Permutation entropy of the electroencephalogram: a measure of anaesthetic drug effect

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Background. It would be useful to have an open-source electroencephalographic (EEG) index of γ-amino-butyric acid (GABA)-ergic anaesthetic drug effect that is resistant to eye-blink artifact, responds rapidly to changes in EEG pattern, and can be linked to underlying neurophysiological and neuropharmacological mechanisms that control the conscious state.

Methods. The EEG waveform can be described as a sequence of ordinal patterns. The permutation entropy (PE) describes the relative occurrence of each of these patterns. It is high (≈1.0) when the signal has predominantly high frequencies and low (≈0.4) when the signal consists of only low frequencies. The response of the PE to various computer-generated EEG-like waveforms was assessed. A composite PE index (CPEI) was developed, which was the sum of two simple PEs and included a small measurement-noise threshold (0.5 μV). We also applied the CPEI to two small pilot EEG data sets from patients receiving sevoflurane (n=21) or propofol (n=9) anaesthesia.

Results. With minimal pre-processing or artifact rejection, the CPEI reliably tracked the anaesthetic-related EEG changes, namely loss of high frequencies, spindle-like waves, and delta waves. Using NONMEM, it was possible to construct adequate pharmacokinetic–pharmacodynamic models from the data. The CPEI was comparable with models derived using the bispectral index \( R^2 = 0.88 \) (0.08) vs CPEI \( R^2 = 0.91 \) (0.06) for the propofol data and M-entropy indices \( M\text{-entropy} R^2 = 0.91 \) (0.06) vs CPEI \( R^2 = 0.87 \) (0.09) for the sevoflurane data.

Conclusions. PE of the EEG shows promise as a simple measure of GABAergic anaesthetic drug effect.

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There already exist many ‘depth-of-anaesthesia’ encephalographic (EEG) measures, and we do not want to add yet another to this collection. However, there is a need for the development of an ‘open source’ EEG index for use in quantifying the hypnotic brain effects of general anaesthetic drugs. This index could be used in pharmacokinetic–pharmacodynamic (PK–PD) modelling. Problems with existing EEG measures of central nervous system drug action include: (i) sensitivity to blink and other artifacts in the awake subject, (ii) the fact that commercially available EEG indices have undisclosed parts of their algorithms that make interpretation of drug effects unclear, and (iii) there are uncertain and variable time delays as part of the data smoothing process in the algorithms for commercial EEG indices of anaesthetic depth. This makes these indices unreliable when studying rapid drug effects. A good measure of anaesthetic drug effect should therefore be: freely available and easy to use, robust to wakefulness artifacts, and able to be consistently related to the known neurophysiological changes that occur during γ-amino-butyric acid (GABA)-ergic anaesthetic drug administration. In the first instance, we attempted to produce and understand an EEG index that measures hypnotic drug effect. Because of the additional complexities introduced by the estimation and measurement of the activity of different arousal systems, all data in this paper were obtained without the confounding effects of surgical stimulation. The effects of surgical stimulation on the index will be the topic of subsequent research.

Enhancement of GABA activity is a prominent feature in the action of most commonly used general
anaesthetic drugs.\textsuperscript{1–3} We will therefore confine our methods to measuring EEG effects induced by the so-called ‘GABAergic’ drugs, such as propofol and volatile general anaesthetic agents. We acknowledge that these drugs (especially volatile anaesthetic agents) have other known and unknown neurodepressant mechanisms of action, but we seek to measure the predominant EEG effects that are, to a large degree, common to all members of this group of agents.\textsuperscript{1, 2} To be a plausible index of general anaesthetic effect, it is essential that the proposed EEG index be directly related to EEG changes that are known to be linked with underlying neurophysiological and neuropharmacological mechanisms that control the conscious state. The neurophysiological mechanisms underlying these changes are quite well studied\textsuperscript{4, 5} and have some commonality with natural sleep processes.\textsuperscript{6} There are three main components of anaesthetic-induced EEG changes, which must be detectable by any proposed measure of GABAergic anaesthetic drug effect. First, the EEG loses power in the high-frequency range, which is associated with a marked decrease in the mean firing rate in the cortex.\textsuperscript{3, 7} Secondly, large waxing and waning ‘spindle-like’ waves appear. The frequency of these waves is related to anaesthetic drug concentration. At low anaesthetic concentrations, their frequency is in the beta range (about 20 Hz), but the frequency slows to about 8 Hz as the drug concentration increases. The importance of this pattern is that once the frequency lies below 12 Hz, it indicates thalamic hyperpolarization, bursting modes of neuronal firing, and the presence of increasing arousal blockade.\textsuperscript{8–10} The spindle waves may or may not occur with large amplitude delta and sub-delta waves. Finally, deep anaesthesia gives rise to the burst suppression pattern.\textsuperscript{11}

In this paper, we present the methodology of using the permutation entropy (PE) of the EEG as a simple, yet robust, measure of GABAergic drug effect that fulfils many of the criteria for a useful indicator of hypnotic effect in the brain. Like the Lempel–Ziv complexity, the PE is an example of the application of an ordinal approach to the extraction of information from the EEG signal. We first describe in detail how the PE is calculated, and how it responds to various synthetic ‘pseudo-EEG’ signals. We then apply it to two small clinical EEG data sets, as examples to demonstrate its resistance to low-frequency blink artifacts and relationship to the neurophysiological effects induced by GABAergic drugs.

**Methods**

**Ordinal statistics and the calculation of the PE**

With the possible exception of zero-crossing rate, most EEG indices use the EEG signal as a continuously variable signal (to the limits of the measuring equipment). In contrast, ordinal statistics rank the data from smallest to largest, and then compare the rankings. Therefore, the use of ordinal descriptions of EEG may have the advantage of being resistant to large artifacts that occur with low frequencies. In this article, we will refer to the elemental patterns that are extracted from the EEG signal as ‘motifs’ (see Fig. 1 for graphical explanation). The EEG signal can therefore be considered to consist of a sequence of ordinal motifs.

The use of PE to quantify EEG changes in seizures was originally proposed by Bandt and Pompe,\textsuperscript{12} and this work has been further developed by Cao and colleagues.\textsuperscript{13} The algorithm of the calculation of the PE is quite simple and is depicted diagrammatically in Figure 1 as follows:

1. fragment the continuous EEG signal (dotted line in the lower diagram of Fig. 1), into a sequence of motifs (some examples are shown in grey);
2. identify each motif as belonging to one of the six possible types (as shown in the middle row of diagrams in Fig. 1)—according to their shape [we describe the six types as two varieties each of ‘slopes’ (motifs #2 and #5 in Fig. 1), ‘peaks’ (motifs #1 and #6), and ‘troughs’ (motifs #3 and #4)];
3. count the number of motifs of each of the six categories, to obtain the probability of occurrence of each motif in the signal ($p_i$) (upper diagram in Fig. 1);
4. calculate the PE of the resultant normalized probability distribution of the motifs, using the standard Shannon uncertainty formula:

$$PE = - \frac{\sum p_i \times \ln(p_i)}{\ln (\text{number of motifs})}$$

Matlab code for the calculation of these quantities is given in the Appendix. Thus, the PE is a way of quantifying the relative occurrence of the different motifs. Like other entropies, the PE is simply a measure of the ‘spread-outness’, or ‘flatness’, or ‘uncertainty’ in the frequency distribution. When the EEG signal is dominated by high frequencies, there will be almost equal numbers of each species of motif in each EEG segment analysed. The properly normalized entropy is maximal (PE=1.0), if there is an equal distribution of motifs between each of the six patterns. Conversely, when the signal consists of slow delta waves, there will be relatively more of the ‘slope’ motifs (motifs #2 and #5 in Fig. 1), and fewer of the other ‘peak’ and ‘trough’ motifs, and the entropy decreases. The PE of a signal consisting of a single motif (such as one very long ‘up-slope’) is zero. However, the effective realistic minimum value of the PE is about 0.4. It is important to note that the PE is very different from the spectral entropy in its frequency response. The PE tends to decrease as the frequency decreases (Fig. 2), whereas the value of the spectral entropy is completely independent of frequency per se, but only measures the sharpness of the frequency peak. To test the responses of the various PEs to variations in frequency, artificial ‘pseudo-EEG’ signals...
were generated, using a Matlab computer program which allowed known amounts of white noise to be added to various pure sine wave frequencies (Fig. 2).

**Parameters and ties**

The PE has two predefined parameters. (i) The ‘order’ of the PE is the number of data points that are included in each motif. We restricted our study to include only short motifs of just three points (order=3). Exploratory data analysis suggested that the use of longer motifs did not contribute to a better index of depth of anaesthesia. (ii) The ‘lag’ (\(\tau\)) of the PE is the number of sample points spanned by each section of the motif. In the lower diagram in Figure 1, the dark grey motifs are of lag \(\tau=1\), because they are made up of adjacent data points. The longer light grey motif is of lag \(\tau=2\), because the length of each section of the motif is two data points—not one as in the case of lag \(\tau=1\). The importance of the lag is that it gives the resultant PE different frequency characteristics (Fig. 2). Most of the anaesthetic-related information in the EEG can be extracted using a lag (\(\tau=1\)) of one sample step (assuming a sampling frequency of 100 or 128 s\(^{-1}\)). However, as described below, the inclusion of lag (\(\tau=2\)) helped differentiate deeper planes of anaesthesia, and resulted in a better PK–PD modelling. Thus in our data, we were using effective lags of 10 or 7.8 ms (one sample step) and 20 or 15.6 ms (two sample steps).

It is possible that two (or indeed all three) of the data points in a motif may have the same measured voltage because of the limited resolution of the analogue–digital conversion, and therefore are not able to be ranked. Although this occurrence may seem to be very unlikely, it raises the important issue of how to deal sensibly with
In this paper, we have chosen the value of 0.5 which, most of the ‘signal’ is thought to consist of noise. We can rarily assign a third parameter—the threshold level, below present during deep anaesthesia. One solution is to arbitra-

Appropriate fluctuations in the signal—and its value typically increases. Unfortunately, these fluctuations are made up largely of various types of measurement noise, and are not reflecting drug actions on the cerebral cortex. This is most apparent when the burst suppression EEG pattern is

In summary, the PE quantifies the probability distribution of motifs present in the signal, and is determined both by the dominant frequency in the EEG signal and by the bandwidth. Because of the ordinal (counting) nature of the PE, this is dominated by the presence of higher EEG frequencies, even if they have quite small amplitudes.

Application to real EEG signals

To be useful, a putative EEG parameter must be able to capture information specific to the effects of general anaesthetic drugs. To capture the transition from the awake state to the anaesthetized state, the EEG parameter must be reasonably resistant to the huge blink and eye-motion artifacts that are almost always present in the

Threshold level as a compromise between losing the artifact resistance of the PE vs the inability of the PE to decrease appropriately in response to the development of the burst suppression pattern in the EEG. The entropy of these ‘discarded’ motifs is almost always very close to 1, indicating that we are discarding something similar to white noise. We have termed the resultant PE statistic, the PEtie.

Thus there exists a family of PEs that are defined by the three parameters:

(i) order (motif pattern consists of three points),
(ii) lag (τ=1 or τ=2 data points within each part of the motif), and
(iii) noise threshold (tie <0.5 μV).

Which is the best PE to use in measuring anaesthetic drug effect?

To combine the ability of the PEtie<0.5, τ=1 to distinguish periods of delta waves, with the ability of the PEtie<0.5, τ=2 index to distinguish mid-frequency oscillations from very slow delta oscillation, we made a composite EEG index of anaesthetic drug effect called the ‘composite PE index’ (CPEI). This index takes advantage of the natural summation of entropies, and simply sums the components of the (tie<0.5 μV, τ=2) and (tie<0.5 μV, τ=1) PEs.

\[
\text{CPEI} = -\sum p_i \ln (p_i), \text{tie}<0.5, \tau=1 + \sum p_i \ln (p_i), \text{tie}<0.5, \tau=2 / \ln (49)
\]

To obtain the correct normalization denominator, we need to include six motifs for each of the PEi,s and one each for the PEtie,s, making a total of 49 (7×7). The CPEI is the index used in subsequent PK–PD modelling because we found it to give better model fitting, when compared with the use of the raw PEs. The Matlab code is presented in the Appendix. (A discussion of measures of complexity, and examples of various matlab codes can be found at http://www.nbb.cornell.edu/neurobio/land/PROJECTS/Complexity/index.html)

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To be useful, a putative EEG parameter must be able to capture information specific to the effects of general anaesthetic drugs. To capture the transition from the awake state to the anaesthetized state, the EEG parameter must be reasonably resistant to the huge blink and eye-motion artifacts that are almost always present in the
prefrontal EEG of the awake patient before an operation. As a preliminary step, we applied the PE to a databank of EEG records that have been collected as part of previous studies on the effects of sevoflurane (n=21) and propofol (n=9) on the EEG. The details of the experimental protocols can be obtained from these papers. It must be noted that the only pre-processing and artifact rejection applied to the signal was: to reject EEG segments with a maximum amplitude of >500 μV and to remove frequencies above 45 Hz (ninth-order Butterworth filter). Less than 5% segments were rejected. The prefrontal EEG was digitized at either 100 s⁻¹ (sevoflurane study) or 128 s⁻¹ (propofol study), and 12 bit resolution, and sequential 30 s segments analysed (updated every 5 s). We used these long (30 s) EEG segments in order to obtain meaningful comparison with the commercial indices, which themselves have a smoothing delay in the order of 30 s.

In brief, the first study involved the induction of inhalation sevoflurane (3% for 2 min then 7%) anaesthesia in adult (aged 18–63 yr, ASA I–II) patients to achieve a target state entropy index (M-entropy S/5 TM Module, GE Healthcare, Helsinki, Finland) of 20. During this period, the raw EEG data were recorded using the S/5 TM Module. Electrode skin impedance was checked to be <7.5 kOhm. After 2 min of the state entropy index <20, the sevoflurane administration was stopped and the anaesthesia allowed to partially wear off until a state entropy index value of 70 was reached. None of the patients was responsive to verbal command at this point. The anaesthesia was then adjusted according to clinical requirements and surgery commenced. Originally, the aim of second study was to determine the effects of deep sedative doses of propofol on auditory consciousness and memory. Adult subjects were given a slow i.v. infusion of 10 mg ml⁻¹ propofol (150 ml h⁻¹) until they dropped a 50 ml syringe full of water, and were checked to be unresponsive to verbal command—at which point, the propofol infusion was stopped and the subject allowed to awaken fully. The scalp EEG data were recorded from silver/silver-chloride electrodes in a bipolar (Fp1–F7, earth–FpZ) configuration (electrode impedance <5 kOhm). The bispectral index (BIS, version 3.12, Aspect Medical Systems, Newton, MA, USA) was recorded concurrently, and this study allowed direct comparison of the performance of the CPEI with the BIS. Goodness-of-fit was quantified using the coefficient of determination (R²).

**PK–PD modelling**

The anaesthetic concentration–effect data were analysed with the pharmacodynamic model as described by Olofsen and Dahan, and model parameter values were estimated with NONMEM version V, level 1.1 (a data analysis program for non-linear mixed-effects modelling). The pharmacodynamic model consisted of a hypothetical effect compartment combined with a sigmoid E_max model described by the equations:

\[
\frac{dC_e(t)}{dt} = -k_{e0} \times |C(t) - C_e(t)|
\]

\[
E(t) = E_{\text{max}} + (E_{\text{min}} - E_{\text{max}}) \times \frac{C_e(t)}{C_{50}^2(t) + IC_{50}^{-2}}
\]

where C is end-tidal sevoflurane concentration or blood propofol concentration; k_e0 the rate constant determining the speed of equilibrium (we estimated the effect-site equilibration half-time t_1/2_k_e0); C_e the effect-site concentration; E the effect measure (CPEI, M-entropy, or BIS); E_{\text{max}} and E_{\text{min}} are the maximal and minimal values of E; IC_{50} is the concentration that places E halfway between E_{\text{min}} and E_{\text{max}}; and \gamma the steepness parameter. In the mixed-effects analysis, all parameters were assumed to be lognormally distributed, and that residual error was normally distributed. The blood propofol concentrations were not measured but assumed to be adequately described by the three-compartment model with parameters by Gepts and colleagues.

**Comparison with other EEG indices**

As a pilot investigation, we compared the PE calculated in the sevoflurane and propofol studies with other EEG indices measured/calculated in these studies: (i) two commercially available indices, the BIS and the M-entropy (response entropy), and (ii) two open-source indices, the approximate entropy (embedding dimension m=2, lag=2) and the crude spectral entropy (1–47 Hz). However, because of the awake eye-blink artifacts, it was not feasible to obtain reasonable convergence of the NONMEM modelling of the approximate entropy and crude spectral entropy.

**Results**

**Frequency responses of PE**

Figure 2a shows how the PE_{\text{dose=0, } t=1} and the PE_{\text{dose=0, } t=2} decrease with decreasing frequency of sine waves (1–43 Hz). The frequency dependence of PE_{t=2} is markedly different, and more complex, than that of PE_{t=1}. The effect of adding a small amount of white noise to the signal (amplitudes 0.1 and 0.02 of the oscillation amplitude) is shown in Figure 2n. This is the reason why the PE is extremely resistant to low-frequency blink artifacts. The slow blink and eye-movement artifacts (about 1–2 Hz) are dominated by the ‘white noise-like’ high-frequency awake EEG/EMG. The effect of adding a second fixed frequency (12 Hz) sine wave oscillation is shown in Figure 2c. It can be seen that the PE of the combined signal measures that of the higher frequency of the combination.
Application to real EEG signals

Figure 3 shows an example of the EEG changes that occur during the sevoflurane induction. The changes are most economically presented in the form of a spectrogram. The colours clearly show the alterations in frequency content of the EEG that were induced by the increasing, and then decreasing, concentrations of sevoflurane. At 16 min, the patient was given 100 mg i.v. propofol, and the EEG abruptly changes to a burst suppression pattern. In this record can be found good examples of the four main EEG patterns associated with GABAergic anaesthesia: (i) artifact-ridden awake EEG, (ii) mixed slower frequencies including sleep spindle-like activity on top of slower frequencies, (iii) pure high-amplitude delta waves, and (iv) burst suppression patterns. In Figure 4, we use examples of these four patterns to illustrate how the various PE indices can be related to the anaesthetic drug effects.

The awake EEG and blink artifact resistance

The top waveform of Figure 4 is part of an EEG waveform from early in the record. It helps us to understand the extreme resistance of the PE to common blink and eye-movement artifact. This is the EEG of a slightly anxious person, who is in an active cognitive state. In the awake patient, the high frequencies present in the underlying EEG and EMG signals dominate the PE, but are almost completely unaffected by the huge, but slow, blinks. This is the main advantage of the PE over the approximate entropy.
Indeed, because of the eye-blink artifacts in the awake EEG signal, it was not feasible to obtain sensible modelling, and hence comparison, with the older open-source indices—approximate entropy, raw spectral entropy, and spectral edge. The resistance to blinks depends on the relative slopes of the slow waves and the fast waves. If the slow waves are steep enough, they will convert the predominance of four ‘peaks’ patterns to two ‘slope’ patterns, and hence cause a falsely low PE value. If the slow waves are not steep enough, the high-frequency EEG/EMG pattern will predominate and hence maintain a high PE value.

Unconsciousness and signs of adequate arousal blockade

Taken as a whole, all the different PE indices decreased as the sevoflurane concentration increased, the patient lost consciousness, and the EEG lost high frequencies and took on a delta wave pattern. Consistent with the results shown in Figure 2, the decrease was least in the PE \( t=2 \) index. As the brain sevoflurane concentration recovered in the second half of the recording, the patient’s EEG showed some episodic mid-frequency spindle-like oscillations superimposed on the slow delta waves. Their
frequency correlated well with the sevoflurane concentration, and increased from about 8 Hz to about 15 Hz as the drug effect wore off. This frequency shift was tracked reliably by the PE\(_{r=2}\), in contrast to the PE\(_{r=1}\) which hardly changed. As predicted by the simulated pseudo-EEG (Fig. 2), the gap between the PE\(_{r=2}\) and the PE\(_{r=1}\) acts as an indicator of this mixed spindle-like EEG pattern.

**Burst suppression pattern**

The difference in response induced by adding a noise threshold to the calculation of the PE was most marked in the burst suppression segment (e.g. see lower diagram of Fig. 4). With noise threshold set at zero, both the PE\(_{r=1}\) and the PE\(_{r=2}\) increased to almost 1. Because they were almost invariant to the absolute magnitude of the signal, both indices were dominated by the low-amplitude, high-frequency measurement noise, which becomes apparent during the periods of cortical silence. In contrast, during periods of cortical silence, the inclusion of a noise threshold of 0.5–1.0 \(\mu \text{V}\) put almost all of the motifs into the seventh ‘tied’ category and the resultant PE decreased markedly. However, because we did not have many episodes of burst suppression in our EEG data, the transition to burst suppression needs to be investigated in more detail in further studies.

**Comparison of CPEI with BIS and M-entropy**

The frequent occurrence of blink artifacts precluded the construction of PK–PD models from spectral entropy and approximate entropy. See for an example the effect of blink artifacts on approximate entropy (Fig. 3). In contrast, the excellent artifact rejection algorithms of the commercial BIS and M-entropy monitors enabled a meaningful comparison with the PE.

**Comparison of CPEI with M-entropy: PK–PD analysis of sevoflurane data**

Using the NONMEM package, a standard inverse sigmoid \(E_{max}\) PK–PD model was fitted to the CPEI and M-entropy obtained from the patients in the sevoflurane study. Best, median, and worst examples of the fitted model (line) vs experimental observations (dots) are shown in Figure 5. The [mean (sd)] \(R^2\) for the CPEI model was 0.87 (0.09) and for the M-entropy model was 0.91 (0.06) (Table 1).

**Comparison of CPEI with BIS: PK–PD analysis of propofol data**

Examples of best, worst, and median PK–PD fitting for the CPEI and BIS are shown in Figure 6. The mean (sd) values at the point of loss of responsiveness was 75 (13) for the BIS and 0.80 (0.06) for the CPEI. Although serum propofol samples were not taken, we fitted a combined PK–PD drug effect model to the second group of subjects using the Jepts and colleagues\(^{18}\) three-compartment pharmacokinetic parameter set for propofol. The [mean (sd)] \(R^2\) for the CPEI model was 0.91 (0.06) and for the BIS model was 0.88 (0.08). The overall linear correlation coefficient between the BIS and the CPEI raw values was 0.86. A comparison of the PK–PD parameters for the BIS vs the CPEI is shown in Table 2.

**Discussion**

Ordinal measures of EEG patterns have very different characteristics to traditional methods that use the raw EEG signal. The conceptual difference may be summed up in the phrases: not ‘how large is the pattern?’ but rather ‘how many patterns exist?’. Our preliminary investigations indicate that the CPEI shows promise as a practical EEG measure of GABAergic hypnotic drug effect. It appropriately tracks the qualitative assessment of the EEG pattern from: awake, to sedated/lightly anaesthetized, and to deeply anaesthetized. It requires minimal pre-processing and is very resistant to blink artifacts. It can produce acceptable PK–PD models. It is comparable with the BIS in the spread of values between patients at the point of loss-of-consciousness, and the time-course of induction and recovery from an i.v. propofol infusion. It is computationally efficient and does not require long segments of EEG data. During the preparation of this manuscript, we became aware of simultaneous parallel work using the PE in anaesthesia presented in abstract form by Jordan and colleagues.\(^{19,20}\) They also suggested that the use of the PE helped to differentiate deep anaesthesia from sedation. We hope that our pharmacologically oriented approach will complement their level-of-consciousness studies.

This study was not designed as a comprehensive validation of the use of PE as a measure of ‘depth’ of clinical anaesthesia or for the prevention of intraoperative recall; but rather to understand the inner workings of this index, and to see whether this index correlated with EEG signs of GABAergic drug effect, and hence could be used to construct reasonable PK–PD models for this group of drugs. Careful understanding of the strengths and weaknesses of the index is a necessary preliminary to more widespread heuristic trials of its clinical usefulness. Like all techniques, it is used best if its limitations are well understood. We also have not attempted to produce any hardware specifically for the use of the CPEI; but instead have purposefully tested the algorithm using raw EEG data collected from commonly available commercial EEG monitors. These monitors have largely solved the significant technical problems involved in the collection of EEG data in the (very challenging) noisy intraoperative environment.

**PK–PD modelling**

A wide variety of other EEG indices have been used in PK–PD modelling.\(^{14, 21–27}\) At the present time, the
most commonly used are the commercial ones (BIS, M-entropy, and Narcotrend) or other open-source methods such as the 95% spectral edge and approximate entropy. As described earlier, all these methods have limitations. The open-source indices require extensive and sophisticated artifact handling to achieve acceptable results, and this always runs the risk of distorting the EEG signal. The resistance to blink artifacts (and speed of computation) is a big advantage of the PE over the approximate entropy, producing stable values in the pre- and early induction period. Indeed, it was not feasible to fit the approximate entropy to the data because of the artificially low values caused by blink artifacts during the awake state (Fig. 3). As for all EEG monitors, the CPEI is effectively measuring an EEG signal which is inextricably linked with the frontalis EMG signal. The presence of either or both of these components of the scalp signal is sufficient to maintain a high value of the CPEI when the patient is awake. However, the same reason that makes the CPEI stable during the awake state also makes it very sensitive to episodic high-frequency fluctuations (artifactual, electromyographical, and neurophysiological) during deep anaesthesia (see Fig. 2 for explanation). A characteristic feature of the state of general anaesthesia is the presence of large slow fluctuations in the instantaneous frequency

![Fig 5](image)

**Table 1** Comparison of fitted PK–PD parameters for CPEI and M-entropy (response entropy) for the sevoflurane study. Values are typical (SE). Exponential notation is used for spatial reasons. $t_{1/2}$ is the blood effect-site equilibration constant; $E_{\text{max}}$ and $E_{\text{min}}$ are the maximum and minimum EEG parameter values; IC$_{50}$ is the concentration of sevoflurane causing 50% effect; $\gamma$ the shape parameter; $\omega^2$ the inter-individual variability; and $\sigma^2$ the intra-individual variability.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CPEI</th>
<th>$\omega^2$</th>
<th>M-entropy</th>
<th>$\omega^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$</td>
<td>1.260 (0.242)</td>
<td>0.799 (0.291)</td>
<td>1.250 (0.162)</td>
<td>0.349 (0.087)</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>0.976 (0.002)</td>
<td>—</td>
<td>88.4 (0.526)</td>
<td>—</td>
</tr>
<tr>
<td>$E_{\text{min}}$</td>
<td>0.817 (0.008)</td>
<td>—</td>
<td>16.1 (2.29)</td>
<td>—</td>
</tr>
<tr>
<td>IC$_{50}$ (%)</td>
<td>0.833 (0.063)</td>
<td>0.062 (0.022)</td>
<td>0.839 (0.047)</td>
<td>0.062 (0.019)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>3.67 (0.518)</td>
<td>0.307 (0.097)</td>
<td>5.60 (0.731)</td>
<td>0.308 (0.080)</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>0.00432 (6.23E–5)</td>
<td>—</td>
<td>74.9 (10.5)</td>
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content of the EEG. The most extreme example of this phenomenon is the burst suppression pattern. The fluctuations in the PE may be accurately tracking the (fluctuating) real state of the EEG. This sensitivity to high frequencies, however, will make the PE a poor measure of drug effect, if there is continuing high-frequency activity after loss of consciousness. Falsely elevated EEG indices may occur if the patient develops hypertonus and abnormal movements during induction of anaesthesia—which are common with rapid induction of anaesthesia using propofol, sevoflurane, or high doses of opioids as part of the technique. This is likely to be the cause for the poor PK–PD fit in one of the patients in the sevoflurane study (worst fit of Fig. 5). Although this patient lost responsiveness at 270 s, with concurrent delta wave activity; close inspection of the raw unfiltered EEG waveform and spectrogram showed ongoing high-frequency (>40 Hz) power and some epileptiform spike-like waveforms for another 90 s. This abnormal activity falsely elevated the CPEI.

Only two of the patients displayed any burst suppression patterns, so it is not possible to determine whether, in deep anaesthesia, the CPEI reliably makes a smooth transition to this pattern; further studies are needed, in particular to determine the optimum value of the threshold (tie) parameter. There are both signal processing and

Table 2 Comparison of fitted PK–PD parameters for CPEI and BIS of the propofol study. Values are typical (SE). Exponential notation is used for spatial reasons. $t_{1/2}$ is the blood effect-site equilibration constant; $E_{\text{max}}$ and $E_{\text{min}}$ are the maximum and minimum EEG parameter values; $IC_{50}$ is the concentration of sevoflurane causing 50% effect; $\gamma$ the shape parameter; $\sigma^2$ the inter-individual variability; and $\sigma^2$ the intra-individual variability.

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<tbody>
<tr>
<td>$t_{1/2}k_{e0}$ (min)</td>
<td>2.770 (0.469)</td>
<td>3.20 (0.529)</td>
</tr>
<tr>
<td>$E_{\text{max}}$</td>
<td>0.965 (0.002)</td>
<td>96.5 (0.413)</td>
</tr>
<tr>
<td>$E_{\text{min}}$</td>
<td>0.789 (0.033)</td>
<td>0 (fixed)</td>
</tr>
<tr>
<td>$IC_{50}$ (ng ml$^{-1}$)</td>
<td>2500 (444)</td>
<td>3350 (427)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>3.40 (0.882)</td>
<td>3.35 (0.862)</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>8.91E–5 (1.29E–5)</td>
<td>16.4 (3.84)</td>
</tr>
</tbody>
</table>

Fig 6 Examples of PK–PD modelling of propofol effects. The dots are the experimental CPEI (left) or BIS (right) data points. The lines through the data are the model fits.
neuropharmacological issues with the quantification of this transition. Because the time scale of the suppression and bursts is of the order of seconds to tens-of-seconds, it is necessary to have a long period of processing of the EEG. If a particular short period is dominated by a burst, the CPEI will be high, whereas if it is dominated by EEG suppression, it will be low. Thus, the CPEI fluctuations could be expected to get larger with deeper anaesthesia. The other possibility is that burst suppression may be associated with different modes of drug actions; and that this change in state of the brain is an abrupt process, not a continuous one.28

When comparing PK–PD models of sevoflurane effect (CPEI vs M-entropy) and propofol effect (CPEI vs BIS), the parameter values were very similar. We used 30 s segments of EEG data to calculate the CPEI for comparison with the commercial EEG indices. Although this smoothing decreases ‘pure’ random errors, it concomitantly increases ‘lack-of-fit’ errors. This is seen particularly around the point of loss of consciousness where both the BIS and the M-entropy tend to have a delayed, but then more step-like abrupt decrease in values, compared with the smoother transition seen with the CPEI (Figs 5 and 6). However, it could be argued that a shorter segment length (5 s) may be preferable when using the CPEI for PK–PD modelling; because the CPEI can respond faster, and shows less autocorrelation of the residuals, which might give better parameter estimates. The reason for the very short $t_{1/2}k_{e0}$ in the sevoflurane study is unclear, but may relate to the rapid induction with high dose sevoflurane that was used in this study. High-dose sevoflurane increases brain blood flow and consequently may shorten $t_{1/2}k_{e0}$. See also the discussion in the paper by Olofsen and Dahan.16 In another paper comparing different EEG indices during induction with sevoflurane and remifentanil, Olofsen and colleagues found a similar wide, and unexplained, disparity in the $t_{1/2}k_{e0}$ when modelled using the spectral edge frequency (1.91 min) when compared with models using the BIS (3.11 min).

We would conclude that the CPEI shows promise as a simple open-source method of quantifying the brain effects of GABAergic drugs, and hence may be useful for PK–PD modelling. However, further work is required to accurately quantify the transition to burst suppression patterns. The CPEI performance is comparable with the M-entropy and BIS, and better than spectral and approximate entropy. The use of a composite index of PE allows the graded differentiation of different anaesthesia-induced EEG patterns, and the handling of low-amplitude measurement noise.

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**Appendix**

**Matlab function to calculate CPEI**

```matlab
function [pepi, p1, p2, p1tie, p2tie, pk12] = CPEI(y, epe)
% Permutation Entropy - order set at 3
% Input time series (y) and noise threshold (epe)
% Output all combinations of entropies for tau1 vs tau2 (including Kullback-Leibler)
% Set epe to zero for no ties
% check data and initialize variables
ord = 3;
sd = std(y);
p1=0; p2=0; epeip=0; pk12=0;
if sd==0; return; end
% check and turn y vector to correct direction
y = y-mean(y);
end
% CALCULATE PE for tau = 1 & 2---- and threshold = epe
--------
c1=[132;131;123];
perm1 = permute(ones(ord));
tie1=0;
tie2=0; % initial ties bin
tie1(1:length(perm1)+1)=0; % init tau=1 bins
tie2(1:length(perm2)+1)=0; % init tau=2 bins
for j=3:ly-2;
   seg=y(i+j-2:j);
   % total segment
   seg1=[seg(1:2),seg(3),seg(4)]; %seg for tau=1;
   seg2=[seg(1),seg(3),seg(5)]; %seg for tau=2;
   % sorts ordinate section of seg
   [a1i,v1]=sort(seg1);
   % sorts ordinate section of seg1
   [a2i,v2]=sort(seg2);
   % sorts ordinate section of seg2
   % gets bins =epe and 6 other motifs for PE tau=1------------
da1=abs(diff(a1)); % find difference between points in the motif
   if (min(da1))<epe;
      if <threshold add to 7th bin
                     etie1=etie1+1;
   else
      for ji=1:length(perm1);
         if perm1(ji)>i-iv1==0
            c1(ji) == c1(ji) + 1; %accumulates into the correct bin
            end
            end
            %if min da1
            % repeats for tau=2
            end
            da2=abs(diff(a2));
            if (min(da2))<epe;
               c1e2=c1e2+1;
            else
               for ji=1:length(perm2);
                  if perm2(ji)>i-iv2==0
                     c2(ji) == c2(ji) + 1;
                     end
                     end
                     %if min da2
                     end
                     len1=g1-3;
                     % effective length
                     p1 = c1/len1; % normalizes to total area
                     p2 = c2/len2;
                     ptie1=etie1/len1;
                     ptie2=etie2/len2;
                     zix=find(p1=0);
                     % handle p*log(p)>0
                     z1 = -sum(p1(zix) * log(p(zix))) + 0;
                     z2 = sum(p2(zix) * log(p2(zix))) + 0;
                     if p1>0;
                        etie1 = etie1 * log(ptie1);
                        else etie1=0;
                        end
                        if ptie2>0;
                           etie2 = etie2 * log(ptie2);
                           else etie2=0;
                           end
                            p1tie==etie1;
                            p2tie=etie2;
                            p1=-(e1-etie1)/log(7);
                            p2=-(e2-etie2)/log(7);
                            epe1=p1-p2/2+log7;
                            pk12 = -sum(p2*log(p2/p1));
                            return;
end
```

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