Journal of Clinical Monitoring and Computing (2019) 33:1089–1096
https://doi.org/10.1007/s10877-019-00254-7

ORIGINAL RESEARCH

Non-sinusoidal waves in the EEG and their simulated effect on anaesthetic quantitative EEG monitors

Rebecca M. Pullon[1] · Samuel McCabe[1] · Amy Gaskell[1] · Jamie W. Sleigh[1]

Received: 22 July 2018 / Accepted: 3 January 2019 / Published online: 22 January 2019

Abstract
The effect of anaesthetic drugs on the cortex are commonly estimated from the electroencephalogram (EEG) by quantitative EEG monitors such as the Bispectral Index (BIS). These monitors use ratios of high to low frequency power which assumes that each neurological process contributes a unique frequency pattern. However, recent research of the effect of deep brain stimulation on EEG beta oscillations suggests that wave shape, a non-sinusoidal feature that is only measurable in the time-domain, can change the frequency 'signature' of a neurological rhythmical process by the inclusion or removal of harmonic frequencies. If wave shape variations are present in the EEG of anaesthetised patients, then quantitative EEG monitors likely overestimate the anaesthetic drug effect. The purpose of this paper is to investigate alpha-wave shape in the EEG of anaesthetised patients and demonstrate the effect of wave shape on the frequency ratios that are commonly utilised in the BIS quantitative EEG monitor. EEG data, demographic information, and surgery details were collected prospectively from 305 patients undergoing a general anaesthetic for elective surgery. Alpha-wave shape was categorised by triangularity of the EEG extrema, a measure of how peaked (towards a sawtooth wave) or flat (towards a square wave) the extremum was. The alpha-wave was then artificially modified to either a sawtooth wave or square wave, and BetaRatio and PowerFastSlow metrics calculated. Age was found to be the only significant predictor of alpha wave triangularity. The artificially modified square-alpha waves increased the power in the frequency spectrum at 26 Hz by 1–5 dB, and increased the BetaRatio by 0.7. The alpha-wave of anaesthetised patients contains non-sinusoidal components which likely impact depth of anaesthesia calculations.

Keywords Depth of anaesthesia · EEG · Wave shape · Triangularity · Non-sinusoidal waves

1 Introduction

The electroencephalogram (EEG) is often used to monitor the effect of anaesthetic drugs on the cortex, and consequently provide an estimate of level of consciousness during surgery [1]. Analysis in the frequency domain, using techniques such as the Fourier transform which decompose a signal into its component sinusoids, is common for such monitors, which typically rely on the ratio of high frequency to low frequency power. However, these techniques assume that each neuronal process has a characteristic frequency 'pattern'. In reality, this frequency pattern can be altered by wave shape, a non-sinusoidal feature only measurable in the time-domain. For example, Cole et al. [2] demonstrated that with deep brain stimulation, the beta waveform of Parkinson's patients changed from a sawtooth-like wave towards a smooth sinusoid. Sawtooth waves are thought to reflect greater synchrony of synaptic input. In the frequency domain, a sawtooth wave contains high frequencies to capture the sharp changes in direction (i.e. odd harmonics of the fundamental frequency), whereas a smooth sinusoidal signal only contains power at the fundamental frequency. Therefore the change in stimulation caused the frequency pattern of the beta wave to apparently change from power spread over several frequencies to power at a single frequency.

If not interpreted carefully, the presence of non-sinusoidal features can result in a lack of accurate correspondence

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10877-019-00254-7) contains supplementary material, which is available to authorized users.

✉ Rebecca M. Pullon
r.pullon@auckland.ac.nz

1 Department of Anaesthesiology, Waikato Clinical School, University of Auckland, Hamilton, New Zealand

between the frequency spectrum and the actual biological activity. In the example above, the authors showed that the sharp beta waves (13–30 Hz) in the primary motor cortex were the origin of increased high gamma power (50–200 Hz) in the frequency spectrum rather than a change in the biological processes that typically oscillate in gamma frequencies. Contreras et al. [3] reported the presence of non-sinusoid components in posterior alpha rhythms. These components have been reported to cause cross frequency coupling despite the absence of functional interaction between sources [4, 5]. Applications of non-sinusoidal features have thus far been largely explored only in neurological research; however we hypothesise that these discoveries may also apply to the interpretation of EEG signals by anaesthetists during general anaesthesia. Low frequency brain processes are many orders of magnitude greater in amplitude than the high frequency processes and thus even small changes in wave-shape may affect the calculations of quantitative EEG monitors [6].

We aimed to determine whether non-sinusoidal waves are found in frontal EEG signals during routine surgical anaesthesia, and consequently what effect these would have on two frequency ratios used by the Bispectral Index (BIS) quantitative EEG monitor.

2 Methods

An overview of our methods is as follows: firstly we examined the wave shape of the extended alpha-range (7–17 Hz) waves obtained from clinical EEG data from a previous study [7]. We sought to describe the natural distribution of variation in shape and the relationship between wave shape and various associated demographic factors. Secondly, we illustrated the effect of sawtooth and square waves on frequency ratios used by the BIS monitor by replacing the dominant alpha frequency component in the EEG with an artificially generated sawtooth or square wave, and then quantifying the frequency domain effect of this manipulation. This allowed us to confirm the usefulness of our measure of triangularity, and to quantify the maximum possible effect of wave shape on measures of anaesthetic depth.

All analysis was performed in the Matlab programming environment (version R2017b, MathWorks, Inc., Natick, MA).

2.1 Dataset

Frontal EEG (Fpz-Fp1 or Fp2) was recorded for 305 adult patients undergoing surgery under general anaesthesia at Waikato Hospital, New Zealand. A Bispectral Index® (BIS®, Aspect Medical Systems, Newton, MA, USA, with a sampling rate (*fs*) of 128 Hz) or entropy (GE Healthcare, Helsinki, Finland, with a sampling rate of 100 Hz) monitor was used to record EEG data. Relevant clinical data, such as end-tidal anaesthetic gas concentrations, were recorded using an S/5 anaesthesia monitor (GE Healthcare, Helsinki, Finland).

The study was approved by the New Zealand Health and Disability Ethics Committee (Ref. 12/CEN/56), all patients gave written informed consent and the study had institutional research committee approval. Analysis of the pattern of alpha-waves from this observational dataset has previously been published [6].

2.2 Pre-processing of EEG

All EEG recordings were upsampled to 500 Hz using cubic spline interpolation, and detrended. A 40 s epoch was taken from the middle of each EEG recording, during the maintenance phase of surgical anaesthesia. Each epoch was examined for motion artefacts and burst suppression by visual inspection of the raw signal and spectrogram. If an artefact or burst suppression was present, a different 40 s epoch was selected. All chosen epochs were within 15 min of the middle of the recording.

2.3 Triangularity of the alpha-wave

Non-sinusoidal waves can be either towards a square (flat) wave, or a sawtooth (peaked) wave. As non-sinusoidal waves contain multiple frequencies (i.e. odd harmonics), it is, by definition, not possible to determine their presence by frequency analysis alone. The shape of the extended alpha-band *time-domain* signal was therefore analysed to determine non-sinusoidal components [2].

We use *Triangularity* to quantify the peakedness of an extremum (peak or trough), and therefore to describe the continuum between a square wave and a sawtooth wave. The procedure for calculating triangularity of an alpha-oscillation is as follows. First, the extended alpha-band range (7–17 Hz) was extracted by filtering. A 10th order high-pass Butterworth filter (cut-off at 6.5 Hz) was used to attenuate low frequencies, and a Whittaker function (scale parameter: $\lambda = 0.4\,fs$) used to attenuate high frequencies, chosen due to its slow roll-off which largely retains wave shape [8].

Time points of rising and falling zero-crossings of the extended alpha-band signal were identified. A "peak" was considered as the signal between a rising zero-crossing and a falling zero-crossing, and a "trough" as the signal between a falling zero-crossing and a rising zero-crossing. The shape of the extrema were quantified by the interquartile range of the absolute distribution of their derivative (rate of change), referred to as *BasicTriangularity*. Figure 1 illustrates the process of calculating *BasicTriangularity* and the difference in derivative distributions between a square peak and a sawtooth peak.

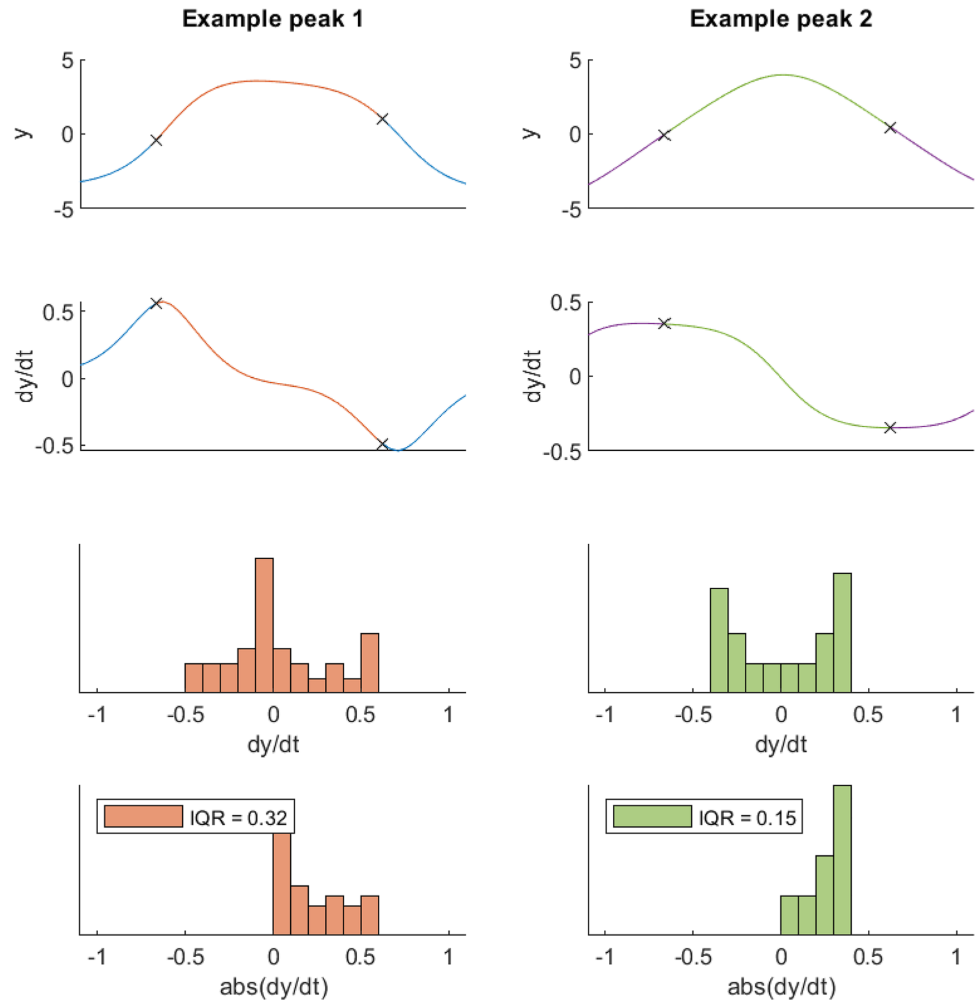

Fig. 1 The process of calculating triangularity for a square-like peak (left column) and triangular-like peak (right column) in the EEG. Top: time domain signal with the start and end of the peak identified by zero-crossings. Second plot: derivative of the time-domain signal. Third plot: histogram of the derivative of the peak. For a square peak (left) the derivative is often near zero, whereas for a sawtooth peak (right) the derivative only passes through zero as it transitions from a stead positive gradient to a steady negative gradient. Bottom: histogram of the absolute derivative of the peak. The interquartile range (IQR) of this distribution is the BasicTriangularity. After standardising with the IQR of a similar sinusoid peak, the Triangularity of peak 1 (left) is −2.23 and for peak 2 (right) is 1.64

For each peak and trough, a sinusoid with the same width and height was created. The interquartile range of the absolute distribution of the sinusoid's derivative (the *SinusoidTriangularity*) was used to standardise *BasicTriangularity* to account for changes in voltage and frequency between extrema. Thus for extremum *i, Triangularity* is calculated as:

$$\text{Triangularity}_\text{i} = 10 * \log_{10} \frac{\text{SinusoidTriangularity}_i}{\text{BasicTriangularity}_\text{i}}$$

A triangularity of zero therefore indicates a perfect sinusoid, a triangularity less than zero indicates the extremum is towards a square wave, and a triangularity greater than zero indicates the extremum is towards a sawtooth wave. Matlab code to calculate triangularity is provided in the Online Resource.

An epoch's triangularity was summarised by the *median* triangularity of all the extrema in that epoch.

2.4 Predictors of wave shape

In order to determine the circumstances which affect wave shape of the extended-alpha-band, an epoch's median Triangularity was correlated with age, sex, opioid concentration, type of anaesthetic agent, and MAC concentration of the anaesthetic agent.

2.5 The effect of non-sinusoid waves on anaesthetic depth measures

To determine whether non-sinusoidal alpha waves could cause significant changes in frequency ratios used in the BIS quantitative EEG monitor, the EEG epochs were artificially modified to contain a sawtooth or square wave at their dominant alpha frequency.

For each EEG epoch, the frequency between 7 and 17 Hz with the largest magnitude was selected as the dominant alpha frequency. The EEG signal was then bandpass filtered with a 3rd order Butterworth filter with frequency cut-offs 1 Hz either side of the dominant alpha frequency. The resulting signal is referred to as the "sinusoid-alpha", and the remainder of the EEG signal as the "stopband". We only modify the sinusoid-alpha signal rather than the extended-alpha signal to minimise changes in the frequency spectrum outside the alpha frequency.

As in the estimation of triangularity (Sect. 2.3), the rising and falling zero-crossings of the sinusoid-alpha signal were identified to identify the extrema. A *square-alpha* signal was generated by selecting the maximum (peak) or minimum (trough) voltage of the extrema for its duration. A *sawtooth-alpha* signal was generated by connecting extrema voltages at their middle time-point with straight lines. The amplitude of the sawtooth-alpha and square-alpha signals were normalised such that the power at the dominant alpha frequency was the same as in the sinusoid-alpha wave. The stopband was added to the sawtooth-alpha signal and square-alpha signal to create a reconstructed sawtooth-EEG and square-EEG, respectively. An example of this process is shown in Fig. 2.

The frequency spectrum of the reconstructed sawtooth-EEG and square-EEG signals were compared with the frequency spectrum of the original EEG signal using two metrics utilised in the calculation of the Bispectral Index (BIS) [1]. The *BetaRatio* is the log ratio of power in the 30–47 Hz band to power in the 11–20 Hz band. *PowerFastSlow* is the log ratio of power in the 40–47 Hz band to that in the 1–47 Hz band. We used the PowerFastSlow (spectrum) as an approximation to the SynchFastSlow (bispectrum) that is used in the commercial monitor. For these calculations, the EEG spectra were calculated using Welch's power spectral density estimate with 129 frequency steps, 1 s segments, and 50% overlap.

2.6 Statistics

All distributions and changes in distributions were assumed to be non-Gaussian and therefore summarised by their median and interquartile range (IQR). Unless otherwise stated, the Wilcoxon rank sum test was used to compare distributions, where $p < 0.05$ was considered statistically significant. Spearman's correlation coefficient (ρ) was used to as an indication of linear relationship between continuous variables.

3 Results

Of the 305 patients recruited to the study, EEG data were not able to be obtained for 20 patients due to cancelled surgery or technical failure. EEG recordings from 285 patients were therefore used for analysis. Patient age ranged from 18 to 90 years with a median (IQR) of 64 (28) years. 143 (50.2%) were female. 194 (68.1%) patients received sevoflurane as the main anaesthetic agent, 74 (26.0%) received desflurane, and 17 (6.0%) received propofol. The most common type of surgery was general surgery (117, 41.1%), followed by vascular (73, 25.6%), urology (41, 14.4%), and gynaecology (32, 11.2%).

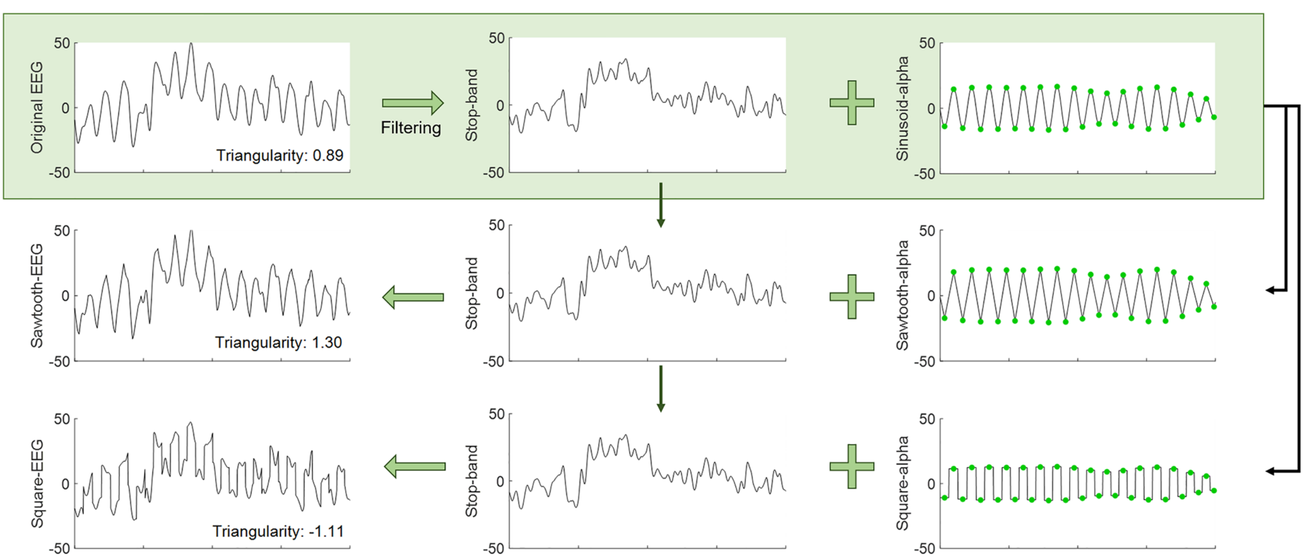

Fig. 2 Illustration of the construction of the sawtooth-alpha and square-alpha (right column) from the sinusoid-alpha of the original EEG epoch, and the consequent reconstruction of the EEG by addition to the stop-band signal

3.1 Triangularity in the unaltered alpha band of the EEGs during routine general anaesthesia

We identified 228,055 extrema in the alpha-band signal of the 285 40-s EEG epochs used for analysis. Triangularity was calculated for all extrema and found to be more sawtooth rather than square. Values were normally distributed (Kolmogorov–Smirnov test, $p < 0.001$) with a median (IQR) of 0.75 (2.04) and 95% of the values between −2.44 (towards a square waveform) and 3.97 (towards a sawtooth waveform). The median triangularity for each participant was also found to be sawtooth [0.77 (0.16)] with an IQR of 2.04 (0.39). There were 795 (90) extrema per epoch, a range of 655 to 994 extrema.

Example extrema and their triangularity values are shown in Fig. 3.

3.2 Univariable predictors of wave shape

The relationship between median triangularity and the continuous predictors of patient age, MAC value, and fentanyl concentration are shown in Fig. 4. Data were binned and visually summarised by the mean and standard deviation to highlight any trends present. There was some negative correlation between age and median triangularity ($\rho = -0.34$). This difference was significant between those less than 35 years [n = 36; 0.82 (0.12)] and those greater than 75 years [n = 49; 0.70 (0.18), $p < 0.001$]. Drug dosage did not affect triangularity ($\rho = 0.03$ for MAC and $\rho = -0.04$ for fentanyl concentration).

The effect of categorical predictors—patient sex, type of anaesthetic agent, and surgery type—on median triangularity were also investigated (Fig. 5). There was no difference in median triangularity between female and male participants ($p = 0.860$), or between sevoflurane and desflurane volatile anaesthetics ($p = 0.104$). Since only a small number of patients received propofol as their primary anaesthetic agent, propofol was not included in the analysis.

Surgery types with more than 30 patients (general, gynaecology, urology, and vascular) were considered as candidate explanatory variables for triangularity. However, the grouped Kruskal–Wallis test showed no significant difference in the median triangularity between groups ($\chi^2 = 4.6$; $p = 0.201$).

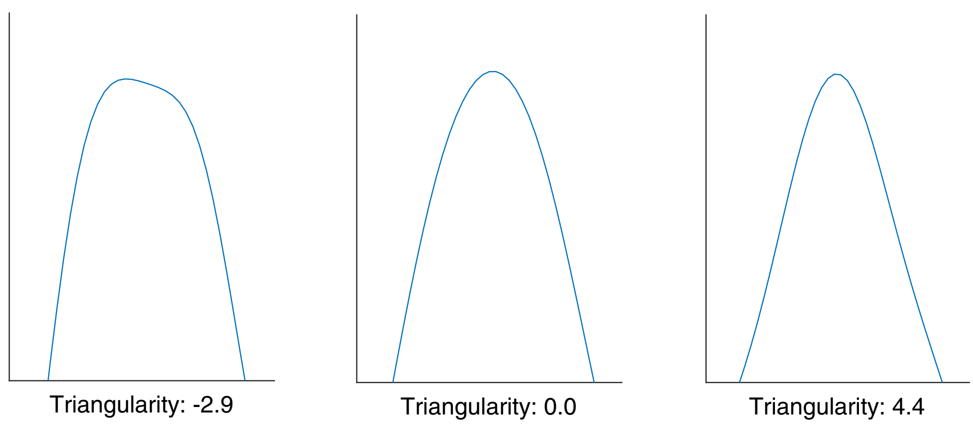

Fig. 3 Example extrema with a negative triangularity (left, towards a square wave), triangularity of zero (middle, a sine wave), and a positive triangularity (right, towards a sawtooth wave)

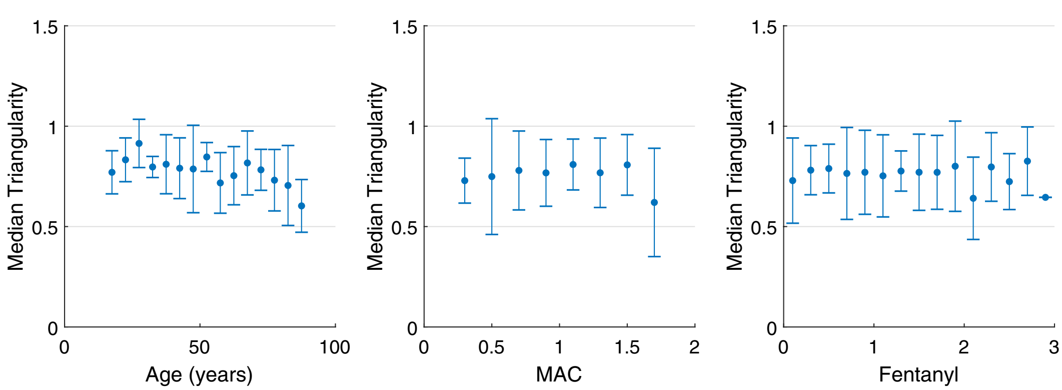

Fig. 4 Relationship of patient age, volatile anaesthetic concentration, and opioid concentration, with median triangularity. Presented as median (dot) ± IQR (error bars)

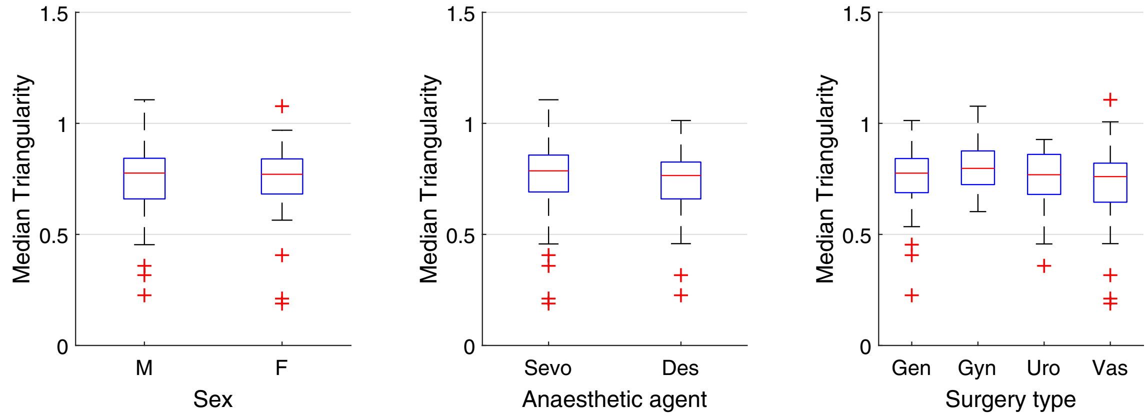

Fig. 5 Relationship of patient and surgery with median triangularity. The boxplots represent the median (central line), IQR (box), and range (whiskers). Abbreviations: female (F), male (M), sevoflurane (sevo), desflurane (des), general surgery (gen), gynaecology (gyn), urology (uro), and vascular surgery (vas)

3.3 The effect of introducing non-sinusoidal alpha-wave shapes to the raw EEG

Introducing non-sinusoidal alpha-wave shapes into the EEG signal altered the median triangularity of the EEG epochs. The original signals were already somewhat sawtooth-shaped. The reconstructed sawtooth-EEG *increased* the median triangularity by 0.08 (0.12) ($p < 0.001$), and the reconstructed square-EEG *decreased* the median triangularity by 0.36 (0.40) ($p < 0.001$).

The reconstructed signals contain more high frequency components (above 20 Hz) than the original EEG signal with a peak around 26 Hz, the first odd harmonic of the alpha frequency. The median difference in frequency spectrum between the original EEG signal and the reconstructed sawtooth and square wave signals are shown in Fig. 6. At 26 Hz the sawtooth reconstruction increased power by a median (IQR) of 0.23 (1.51) dB, and a larger effect of 1.1 (6.4) dB for the square wave reconstruction.

Altering the shape of the alpha waves caused both the BetaRatio and the PowerFastSlow to increase statistically significantly. The effects were more pronounced for the square wave transformation. The BetaRatio changed from − 1.71 (0.53) to − 1.58 (0.35) for the reconstructed sawtooth-EEG, a median increase of 0.08 (0.16) per recording ($p < 0.001$). BetaRatio was − 0.94 (0.27) for the reconstructed square-EEG, a median increase of 0.71 (0.56) from the original signal ($p < 0.001$). The change in

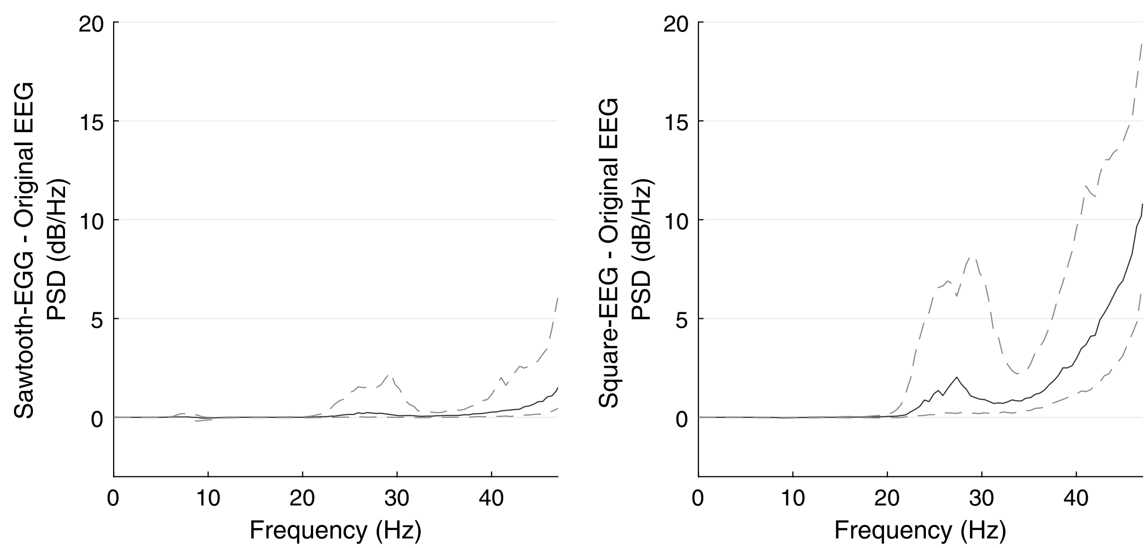

Fig. 6 The change in power spectral density between the original EEG signal and the reconstructed sawtooth-EEG (left) and square-EEG (right). The median (solid line) and lower and upper quartile (dashed line) changes are shown

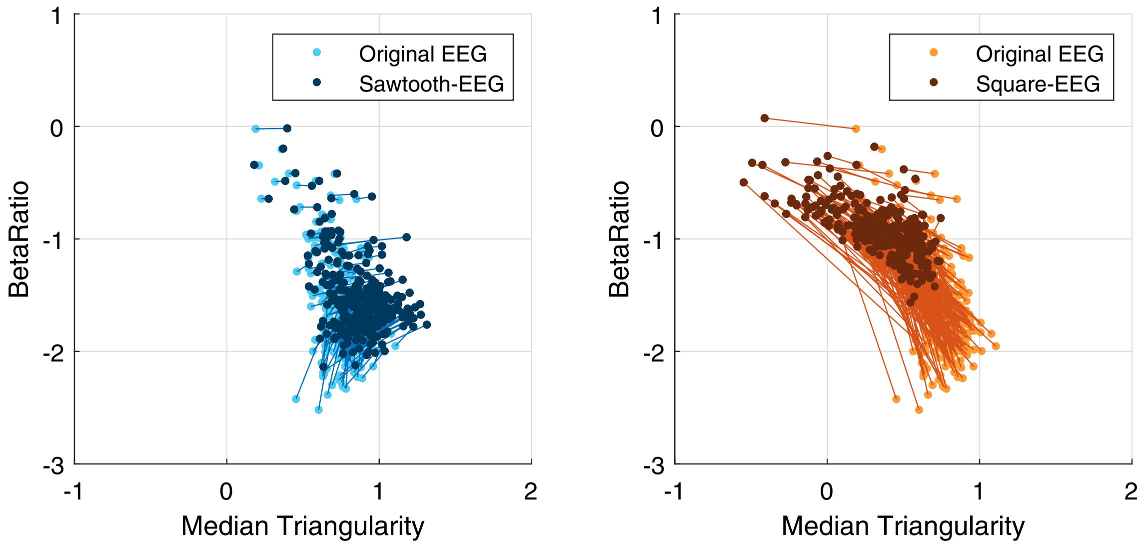

Fig. 7 The change in BetaRatio and median triangularity from the original EEG to the reconstructed sawtooth-EEG (left) and square-EEG (right)

BetaRatio with respect to median triangularity are shown in Fig. 7.

The PowerFastSlow changed from −3.89 (0.53) to −3.62 (0.41) for the reconstructed sawtooth-EEG, a median change of 0.10 (0.29) per recording ($p < 0.001$). PowerFastSlow for the reconstructed square-EEG was −2.81 (0.90), a median increase of 0.90 (1.08) from the original signal ($p < 0.001$). BetaRatio and PowerFastSlow are correlated measurements with a Spearman's correlation coefficient of 0.69.

4 Discussion

We found that the alpha oscillation in adult patients under routine volatile general anaesthesia tended towards being sawtooth in shape (positive triangularity), rather than being strictly sinusoidal. Univariable analysis showed that greater sawtooth shape was associated with patient age.

The triangularity metric presented here quantifies an extremum's shape by the spread of its derivative distribution. This is a variation on the "sharpness" metric presented by Cole et al. [2] which calculated the average gradient surrounding identified extrema. We found that Cole's method worked well for sinusoidal and sawtooth peaks but was not adequate for identifying and describing the shape of square-like waves. Square waves have a steep rising and falling edge with a flat, or near-flat, section in between. With added high frequency noise, this square wave can appear as two peaks with a trough in between, and thus identifying a single maximum does not capture the entire square wave. Quantifying an extremum as the period between two zero-crossings of time-domain EEG signal addresses this problem, and taking the derivative over this whole period is a natural extension when the centre of the peak is not known. The interquartile range, rather than the median, was used to summarise the derivative's distribution to distinguish between sawtooth and sinusoidal peaks since their medians are similar.

We found that triangularity of extrema varied between sawtooth and square wave shapes within each individual's 40-s EEG epoch. However, the spread of median triangularity between individuals was narrow, lying between 0.46 and 0.96 for 95% of the participants, compared to between −2.44 and 3.97 for individual extrema. The ability to assess the effectors of triangularity was therefore limited, and we found that age was the only significant predictor of wave shape. Further analysis should examine the relationship of possible surgical predictors with triangularity *within* a participant on epochs longer than 40 s.

BetaRatio and PowerFastSlow both increased with the small changes in triangularity from alpha-sawtooth reconstruction (positive triangularity) and alpha-square wave reconstruction (negative triangularity). Both sawtooth and square waves contain sharp corners, and thus contain very short segments of high frequencies. As BetaRatio and PowerFastSlow are measures of the frequency distribution, this change is intuitively reasonable. Therefore any artefactual increase in triangularity could result in artificial elevation of the BIS index and misguide patient management. Because the derivation of the BIS value from its subcomponents is proprietary, we are not able to exactly state how much the BIS would be influenced, but it is hard to imagine that the changes in BetaRatio—caused by quite modest variation in alpha wave triangularity—would not alter the BIS value significantly. Furthermore, although only the BIS index is known to explicitly use the BetaRatio, all presently available commercial EEG depth of anaesthesia monitors similarly quantify the loss of high frequencies in the EEG, and therefore they would be sensitive to these changes.

These results have more general consequences for all sorts of EEG spectral analysis. Our simulation showed that a sawtooth waveform would be expected to increase the power in the beta waveband by up to 2 dB. A square-wave waveform is quite rare, but would have even larger effect. This is in agreement with well-established theory. Square wave harmonics reduce in amplitude with 1/k (where k is the harmonic number), while triangle wave (e.g. sawtooth) harmonics fall with $1/k^2$ and thus contribute less power to high frequencies. We would suggest that any studies which report (purported) important changes in beta and gamma EEG power—in the presence of a co-existing alpha peak—should have to demonstrate that the observed changes in beta and gamma power are not signal processing artefacts caused by changes in shape of the alpha oscillation waveform.

5 Limitations

We used the Whittaker filter to extract the extended alpha component of the EEG signal before estimation of its triangularity. Although this method retains the underlying waveform with less distortion than a conventional Fourier-based filter, it is still a compromise between being able to follow abrupt changes in the true 'alpha' waveform and being overly influenced by true non-alpha high frequency EEG activity. Because of this we are, if anything, underestimating the distribution and effects of waveform shape in this paper.

Our triangularity metric is limited in its ability to distinguish between symmetric and asymmetric extrema. Incorporating symmetry into the triangularity metric could provide additional insights into the causes of non-sinusoidal EEG features.

6 Conclusions

We found that there is some variation in the shape of the alpha waveform in patients during general anaesthesia. It is commonly somewhat sawtooth-shaped, and has the effect of artificially increasing quantitative EEG monitor indices. This also suggests that some apparent high frequency spectral power is, in fact, generated as part of the alpha oscillatory processes.

Acknowledgements The authors acknowledge the funding of the James S. McDonnell Foundation which supported the collection of the data analysed in this paper, and Darren Hight who collected the data. The authors also acknowledge the University of Auckland, School of Medicine E G Shrimpton Fund which supported the analysis presented in this paper.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Miller A, Sleigh JW, Barnard J, Steyn-Ross DA. Does bispectral analysis of the electroencephalogram add anything but complexity? Br J Anaesth. 2004;92(1):8–13. https://doi.org/10.1093/bja/aeh003.
2. Cole SR, van der Meij R, Peterson EJ, de Hemptinne C, Starr PA, Voytek B. Nonsinusoidal beta oscillations reflect cortical pathophysiology in Parkinson's disease. J Neurosci. 2017;37(18):4830–40. https://doi.org/10.1523/jneurosci.2208-16.2017.
3. Contreras D, Destexhe A, Sejnowski TJ, Steriade M. Spatiotemporal patterns of spindle oscillations in cortex and thalamus. J Neurosci. 1997;17(3):1179–96.
4. Gerber EM, Sadeh B, Ward A, Knight RT, Deouell LY. Non-sinusoidal activity can produce cross-frequency coupling in cortical signals in the absence of functional interaction between neural sources. PLoS ONE. 2016;11(12):e0167351. https://doi.org/10.1371/journal.pone.0167351.
5. Lozano-Soldevilla D, ter Huurne N, Oostenveld R Neuronal oscillations with non-sinusoidal morphology produce spurious phase-to-amplitude coupling and directionality. Front Comput Neurosci. 2016;10 (87). https://doi.org/10.3389/fncom.2016.00087.
6. Chander D, García PS, MacColl JN, Illing S, Sleigh JW. Electroencephalographic variation during end maintenance and emergence from surgical anesthesia. PLoS ONE. 2014;9(9):e106291.
7. Hight DF, Voss LJ, García PS, Sleigh JW. Electromyographic activation reveals cortical and sub-cortical dissociation during emergence from general anesthesia. J Clin Monit Comput. 2017;31(4):813–23. https://doi.org/10.1007/s10877-016-9911-z.
8. Whittaker ET On a new method of graduation. Proc Edinb Math Soc. 1922;41:63–75. https://doi.org/10.1017/S0013091500077853.