Measuring Depth of Anesthesia using Electroencephalogram Entropy Rates

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Abstract

Background

Electroencephalogram (EEG) entropy rate estimation has been proposed as a measure of anesthetic depth. The authors explore the principles of entropy rates measurement for the purpose of extracting depth of anesthesia information from the EEG, and apply entropic measures to EEG data from patients undergoing general anesthesia. These are compared with traditional spectral indices.

Methods

The following were assessed: Conditional Entropy (CEn); Corrected Conditional Entropy (CCEn); Approximate Entropy (ApEn); Coarse-grained Entropy rates (CGEn); Gaussian Process Entropy rates (GPEn); and Spectral Entropy (SpEn). For comparison, Spectral Edge 95 (SE95) and Bispectral Index Scale (BIS) were used. EEG data were logged using an Aspect A-2000 BIS monitor from adult patients undergoing elective surgery. Eight EEG series were investigated. Two representative parts of these EEG series were used to quantify discriminative power of each method: a series containing moderate and light anesthesia; and one containing emergence from anesthesia. Discrimination of each measure was measured in units of baseline variance. All measures (except BIS) were calculated off-line. Where data quantization was required two methods were compared. A range of subparameters were evaluated where relevant.

Results

All measures gave some indication of depth of anesthesia. A high level of correlation among the all entropy rates measures was observed (Spearman's ranked correlation coefficient SRC $>$ 0.8). The entropy rates measures were as good as, or better than the spectral methods at distinguishing light from moderate anesthetic depth. CGEn showed the greatest discriminative power. Equiquantization improved discrimination in all cases.

Conclusions

This study confirms entropy rate estimations as potentially useful measures of anesthetic depth. Correction terms for limited data should be employed and equiquantization is preferred. CGEn was consistently the best measure in this study and is worthy of further investigation.

Introduction

Frequency power spectrum techniques

A variety of methods of assessing anesthetic depth have been explored[1]. The electroencephalogram (EEG) shows obvious frequency changes associated with anesthesia and indices derived from the EEG frequency power spectrum have enjoyed some success. These indices mainly measure EEG slowing (shift to predominantly lower frequencies) associated with increasing anesthetic depth. The most recent of these is the bispectral index scale (BIS), a proprietary combination of spectral measures optimised on a large clinical database (Aspect Medical Systems Inc., Newton, MA)[a].

Nonlinear measures

Noting that central nervous system neurons exhibit nonlinear behavior, researchers applied measures derived from nonlinear dynamics and deterministic chaos theories to the EEG time series.[2,3] This must be done with care: in particular the EEG signal is non-stationary, and the number of data points that can be used for any measure is therefore limited. However, initial studies suggested that these new measures contained useful information about anesthetic depth.[4,5,6]

Entropy Rates

Entropy rates are measures designed to quantify the regularity of a time series or the predictability of new values based on previous observations. The complexity of a stochastic process evolving in time can be represented by the rate that the system loses information about previous states. This complexity can be described using entropy rates, which tend to zero for processes with periodic repetition and conversely tend to high values for processes with aperiodic or random behavior.

For a dynamical system evolving in some measurable state space, the entropy rates are related to Kolmogorov-Sinai entropy (KSE).[7] This allows the measurement of entropy rates not only when a time-series is considered as a projection of a trajectory of a dynamical system (e.g. low-dimensional chaotic system) but also when a general linear or nonlinear stationary stochastic process is assumed.

Problems arise when entropy rates or KSE has to be estimated from a finite number of observations containing a relatively high noise component - as EEG data under anesthesia. The authors studied three groups of algorithms designed to approximate entropy rates under these conditions.

The entropy rates measures assessed and compared

The following EEG entropy rates measures were assessed: Conditional Entropy (CEn), Corrected Conditional Entropy (CCEn), Approximate Entropy (ApEn), Coarse-grained Entropy rates (CGEn) and Gaussian Process Entropy rates (GPEn).

CEn estimates entropy rates directly by computing empirical probability distribution functions from quantized data. CCEn is a variant of CEn which incorporates a correction term

[a] `http://www.aspectms.com`

when numbers of data points are limited. CGEn estimates entropy rates based on the asymptotic relation of the marginal redundancies (see below) and KSE. These marginal redundancies are estimated from quantized EEG data. In contrast ApEn estimates entropy rates from unquantized data. All these measures are designed to discriminate data series with different regularity and predictability properties rather than to provide exact entropy rate values. They are therefore relative measures and their proximity to absolute entropy values depends on the sub-parameters selected. Other researchers have highlighted the importance of unification of sub-parameters in the case of ApEn.[4] Where the process generating EEG data is a stationary Gaussian stochastic process, entropy rates may be estimated from its spectrum - GPEn. This provides a straightforward connection to the Spectral Entropy measure (SpEn) described below.[8]

Study aim

The aim of this study was to determine which entropy rates measure was most suitable for assessing the EEG waveform considering the limited data amounts available. Where relevant a range of sub-parameter settings were evaluated; as was the effect of two quantization methods; and the impact of using a correction term for limited data.

Materials and Methods

Clinical anesthesia, patients

This study used EEG waveform data measured in eight adult patients undergoing routine elective surgery. The patients were all between the ages of 30 and 75 years old, and were ASA I-III. The surgical specialties represented were orthopaedics, gastro-intestinal surgery, and ophthalmology. The anesthetic technique was not standardised and including target controlled infusions of propofol as well as inhalational anesthesia. EEG data were tagged with relevant clinical data which included premedicant and sedative medication, hypo or hyperthermia, thyroid disease, target propofol concentration, end-tidal agent concentration, and clinical events such as gagging or eye-opening. The study met the requirements of the local Ethical Committee.

Equipment

Capnomac (Datex, Copenhagen, Denmark), Aspect A-2000 BIS monitor (Aspect Medical Systems, Natick, MA, USA), Electrodes - Blue Sensor (Medicotest, Olstykke, Denmark), Skin abrasion - One-step skin prep (3M, Ontario, Canada).

Techniques

The EEG was recorded continuously from a bifrontal montage (Fp1-Fpz, Fp2-Fpz, international 10-20 system, Aspect A-2000 monitor). The raw EEG data were manually cleared of artifacts which were unphysiological, and data identified by BIS monitor as corrupted were removed. This left approximately 500 minutes of detailed tagged EEG data. The raw EEG was digitized at 128Hz and filtered between 0.5 - 30Hz. EEG epochs of 1204 data points (8sec) were used for computation of individual measures employed in the study. The epochs were taken in steps of 128 data points (1sec). The BIS values are computed from 60 second EEG segments and averaged over 15sec intervals (Aspect Medical Systems Inc.).

Entropy rates assessment

Consider a stochastic process $\{X_i\}$, i.e. an indexed sequence of random variables characterized by the joint probability distribution function $p^m(x_1, \cdots, x_m) = \Pr[(X_1, \ldots, X_m) = (x_1, \ldots, x_m)]$, where $\{x_i \in \mathcal{X}\}$ is a realization of $\{X_i\}$ drawn from the set of all possible values $\mathcal{X}$. Thus we have the following definition of the *entropy rate* h

$$\lim_{m\to\infty} \frac{H(X_1, X_2, \ldots, X_m)}{m} = h \tag{1}$$

where

$$H(X_1, X_2, \ldots X_m) = -\sum_{x_1,\cdots,x_m} p^m(x_1, \cdots, x_m) \ln p^m(x_1, \cdots, x_m)$$

is the (Shannon) entropy of the random vector $\mathbf{X}_m = (X_1, \ldots, X_m)$.[9] Alternatively for stationary random processes we have

$$\lim_{m\to\infty} H(X_m/X_1, \ldots, X_{m-1}) = \lim_{m\to\infty} [H(\mathbf{X}_{m+1}) - H(\mathbf{X}_m)] = h \tag{2}$$

where $H(X_m/X_1,\cdots,X_{m-1})$ is the conditional entropy.[9] The existence of limits (1) and (2) are basic properties of stationary processes.

Practically we can consider the time series $\{x(t), t = 1, 2, \ldots, N\}$; i.e the observed measurements at time points t, to be a realization of a stationary and ergodic stochastic process $\{X_i\}$. The ergodicity allows us to estimate the statistics of $\{X_i\}$ from a single realization (time series); i.e we can replace ensemble averages by equal time averages. Thus, we can assume the variables X_i to be

$$X_i = x(t + (i-1)\tau)$$

where τ is a time delay, and we may construct m-dimensional embedding vectors $\{\mathbf{x}(t) = [x(t), x(t-\tau), \ldots, x(t-(m-1)\tau)]\}_{t=1}^{N-m+1}$. In practice we can not compute exact entropy rates from a finite number of measurements, the precise measurement of entropy rates is restricted to specific cases.[9]

i) Gaussian process entropy rates

If the observed time-series is a realization of a zero-mean stationary Gaussian process; i.e. linear stochastic process, we can estimate entropy rates through its spectral density function $f(\omega)$ which fully describes the dynamics of the process.[10,11,12] In our study for each epoch of EEG data we computed the Gaussian proccess entropy rate (GPEn) based on the approximation of spectral density by a periodogram evaluated from 512 points. GPEn is then estimated as the average over the individual periodogram bins. It is clear that GPEn is a linear measure which can fully describe an underlying stationary Gaussian process but can not describe data generated by a process involving nonlinearity. In such a case the nonlinear measures described below may be employed.

ii) Approximate entropy

The concept of approximate entropy (ApEn) was proposed by Pincus et. al.[13] Assuming an observed time-series of length N from which the set of m-dimensional time-delay embedding vectors $\{\mathbf{x}(j) = [x(j), x(j-1), \ldots, x(j-(m-1))]\}_{j=1}^{N-m+1}$ was constructed ApEn can be defined as

$$\text{ApEn} = \Phi^m(r) - \Phi^{m+1}(r) \tag{3}$$

where

$$\Phi^m(r) = \frac{1}{N-m+1} \sum_{i=1}^{N-m+1} \ln C_i^m(r) \tag{4}$$

$C_i^m(r) = \sum_{j=1}^{N-m+1} \theta(\|\mathbf{x}(i) - \mathbf{x}(j)\| - r)$ is a correlation sum, θ stands for the Heaviside function

$$\theta(u) = \begin{cases} 0 & : \quad u < 0 \\ 1 & : \quad u \geq 0 \end{cases}$$

$\|.\|$ represents a norm in a phase space of embedded vectors (usually the maximum norm is utilized) and the parameter r is the diameter of the phase space partition (grain). Heuristically, ApEn measures the (logarithmic) probability that m-dimensional patterns that are close to each other will continue to stay close when their dimension increases. The frequency of m-dimensional patterns similar to the pattern $\mathbf{x}_i$ is measured by the correlation sum $C_i^m(r)$ where the parameter r defines the proximity of the patterns. The decrease of $C_i^{m+1}(r)$ in

relation to $C_i^m(r)$ indicates the deviation of patterns from the base pattern $\mathbf{x}(i)$ when the length of the pattern is increased to $m+1$ leading to an increase in ApEn. It is clear, that for data generated randomly without any regular structure ApEn will tend to higher values. In contrast, for a rigorously periodic pattern $\mathbf{x}(i)$, whose period can be 'captured' by the m-dimensional embedding vector, the increase of the embedding dimension to $m+1$ will not decrease $C_i^{m+1}(r)$ and ApEn will tend to zero. The final ApEn value is then averaged over 'regularity' of all possible patterns $\mathbf{x}(i)$.

iii) Corrected conditional entropy

By using estimates of conditional entropy (CEn)[b] in (2) the exact entropy rate h can be approximated. However, in practice we usually restrict m to a finite number and compute CEn from empirical probability distribution functions derived from observed data. Thus, we can consider ApEn as an analog of CEn where correlation sums are used instead of empirical probability distribution functions. Moreover the related concept of measuring pattern regularity when pattern dimensionality is incremented can be used here.[14]

The empirical probabilities may have to be estimated from a finite (usually small) number of observed points. With increasing dimensionality m and quantization level Q the number of bins will increase as Q^m (see below). CEn then tends to zero values even for a random signal.[14] This source of error also occurs with ApEn causing Pincus et. al.[13] to restrict the range of embedding dimensions to $m \leq 2, 3$ when approximately 1000 data points were used. As a logical extension of this for higher values of m and Q Porta et. al.[14] proposed a correction term where the conditional entropy was estimated from smaller numbers of observations. CCEn is then defined as

$$\mathrm{CCEn}(X_{m+1}/\mathbf{X}_m) = \mathrm{CEn}(X_{m+1}/\mathbf{X}_m) + perc(X_{m+1})\hat{H}(X_1)$$

where $perc(X_{m+1})$ is a parentage of single points in the $m+1$ dimensional phase space (i.e. number of $m+1$ dimensional bins containing one sample) and $\hat{H}$ stands for a estimate of Shannon entropy for $m=1$. The CCEn as a function of the parameter m is measured, the minimum value being the best estimate of exact conditional entropy.

iv) Coarse-grained entropy rates

CGEn were proposed and successfully used to assess complexity or regularity in physiological signals.[15,16] To describe CGEn requires defining marginal redundancies; i.e. measures quantifying the average amount of information about the variable X_{m+1} contained in the vector of variables $\mathbf{X}_m = (X_1, \ldots, X_m)$

$$\rho_\tau^{m+1}(X_{m+1}; \mathbf{X}_m) = \sum_{x_1,\ldots,x_{m+1}} p^{m+1}(x_1, \ldots, x_{m+1}) \ln \frac{p^{m+1}(x_1, \ldots, x_{m+1})}{p^m(x_1, \ldots, x_m)p(x_{m+1})}$$

where the subscript τ is used to stress the fact that the marginal redundancies are also functions of the time-delay τ used to construct m-dimensional embedding vectors. We can also write

$$\rho_\tau^{m+1}(X_{m+1}; \mathbf{X}_m) = H(\mathbf{X}_m) - H(\mathbf{X}_{m+1}) + H(X_{m+1}) = -H(X_{m+1}/\mathbf{X}_m) + H(X_{m+1})$$

[b] We denote by CEn the estimate of the exact conditional entropy.

giving the relationship of CGEn to CEn and ApEn, respectively.[17]

It has been shown[18,19] that for some values of τ there exists an asymptotic relationship between the marginal redundancies and the KSE of a dynamical system, or entropy rates of a stationary stochastic process. In practice, using this result, Paluš proposed computing CGEn rather than estimating the exact entropy rates.[15,16] He defined CGEn as

$$\mathrm{CGEn} = \frac{\rho_{\tau_0}^{m+1}(X_{m+1}; \mathbf{X}_m) - \|\rho^{m+1}\|}{\|\rho^{m+1}\|} \; ; \qquad \|\rho^{m+1}\| = \frac{\sum_{\tau=\tau_0}^{\tau_{max}} \rho_{\tau}^{m+1}(X_{m+1}; \mathbf{X}_m)}{\tau_{max} - \tau_0}$$

and suggests setting τ_{max} to the value where $\tau \geq \tau_{max} : \rho_{\tau}^{m+1}(X_{m+1}; \mathbf{X}_m) \approx 0$ and also setting τ_0 to zero. On several EEG epochs we observed that $\rho_{\tau}^{m+1}(X_{m+1}; \mathbf{X}_m)$ (for different m and Q values) tends to zero for the value $\tau_{max} \approx 150$ and we therefore used this value in all our future analyses.

Quantization effect

The CEn, CCEn and CGEn algorithms assume prior knowledge of the probability distribution functions of the individual constructed embedding vectors. In our study these probabilities were estimated based on the computation of empirical probability distribution functions using the technique of histograms. Consider a time series with K distinct values. We can merge the values of time series $\{x(t)\}$ into Q categories (bins) for any Q in the range $1 \leq Q \leq K$. However, as we have already noted the number of bins increase as Q^m and when Q and m are increased without a corresponding increase in the number of data samples many empty bins occur. This may significantly decrease the accuracy of estimates of probability distribution functions. It has been shown that the number of data points N must be at least five times the number of bins[20] ; i.e. $N \geq 5Q^m$, to provide accurate estimates of m-dimensional entropies or marginal redundancies. Commonly, however, this length of time series is not available. In the case of depth of anesthesia monitoring only on-line or almost on-line systems have practical meaning. Hence an appropriate trade off between these requirements has to be found.

Quantization of the original data into Q levels can be performed in different ways. The basic aim is to divide the data into a predefined number of ranges Q. One obvious method is to allocate the variables to Q equally spaced segments. This procedure broadly preserves information about the distribution of individual variables, but may be misleading where extreme values occur. Also, in the case of the estimation of m-dimensional entropies or marginal redundancies we are not interested in the distribution of individual variables, but intervariable relations; i.e. the structure of the system. It was suggested[20] that the quantization of the variables into equally (or almost equally) populated bins - *equiquantization* - may be preferred. Equiquantization is more sensitive to the internal details of the distribution, embodies more information about it, and preserves more structural information than standard quantization into bins of equal length. Equiquantization generally provides a more 'dense' m-dimensional histogram in the sense of a lower number of zero bins. Note, that when equiquantization is applied during computation of CCEn we have to compute the estimate $\hat{H}(X_1)$ based on quantization into equal bins to match the correction term with that in the original proposal[14]; i.e. to preserve the actual distribution of the time series as much as possible.

Spectral Entropy

Spectral Entropy (SpEn) was introduced and defined as Shannon entropy computed over the normalized power spectral density function.[8] It is an entropic measure which can be used as

a measure of system complexity and is therefore included in this study. However, here the complexity of the system is understood as the number of different processes making up the time series rather than measure of complexity in the sense of regularity as understood in the case of previously described entropy rates measures.

Spectral Entropy (SpEn) is defined as

$$\mathrm{SpEn} = -\sum_{i=1}^{k} p(\omega_i)\ln p(\omega_i)$$

where $p(\omega_i)$ is the probability density function (pdf) value at frequency ω_i. The pdf is obtained by normalization of the power spectral density function given by Fourier Transform. High SpEn reflects a large number of processes, while lower values of SpEn indicate a smaller number of dominating processes creating the time series. Regular, periodic process with a single dominant frequency lead to zero values of SpEn whilst random white noise provide maximum values of SpEn due to a 'flat' power spectral density function.

Significant SpEn changes would be grossly visible in graphical displays of the EEG frequency spectrum, and would certainly have been described in early studies of the EEG effects of anesthesia. SpEn provides a single index value to quantify these changes. SpEn is a linear measure and its use to fully describe the dynamics of a stochastic process is limited to the case of stationary Gaussian processes. SpEn is therefore closely related to GPEn.

Statistical analysis

The entropy rates traces obtained, and the spectral based measures BIS, SEF95 and SpEn were charted against clinical and monitoring data to display an overall impression of each measure's ability to differentiate different depths of anesthesia. Correlation between traces was measured using Spearman's ranked correlation coefficients (SRC) - for both unsmoothed values, and values under a range of smoothing windows.

Two representative EEG series were selected for detailed evaluation and used to quantify the performance of each method. The first contained a period of moderate anesthetic depth (blood propofol concentration 6mg/L) followed by a period of lighter anesthesia (4mg/L). This EEG series was used to assess each measure's ability to discriminate light and moderate anesthetic depth. The initial trace was considered as a reference level and individual measures were plotted and investigated as difference from mean divided by standard deviation computed from the reference part. This provides a relative scale in units of standard deviation. During each period anesthesia and surgical stimulus were stable, and an ideal measure would contain little fluctuation. Discriminative power is therefore reflected by the difference between the means, expressed in units of reference standard deviation.

A second EEG series containing a period of steady anesthesia (blood propofol concentration 4mg/L) followed by discontinuation of anesthesia and clinical emergence was assessed. The discriminant ability of each method was assessed using units of baseline standard deviation as above. The onset of gagging, and spontaneous eye-opening are noted.

Results

Visually comparing measures, in the light of the clinical data, showed some level of correlation with the perceived depth of anesthesia in all cases. Figure 1 shows a typical plot of measures computed over the first 35min of a general anesthetic.

Selecting sub-parameters for each measure, and varying the averaging of the observed values provided a wide range of different settings for estimating correlation among the measures. However, generally we observed high correlation between the entropy rates measures (SRC > 0.8). We also observed high correlation between particular entropy rates measures when equiquantization and standard quantization was used (SRC > 0.9). Spectral measures (SE95, SpEn and GPEn) showed high correlation with nonlinear entropy rates measures (SRC 0.7 - 0.95). A slightly lower correlation was usually found between BIS and other measures (SRC 0.5 - 0.9). This may simply be due to poor synchronization between the recorded BIS values and measures computed from raw EEG data. As we do not have access to the formula for computing BIS we can not comment further on the level of correlation between BIS and other measures. SRC for all measures applied to the case depicted in Figure 1 are shown in Table 1.

The ability of each measure to discriminate stages of anesthesia was assessed. This was derived from two examples which provided traces suitable for quantifying this discriminative power.

Transition from moderate to light anesthesia

Each measure's ability to discriminate moderate (propofol level 6mg/L) and light (propofol level 4mg/L) anesthetic depth is shown in Figure 2 where the individual measures are averaged over 15sec intervals (BIS is internally averaged over the same time interval). The graph shows good separation of stages without significant overlapping of the values computed during the individual anesthesia periods. This data is presented as boxplots in Figures 3 and 4. These show the lower quartile, median, and upper quartile values and a whisker plot and are plotted in pairs computed over the first period (propofol 6mg/L) (left) and over second period started 4min after achieving a target level of propofol 4mg/L (right). First in Figure 3 the boxplots computed from unaveraged values are depicted (BIS is not included as the unaveraged values are not available from the BIS monitor). In all cases overlapping values are seen, however non-overlapping of the upper and lower quartiles indicates a relatively high discriminative power. The boxplots show that in this case entropy rates measures provide better discrimination between the two levels of anesthesia with CGEn performing best. Figure 4 shows the same boxplot using 15sec averaged values. Again as Figure 2 no overlaps between the values from different anesthesia stages indicate high discrimination of all the measures. Although BIS clearly discriminates the two stages we observed paradoxical behavior of BIS in this case and in Figure 5 we plotted BIS and Signal Quality Index (SQI)[c] as recorded from the monitor. The SQI changes approximately 6min after the beginning and this might cause a small change in BIS at that time. However the values of SQI are greater than 70% more than 3min prior to decreasing the target level of propofol from 6mg/L to 4mg/L (first vertical line). The sudden increase of BIS preceding this event therefore cannot be readily explained by a deterioration in signal quality.

[c]The values of SQI between 50%-100% indicate a good quality signal and hence reliable values of BIS. BIS values are not provided where SQI is less than 15% (Aspect Medical Systems Inc.).

Emergence from general anesthesia

Figure 6 shows the measures applied to emergence from anesthesia. Entropy rates increase progressively as anesthesia lightens. The increase in BIS is not as dramatic and shows a paradoxical decrease after eye-opening in response to speech. The spectral measures SE95 and GPEn clearly reflect anesthetic emergence.

Parameters and type of quantization selection

The parameters of all entropy rates measures were tuned using appropriate ranges and compared on the two examples investigated in detail. For measures computed from empirical probabilities (CEn, CCEn, CGEn), remembering the restriction to the minimum number of data points, we did not see significant changes in the discriminative power of the measures. Using the correction term in CCEn allowed us to increase the number of quantization levels Q up to 8 when an embedding dimension $m = 5$ or $m = 6$ was assumed, however the results were similar to the results provided by CEn using the lower values of Q and m parameters (typically $Q = 5, m = 3$). As predicted increasing the embedding dimension to 5 or 6 degraded the performance of CEn. In all cases equiquantization produced superior results to standard quantization, Figure 7.

Finally, in the case of ApEn, assuming a fixed number of data points, the performance of the measure is influenced by varying the sub-parameters grain r and embedding dimension m. As we have already noted in the case of approximately 1000 data points the embedding dimension should be kept low, and we observed that $m = 2$ or $m = 3$ provided good results. The grain parameter is usually proportional to the standard deviation (SD) of the investigated EEG epoch. We also observed that increasing r values resulted in smoother estimates, in agreement with the theoretical assumption of inherent noise filtering. High r values, however, may lead to the loss of important system information. We investigated this trade off in the case of transition from moderate to lighter anesthesia as described above. In Figure 8, where a range of r parameters are plotted against the averages of the ApEn values from the second stage (values computed over final 30 minutes were used) referenced to the mean value of the first stage. The corresponding variance of ApEn values over the first stage is also depicted. It can be readily seen that values around 0.5*SD may provide a good trade off between discriminative power and loss of detailed system information due to the selection of too high values of r.

Discussion

This study has confirmed entropy rate estimates as useful measures of depth of anesthesia, with individual entropy rate measures differing in their ability to identify levels of light anesthesia. These differences have been explored in some depth in order to identify the factors involved and their significance. The limited size of this study does not permit definite and detailed conclusions about the applicability of these techniques to the wide range of conditions encountered in clinical practice.

Physiological justification

During transition from the awake to the anesthetised state the EEG shows increasing influence from thalamic oscillators, and this synchronisation may provide physiological relevance for measuring EEG entropy rates. The function of these oscillators is unknown, but EEG regularity and predictability may change as a result of this process and entropy rates can be used to measure these changes. Entropy rates tend to zero for processes with periodic repetition and tend to high values for processes with aperiodic or random behavior.

One estimate of EEG entropy rates (ApEn) has been shown to decrease progressively as anesthesia deepens.[4] It has also been demonstrated that ApEn is low when measured on burst suppressed data - tempting speculation that entropy rates might be a unified measure of anesthetic depth.[5] The authors here considered whether other estimates of entropy rates might be more suited to measuring depth of anesthesia.

Entropy rates measures

Of the six entropic measures assessed, four had been previously applied to physiological data, but not to EEG data recorded during anesthesia (CEn, CCEn, CGEn, GPEn); the other two had been investigated individually as measures of anesthetic depth (ApEn, SpEn). All these measures can accurately assess entropy rates given large amounts of stationary and noise-free data, so correlation between them was expected, and confirmed. However the noisy and non-stationary nature of the EEG recorded in a typical operating theatre environment would inevitably reduce the accuracy of entropy rate measures.

Quantifying differences between entropy rates measures

Although differences between these measures were obvious on visual inspection of the traces, quantifying these differences is difficult since there is no benchmark measure that can be used as a comparator when the anesthetic technique is not standardized. Standardizing the anesthetic technique is unhelpful as many EEG measures have been shown to be agent-specific, and therefore validating measures using a single-agent technique can be misleading. Having visually noted consistent performance across inhalational and propofol anesthesia, we then quantified the differences between these measures using traces where the only varying factor was the blood propofol concentration. This is a circumstance where BIS is known to perform reliably, and would provide a useful comparison. All the traces studied reflected moderate to light depth of anesthesia - less than 3 percent showed burst-suppression.

CCEn incorporates a term specifically to correct for insufficient data. Several of these algorithms incorporate inherent filtering of noise when data is quantized: equiquantization consistently producing better results than traditional quantization. The varying performance

of these measures may therefore be accounted for by their suitability for assessing limited amounts of noisy data.

The non-stationary nature of the EEG time-series limits measurement to less than 15-30sec windows which may contain significant amounts of noise. This limits the data available for analysis and it would seem appropriate to use the correction term included in CCEn and to use equiquantization rather than standard quantization.

SpEn is an alternative measure quantifying those changes in the frequency domain which correspond to varying EEG data characteristics. We pointed out the close relation between SpEn and entropy rates computed from the periodogram - where a stationary Gaussian process is considered to generate the EEG. Assessing any non-linear component in the EEG would however require one of the other techniques studied here.

Correlation between entropy rates measures

Although individual entropy rates measures are derived from similar theoretical assumptions they have different numerical properties. A high level of correlation among entropy rates measures was observed suggesting similar characteristics of each measure. This correlation was seen across all the cases studied here, despite no standardization of anesthetic technique.

The detailed results reported here indicate that the entropy rates measures CCEn, CEn, CGEn and ApEn may provide better discrimination between two different stages of anesthesia than spectral measures (SpEn, SE95 and GPEn). This is not necessarily due to some nonlinear component of the EEG but may simply reflect better numerical properties of the measures. Other researchers have also reported a significant difference in discriminative power between GPEn and CGEn when used to assess the pre/ictal EEG.[16] However when EEG surrogate data[d] were used to compute CGEn a smaller difference was observed. Regarding the numerical properties of individual methods, it has been suggested[16] that the superior performance of nonlinear entropy rates measures is based on inherent filtration which can be identified in all these methods (quantization into Q levels in the case of CEn, CCEn and CGEn and the selection of grain parameter r in the case of ApEn).

This contrasts with the measures derived from frequency characteristics where noise in the original EEG trace is necessarily incorporated in the final estimates. Further confirmation of this source of error is that 'optimal' values for the r parameter in ApEn are higher (0.5*SD) than the recommended values 0.1-0.25*SD.[13] Our findings suggest that this loss of detailed system information may not matter when the objective is to discriminate between different anesthetic states.

Multiple component strategies

Multiple component strategies have been used. For example BIS uses a proprietary combination of three different measures (burst suppression ratio, relative alpha/beta ratio, and bicoherence between individual frequencies) optimised using multivariate regression on a large clinical database (Aspect Medical Systems Inc.). Combining spectral and the described entropy rates measures in this way may produce solutions which combine the relative merits of both these approaches.

Further research

[d]Surrogate data reflects linear properties of the original data (sample aurocorrelation, sample amplitude distribution), however, the nonlinear structure is destroyed by phase randomization.[21]

Simple spectral measures are known to provide useful information about anesthetic depth and are generally not sensitive to the values of the parameters used. This contrasts with entropy rate measures which present the user with the problem of selecting appropriate parameter values. For example, the most appropriate parameters for ApEn identified in this study differed from those suggested by Bruhn et. al.[4] Further and larger clinical studies will be required before definitive statements can be made about the optimum values of these parameters. This study suggests that in isolation entropy rate measures provide superior discrimination of anesthetic depth over spectral measures. It is still unknown how well entropy rates measures will generalize across widely differing anesthetic drug regimens.

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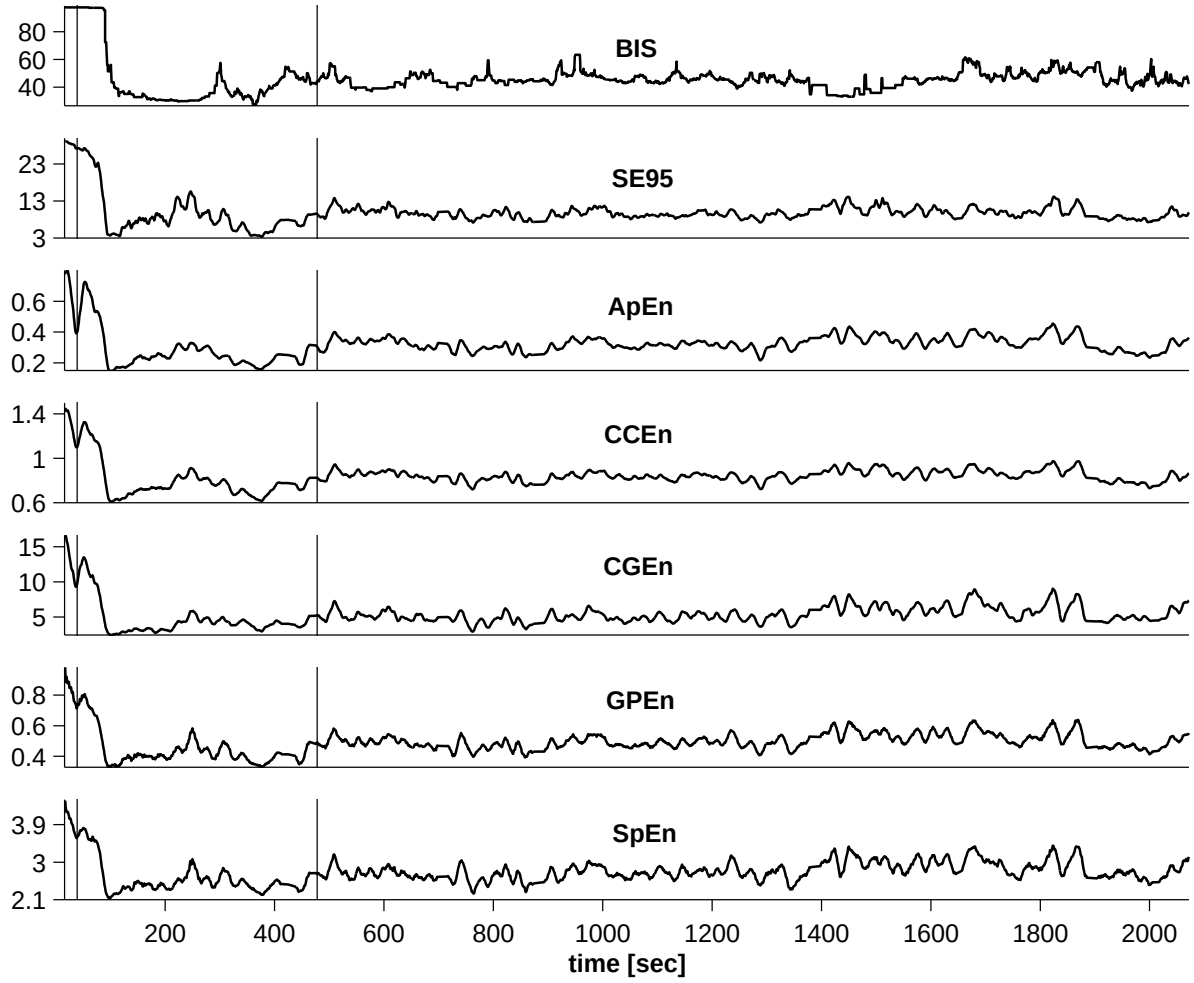

Figure 1: Traces of individual measure over approximately 35min covering induction and maintenance of general anesthesia. First vertical line: i.v. propofol 2mg/kg. From second vertical line to end: end-tidal desflurane concentration maintained between 3.4% and 4.5%. ApEn($r = 0.5\text{SD}, m = 2$), CCEn($Q = 6, m = 4$), CGEn($Q = 5, m = 3$).

Table 1: **Entropic and Spectral Measures: Spearman's ranked correlation coefficients**

	BIS	SE95	SpEn	ApEn	CCEn	eCCEn	CEn	eCEn	CGEn	eCGEn	GPEn
BIS	1	0.48	0.52	0.52	0.51	0.51	0.51	0.51	0.51	0.5	0.52
SE95	0.48	1	0.89	0.95	0.85	0.96	0.84	0.95	0.89	0.9	0.93
SpEn	0.52	0.89	1	0.93	0.82	0.93	0.82	0.93	0.97	0.97	0.98
ApEn	0.52	0.95	0.93	1	0.91	0.98	0.91	0.98	0.93	0.93	0.97
CCEn	0.51	0.85	0.82	0.91	1	0.86	1	0.86	0.82	0.82	0.86
eCCEn	0.51	0.96	0.93	0.98	0.86	1	0.86	1	0.93	0.95	0.96
CEn	0.51	0.84	0.82	0.91	1	0.86	1	0.86	0.82	0.82	0.86
eCEn	0.51	0.95	0.93	0.98	0.86	1	0.86	1	0.93	0.95	0.95
CGEn	0.51	0.89	0.97	0.93	0.82	0.93	0.82	0.93	1	0.98	0.97
eCGEn	0.5	0.9	0.97	0.93	0.82	0.95	0.82	0.95	0.98	1	0.96
GPEn	0.52	0.93	0.98	0.97	0.86	0.96	0.86	0.95	0.97	0.96	1

Spearman's ranked correlation coefficients computed from individual values averaged over 15sec intervals. EEG data recorded during general anesthesia. CGEn($Q = 5, m = 3$), CEn($Q = 5, m = 3$), CCEn($Q = 8, m = 5$), ApEn($r = 0.5\text{SD}, m = 2$). Measures prefixed with e were computed using equiquantization.

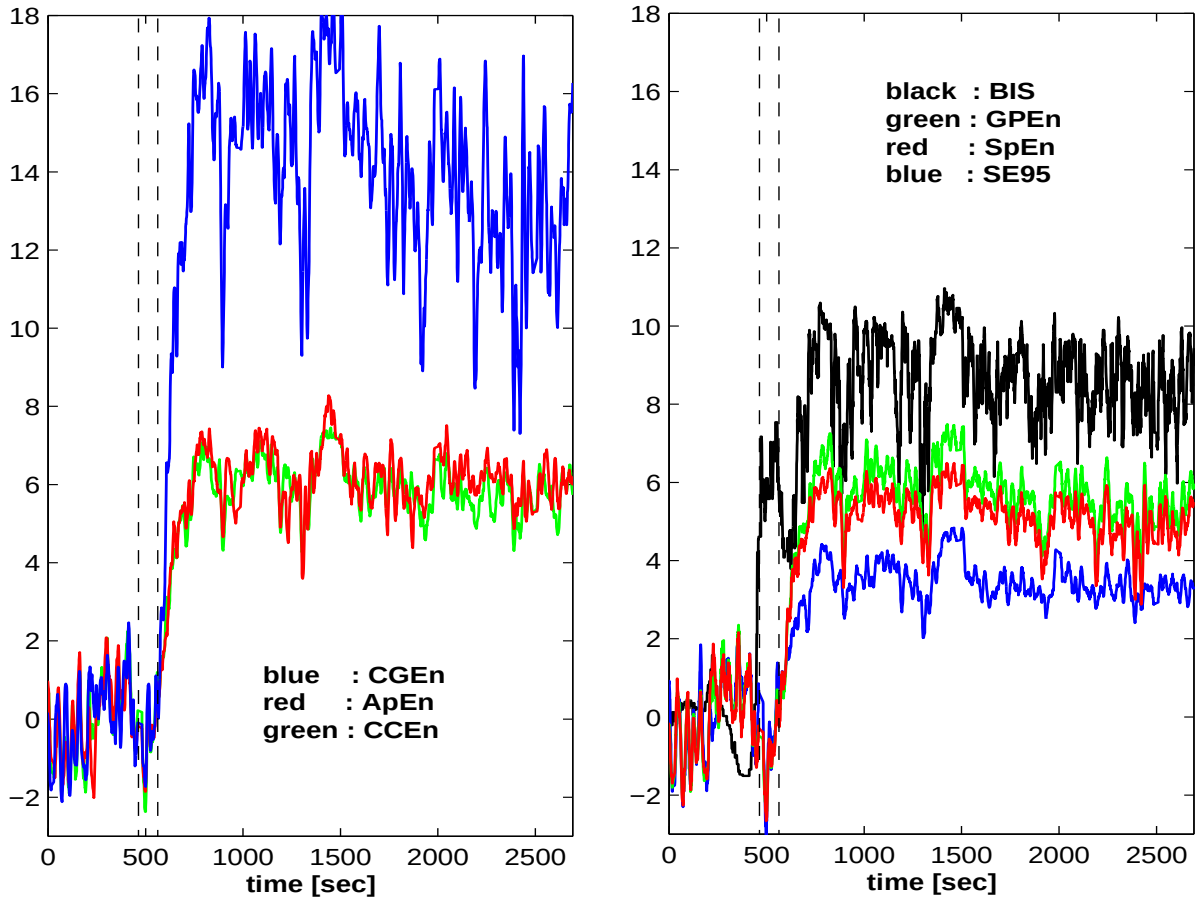

Figure 2: ApEn($r = 0.5\text{SD}, m = 3$), CCEn($Q = 6, m = 4$), CGEn($Q = 5, m = 3$), BIS, GPEn, SpEn and SE95 during the transition from moderate to light anesthesia. The measures are plotted in a relative scale reflecting the difference between the means during moderate and light anesthesia (propofol levels 6mg/L and 4mg/L respectively) in units of standard deviation (SD) computed during the stage of moderate anesthesia. Prior to the first vertical line the TCI propofol level was 6mg/L; the first vertical line shows where TCI propofol target was set to 4mg/L; the second vertical line shows the point when 4mg/L was achieved. The values of individual measures were averaged over 15sec intervals. Equiquantization was used in the case of CCEn and CGEn.

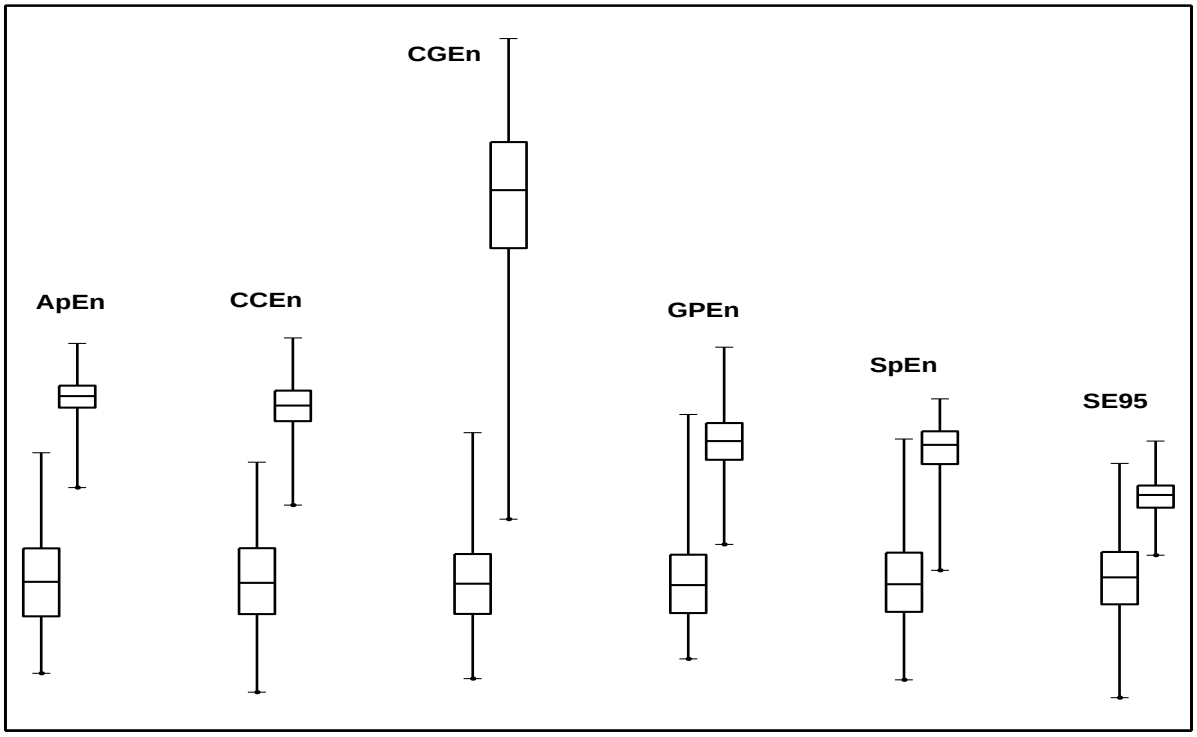

Figure 3: Boxplots of the data presented in Figure 2. The lefthand boxplot of each pair represents a TCI propofol level of 6mg/L, the righthand boxplot represents a TCI propofol level of 4mg/L. ApEn($r = 0.5\text{SD}, m = 3$), CCEn($Q = 6, m = 4$), CGEn($Q = 5, m = 3$). The values of individual measures were not averaged. Equiquantization was used in the case of CCEn and CGEn.

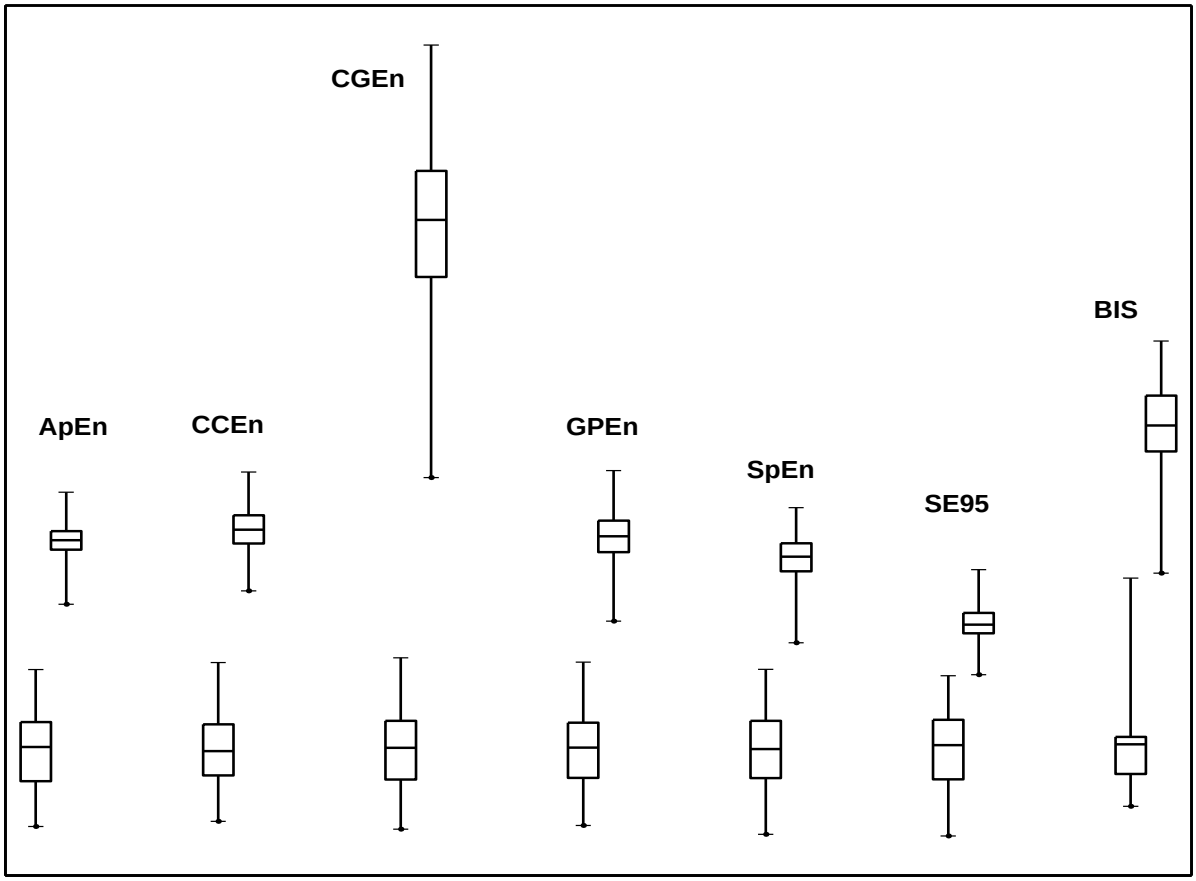

Figure 4: Boxplots of the data presented in Figure 2. The lefthand boxplot of each pair represents a TCI propofol level of 6mg/L, the righthand boxplot represents a TCI propofol level of 4mg/L. ApEn($r = 0.5\text{SD}, m = 3$), CCEn($Q = 6, m = 4$), CGEn($Q = 5, m = 3$). The values of individual measures were averaged over 15sec intervals. Equiquantization was used in the case of CCEn and CGEn.

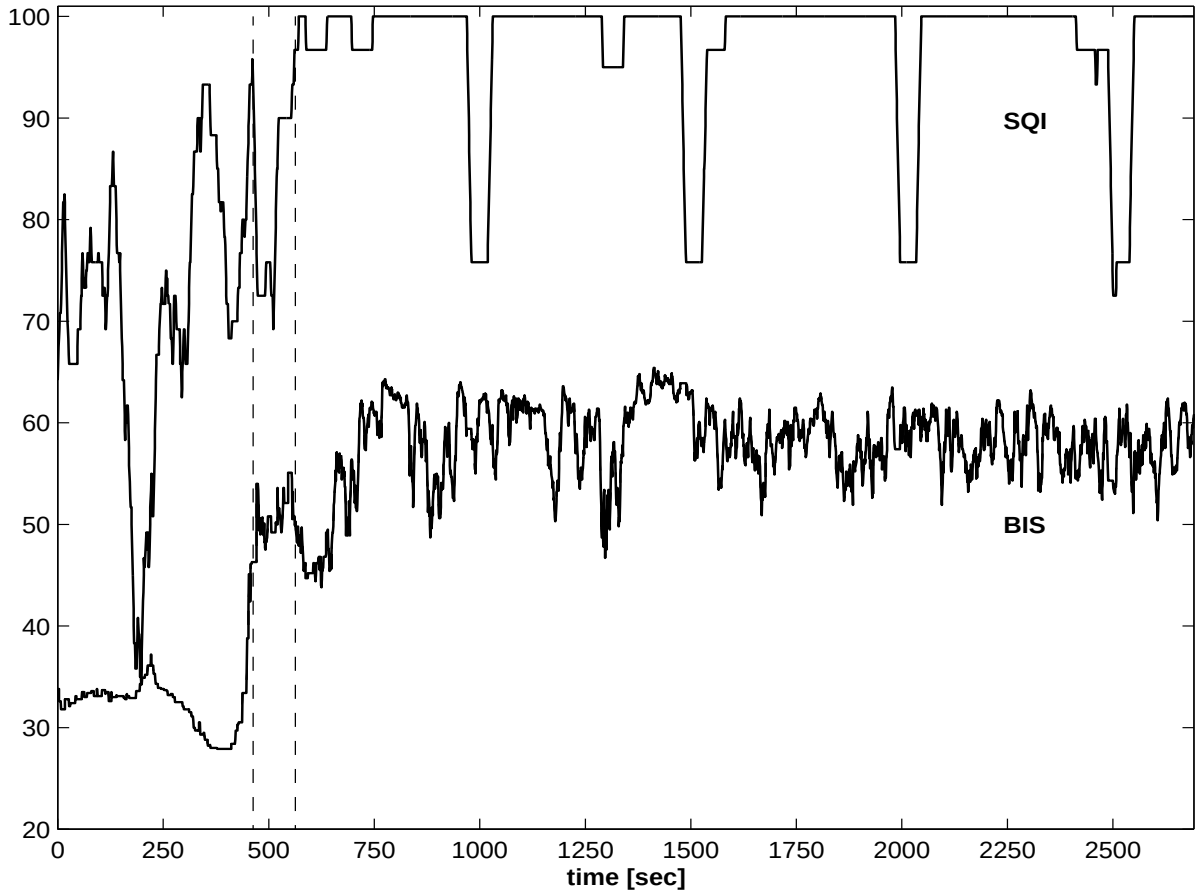

Figure 5: BIS (lower trace) and Signal Quality Index (upper trace) recorded during the period of transition from moderate to light anesthesia. Prior to the first vertical line the TCI propofol level was 6mg/L; the first vertical line shows where TCI propofol target was set to 4mg/L; the second vertical line shows the point when 4mg/L was achieved.

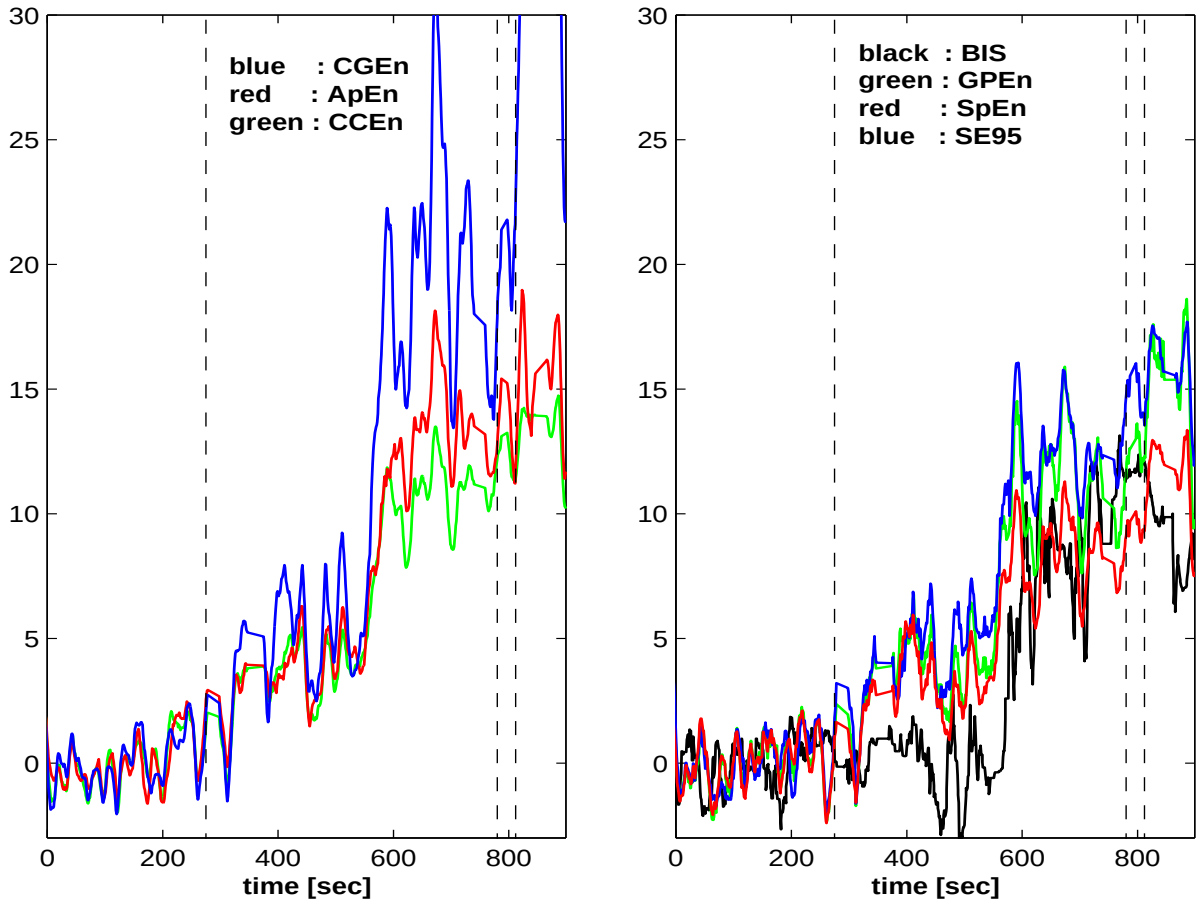

Figure 6: ApEn($r = 0.5$SD$, m = 2$), CCEn($Q = 6, m = 4$), CGEn($Q = 5, m = 3$), BIS, GPEn, SPEn and SE95 during emergence from general anesthesia. The measures are plotted in a relative scale established prior to the first vertical line. The baselines were set to the mean values, and the values then charted in units of standard deviation (SD). The first vertical line indicates when TCI propofol level of 4mg/L was set to 0mg/L. The second vertical line shows when the patient began to gag with the Laryngeal Mask Airway in situ, and the third line denotes eye-opening in response to speech. The values of individual measures were averaged over 15sec intervals. Equiquantization was used in the case of CCEn and CGEn.

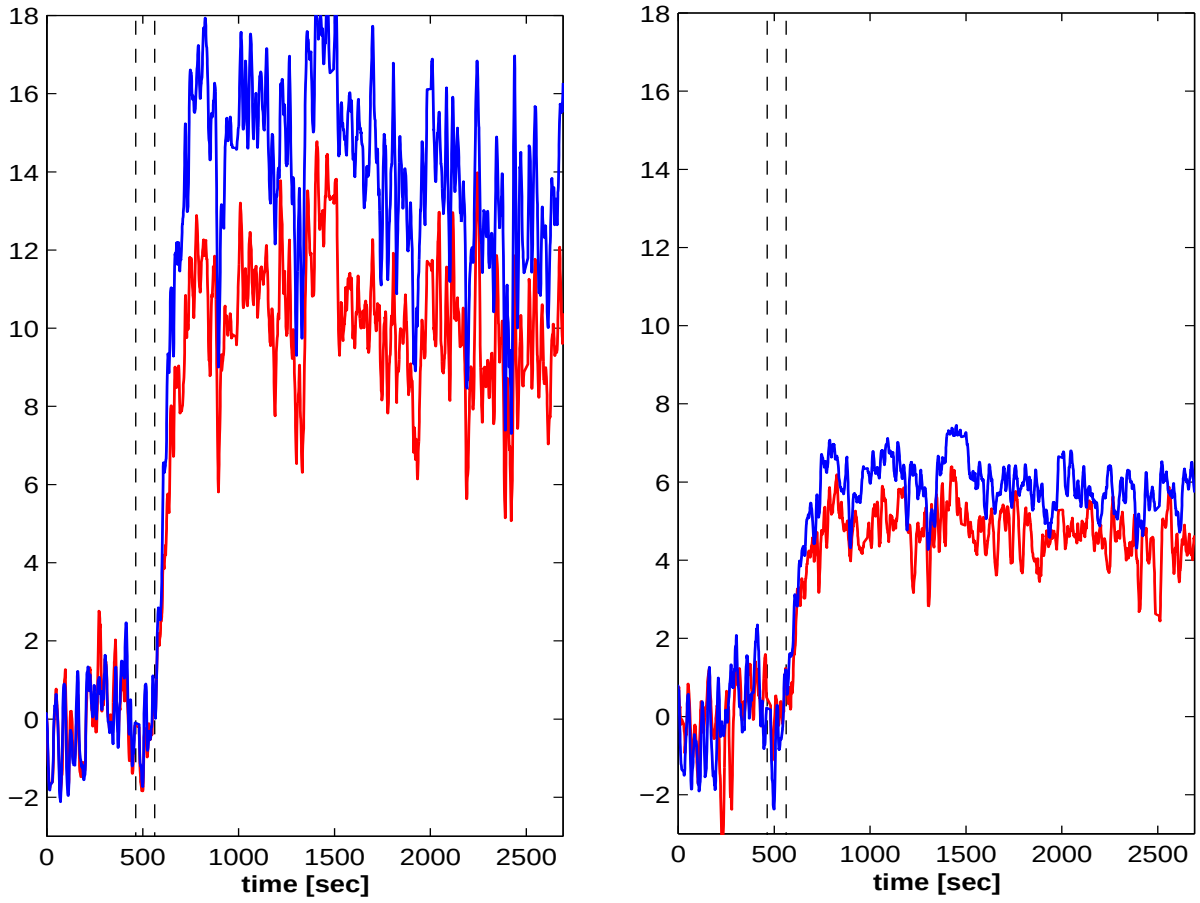

Figure 7: A comparison of two quantization methods - equiquantization (blue) and standard quantization (red) - used to compute CGEn($Q = 5, m = 3$) (left) and CCEn($Q = 6, m = 4$) (right). The graphs show the transition from moderate to light anesthesia. For the description of the plotted values and the vertical lines see Figure 2.

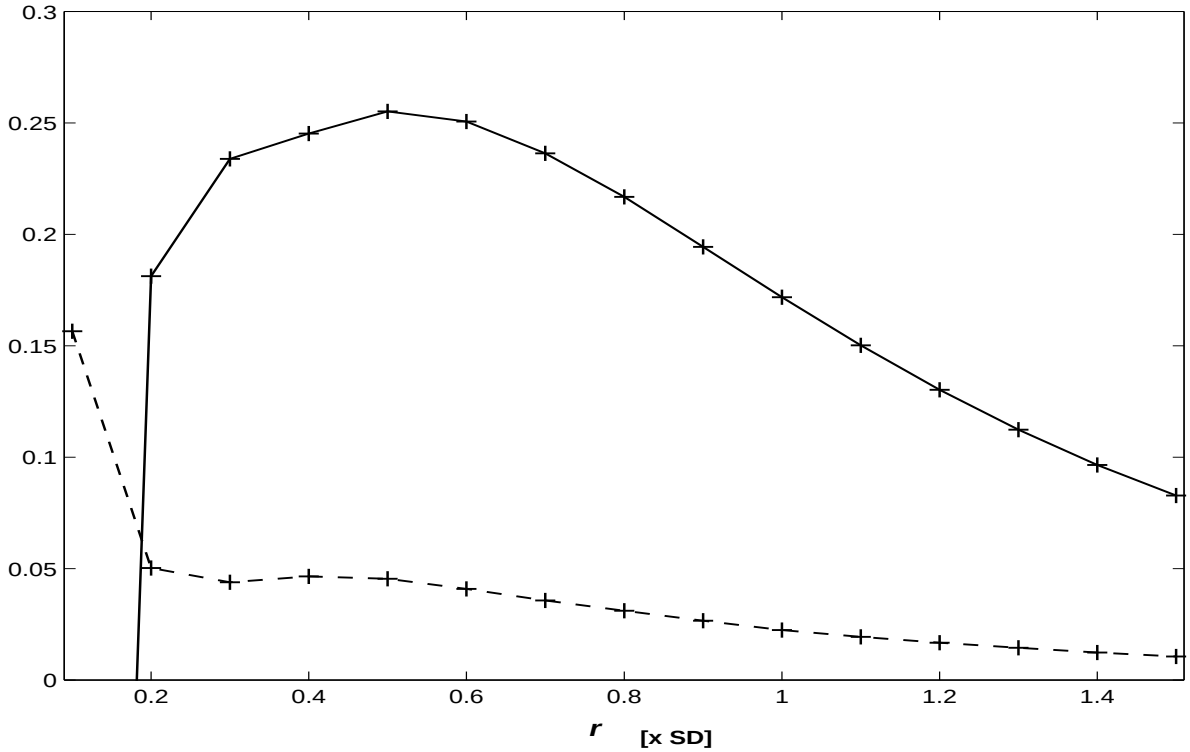

Figure 8: ApEn performance showing the effects of varying the grain parameter r. Source data was from the transition between moderate and light anesthesia (as Figure 2). The solid line shows the difference between the means for the two stages of anesthesia (TCI propofol 6mg/L; and 4mg/L). Following 6 minutes for equillibration, 30 minutes of data were used to compute stage 2 mean values. The dashed line shows the standard deviation measured during the baseline stage (TCI propofol 6mg/L).