Behavior of Entropy/Complexity Measures of the Electroencephalogram during Propofol-induced Sedation

Dose-dependent Effects of Remifentanil

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Background: Several new measures based on the regularity of the electroencephalogram signal for the assessment of depth of anesthesia/sedation have been proposed recently. In this study we analyze the influence of remifentanil and electroencephalogram frequency content of the performance of a set of such measures.

Methods: Forty-five patients with American Society of Anesthesiologists physical status I were randomly allocated to one of three groups according to the received dose of predicted effect compartment–controlled remifentanil (0, 2, and 4 ng/ml). All 45 patients received stepwise increased effect site concentration–controlled dose of propofol. At every step of propofol increase, the Observer's Assessment of Alertness/Sedation score was assessed. The following measures were calulated from the electroencephalographic signal: spectral entropy, approximate entropy, Higuchi fractal dimension, Lempel-Ziv complexity, relative β ratio, and SyncFastSlow measure.

Results: The behavior of the electroencephalogram-based measures is highly sensitive to the frequency content of the signal and the dose of remifentanil. The prediction probability with respect to the Observer's Assessment of Alertness/Sedation score of the most discriminative measure, the Higuchi fractal dimension, dropped from 0.90 (electroencephalographic frequency band 6–47 Hz, no remifentanil) to 0.55 when the frequency band was changed to 0.5–19 Hz and to 0.83 when remifentanil concentration was increased to 4 ng/ml. The co-effect of remifentanil on electroencephalographic regularity is bimodal depending on the frequency band of the signal.

Conclusions: Cutting off high frequencies from the electroencephalogram and increased remifentanil concentration deteriorate the performance of the electroencephalogram-based entropy/complexity measures as indicators of the depth of propofol sedation.

SINCE 1996 when Aspect Medical Systems Inc. introduced the Bispectral Index or BIS (A-2000 BIS® monitor; Aspect Medical Systems Inc., Newton, MA), monitoring of anes-thetic depth using electroencephalogram-based methods has become a common practice in numerous hospitals all over the world. During the past decade, several other algorithms based either on the spontaneous electroencephalogram or auditory evoked responses, such as the Patient State Index (PSI®; Hospira, Lake Forrest, IL), the Narcotrend index (Narcotrend®; Schiller AG, Baar, Switzerland), the State and Response Entropy indices (M-entropy® module; GE Healthcare Finland Oy, formerly Datex Ohmeda, Helsinki, Finland), the Cerebral State Index or CSI®, and the A-Line ARX index or AAI® (both by Danmeter A/S, Odense, Denmark), have been developed for use in commercial monitoring devices. In addition, several measures calculated from the electroencephalographic signal, *e.g.*, nonlinear correlation index, Shannon entropy, approximate entropy, Lempel-Ziv complexity, have been proposed in the literature for the assessment of depth of hypnosis.[1–5] An overview of the algorithms used for monitoring anesthetic depth was recently published by Lipping *et al.*[6]

When comparing or evaluating the various methods available for anesthesia/sedation monitoring, one is faced with several problems. First, the neural mechanisms of action vary for different anesthetic agents, other medications causing changes in the electroencephalographic signal might be used, and the state of the subjects may vary from study to study. Second, the results are sensitive to the frequency content of the electroencephalogram determined by the analog and digital prefilters, and the calculation of the indices often involves predefined parameters whose suitable values are difficult to determine.

In this work, we apply several measures—approximate entropy, spectral entropy, Lempel-Ziv complexity, and Higuchi fractal dimension—to quantify the entropy/complexity of the electroencephalographic signal during propofol–remifentanil anesthesia. In comparison, relative β ratio and SyncFastSlow measure, obtained using bispectrum magnitude as well as bicoherence, are considered. Two main objectives underlie this study. First, the influence of the frequency band of the electroencephalogram on the behavior of the mentioned measures is studied. Second, the effect of remifentanil on the performance of the measures is addressed.

Methods and Materials

Clinical Protocol

After institutional ethics committee (Ghent University Hospital, Gent, Belgium) approval, informed consent

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was obtained from 45 patients with American Society of Anesthesiologists physical status I, aged 18–60 yr, scheduled to undergo ambulatory surgery. Exclusion criteria included weight less than 70% or more than 130% of ideal body weight (following the table of Desirable Weights, Metropolitan Life Insurance, 1983), neurologic disorder, and recent use of psychoactive medication, including alcohol. The patients were randomly allocated to one of three groups using block randomization (permuted block design, three blocks of 15 patients with a 1:1:1 ratio). In group remi0, no remifentanil was given. In groups remi2 and remi4, the effect compartment–controlled infusion of remifentanil targeted at 2 or 4 ng/ml, respectively, was started 4 min before the start of propofol. In all groups, patients received a "staircase" computer-controlled infusion of propofol, targeting the effect compartment. Initially, an effect site concentration of 0.75 μg/ml was targeted, increased every 4 min by 0.25–0.30 μg/ml until loss of response to all relevant clinical measures of anesthetic depth was observed.

Propofol and remifentanil were administered *via* a computer-assisted continuous infusion device to a target effect site concentration (RUGLOOP II; Demed, Temse, Belgium) using a three-compartment model enlarged with an effect site compartment. For propofol, the pharmacokinetic–dynamic model previously published by Schnider *et al.*[7,8] was used. For remifentanil, the pharmacokinetic–dynamic model previously published by Minto *et al.*[9,10] was used. Predicted effect site propofol concentration (CePROP) was computed to yield a time to peak effect[11] of 1.6 min after bolus injection, as also published by Schnider *et al.*[7,8] and clinically confirmed by Struys *et al.*[12] For remifentanil, an age-dependent ke0 value of $0.595 - 0.007 * (\text{Age} - 40) \text{ min}^{-1}$ was applied as published by Minto *et al.*[9,10] Propofol and remifentanil infusion were administered using a Fresenius Modular DPS Infusion Pump connected to a Fresenius Base A (Fresenius Vial Infusion Systems, Brésin, France). RUGLOOP II steers the pump at infusion rates between 0 and 1,200 ml/h *via* an RS-232 interface. By using this infusion technique, we were able to obtain a steady state condition for both propofol and remifentanil at every target level after 4 min of infusion. Hereby, steady state is defined as the equilibration between the calculated plasma and effect site concentration of the drug. Remifentanil and propofol were infused *via* a large left forearm vein. Every patient received approximately 200 ml crystalloid fluid during the study period. No fluid load was given before induction. No patient received preanesthetic medication. No other drugs were given. All patients maintained spontaneous ventilation *via* facemask delivering 6 l/min O_2.

Data Acquisition

For safety, heart rate, noninvasive blood pressure, oxygen saturation measured by pulse oximetry, and capnography were monitored continuously using an S/5 Anesthesia Monitor (GE Healthcare Finland Oy) and recorded electronically using RUGLOOP II data management software. All changes in hemodynamics and capnography were within clinical limits (data not presented). Electroencephalographic signal was recorded using the M-Entropy® module of the S/5 Anesthesia Monitor. This module is able to collect the raw electroencephalogram and transform it into the Entropy® index. The signal was derived using the standard entropy sensor of the S/5 monitor; however, the location of the sensor was slightly modified to be more suitable for the analysis in question. In this modified setup, the two recording electrodes of the entropy sensor were located bilaterally on the forehead, approximately 5 cm above the eyebrows. The distance of the electrodes from the midline was approximately 4 cm to either direction with the ground electrode located between the recording electrodes. The signal was sampled at 400 Hz and stored on a hard disk using S5-collect software (GE Healthcare, Helsinki, Finland). Two commercially available spectral entropy measures, state entropy (SE) and response entropy (RE), were calculated on-line by the algorithms incorporated in the M-Entropy® module (GE Healthcare). Data were also electronically stored using RUGLOOP II software. The SE value ranges from 91 to 0, and the RE value ranges from 100 to 0. SE is computed over the frequency range from 0.8 to 32 Hz. The time windows for SE are chosen optimally for each particular frequency component and range from 60 s to 15 s. RE is computed over a frequency range from 0.8 to 47 Hz. The time windows for RE are chosen optimally for each frequency, with the longest time window equal to 15.36 s and the shortest time window, applied for frequencies between 32 and 47 Hz, equal to 1.92 s. The description of the full algorithm is reported elsewhere.[13]

It is important to note that due to the modified electrode location, the results for RE and SE reported in this work are not totally comparable with those achieved using the standard commercial electrode setup. However, all the data are valid for comparison within this study.

Off-line Signal Processing

The recorded raw electroencephalographic data were preprocessed as follows. First, artifacts caused by eye movements, movements of the subject, or equipment noise were marked by visual inspection. Subsequently, the signal was segmented into 15-s segments overlapping by 5 s. The segments containing artifacts were discarded.

In total, seven measures based on the electroencephalographic signal were calculated off-line from the signal segments. Three of them, based on spectral or bispectral analysis, were included because they are applied as components of algorithms used in commercial anesthesia

monitoring devices (*e.g.*, in the BIS® monitor). The other four measures quantify the entropy/complexity of the electroencephalogram and have previously been proposed in the literature for monitoring anesthetic depth. These measures are considered here as they depend on the electroencephalographic frequency band and remifentanil concentration in a different manner and have never been compared in a similar setup.

The entropy/complexity measures include the following:

Spectral entropy (SpEn) is calculated by transforming the signal power spectrum over the Shannon function. SpEn depends solely on the power spectrum of the signal, quantifying its "flatness." For example, spectral entropy of a pure sine wave, having a single spectral peak, is 0, whereas white noise is characterized by maximum spectral entropy (spectral entropy of value 1 in the normalized case). SpEn is used in the M-Entropy® module of the S/5 Anesthesia Monitor as mentioned above.

Lempel-Ziv complexity (LZC) quantifies the recurrence of patterns of symbols in a signal. In the calculation of LZC, the signal is first turned into a sequence of symbols, after which the symbol recurrence is analyzed. LZC has been proposed for the assessment of depth of hypnosis by Zhang *et al.*,[5] for example.

Approximate entropy (ApEn) is an approximation of Kolmogorov entropy having its roots in nonlinear dynamics. The calculation of ApEn involves embedding of the signal onto phase space. It basically estimates the rate of increase in the number of phase space points fitting within a hyperball of radius r as the phase space dimension is increased from predefined value m to $m + 1$. ApEn has been evaluated as a measure of anesthetic depth by Bruhn *et al.*[3] and Bouillon *et al.*,[4] for example.

Higuchi fractal dimension (HFD) is another signal measure having its roots in nonlinear dynamics; however, it can be calculated solely in time domain, and its calculation is therefore of very low computational complexity. HFD measures the rate of increase in the difference of signal amplitude values as the signal samples are picked increasingly sparsely. HFD, calculated from the electroencephalographic signal, has proved to be a sensitive measure of the level of hypnosis.[14,15]

A more formal treatment of these measures together with corresponding references and values of algorithm parameters used in the present study are given in the appendix.

The following spectral/bispectral measures are applied:

Relative β ratio (RBR), calculated as

$$RBR = \log\left(\frac{P_{30...47}}{P_{11...20}}\right), \qquad (1)$$

where $P_{30...47}$ and $P_{11...20}$ denote signal power in frequency ranges 30 . . . 47 and 11 . . . 20 Hz, respectively.

SyncFastSlow measure (SFS), calculated in the bispectral domain as

$$SFS = \log\left(\frac{B_{0.5...47.0}}{B_{40.0...47.0}}\right), \qquad (2)$$

where $B_{0.5...47.0}$ and $B_{40.0...47.0}$ denote the sum of bispectrum magnitude values in frequency ranges 0.5 . . . 47.0 and 40.0 . . . 47.0 Hz, respectively.

SyncFastSlow calculated using bicoherence (SFSBIC). Often in bispectral analysis, bicoherence is used instead of bispectrum magnitude. Bicoherence is obtained by normalizing the bispectrum magnitudes:

$$BIC(\omega_1, \omega_2) = \frac{B(\omega_1, \omega_2)}{\sqrt{P(\omega_1)P(\omega_2)P(\omega_1 + \omega_2)}}, \qquad (3)$$

where $B(\omega_1, \omega_2)$ and $P(\omega)$ denote the magnitude of the bispectrum and the power spectrum, respectively. SFSBIC is subsequently calculated as the log-ratio of the sums of bicoherence values in the same frequency ranges as SFS (see equation 2).

As can be seen, the definitions of the spectral and bispectral measures described above involve frequency ranges; therefore, the prefilter settings have no impact on their values as far as the cutoff frequencies are outside the effective frequency bands. If this assumption is not fulfilled, the measures should be redefined for the particular prefilter parameters. The behavior of the four entropy/complexity measures, however, is sensitive to the frequency band of the electroencephalographic signal underlying their calculation. We studied this dependence by prefiltering the electroencephalographic signal using nine different sets of cutoff frequencies:

0.5–19.0 Hz; 2.0–19.0 Hz; 6.0–19.0 Hz
0.5–32.0 Hz; 2.0–32.0 Hz; 6.0–32.0 Hz
0.5–47.0 Hz; 2.0–47.0 Hz; 6.0–47.0 Hz

The particular frequencies were chosen according to the values used in some anesthesia monitors; however, their exact values are not crucial from the point of view of our analysis. The prefilters were of linear-phase equiripple design with pass- and stop-band attenuation of 0.01. They were applied to the signal after segmentation.

The behavior of the electroencephalographic measures at increasing steady state concentrations of propofol and remifentanil were compared with a clinical score of alertness and sedation, the Observers' Assessment of Alertness/Sedation (OAA/S)[16] score (table 1). This comparison was performed in the following manner. The measures were obtained over the time period preceding each propofol concentration increase by 65 . . . 20 s, averaging the calculated values of four (or fewer if some of the segments were discarded because

of artifacts) 15-s segments (5-s overlap). Ten seconds before the propofol increase, clinical assessment of the level of sedation was made using a modified OAA/S scale. This scale is assessed by applying progressively more intense stimulation, ranging from a moderate speaking voice to physical shaking or moderate noxious stimulus (trapezius squeeze) until response is observed. Patients were considered responsive at OAA/S levels 5, 4, or 3 and scored as unresponsive at OAA/S levels 2, 1, or 0. Patients were considered to have loss of consciousness at the transition between levels 3 and 2. The overall sequence of testing was always the same: first the electroencephalographic measures, then the OAA/S score.

Statistical Analysis

To assess the ability of the electroencephalographic measures to indicate the subjects' level of sedation, prediction probabilities were calculated. Prediction probability (P_K), developed by Smith *et al.*,[17,18] compares the performance of independent variables having different units of measurements. Consider an independent variable and a "gold standard" measure of anesthetic depth such as the multilevel OAA/S score or the two-level responsiveness (yes/no) to noxious stimulus. Then, a P_K of 1 for this independent variable would mean that the value of the variable always increases or decreases as the sedation gets lighter (increasing OAA/S values) or deeper (decreasing OAA/S values), respectively, according to the gold standard. Such an independent variable can perfectly measure anesthetic depth. Alternatively, a P_K value of 0.5 would mean that there is no correlation between any direction of change in clinically determined depth of anesthesia and the direction of change in the corresponding values of the independent variable. In this study, prediction probability was calculated using a custom spreadsheet macro, P_KMACRO, developed by Smith *et al.*,[17,18] for each electroencephalographic measure in each subject group. The jackknife method was used to compute the standard error of the estimate, based on the assumption that all assessments were independent.[17,18]

Table 1. Responsiveness Scores of the Modified Observer's Assessment of Alertness/Sedation Scale

Score	Responsiveness
5	Responds readily to name spoken in normal tone
4	Lethargic response to name spoken in normal tone
3	Responds only after name is called loudly and/or repeatedly
2	Responds only after mild prodding or shaking
1	Responds only after painful trapezius squeeze
0	No response after painful trapezius squeeze

Results

Dependence of the Electroencephalographic Measures on the Frequency Content of the Signal

In figure 1, the behavior of the entropy/complexity measures in the course of the whole recordings and for all of the tested frequency bands is presented. Different measures are presented by separate sets of curves with corresponding scales of values indicated at the left side of each plot. The curves represent the median values of the measures in the three patient groups. It is important to note that the curves corresponding to patient groups remi2 and remi4 are shorter compared with those corresponding to the patient group remi0 because the higher the remifentanil dose was, the sooner the endpoint of no response to stimuli was achieved and the recording stopped. The mean (SD) duration of the recordings was 46′2″ (8′22″), 34′13″ (5′25″), and 30′13″ (6′22″) for groups remi0, remi2, and remi4, respectively.

Figure 1 shows that the nearly monotonic decrease of the calculated measures with increasing propofol concentration (seen in the lower right panel) is lost when low frequencies are incorporated and/or high frequencies are cut off. The most suitable frequency band for estimating anesthetic depth from the entropy/complexity of the electroencephalographic signal seems to be that of 6–47 Hz. Among the tested entropy/complexity measures, HFD is relatively insensitive to the presence of low frequencies. Figure 2 presents similar results for the three spectral/bispectral measures. Whereas SFS shows roughly monotonous relationship, scaling the bispectrum magnitude by the autospectra (equation 3) destroys the correlation. RBR has the disadvantage of biphasic behavior, and its correlation with propofol concentration deteriorates with remifentanil.

Effect of Remifentanil on the Correlation of the Electroencephalographic Measures with the OAA/S Score

Figures 3 and 4 present the mean values of SpEn and HFD, respectively, corresponding to each OAA/S score, the three subject groups, and the nine frequency bands. Only SpEn and HFD are presented here, because the behavior of the other two entropy/complexity measures, ApEn and LZC, is similar. It can be seen that when low frequencies are considered (see, *e.g.*, the upper left panel of figs. 3 and 4) and/or during light sedation, increasing remifentanil concentration tends to turn the electroencephalogram more regular, decreasing its entropy/complexity. However, when high frequencies are considered (*e.g.*, lower right panel) and/or during deep sedation, the effect is reversed. Figure 5 presents similar results for the spectral/bispectral measures, showing that the effect of remifentanil on the properties of the electroencephalogram is nonlinear, *i.e.*, the change in a
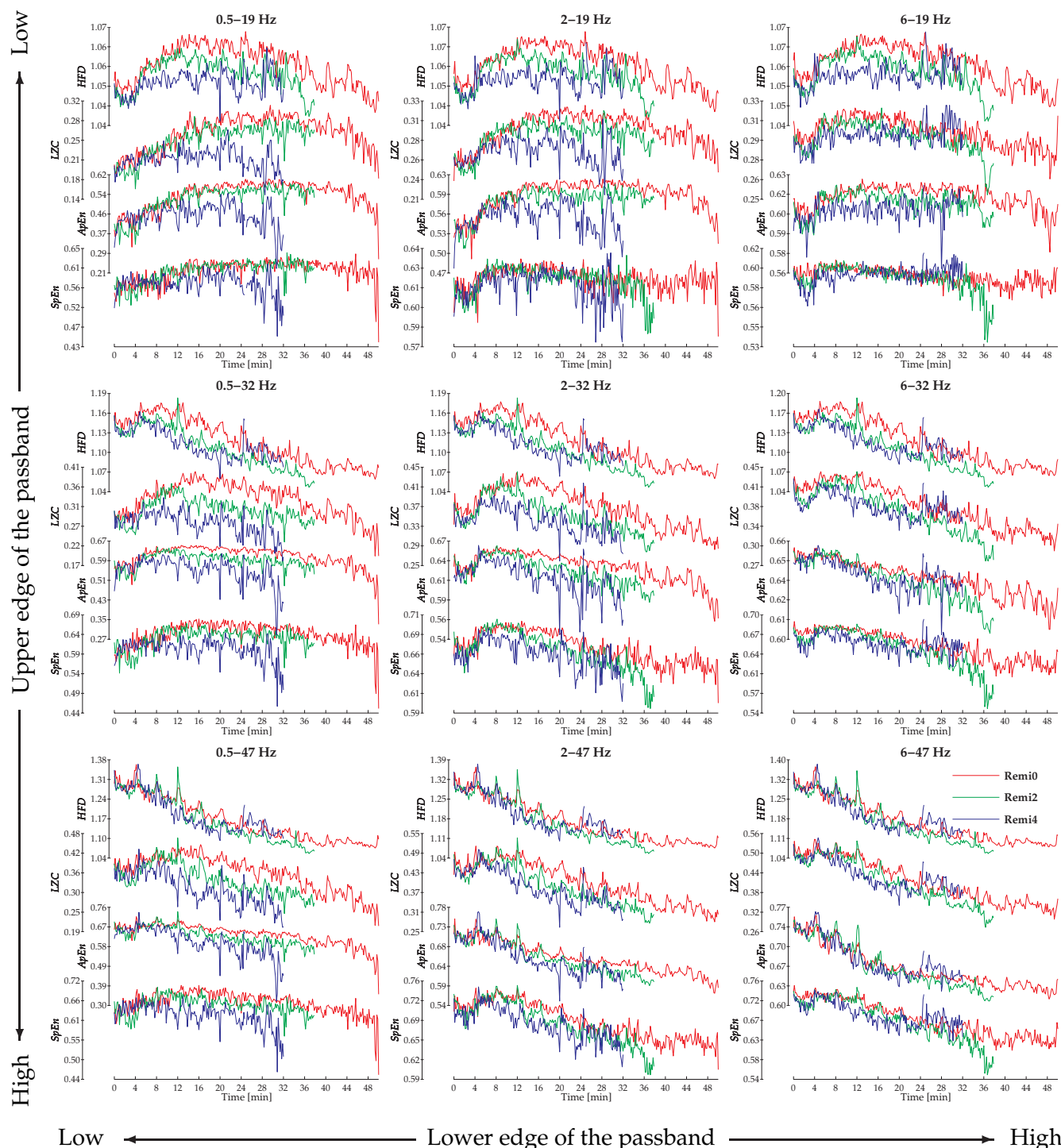
Fig. 1. Time-varying entropy/complexity of the electroencephalographic signal. The sets of *curves* corresponding to Higuchi fractal dimension (HFD), Lempel-Ziv complexity (LZC), approximate entropy (ApEn), and spectral entropy (SpEn) are plotted below each other, with corresponding *scales* at the left of each panel. *Red*, *green*, and *blue curves* correspond to subject groups remi0, remi2, and remi4, respectively. The nine *panels* correspond to the nine frequency bands as indicated at the top of each panel. The signal frequency band is shifted from low frequencies toward higher frequencies while moving from the upper left panel toward the lower right panel of the figure. Monotonic behavior of the presented electroencephalographic measures is lost when high frequencies are cut off and/or low frequencies are preserved.

particular measure from the case of no remifentanil to that of moderate dose might be opposite to the change from moderate dose to high dose. This is revealed also by the results in figures 3 and 4 and is especially prominent

around OAA/S scores 3 and 2, marking the loss of consciousness.

Table 2 presents the prediction probabilities of the entropy/complexity measures for the nine frequency
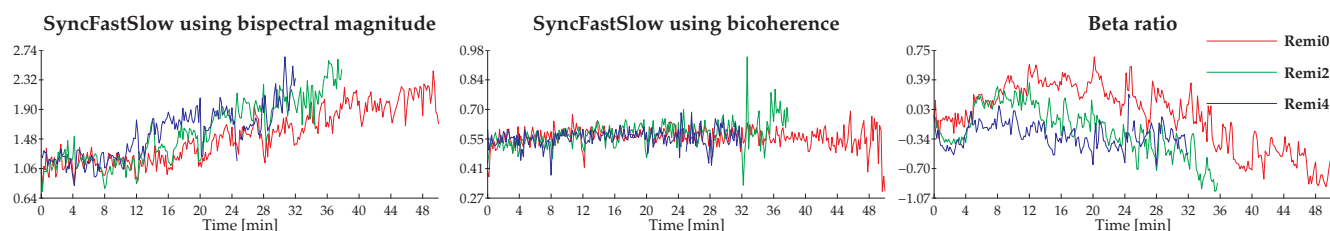
Fig. 2. Time-varying spectral/bispectral measures of the electroencephalographic signal. *Left*: SyncFastSlow measure calculated using bispectral magnitude; *middle*: SyncFastSlow measure calculated using bicoherence; *right*: relative β ratio. Correlation of the bispectral measures with anesthetic depth is lost when bispectrum is normalized in the calculation of bicoherence. Relative β ratio shows biphasic behavior.

bands as well as for SE, RE, RBR, SFS, SFSBIC, and CePROP. The OAA/S level is taken as the gold standard. It can be seen that shifting the frequency band toward lower frequencies as well as increasing the remifentanil concentration tends to deteriorate the performance of the electroencephalographic measures as indicators of
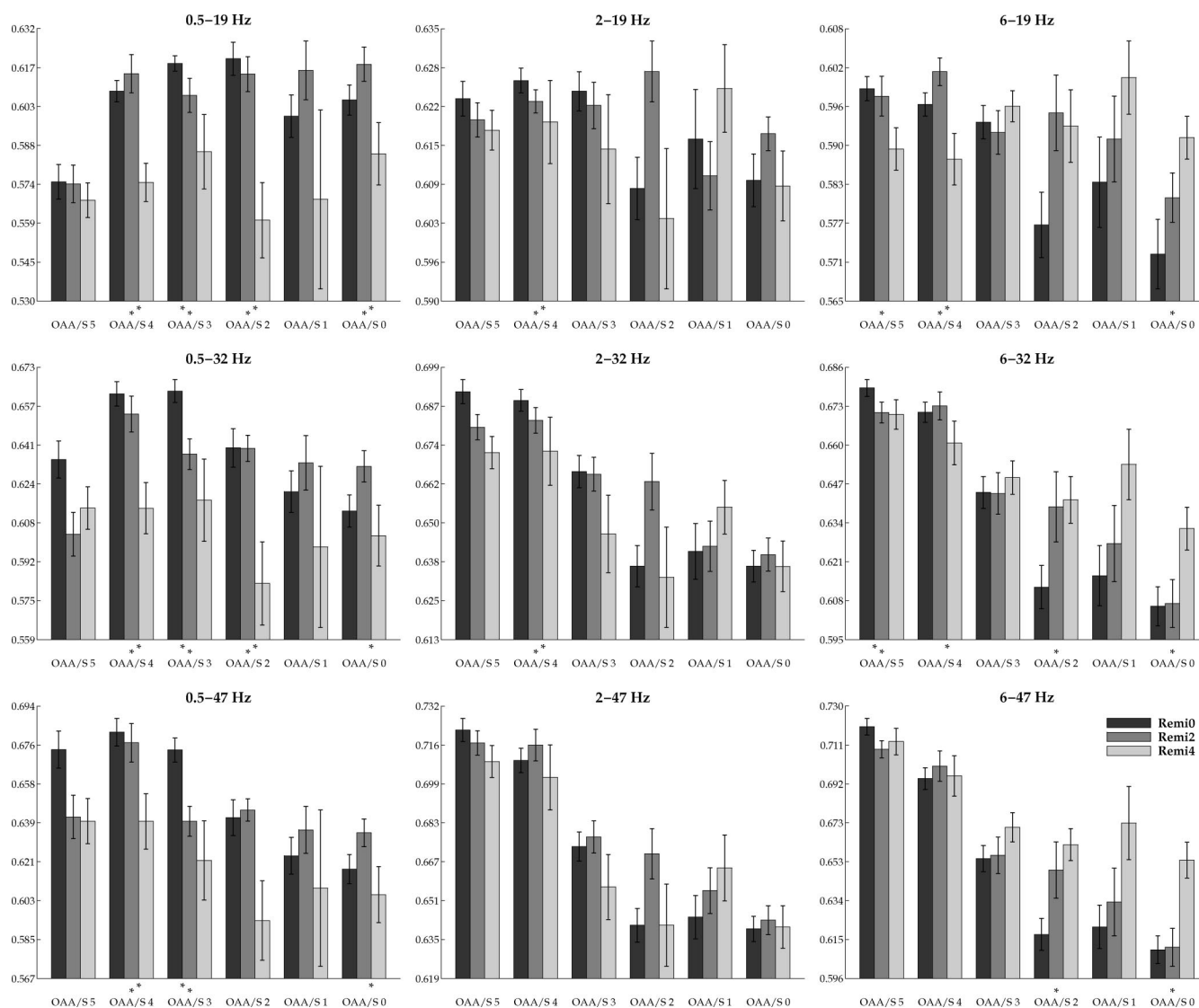

Fig. 3. Spectral entropy of the electroencephalographic signal corresponding to different Observer's Assessment of Alertness/Sedation (OAA/S) levels (mean and standard error). The bars of different shades of gray correspond to the patient groups remi0 to remi4: The *darkest bar* represents patients receiving no remifentanil (group remi0), the *middle bar* represents patients receiving remifentanil dose of 2 ng/ml (group remi2), and the *lightest bar* represents patients receiving remifentanil dose of 4 ng/ml (group remi4). Statistical significance (*P* < 0.05) of the differences between the results of the patient groups is denoted by an *asterisk* below and between the corresponding bars. An *asterisk* at a lower position in the middle of a group of three bars marks significant difference of patient groups remi0 and remi4. The effect of remifentanil is reversed as the frequency band of the signal is shifted toward higher frequencies.
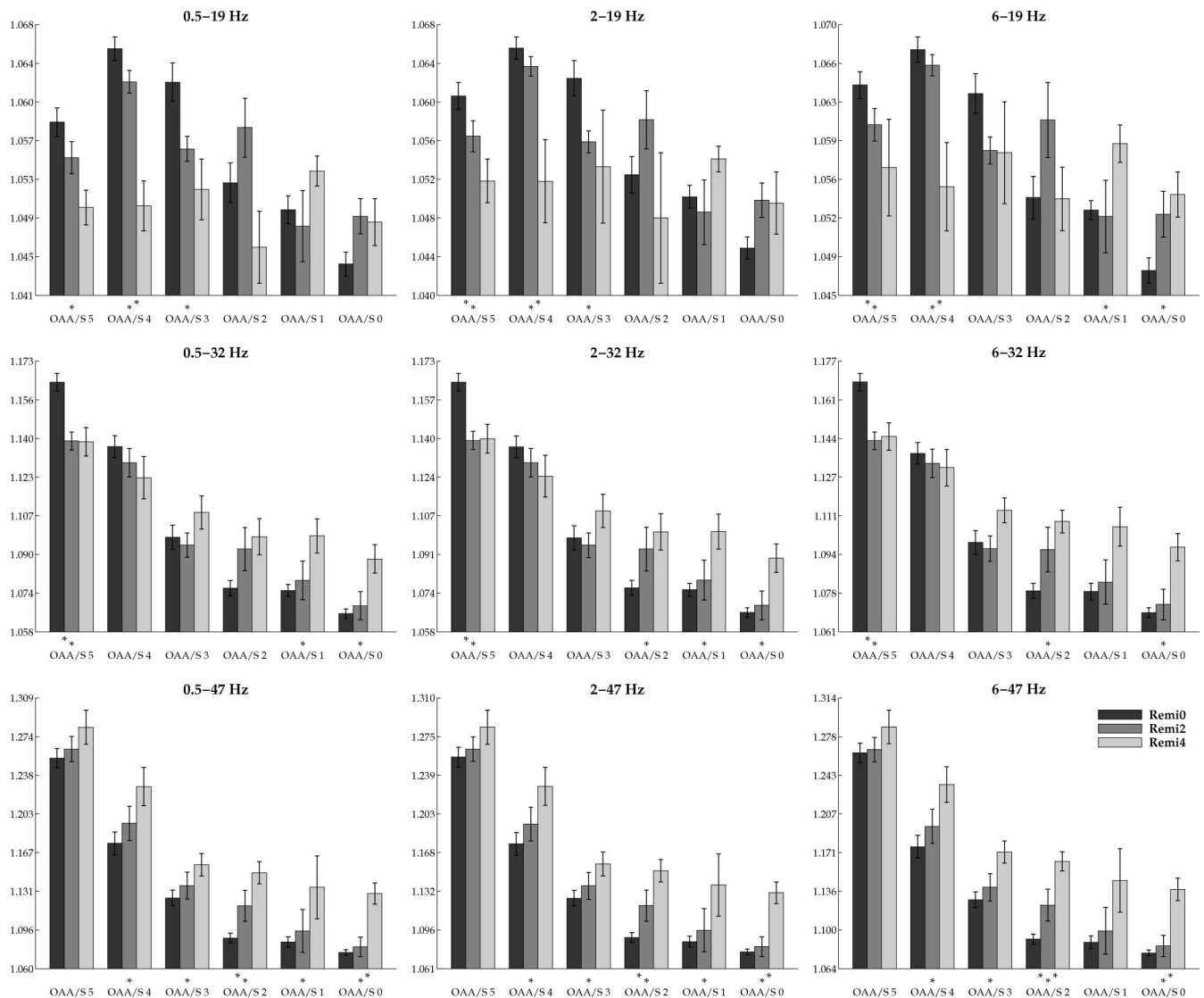
Fig. 4. Higuchi fractal dimension of the electroencephalographic signal corresponding to different Observer's Assessment of Alertness/Sedation (OAA/S) levels (mean and standard error). The bars of different shades of gray correspond to the patient groups remi0 to remi4: The *darkest bar* represents patients receiving no remifentanil (group remi0), the *middle bar* represents patients receiving remifentanil dose of 2 ng/ml (group remi2), and the *lightest bar* represents patients receiving remifentanil dose of 4 ng/ml (group remi4). Statistical significance ($P < 0.05$) of the differences between the results of the patient groups is denoted by an *asterisk* below and between the corresponding bars. An *asterisk* at a lower position in the middle of a group of three bars marks significant difference of patient groups remi0 and remi4. Preserving frequencies down to 0.5 Hz does not significantly deteriorate the behavior of Higuchi fractal dimension.

anesthetic depth. If the most favorable frequency band (6–47 Hz) is considered, the prediction probabilities for all of the entropy/complexity measures is between 0.83 and 0.90 for the patient group remi0, between 0.81 and 0.87 for group remi2, and between 0.74 and 0.83 for group remi4. HFD performs best having, in the mentioned frequency band, slightly higher P_K than RE or SE. It is interesting to note that the correlation of OAA/S with CePROP is not perfect either. In each subject, the OAA/S score decreased monotonically with increasing CePROP; however, when merging the data from different subjects, lower CePROP could correspond to lower OAA/S (higher level of sedation) in some cases. In fact, in

group remi0, HFD has slightly higher P_K compared with CePROP.

Discussion

There has recently been a boom of studies applying newly developed indices and electroencephalographic measures to anesthesia/sedation monitoring. The results are often difficult to compare because of different recording setup, parameter values, and/or prefilter settings. Sometimes the results appear contradictory, *e.g.*, the finding that the Shannon entropy increases with
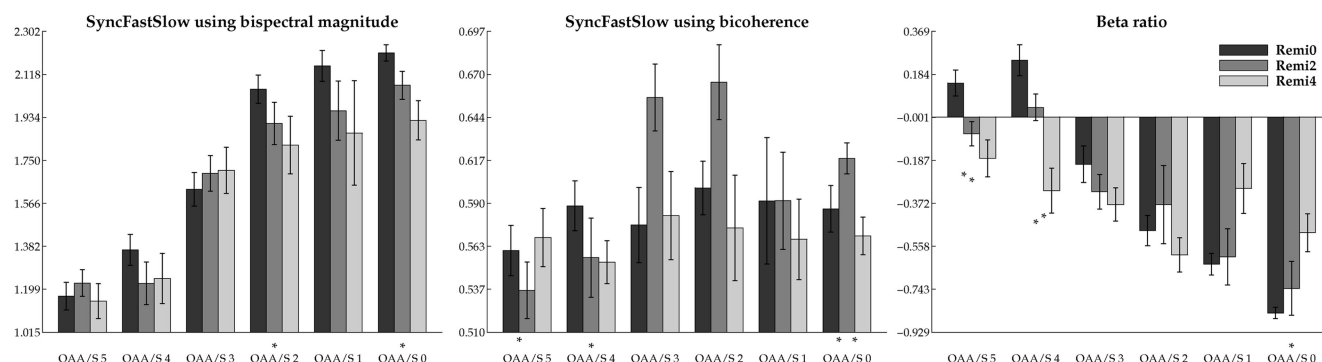
Fig. 5. Spectral/bispectral electroencephalographic measures corresponding to different Observer's Assessment of Alertness/Sedation (OAA/S) levels. *Left*: SyncFastSlow measure calculated using bispectrum magnitude; *middle*: SyncFastSlow measure calculated using bicoherence; *right*: relative β ratio. Statistical significance ($P < 0.05$) of the differences between the results of the patient groups is denoted by an *asterisk* below and between the corresponding bars. An *asterisk* at a lower position in the middle of a group of three bars marks significant difference of patient groups remi0 and remi4. The results for the SyncFastSlow measure calculated using bicoherence demonstrate nonlinear nature of the remifentanil effect.

deepening sedation whereas usually it is assumed that the electroencephalographic signal becomes more regular (entropy decreases) with deepening anesthesia/sedation.[2] We have previously pointed out that the various algorithms for the calculation of signal entropy are sensitive to different signal properties and that Shannon entropy has the disadvantage of not taking into account the time order of the signal samples, important in the analysis of the electroencephalogram.[14]

The set of measures chosen for the current analysis contains two on-line measures from the M-Entropy® module of the S/5 Anesthesia Monitor, three components of the algorithms used in, *e.g.*, the commercial BIS® index, as well as four measures quantifying the

Table 2. Prediction Probabilities of the Electroencephalographic Measures and CePROP with Respect to the OAA/S Score for the Patient Groups Remi0, Remi2, and Remi4

	Remi0	Remi2	Remi4	Remi0	Remi2	Remi4	Remi0	Remi2	Remi4
	0.5–19 Hz			2–19 Hz			6–19 Hz		
SpEn	0.66 (0.03)	0.69 (0.04)	0.57 (0.05)	0.54 (0.03)	0.54 (0.04)	0.55 (0.05)	0.67 (0.03)	0.61 (0.04)	0.53 (0.04)
HFD	0.55 (0.04)	0.52 (0.05)	0.52 (0.04)	0.60 (0.04)	0.55 (0.05)	0.57 (0.04)	0.65 (0.03)	0.58 (0.05)	0.55 (0.04)
LZC	0.66 (0.03)	0.66 (0.04)	0.55 (0.04)	0.55 (0.04)	0.55 (0.05)	0.50 (0.04)	0.65 (0.03)	0.60 (0.04)	0.51 (0.04)
ApEn	0.69 (0.03)	0.66 (0.04)	0.55 (0.04)	0.61 (0.03)	0.56 (0.04)	0.52 (0.04)	0.55 (0.03)	0.58 (0.04)	0.54 (0.04)
	0.5–32 Hz			2–32 Hz			6–32 Hz		
SpEn	0.54 (0.03)	0.55 (0.04)	0.50 (0.04)	0.70 (0.03)	0.69 (0.04)	0.61 (0.04)	0.80 (0.02)	0.75 (0.03)	0.66 (0.04)
HFD	0.86 (0.02)	0.83 (0.03)	0.77 (0.03)	0.86 (0.02)	0.83 (0.02)	0.77 (0.03)	0.87 (0.02)	0.83 (0.02)	0.78 (0.03)
LZC	0.57 (0.04)	0.58 (0.04)	0.62 (0.04)	0.74 (0.03)	0.73 (0.04)	0.68 (0.03)	0.86 (0.02)	0.80 (0.03)	0.73 (0.03)
ApEn	0.55 (0.03)	0.57 (0.04)	0.58 (0.04)	0.73 (0.03)	0.72 (0.04)	0.67 (0.03)	0.82 (0.02)	0.82 (0.03)	0.73 (0.03)
	0.5–47 Hz			2–47 Hz			6–47 Hz		
SpEn	0.56 (0.03)	0.52 (0.04)	0.56 (0.04)	0.77 (0.03)	0.77 (0.03)	0.69 (0.03)	0.83 (0.02)	0.81 (0.03)	0.74 (0.03)
HFD	0.89 (0.02)	0.86 (0.02)	0.83 (0.03)	0.89 (0.02)	0.86 (0.02)	0.83 (0.03)	0.90 (0.02)	0.86 (0.02)	0.83 (0.03)
LZC	0.71 (0.03)	0.72 (0.04)	0.72 (0.03)	0.84 (0.02)	0.81 (0.03)	0.76 (0.03)	0.88 (0.02)	0.85 (0.02)	0.79 (0.03)
ApEn	0.71 (0.03)	0.71 (0.04)	0.71 (0.03)	0.84 (0.02)	0.83 (0.03)	0.79 (0.03)	0.87 (0.02)	0.87 (0.02)	0.82 (0.03)
SE	0.87 (0.02)	0.85 (0.03)	0.79 (0.02)						
RE	0.87 (0.02)	0.87 (0.02)	0.81 (0.03)						
RBR	0.71 (0.03)	0.74 (0.04)	0.71 (0.03)						
SFS	0.71 (0.03)	0.75 (0.03)	0.70 (0.04)						
SFSBIC	0.57 (0.03)	0.58 (0.04)	0.56 (0.04)						
CePROP	0.87 (0.02)	0.92 (0.01)	0.91 (0.02)						

Data are mean (standard error). For the entropy/complexity measures, prediction probabilities are given for the nine frequency bands described in the Materials and Methods.

ApEn = approximate entropy; CePROP = predicted effect site propofol concentration; HFD = Higuchi fractal dimension; LZC = Lempel-Ziv complexity; OAA/S = Observer's Assessment of Alertness/Sedation; RBR = relative β ratio; RE = response entropy; Remi0 = patient group receiving no remifentanil; Remi2 = patient group receiving 2 ng/ml remifentanil; Remi4 = patient group receiving 4 ng/ml remifentanil; SE = state entropy; SFS = SyncFastSlow measure calculated using bispectrum magnitude; SFSBIC = SyncFastSlow measure calculated using bicoherence; SpEn = spectral entropy.

entropy/complexity of the electroencephalographic signal and previously proposed for monitoring anesthetic depth. A large set of measures based on the spontaneous electroencephalogram (19 measures) as well as on auditory evoked potentials (23 measures) has recently been evaluated for the detection of consciousness in Schneider *et al.*[19] Monotonicity of a set of linear and nonlinear electroencephalographic measures with respect to anesthetic depth has been addressed, *e.g.*, in Jordan *et al.*[20] and Koskinen *et al.*[21] Our study, however, includes several new aspects. First, the recordings are divided into three groups according to the dose of remifentanil, allowing us to study the influence of remifentanil on the ability of the calculated measures to follow anesthetic depth. Second, the influence of the electroencephalographic frequency band (and thus the role of various electroencephalographic rhythms) on the entropy/complexity measures has been studied. It occurs that although the calculation of these measures does not involve power spectrum (except for SpEn), they are still highly sensitive to the frequency content of the signal. Third, we have incorporated HFD, a relatively uncommon measure in electroencephalographic analysis, into our study. HFD shows the highest prediction probability among the tested measures while preserving monotonic behavior also in the presence of low frequencies.

Most of the measures incorporated into this study are not applied in any commercial anesthesia monitor as such. Comparing the performance of commercial monitoring systems, such as those mentioned in the introduction, is complicated and could, in principle, be done either by using several devices in parallel in the recording setup or by recording the signals and calculating the indices off-line. Because the commercial algorithms are mostly proprietary, the latter way is not possible in practice. Applying several monitoring devices in parallel makes the recording setup complex and is not feasible if the number of systems to be compared exceeds two or three. Despite the fact that the measures compared in this work are not exactly those used in commercial systems, the current study has, besides merely academic value, also the following impact on clinical practice. First, given the great interest in anesthesia/sedation monitoring, it is probable that the different measures quantifying the entropy/complexity of the electroencephalogram will end up in a commercial monitoring device in the future. Second, available monitoring devices use different frequency bands. For example, the lower cutoff frequency of the signal passband varies from 0.1 Hz (the SNAP® monitor; Viasys Healthcare, Madison, WI) to 6 Hz (the CSI® monitor). Our results give a hint of how they might behave in the case of relatively high doses of opiates.

In figures 1 and 2, the behavior of the measures was presented throughout the whole recordings. In these figures, the points of similar propofol concentration but,

because of the potentiating effect of remifentanil on propofol as an anesthetic, not necessarily of similar anesthetic depth fall at any particular timeline. The curves corresponding to different patient groups become comparable if one "drags" the shorter curves from their corresponding endpoints to become as long as the curve of the patient group remi0. The peaks at 4, 8, 12, and 16 min in some of the panels of figure 1 are due to the stimuli related to the OAA/S assessments and show the reactivity of the measures to transient changes in the state of the patient.

In our study, we assumed that steady state in the patients' condition is achieved within 2–3 min after each OAA/S assessment and increase in propofol concentration. This issue was carefully considered by analyzing the trend in the calculated measures within 2 min preceding each OAA/S assessment (not shown in the Results). No significant trend was observed, suggesting that, at least as far as the calculated measures are concerned, the state of the patients can be considered stable. This does not necessarily show as a steady plateau in the curves presented in figure 1, because each of these curves is a median value of the results from 15 patients and is thus subject to statistical fluctuation. Also, within a single recording, electroencephalogram-based measures tend to fluctuate even when a subject is pharmacologically in a steady state, because the state may manifest itself in different electroencephalographic patterns.

When analyzing the dependence of the behavior of the calculated measures on remifentanil concentration, two important results have been presented: the reversal of the remifentanil effect with shifting the signal frequency band toward higher frequencies and the nonlinear nature of this effect. These findings suggest that using different remifentanil concentrations and electroencephalographic measures calculated over different frequency bands may give contradicting results on the direction and magnitude of the effect. Also, the output of the commercial anesthesia monitors using higher frequency band may react to opiates in an opposite manner compared with those using a lower band. It is noteworthy that in many cases (*e.g.*, RBR in fig. 5) the reversal of the remifentanil effect occurs around the point of loss of consciousness (*i.e.*, around OAA/S scores 2 and 3). Whether these two phenomena are related to each other remains to be studied.

Changes in the electroencephalogram are commonly described by the dynamics of rhythms of predefined frequencies. Therefore, it is natural that the behavior of the measures used for anesthesia/sedation monitoring is sensitive to the frequency content of the signal. An example of this phenomenon is seen in figure 1—the variance of the blue curve, corresponding to the subject group receiving a relatively high dose of remifentanil, becomes high toward the end of the recordings, especially when low frequencies are incorporated, indicating

the appearance of delta rhythm typical to remifentanil. We suggest that the goal in the frequency analysis of the electroencephalogram for anesthesia monitoring should not just be to select the "right" frequency band but to detect the various physiologically meaningful electroencephalographic rhythms and to follow their evolution.

In conclusion, our study shows that the electroencephalographic depth-of-sedation measures are extremely sensitive to the frequency content of the signal as well as the dose of opiates administered. These relations may be complex as indicated by the reversed and nonlinear effect of remifentanil concentration on the tested measures. More informative monitoring of sedation as well as well-being of the brain in the intensive care unit could be achieved by detecting and tracking the electroencephalographic rhythms and patterns caused by the particular drugs.

Appendix

Spectral Entropy

The idea of spectral entropy, H_{Sp}, is straightforward in the sense that the amplitude probability density function p in the equation of Shannon entropy $H_{Sh} = \sum p \log p$ is replaced by the power density P from the frequency spectrum of the signal (normalized so that $\sum P_n = 1$):

$$H_{Sp} = -\sum_{i=f_l}^{f_b} P_i \log P_i \qquad (A1)$$

where f_l and f_b define the frequency band we are interested in.[22,23]

Usually spectral entropy is normalized to the range of values between 0 and 1:

$$\text{SpEn} = \frac{H_{Sp}}{\log N_f} \qquad (A2)$$

where N_f is the number of frequency components in the range $[f_l, f_b]$.[13]

Approximate Entropy

Approximate entropy, ApEn, introduced by Pincus, is a measure quantifying the unpredictability or randomness of the signal.[24] ApEn is originated from nonlinear dynamics. It is an approximation of the Kolmogorov entropy in the sense that the limits ($r \to 0$, $N \to \infty$, $m \to \infty$) can be relaxed. Therefore, it can be applied to signals of finite length.[3,23–25]

The calculation of ApEn of signal s of finite length N is performed as follows. First, fix a positive integer m and a positive real number r. Next, from the signal s the $N - m + 1$ vectors $\mathbf{x}_m(i) = \{s(i), s(i + 1) \ldots, s(i + m - 1)\}$ are formed. After that, for each i, $1 \le i \le N - m + 1$, the quantity $C_i^m(r)$ is calculated using

$$C_i^m(r) = \frac{\text{number of such } j \text{ that } d[\mathbf{x}_m(i), \mathbf{x}_m(j)] \le r}{N - m + 1}, \qquad (A3)$$

where the distance d between the vectors $\mathbf{x}_m(i)$ and $\mathbf{x}_m(j)$ is defined as

$$d[\mathbf{x}_m(i), \mathbf{x}_m(j)] = \max_{k=1,2,\ldots,m} (|s(i + k - 1) - s(j + k - 1)|). \qquad (A4)$$

Next, the quantity $\Phi^m(r)$ is calculated as

$$\Phi^m(r) = \frac{1}{N - m + 1} \sum_{i=1}^{N-m+1} \log C_i^m(r). \qquad (A5)$$

Finally, the approximate entropy is defined as follows:

$$\text{ApEn}(m, r, N) = \Phi^m(r) - \Phi^{m+1}(r). \qquad (A6)$$

The parameter r corresponds to an *a priori* fixed distance between the neighboring trajectory points; therefore, r can be viewed as a filtering level, and the parameter m is the embedding dimension determining the dimension of the phase space.

Frequently, r is chosen according to the signal's SD; in this article, we use the values $r = 0.2$ SD and $m = 2$.[3,25]

Lempel-Ziv Complexity

The normalized complexity, C_α, as introduced by Lempel and Ziv, is a measure reflecting the rate of new pattern generation along given sequence of symbols.[26] That is, C_α characterizes the structure or, as the name implicates, the complexity of the signal—whether the signal is predictable (has simple structure) or nonpredictable (has complex, random structure).[5]

The calculation algorithm of C_α for the sequence of symbols $\mathbf{x}_1^N = x_1, x_2, x_3, \ldots, x_N$ of length N is defined as follows. A block B of length l ($1 \le l \le N$) is a subsequence of l consecutive symbols, $B = \mathbf{x}_{i+1}^{i+l} = x_{i+1}, x_{i+2}, \ldots, x_{i+l}$ ($0 \le i \le N - l$). The first block, B_1, is set equal to the first symbol of the sequence $\mathbf{x}_1^N$, *i.e.*, $B_1 = \mathbf{x}_1^1 = x_1$. Next,

$$B_{k+1} = \mathbf{x}_{n_k+1}^{n_{k+1}} \quad (n_k + 1 \le n_{k+1} \le N) \qquad (A7)$$

is defined to be the following consecutive block of minimal length such that it does not occur in the sequence $\mathbf{x}_1^{n_{k+1}-1}$. Therefore, by continuing this recursive procedure until the last symbol of $\mathbf{x}_1^N$ is reached, it is possible to obtain the decomposition of $\mathbf{x}_1^N$ into minimal blocks:

$$\mathbf{x}_1^N = B_1, B_2, \ldots, B_n. \qquad (A8)$$

The complexity c_α of $\mathbf{x}_1^N$ is defined as the number of blocks in the decomposition, n:

$$c_\alpha \equiv n = n(\alpha), \qquad (A9)$$

where α is the number of possible different symbols in $\mathbf{x}_1^N$. The normalized complexity, C_α, is defined as

$$C_\alpha = \frac{c_\alpha(\mathbf{x}_1^N)}{N/\log_\alpha N} = \frac{n(\alpha)}{N} \log_\alpha N. \qquad (A10)$$

Before applying the above described algorithm, the signal s must be converted into a sequence of symbols, which can be done as follows. Depending on the number of different symbols α, $\alpha - 1$ thresholds T_i must be selected within the signal range $s_{min} < \ldots < T_i < \ldots < s_{max}$, where s_{min} and s_{max} are the minimum and maximum values of the signal s, respectively. For example, if $\alpha = 2$, *i.e.*, two symbols, 0 and 1, are used, there is only one threshold T_1, and by comparing the samples of s with this threshold, the signal is converted into the sequence of symbols: If $s(i) < T_1$ then $x_i = 0$, otherwise $x_i = 1$. For larger α, the conversion procedure is analogous.

Higuchi Fractal Dimension

Fractal dimension is another measure of signal complexity, generally evaluated in phase space by means of correlation dimension. However, to obtain a reliable estimate long signal segment is required and, in addition, the calculation process is time-consuming. Higuchi proposed an algorithm for the estimation of fractal dimension directly in the time domain without reconstructing the strange attractor.[27] This method

Table 3. Summary of the Algorithm Parameter Values of the Entropy/Complexity Measures

Method	Parameter	Value
Spectral entropy	Lowest frequency, f_l	0
	Highest frequency, f_h	Sampling frequency/2
Approximate entropy	Embedding dimension, m	2
	Filtering level, r	0.2 * (SD)
Lempel-Ziv complexity	Number of symbols, α	2
	Threshold, T	Mean of signal segment
Higuchi fractal dimension	Maximum interval time, k_{max}	8

Note that the frequency band of spectral entropy calculation is actually limited by the prefilter settings.

gives reasonable estimate of the fractal dimension in the case of short signal segments and is computationally fast.[27,28]

Higuchi's algorithm is based on the following scheme: From a given signal $s = \{s(1), s(2), ..., s(N)\}$, k new curves s_m^k are constructed as follows:

$$s_m^k = \{s(m), s(m + k), \ldots, s(m + \lfloor (N - m)/k \rfloor \cdot k)\}$$
(A11)

$$m = 1, 2, \ldots, k,$$

where both m and k are integers and they indicate the initial time and the time interval, respectively. The length, $L_m(k)$, of each curve s_m^k is calculated as

$$L_m(k) = \frac{1}{k} \left[\left(\sum_{i=1}^{\lfloor \frac{N-m}{k} \rfloor} |s(m + ik) - s(m + (i - 1)k)| \right) \cdot \frac{N - 1}{\lfloor \frac{N - m}{k} \rfloor k} \right]. \quad (A12)$$

The length of the curve for time interval k, $L(k)$, is calculated as the average of the m curves $L_m(k)$ for $m=1,...,k$. If $L(k) \propto k^{-D}$, the signal is fractal-like with the dimension D. Therefore, if $L(k)$ is plotted against $1/k$, where $k = 1, \ldots, k_{max}$, in double logarithmic plot, the data points should fall into straight line with the slope D. Finally, linear fitting by the means of least-squares is applied to the pairs $(\log 1/k, \log L(k))$, $k = 1, \ldots, k_{max}$, and the slope of the obtained line is calculated giving the estimate of the fractal dimension D.

For a summary of the selected parameter values, for each measure considered herein, see table 3.

References

1. Widman G, Schriber T, Rehberg B, Hoeft A, Elger CE: Quantification of depth of anesthesia by nonlinear time series analysis of brain electrical activity. Phys Rev E 2000; 62:4898-903

2. Bruhn J, Lehmann LE, Röpcke H, Bouillon TW, Hoeft A: Shannon entropy applied to the measurement of the electroencephalographic effects of desflurane. ANESTHESIOLOGY 2001; 95:30-5

3. Bruhn J, Röpcke H, Hoeft A: Approximate entropy as an electroencephalographic measure of anesthetic drug effect during desflurane anesthesia. ANESTHESIOLOGY 2000; 92:715-26

4. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. ANESTHESIOLOGY 2004; 100:1353-72

5. Zhang X-S, Roy RJ, Jensen EW: EEG complexity as a measure of depth of anesthesia for patients. IEEE Trans Biomed Eng 2001; 48:1424-33

6. Lipping T, Jäntti V, Yli-Hankala A: Monitoring in anesthesia, Wiley Encyclopedia on Medical Devices and Instrumentation, 2nd edition. Edited by Webster JG. Hoboken, New Jersey, John Wiley & Sons, Inc., 2006, pp 555-65

7. Schnider TW, Minto CF, Shafer SL, Gambus PL, Andresen C, Goodale DB, Youngs EJ: The influence of age on propofol pharmacodynamics. ANESTHESIOLOGY 1999; 90:1502-16

8. Schnider TW, Minto CF, Gambus PL, Andresen C, Goodale DB, Shafer SL, Youngs EJ: The influence of method of administration and covariates on the pharmacokinetics of propofol in adult volunteers. ANESTHESIOLOGY 1998; 88:1170-82

9. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJ, Gambus PL, Billard V, Hoke JF, Moore KH, Hermann DJ, Muir KT, Mandema JW, Shafer SL: Influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanil: I. Model development. ANESTHESIOLOGY 1997; 86:10-23

10. Minto CF, Schnider TW, Shafer SL: Pharmacokinetics and pharmacodynamics of remifentanil: II. Model application. ANESTHESIOLOGY 1997; 86:24-33

11. Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug effect with a computer-controlled infusion pump. J Pharmacokinet Biopharm 1992; 20:147-69

12. Struys MM, De Smet T, Depoorter B, Versichelen LF, Mortier EP, Dumortier FJ, Shafer SL, Rolly G: Comparison of plasma compartment *versus* two methods for effect compartment–controlled target-controlled infusion for propofol. ANESTHESIOLOGY 2000; 92:399-406

13. Viertiö-Oja H, Maja V, Särkelä M, Talja P, Tenkanen N, Tolvanen-Laakso H, Paloheimo M, Vakkuri A, Yli-Hankala A, Meriläinen P: Description of the Entropy™ algorithm as applied in the Datex-Ohmeda S/5™ Entropy Module. Acta Anaesthesiol Scand 2004; 48:154-61

14. Ferenets R, Lipping T, Anier A, Jäntti V, Melto S, Hovilehto S: Comparison of entropy and complexity measures for the assessment of depth of sedation. IEEE Trans Biomed Eng 2006; 53:1067-77

15. Anier A, Lipping T, Melto S, Hovilehto S: Higuchi fractal dimension and spectral entropy as measures of depth of sedation in intensive care unit, Proceedings of the 26th IEEE EMBS Annual International Conference. September 1-5, 2004; San Francisco, California. Piscataway, New Jersey, Institute of Electrical and Electronics Engineers, Inc., pp 526-9

16. Chernik DA, Gillings D, Laine H, Hendler J, Silver JM, Davidson AB, Schwam EM, Siegel JL: Validity and reliability of the Observer's Assessment of Alertness/Sedation Scale: Study with intravenous midazolam. J Clin Psychopharmacol 1990; 10:244-51

17. Smith WD, Dutton RC, Smith NT: Measuring the performance of anesthetic depth indicators. ANESTHESIOLOGY 1996; 84:38-51

18. Smith WD, Dutton RC, Smith NT: A measure of association for assessing prediction accuracy that is a generalization of non-parametric ROC area. Stat Med 1996; 15:1199-215

19. Schneider G, Hollweck R, Ningler M, Stockmanns G, Kochs EF: Detection of consciousness by electroencephalogram and auditory evoked potentials. ANESTHESIOLOGY 2005; 103:934-43

20. Jordan D, Schneider G, Hock A, Hensel T, Stockmanns G, Kochs EF: EEG parameters and their combination as indicators of depth of anaesthesia. Biomed Tech 2006; 51:89-94

21. Koskinen M, Seppänen T, Tong S, Mustola S, Thakor NV: Monotonicity of approximate entropy during transition from awareness to unresponsiveness due to propofol anesthetic induction. IEEE Trans Biomed Eng 2006; 53:669-75

22. Inouye T, Shinosaki K, Sakamoto H, Toi S, Ukai S, Iyama A, Katsuda Y, Hirano M: Quantification of EEG irregularity by use of the entropy of the power spectrum. Electroenceph Clin Neurophysiol 1990; 79:204-10

23. Rezek IA, Roberts SJ: Stochastic complexity measures for physiological signals analysis. IEEE Trans Biomed Eng 1998; 45:1186-91

24. Pincus SM: Approximate entropy as a measure of system complexity. Proc Natl Acad Sci U S A 1991; 88:2297-301

25. Richman JS, Moorman JR: Physiological time-series analysis using approximate entropy and sample entropy. Am J Physiol Heart Circ Physiol 2000; 278:2039-49

26. Lempel A, Ziv J: On the complexity of finite sequences. IEEE Trans Information Theory 1976; IT-22:75-81

27. Higuchi T: Approach to an irregular time series on the basis of the fractal theory. Physica D 1988; 31:277-83

28. Accardo A, Affinito M, Carrozzi M, Bouquet F: Use of the fractal dimension for the analysis of electroencephalographic time series. Biol Cybern 1997; 77:339-50