG during dialysis treatments. The protocol was approved by the West Midlands Research Ethics Committee and participants gave written informed consent.

As shown in previous studies [5], the spectral parameters of HRV can describe and categorise patients response to HD and could eventually predict morbidities, for example, intradialytic hypotension. It is recommended [3], to visually inspect ECG data and, if necessary, correct it prior to HRV analysis to minimize any interference that may compromise results [7]. This is highly impractical for large data sets obtained in clinical studies (such as iTrend) which are;

- significant in volume per patient treatment, involving 3 recordings of 4 hours in duration from 50 patients),
- suffers from artefacts due to patient movement or occasionally the influence of electromagnetic interference [8],
- missing data due to a loss of signal (for example, if a patient became unwell or otherwise took a break from monitoring during treatment),
- and, in common with other HD patients, the iTrend population experience a significant number of ectopic beats. Cardiac dysrhythmia during dialysis is also common [9] which further complicates the analysis.

The purpose of this work is to demonstrate and evaluate a number of techniques commonly used in the spectral analysis of HRV in order to establish which combination of technologies is the most reliable and most practical for use with data obtained during medical treatments. The first part of this paper will describe the method for generating a power spectral density (PSD) estimation suitable for HRV analysis, the second part will evaluate the effects of RR interval correction on a well-defined synthetic data series and on sample patient data. This work addresses a need to understand the effects of signal processing on the interpretation of spectral parameters in order to better discriminate between those influenced by the patient state, and those generated by the algorithm.

II. Methods

A. Power Spectral Density Estimation

The power content of the LF and HF frequency bands is computed via the PSD estimate of the RR tachogram, most commonly using a Fast Fourier Transform (FFT). While straightforward and fast, FFT requires artificial interpolation of the time-varying heart rate to satisfy the axiomatic requirement of a time-invariant sampling rate. Resampling, in effect a non-linear lowpass filter, also makes an implicit assumption about the form of underlying variation in the data series. Autoregressive (AR) based periodograms have also been employed as they can use shorter segments of data without losing spectral resolution [10]. However, in addition to requiring an evenly sampled data series, AR techniques are complex to implement and highly dependent on the choice of model or model order [4].

An alternative is the Lomb-Scargle (LS) periodogram [11] where time-varying data are weighted on a point-by-point basis, rather than on a per-time basis thus avoiding the requirement to resample data. This method is equivalent to AR and FFT in the case of equally-spaced observations [10][12], but the LS periodogram is less likely to introduce spurious frequencies [4] [13][14] and 'jitter' [10] to the power spectrum when noise is added to the signal. For these reasons, the LS periodogram was selected for use in the iTrend study.

For the time series $x[t_n]$ which is pre-centred around the mean, the normalised LS periodogram is defined as;

$$P_{xx}(f) = \frac{1}{2\sigma^2}\left(\frac{\left[\sum_{n=1}^{N}(x[t_n]-\bar{x})cos(2\pi f[t_n-\tau])\right]^2}{\sum_{n=1}^{N}cos^2(2\pi f[t_n-\tau])} + \frac{\left[\sum_{n=1}^{N}(x[t_n]-\bar{x})cos(2\pi f[t_n-\tau])\right]^2}{\sum_{n=1}^{N}sin^2(2\pi f[t_n-\tau])}\right) \quad (1)$$

Where $\bar{x}$ and σ^2 are the mean and variance of the time series. The sine and cosine coefficients are normalised separately by a frequency-dependent time-delay, τ, in order to make the transformation insensitive to time shifts in the data.

$$\tau = \tan(4\pi f\tau) = \frac{\sum_{n=1}^{N}sin(4\pi f t_n)}{\sum_{n=1}^{N}cos(4\pi f t_n)} \quad (2)$$

There are some practical considerations that should be made when analysing unevenly-sampled data relating to the choice of frequency limits and the grid spacing. The lower limit is well-defined as the fundamental frequency $f_0 = {}^1/_T$ of a sine wave of period equal to the whole interval T and so it is set by the sampling duration. The shortest period over which HRV metrics should be assessed is 5 minutes [3] so the lowest frequency that can be resolved is 1/300=0.003Hz.

The highest frequency that can be coded at a given sampling rate, the Nyquist frequency, is defined as $f_c = {}^1/_{2\Delta T}$, but the sampling interval $\Delta T = {}^T/_N$ might not exist for unevenly-sampled data, and if it does, it tends to be far larger than any limits on the time-invariant case [15]. It is more appropriate to set a pseudo-Nyquist frequency based on the precision of the time measurements as $f_c' = {}^1/_{2p}$ where p is the largest value such that each spacing Δt_i is exactly an integer multiple of this factor.

A different type of frequency limit exists where observations are not instantaneous, but rather consist of short-duration integrations of a continuous signal (such as the RR tachogram). Each observation is effectively a convolution of the underlying ECG signal with a rectangular function of δt. This leads to a 'window' limit of $f_{max} \propto \frac{1}{2\delta t}$, beyond which signals are attenuated to zero. The constant of proportionality depends on the shape of the window describing individual observations and for the RR tachogram, the windowing function is a series of very narrow spikes (reminiscent of the Dirac comb)[15]. By analogy, this gives a maximum frequency of $f_{max} = \frac{1}{T}\frac{1}{2\delta t}$. As the upper frequency limit of the HF band is specified as 0.4Hz [3], this leads to a constraint of $\frac{N}{2T} \geq 0.4$ on the N number of points within the 5-minute segment. This corresponds to a minimum of 240 points and $f_{max} = \frac{f_s}{2T}$.

Data observed through a rectangular window of length T will have sinc-shaped peaks of width 1/T, so in order to ensure the grid sufficiently samples each peak, it is prudent to oversample by some factor. VanderPlas [15] recommends a grid size of $\Delta f = {}^{1}/_{5T}$

B. Synthetic data series

In order to separate the effect of signal processing techniques from underlying data, a synthetic signal with well-defined properties was generated. An artificial tachogram was generated by mixing two sine waves with frequencies at the centre of the LF and HF bands (ω_l=0.095Hz, ω_h=0.275Hz) [13]. The LF component was given an amplitude of A_l = 2 bpm, and the HF band is given a larger amplitude A_h = 2.5 bpm (it will be seen later than RR correction can filter the HF components, so it was emphasised in the synthetic data series. The average heart rate was set at HR_0=60bpm.

$$HR(t) = HR_0 + A_l sin(\omega_l t) + A_h sin(\omega_h t) \quad (3)$$

$$RR(t) = \frac{60}{HR(t)} \quad (4)$$

The first result in the RR tachogram is defined as the first RR interval (RR_1 at t_1). The next RR interval is defined where the RR value equals the time difference between t_n and t_1 [13]. This is generalised as (5) and the result is shown in Fig. 1.

$$RR_n \geq t_i - t_{n-1} \quad (5)$$

The synthetic signal was then distorted by adding uniformly distributed white noise to (3), and then discarding a number of data points at random from the resulting tachogram (5). Fig. 2 shows the limits of the LS periodogram as the amount of data that is randomly discarded is increased from 1% until failure at 64% where there are insufficient data points to perform the computation. The maximum level of data that can be discarded from a 5-minute window is 20%, which is the point at which F_{max}=0.4Hz. This agrees with findings that the PSD for time-invariant data series becomes distorted when more than 20% of the data is in error or corrected [16]. The LS periodogram was more robust to increasing amplitudes of noise and was able to successfully locate the LF and HF peak even when the noise was scaled to have four times the amplitude of the RR tachogram signal, confirming the choice of LS for clinical settings. In combination, the maximum level of distortion that can be applied on the fewest number of points corresponds to a signal-to-noise ratio of 13.4dB with 20% of data discarded at random.

The distorted signal and its power spectrum are shown in Fig. 3, which also demonstrates the calculation of False Alarm Probability (FAP). This important but often neglected evaluation step is used to express uncertainty terms of the heights of the peaks in comparison with the spurious background peaks. FAP is estimated as;

$$FAP(z) \approx 1 - \left[P_{single}(z)\right]^{N_{eff}} \quad (6)$$

If the expected peak width is $\delta f = {}^{1}/_{T}$, then the number of independent frequencies (peaks) in a range $0 \leq f \leq f_{max}$ is assumed to be $N_{eff} = f_{max}T$ [15].

The synthetic and distorted signals are compared in Table I . The addition of noise has increased the total power of the signal by an average of 63% leading to a similar increase of power in both the LF (69%) and HF (65%) bands. Calculation of the 3dB widths show that both peaks are less narrowly defined in the distorted signal. The calculation of LF/HF is via relative power in normalised units, which divides the absolute power for each frequency band by the total power from 0 to 0.4 Hz [13]. The theoretical value of the LF/HF ratio calculated from the amplitude of the sine waves is $\left(\frac{A_l}{A_h}\right)^2 \approx 0.64$, which value is closely approximated in the original, but not the distorted signal. The LS periodogram accurately locates both peaks within a very noisy signal but is better able to locate the HF peak corresponding to the sine wave with the larger (2.5 bpm) amplitude. This is consistent with the lower mean-average RR interval where (5) has selected a greater number of shorter RR intervals (~326) leading to a greater emphasis of the HF band.

Given that the RR tachogram is an unusual signal with time represented on both axes, it is surprising that the frequency is reliably identified but that amplitude is not, but this seems to be affected by the choice of units. As a simple example, a calculation of LF/HF ratio on the basis of linear units (ms^2/Hz), decibels, and percentage results in values of 0.52±0.09, 1.146±1.2 and 1.15±0.03 repsectively. The most consistent approach seems to be to express LF and HF as percentages of total power between the limits of 0.003 and 0.4 Hz.

FFT and AR methods are known to suffer distortion to the resulting spectrum by leakage due to the implicit rectangular window [17]. The fraction of power in the main lobe (within ± 0.01Hz) of each peak shows some evidence that the LS periodogram has a lower degree of spectral leakage which occurs in the LF band.

C. The effects of RR editing on HRV analysis

Other than noise, artefacts in real data would include abnormal heart beats with unusual timing. For example, unusually short RR intervals (ectopic beats) will introduce higher than normal frequency components, causing an overestimation of HF power. Missing data would emphasise longer RR intervals and cause a bias towards LF power. The implication is that any clinical signal would require some form of pre-processing so that doubtful points can be corrected [3].

Considerable methodological diversity is seen in the processing of the data prior to analysis. Aberrant RR intervals are most commonly identified in comparison to a predefined range of expected values based on previous RR intervals [18][19][20][21] or by comparison with a statistical measure of the whole RR tachogram [7][22]. In this work, false beats are detected where a high (+32.5%) or low (-24.5%) threshold for the relative variation in successive RR intervals is exceeded [18][19].

The guidance regarding which techniques are most suitable for correcting aberrant RR intervals is less clear. Methods that exclude outlier values can lead to a systemic loss of information in time-invariant data [23]. Methods to replace outlier values with average values[24][25] or interpolation [26] can change the power of the frequency components in spectral analysis by introducing false shapes and trends [16]. The effect of any of

these approaches when used in conjunction with time-varying PSD estimation is missing from literature. To understand the role of RR editing with the LS periodogram more fully, comparisons were made between 5 different correction methods.

Method 1 – LS periodogram with omitted data. Rather than discarding data at random, only those intervals flagged as in error [19] (on average 15% of the RR intervals over 100 runs) are excluded from the LS estimation. This method will provide a baseline against which other methods are compared, and would be the preferred method as no pre-processing of the signal is required thus limiting the potential for the PSD estimate to be distorted.

Method 2 - Rules Based. An interval that is identified as incorrect will be further analysed in combination with its neighbours and retained if it can be identified as forming part of a physiologically plausible pattern [27]. Otherwise, the aberrant RR interval can be corrected by:

i) summing with two or more neighbouring intervals, which would apply in the case of an ectopic beat occurring between normal beats,

ii) dividing one large interval into two or more intervals of acceptable size, which would apply in the case of missed heart beats,

ii) or adding two or more intervals and dividing the sum into two or more acceptable values. This would occur (or example) when an ectopic beat occurs in the place of a normal (sinus) beat.

The selected correction would be the one that brings the new RR interval closest to the mean average of RR intervals from the previous minute of data.

Method 3 Ornstein-Uhlenbeck third-order Gaussian process filtering (OUGP). The OUGP filter is a reduced form of a Wiener filter, where a one-dimensional series of measurements as a function of time can be solved more efficiently as its inverse matrix via a tridiagonal system of equations. Full details and derivation can be found in [28], but is summarised for a series of measurements x_j and time t_j, j=1,…n, as;

$$\sum_j T_{ij}u_j = \begin{cases} \frac{(x_1-x_2)}{2w_1} & i=1 \\ \frac{(x_i-x_{i+1})}{2w_i}+\frac{(x_i-x_{i-1})}{2w_i} & i=2,\dots,n-1 \\ \frac{(x_n-x_{n-1})}{2w_{n-1}} & i=n \end{cases} \quad (7)$$

Where $\sum_j T_{ij}u_j$ is the sparse tridiagonal system convolving the matrix T and the output of a filtered sequence u. The input w is complex, but the filter is taken to be the real part of the result as

$$Hy = \Re(u),\ \ Ly = y - \Re(u) \quad (8)$$

The OUGP method is implemented here as a bandpass filter, passing frequencies in the range 0.04 – 0.4 Hz. When applied to an unevenly sampled RR tachogram, the OUGP filter exhibits a predictable and stable third-order zero-phase frequency response with explicit -3dB points [29], leading to a recommendation that that it would be suitable for implementation in conjunction with LS periodogram (which motivated its inclusion here).

Method 4 – Denoising by Empirical Mode Decomposition. EMD is a data-driven method to denoise non-linear and non-stationary multi-component time series, x(t) by decomposing it into a finite number of signal-dependent semi-orthogonal zero-mean basis functions called intrinsic mode functions (IMFs), by an iterative process called sifting. IMFs must satisfy two criteria: First, the number of the extrema points (local minima and maxima) and the number of zero crossings must be equal, or differ by one at most; Second, the mean of the envelopes determined by local extrema points should be zero. The sifting algorithm is executed as;

(i) Identify all extrema of x(t) and interpolate between the minima $e_m(t)$, and maxima $e_M(t)$, to find envelope of the signal

(ii) Compute mean of the envelope, $m(t) = [e_n(t) + e_M(t)]/2$

(iii) If m(t) satisfies the requirements, extract the first 'mode' as $x(t) = x(t) - \varphi_i(t)$

(iv) iterate on the residual r(t) until it is constant or a trend.

Hence the original signal can be reconstructed by the sum of the IMDs [30] as described by

$$x(t) = \sum_{i=1}^{L} \varphi_i(t) + r(n) \quad (9)$$

Where L is the number of IMFs. Some methods (in signal processing applications) have proposed the Hurst coefficient as the decision base for which IMF to include in a reconstructed signal [30][31], but this has specific meaning in the context of HRV analysis [32] and could compromise the meaning of long-range correlations that are used to predict pathological states. Souza-Neto et. al. [33] demonstrated that the first three IMFs are sufficient to denoise and recompose the HRV signal in order to analyse LF,HF and LF/HF content. Following this approach the RR tachogram is reassembled by summing values from the original time location for the first three IMFs [33], then reconstructing the new time series from the changed heights of the RR intervals to maintain synchronicity (Fig. 4).

Method 5 – Replacement. All intervals identified as being in error were removed from the HRV tachogram and replaced by a (linear or cubic spline) interpolated value using 3 previous and 1 following neighbour [8], or replaced by the mean average of the previous 60 seconds of RR intervals [27].

D. Experiments and Simulation

Data from a single 'HD patient' from the iTrend study are used to illustrate how a different interpretation of the PSD may arise from different pre-processing techniques (clinically relevant findings from the iTrend population are presented elsewhere). Data from ECG lead II [18] was sampled at 300Hz to avoid issues with QRS detection [4] and then further processed offline [34]. The mean was removed from the RR tachogram prior to application of one of the above methods, and the time series was recalculated to preserve synchronicity where required.

All computer codes were implemented in Matlab version 2020b, but it should be noted that built-in functions for the LS Periodogram, EMD and band-power integrations could not be used (due to the need to specify and test aspects of the algorithms differently, discussed in section II A).

III. RESULTS

A. Synthetic Data

A comparison of data obtained from 100 simulations is presented in Table II. On average, 15% of the RR intervals were classified as in error (5% too long, 10% too short). It was not possible to fully recover the statistical properties of the original signal, but all methods (except replacement) were consistently able to locate both peaks (Fig. 5).

Method 1 involves the exclusion of suspect RR intervals from the periodogram estimate but doesn't lead to a greatly improved estimation of spectral parameters (Table I). The a_l/a_h ratio is much higher which is a consequence of the asymmetrical basis for excluding RR intervals [19]. The smaller tolerance on the lower bound biases the identification of aberrant RR intervals, excluding more HF components from the PSD estimate. This may also explain why the HF peak tends to have a lower amplitude. This method does have the best performance of the five methods, which is a significantly different outcome to previous work based on time-invariant methods where exclusion of RR intervals lead to a systematic loss of information [16].

Although the method 2 was consistently able to locate the two peaks (Table II) it is surprising how poorly it performed given that the rules are based on sound physiological principles. The HF peak exceeds a FAP of 10% in only 88% of the simulations. Method 2 emphasised noise peaks which merged with the true peaks resulting in an inconsistent prediction of power in the LF and HF bands. The PSD estimate of method 2 had the lowest total power, suggesting that it removed a significant amount of all data without discriminating well between noise and signal. Closer inspection of the corrected RR interval tachogram shows that method 2 offers no improvement over interpolation whenever errors occur in clusters.

Method 3 (OUGP) suffered a similar loss of information from the HF band, although it outperformed the method 2 in terms of accurate location of the peaks, and both LF and HF peaks exceeded FAP of 10% in 99% and 96% of simulations respectively. Method 3 has the 'smoothest' PSD with the least variation in RR intervals, which is unsurprising in that it applies to all data points and not just suspicious ones, but offered no improvement in estimation of spectral parameters over method 1.

EMD (method 4) out-performs all others in terms of preserving the statistical features of the underlying signal, providing an accurate estimation of both LF/HF and a_l/a_h, and was the only method able to consistently locate the HF peak in all 100 simulations. The noise peaks never exceed the FAP threshold of 50% suggesting that this might be the most robust method for pre-processing clinical data. However, the resulting PSD does have the highest power content which suggests that some noise is decomposed into the IMFs. It is the subject of future work to establish means by which this could be refined. The challenge of understanding the physiological basis of each IMF (and therefore applying more elaborate denoising approaches [35]) also remains.

The smoothing effect seen in methods 2 and 3 are better understood with reference to Fig. 6. Without question, replacement of aberrant RR intervals leads to the poorest estimation of PSD; power in the HF band is attenuated with the replacement methods acting (in effect) as low pass filters that emphasise different local trends. All replacement methods are particularly poor where aberrant RR intervals occur in clusters as the correction becomes arbitrary. None of these approaches can be recommended in conjunction with the LS periodogram.

B. Patient Data

Fig. 7 which shows the PSD estimate for a five-minute period occurring approximately 3 minutes after the start of dialysis. The 'HD patient' had been sitting at rest for a period of 8 minutes prior to beginning their treatment. Five different methods of editing RR intervals are compared (Table III), but the error selection which is now symmetric and includes RR intervals that deviate by ± 10% from the previous RR interval [7]. This identifies 8% of RR intervals as being in error (with 7% being too short and 1% too long). EMD and OUGP methods were applied to the whole RR interval tachogram, and no further editing of aberrant RR intervals was made.

Given that the original RR tachogram is the same and that the total power is very close, the spectral parameters derived from the PSD estimate should be close, but the different RR editing methods attribute different proportions of power between the LF and HF bands. Multiple peaks exceeding a FAP probability of 50% can be seen in the LF band (Fig. 7); these being LF peaks associated with rhythmic changes in vascular tone, baroreceptor response and respiratory sinus arrythmia [14][16]. LF peaks are distorted and delayed by cubic spline interpolation, which has also introduced and a number of spurious peaks into the PSD estimate. Method 2 (rules) also performs poorly as it is unable to locate any peaks above a FAP of 10%. In a clinical study, lower LF power has been associated with intradialytic hypotension [36], and method 2 would characterise this patient as being hemodynamically unstable (which they are not).

Distortions to the HF band are more striking. The characteristic respiration peak occurs just after 0.15 Hz in all examples, except (again) for cubic spline interpolation. Although present in method 2, the respiration peak falls well below a FAP of 50% and both methods 2 and 5 have attenuated nearly all of the power in the HF band. Only EMD and OUGP were able to locate the respiration peak above a FAP of 50%. This would also be a serious failing in clinical studies, where reduced HF band power is associated with worse patient outcomes [1] [21]. Methods 2 and 5 are also the most commonly used replacement methods reported in literature.

IV. DISCUSSION

The calculation and analysis of PSD for HRV studies is not trivial. Two distinct but overlapping processes generate highly dynamic short-term responses; these being the complex relationship between the sympathetic and parasympathetic nervous system, and the regulatory mechanisms of heart rate, blood pressure and baroreflex in response [23]. As the RR interval tachogram represents time on both axes, it cannot

discriminate between the control and actuation effects, and magnitude is not available in HRV analysis.

Nevertheless, studies of HRV can reveal significant and important diagnostic and prognostic information, both about the patient as an individual [36] and as part of a population [1]. Abnormal HRV primarily reflects the dysregulation between sympathetic and parasympathetic nervous system and has been associated with an increased risk of morbidity [1]. Within populations receiving HD treatment, a low degree of HRV indicates impaired autonomic function and a reducing HRV has been associated with adverse cardiovascular outcomes [37]. Comparisons of HRV taken before and after HD have also proved to be a useful clinical marker in predicting overall mortality[2].

Given the significance of these findings, it is surprising that HRV does not have greater diagnostic use. There may be two reasons for this; the first would relate to the time involved in manually inspecting ECG traces and RR interval tachogram prior to analysis, and the second is in the variability of results [16] which has been shown here to arise from the method of processing in addition to any underlying physiological basis.

This work attempts to address both aspects by demonstrating that the LS periodogram provides a reliable and robust estimate of PSD even in real (as opposed to laboratory) conditions, provided that proper attention is given to the frequency limits, and sampling grid's role in supressing or exaggerating spurious peaks in the PSD. In summary;

- The window limit (F_{max}) provides a hard upper-limit and is a function of the sampling frequency. It is more important than pseudo-Nyquist frequency when unevenly sampled data are analysed.
- Violation of the lower-limit condition leads to an attempt to analyse power below the fundamental frequency limit of the signal. For this reason, total power should be calculated between 0.03Hz and 0.4Hz to avoid boundary effects when integrating the PSD from 0. The effect cannot be assumed to be small.
- The choice of grid spacing is a function of heart rate and should be refined as heart rate increases. This may address criticisms regarding the overly spiky appearance of the LS PSD estimate [14]
- The least number of points that can be analysed in a 5-minute segment is 240, leading to a lower limit of 48bpm on heart rate [13].

A consistent recommendation in literature is that five-minutes segments of data containing more than 20% of suspect or edited RR intervals should not be used for HRV analysis [3] [23], which holds true for the LS method. However, a four-hour HD treatment could generate 48 PSD estimates per patient and so the use of FAP provides an important and additional criterion to understand whether a 5-minute segment is valid for analysis. Its use here has demonstrated that methods employed to edit the RR tachogram via smoothing techniques are unsuitable in conjunction with the LS periodogram. Smoothing methods (in general) act as a low pass filters, emphasising local trends, and filtering high frequencies components of the signal. The different use of RR editing method could explain some of the contradictory results that appear in literature (for example, [5] and [36]).

The investigation performed here also contradicts previous findings that the method of RR interval selection has a greater effect on PSD than the method of RR editing [7]. The real issue seems to be one of bias caused when the method of RR interval selection is asymmetric. The results here suggest that selection criteria should always be symmetrical when used with the LS periodogram, whether a mean average or previous RR interval provides the basis of comparison.

Attempts to edit RR intervals using rules based on physiological plausibility is futile. In reality any RR interval is equally as likely to be in error as its comparator. If editing is required, it should be applied to the whole time-series (such as EMD or OUGP). The recommendation from this work is that EMD is the preferred technique for de-noising and suspicious RR intervals should always be excluded from the LS PSD estimate. It can be argued that EMD also suffers from an implicit assumption that the underlying data can be modelled by cubic splines, and whether the RR intervals can be better linked by a different approach is the subject of future work.

Other criticisms of HRV analysis note that spectral parameters derived from five-minute intervals do not have the prognostic power of time domain measurement derived from 24 hours of data [23], and yet spectral parameters are used (sometimes successfully [2]) to predict long-range outcomes. It is possible that a more deliberate approach to PSD estimation could lead to better correlation between the two time-periods.

V. Conclusions

When using the LS periodogram to estimate spectral parameters of heart rate variability, it is more appropriate to exclude data points than to edit them. The basis for the identification of suspicious RR intervals will lead to identification of a greater or fewer number, and has no further effect provided the method is symmetrical. Should further pre-processing be necessary, EMD is the preferred method for de-noising.

The LS periodogram estimates can only be made when maximum and minimum frequency limits are observed and where the grid spacing is derived from sampling frequency for each 5-minute interval. These could be dynamic within a single time series.

Finally, calculation of FAP should always be performed in deciding whether to accept the PSD estimate of five-minute segment as valid. This decision point can enable greater automation and therefore greater clinical use of the analysis.

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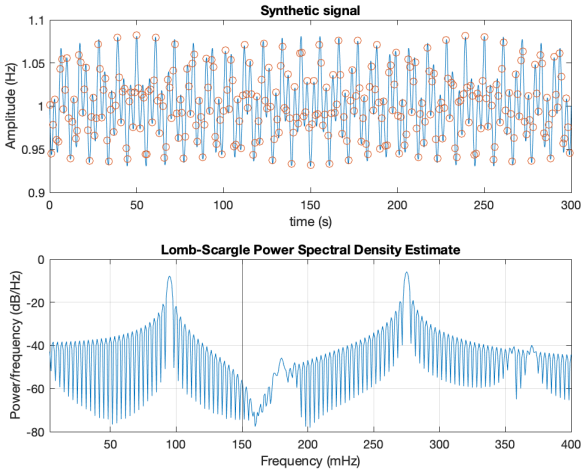

Fig. 1. Synthetic data series with mean frequency of 1 Hz and zero phase, realized from the sum of two sinusoids via (4) with RR intervals (shown as circles) generated from (5) [13]. The resulting LS periodogram accurately locates peaks at ω_l=0.095Hz and ω_h =0.275Hz

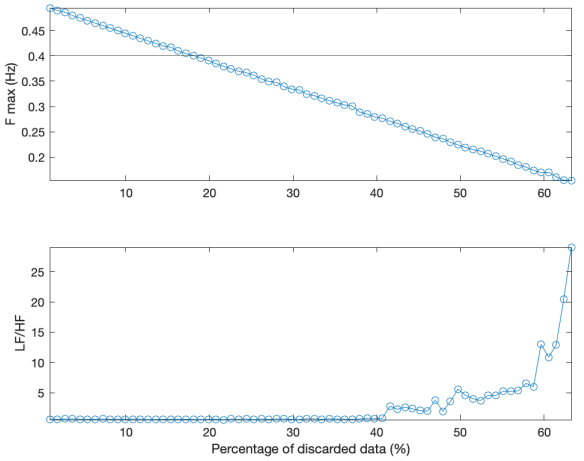

Fig. 2. Illustration of the effect of reducing the number of points in the LS periodogram estimate. The lower pane shows that the LF/HF ratio is relatively well estimated using only 62% of the available data, but the window limit is reached when 20% of the data is discarded, shown in the upper pane.

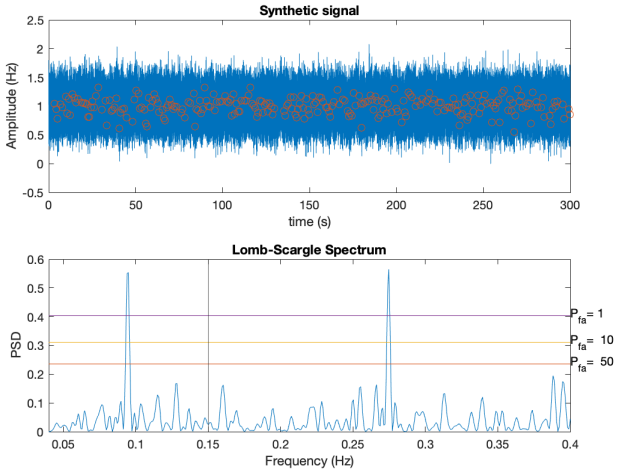

Fig. 3. Signal masked by noise (solid line in upper graph) and with 20% of RR intervals discarded at random (the remaining RR intervals are circles in upper graph). The frequencies of the original sinusoid are both accurately located at ω_l=0.095Hz and ω_h =0.275Hz and are the only peaks to exceed a FAP of 1% in the resulting periodogram.

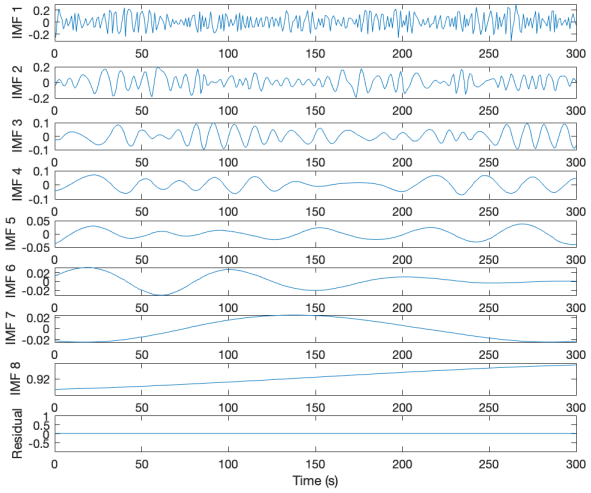

Fig. 4. Coarse to fine IMFs obtained from the distorted synthetic signal shown in Fig. 3. Only the first 3 IMFs are used to reconstruct the RR interval tachogram prior to PSD estimation.

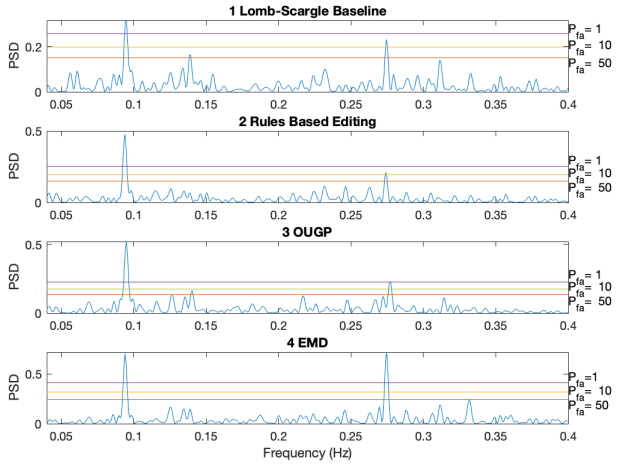

Fig. 5. PSD estimation via the LS periodogram using the same original data series, but with four different methods of editing dubious RR intervals. These four methods are considered successful as they were able to identify the LF and HF peaks corresponding to the sine waves in (3).

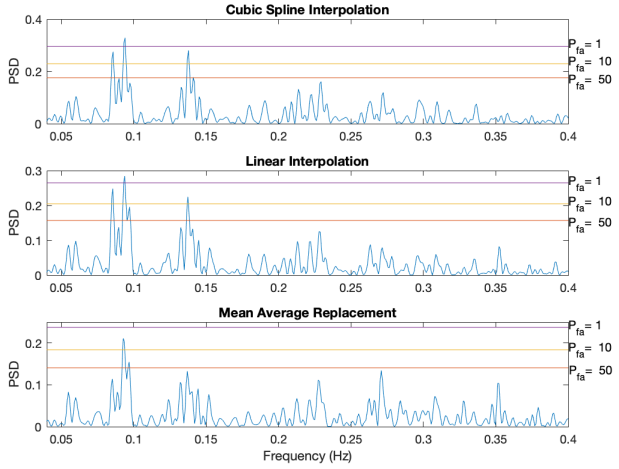

Fig. 6. Example of PSD estimation via the LS periodogram where dubious RR intervals were replaced by cubic spline interpolation, linear interpolation, or by the mean average of one minute of data. These methods are considered unsuccessful as background peaks are emphasized and HF peaks are lost in the noise.

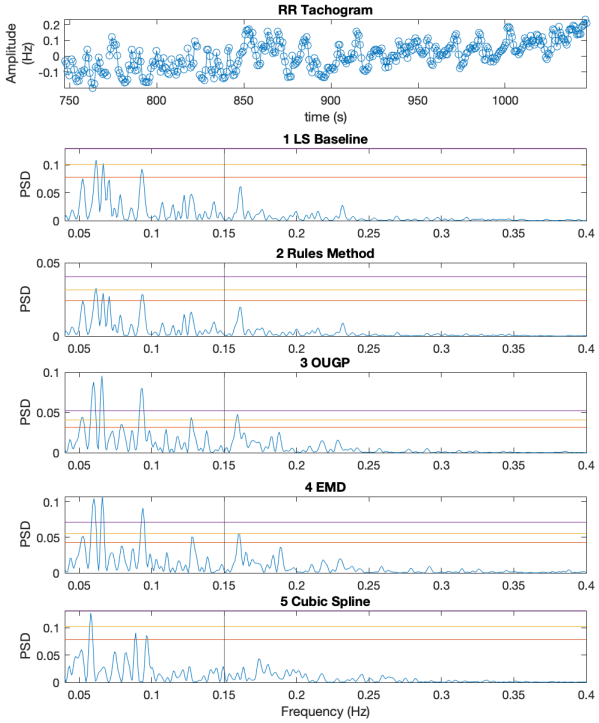

Fig. 7. Comparison of RR editing methods using data from a 'HD patient'. The RR tachogram is shown in the top pane, with a solid line added for clarity. Breaks in the solid line indicate RR intervals that are identified as suspicious and excluded or edited. The cubic spline method is included for illustration as its distorting effects are less obvious with real data.

TABLE I

RESULTS FROM 100 SIMULATIONS OF RANDOM NOISE IN THE 'DISTORTED' SIGNAL COMPARED AGAINST THE LS PERIODOGRAM ESTIMATED FOR THE ORIGINAL SIGNAL.

	Original Signal	Distorted Signal (mean ± std)
Mean average RR interval (sec)	1.009±0.0038	0.9196±0.0061
Range RR intervals	0.151	0.870±0.110
LF power (nu)	0.39	0.32±0.04
HF power (nu)	0.61	0.62±0.04
LF/HF	0.6357	0.52±0.09
LF peak height (ms^2/Hz)	0.1668	0.54±0.16
HF peak height (ms^2/Hz)	0.2601	0.68 ±0.18
A_l/A_h	0.6413	0.79±0.34
LF Peak Location (mHz)	95	97.4±19.6
HF Peak Location (mHz)	275	275.8±9.1
LF Δf_{3dB} (Hz) x 10^{-3}	3.00	3.6±0.11
HF Δf_{3dB} (Hz) x 10^{-3}	2.90	3.4±0.91
Fraction of power within +/-0.01Hz of LF band	0.76	0.69±0.21
Fraction of power within +/-0.01Hz of HF band	0.75	0.86±0.22
Total Power (dB)	-28.46	-17.97±0.41

TABLE II

COMPARISON OF RESULTS OBTAINED FROM 5 DIFFERENT METHODS OF RR EDITING (OVER 100 SIMULATIONS WITH DIFFERENT RANDOM NOISE PROFILES). DATA ARE PRESENTED AS MEAN ± STD

					Method 5 - Replacement		
	Method 1 LS Baseline	Method 2 Rules	Method 3 OUGP	Method 4 EMD	Cubic Spline	Linear	Mean Replacement
Mean RR (sec)	0.94±0.01	0.93±0.01	0.91±0.01	0.92±0.01	0.94±0.05	0.94±0.01	0.94±0.01
Range RR (sec)	0.638	0.724	0.598	0.805	0.743	0.889	0.867
LF (nu)	0.39±0.05	0.42±0.06	0.44±0.04	0.44±0.04	0.43±0.05	0.39±0.05	0.39±0.05
HF (nu)	0.61±0.40	0.48±0.05	0.54±0.04	0.54±0.04	-0.45±0.05	0.51±0.04	-0.51±0.04
LF/HF	0.77±0.16	0.89±0.18	0.82±0.14	0.82±0.14	0.98±0.21	0.77±0.16	0.76±0.15
Ptot (dB)	-19.11±0.46	-19.94±0.45	-19.44±0.46	-19.54±0.38	-18.37±0.47	-19.11±0.47	-19.57±0.42
LF location (mHz)	94.55±3.51	90.62±15.10	95.18±5.95	94.95±3.62	75.57±42.29	71.06±38.51	91.99±30.51
HF location (mHz)	273.18±17.99	251.23±59.65	264.75±49.54	274.92±37.3	155.96±81.59	153.22±79.99	237.12±65.95
A_l/A_h	1.22±0.60	1.76±0.85	1.93±0.94	0.781±0.31	0.88±1.232	1.23±0.93	1.56±0.84
% of LF Peak > FAP 10%	98	93	99	99	84	84	83
% of HF Peak > FAP 10%	98	88	96	100	84	82	70

TABLE III

COMPARISON OF RESULTS OBTAINED FROM 5 DIFFERENT METHODS OF RR EDITING USING PATIENT

	Method 1 LS Baseline	Method 2 Rules	Method 3 OUGP	Method 4 EMD	Method 5 Cubic Spline
Mean RR (sec) ±std	0.77±0.09	0.75± 0.05	0.76±0.06	0.76±0.07	0.77±0.09
Range RR (sec)	0.43	0.25	0.27	0.34	0.43
LF/HF	2.97	0.54	3.76	2.87	3.66
LF (nu)	0.38	0.31	0.69	0.5	0.46
HF (nu)	0.13	0.58	0.18	0.17	0.12
Ptot (dB)	1.002	1.001	1.001	1.001	1.002