MONITORING ANESTHETIC DEPTH
Modification, Evaluation, and Application
of the Correlation Dimension

Een wetenschappelijke proeve op het gebied van de Medische Wetenschappen

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Anesthesia is administered to patients to facilitate surgical and diagnostic procedures. The anesthesiologist generally determines the amount of anesthetics needed on the basis of body weight (or body surface area). However, the inter-individual variation in sensitivity to anesthetics is wide. This also causes a large variability in the time necessary for the patient to awaken and recover from anesthesia. Unnecessary extended periods of anesthesia may be harmful because of dysregulation of vital functions. Because of the natural variability in sensitivity to anesthetics, there is the need for an individualized dosage scheme evident. Therefore the administration of anesthetics should not only be based on body weight, but it should also be related to the anaesthetic effect. The needed level of anesthesia furthermore is determined by the strength of surgical stimulation. Therefore, throughout surgery a constant readjustment of the ‘depth of anesthesia’ (DOA) is necessary. Such adjustments of DOA can only be performed accurately if DOA is monitored. In clinical practice the monitoring is based on the evaluation of multiple physiologic parameters. Which of the individual parameters is most valuable depends on the combination of changes and thus is it difficult to select one single one.

The effect of general anesthesia is the result of interactions with several processes in the CNS. At present monitoring of DOA is based on physiologic reactions resulting from these interactions in the CNS: such as absence of motor responses, changes in blood pressure, heart rate, respiration, carbon dioxide production and temperature. To provide a more direct image of the effects of anesthetics an analysis of the processes in the CNS is needed. The EEG is a well-known, electrically measurable signal that reflects the overall activity of the CNS. The interpretation of the EEG, however, is complex because it is a reflection of the state of the brain, the effects of the surgical procedure and the influence of the anesthetics. The different anesthetics prove to have different effects on the EEG. The difficulty of interpretation of the unprocessed EEG makes its use for routine monitoring of DOA clinically unfeasible. Processing of EEG as applied so far (frequency bands, spectral edge frequency etc.) also is not universally applicable.

Nevertheless, the impression that the EEG informs directly about changes in the physiological state of the patient and the inadequacy of linear measures so far to assess DOA under different circumstances were the main reasons to apply non-linear mathematics to the EEG. Chaos-theory provides new possibilities to analyze the EEG. One variable from chaos-theory that is promising to be representative for the amount of sub-processes or the complexity of the activity of the CNS as reflected in the actual EEG signal: namely correlation dimension (D2) was selected. This thesis describes an adapted algorithm, therefore another abbreviation CD is
introduced to pronounce the difference with $D_2$, to compute CD and evaluates its usefulness to the monitoring of DOA.

The objective of the studies described in this thesis was to investigate the following questions:
- Is CD of the EEG related to DOA?
- Can the CD algorithm be optimized to improve its sensitivity to DOA?
- Can CD of the EEG provide relevant information to the anesthesiologist (practical evaluation)?

To answer these questions, analyzes and experiments were carried out to assess the:
- dependencies of CD to parameters involved in the calculation algorithm.
- relationship between CD and DOA in rat.
- relationship between CD and DOA in human.
- performance of CD under normal circumstances in the operating room.
1 Introduction

1.1 History of anesthetic practice
1.1.1 Arise of anesthetic practice
Before the arise of anesthetic practice the individual’s well being was not genuinely considered until the need for surgical treatment of disease arose; attempts at relieving pain were previously sporadic. It is rather remarkable that the beginning of the development of anesthetic practice did not coincide with the development of surgical practice. An explanation lies in the concepts of disease prevailing at the time. For more than 2,000 years disease was considered to be the result of a disturbed balance of the cardinal humors of the body. When in balance, the body was believed to be healthy, but showed symptoms of disease when upset. In the 18th and 19th centuries Morgagni described the results of a large number of autopsies. Analyzing the results he claimed that most diseases were accompanied by morphological changes of organs. Cure of diseases would be possible by surgical correction of the morphological deviations. However, such surgical correction could not develop freely before the risky influence of pain and infection had been removed. The needs for anesthetic practice became evident.

1.2 Monitoring anesthetic effects
1.2.1 Monitoring variables
The principal tasks of the anesthesiologist are to provide relief of pain for patients during surgery and to provide optimal operative conditions for surgeons, both in the safest manner possible. This task is performed by execution of the functional sequences described in control systems theory. Thus, the anesthesiologist acts as an "external control unit" for various "controlled variables" derived from the cardiovascular system, gas transport, ventilation, and the sensory and motor nervous system. A variety of monitoring devices inform about the level and variability (short and long term, spontaneous and evoked) of these variables. These monitoring devices serve the same goal: the assessment of the patient’s condition with special emphasis on detection of change. The anesthesiologist modulates the patient’s condition with drugs that can be divided into the following three categories: analgesics (pain relief), anesthetics and hypnotics (sleep/consciousness) and muscle relaxants. The effect of general anesthesia is the result of interactions with several processes in the central nervous system (CNS). At present monitoring of anesthetic effects is based on physiologic reactions (changes in heart rate, blood pressure etc.) resulting from these interactions in the CNS. To provide a more direct image of the effects of anesthetics an analysis of the processes in the CNS is needed. The EEG is a well-known, electrically measurable signal that is a direct result of...
the activities of the CNS. The interpretation of the EEG, however, is complex because it is a reflection of the state of the brain, the effects of the surgical procedure and the influence of the anesthetics. The different anesthetics prove to have different effects on the EEG. The complexity of interpretation of the unprocessed EEG makes its use for routine monitoring of the depth of anesthesia (DOA) clinically unfeasible. Processing of EEG as applied so far (frequency bands, spectral edge frequency etc.) neither is universally applicable. The nonlinear approach may provide new variables to analyze the EEG to judge DOA.

1.2.2 “Anesthetic depth”
General anesthesia can be achieved by depression of several functions of the CNS. These functions mainly relate to the following four components: analgesia, consciousness, autonomous reflexes, and indirectly muscle relaxation. Different drugs prove to have specific effects on different physiological subsystems. This enables the anesthesiologist to more specifically control the patient’s condition by choice of the specific drug needed in that situation. However, although the anesthesiologist is able to change the condition of the patient by administering drugs, this does not mean that he also is able to measure these changes. Of course the amount of anesthetics delivered to the patient is known and the apparently major effect can be seen as an anesthetized patient. However the level of suppression of CNS activity is not exactly known. The term “anesthetic depth” is in fact misleading as it suggests that there should exist some sort of physiologic parameter that is measurable, controllable and related to it. In practice “anesthetic depth” is a simple term that is used to indicate whether the patient’s level of anesthesia is sufficient to undergo safe surgery with fast recovery at the end of the operation. In this light too low an anesthetic depth occurs in case of awareness (recall of events during anesthesia) and response to a noxious stimulus. Too deep an anesthetic depth results in dangerous changes in physiologic function and may lead to death. It at least results in a patient that after the operation needs on average substantial more time to awake from anesthesia. Thus, “anesthetic depth”, if interpreted literally does not exist, but in practice it serves to facilitate simple communication about a very complex matter that is mainly being influenced by the components: analgesia, consciousness, muscle relaxants and autonomous reflexes. If in this thesis the term “anesthetic depth” or “depth of anesthesia” (DOA) is used, please keep in mind the previous statement about its interpretation.

1.3 Measuring anesthetic depth
1.3.1 Non-EEG approach
DOA is influenced by different components of the CNS. Anesthetic drugs more or less independently act on these components. A difficulty - despite categorizing patients by gender, age, weight etc. - concerns the large inter- and intra-variability of patients in responses to anesthetics. These phenomena make measuring anesthetic depth a complex matter. An
accepted golden standard and feasible method for a gradually monitoring of DOA is still not found. Therefore measuring the performance of a new indicator of DOA is difficult. An accepted method is the determination of movement of the patient in response to incision. The value of the indicator that prevents movement in response to incision in 50% of the patients serves as a guideline to the assessment of adequacy of inhalation anesthetics (MAC value). Therefore, measuring the performance of a new indicator of DOA is difficult. An accepted method is the determination of movement of the patient in response to incision. The value of the indicator that prevents movement in response to incision in 50% of the patients serves as a guideline to the assessment of adequacy of inhalation anesthetics (MAC value).

Monitoring DOA started with John Snow who defined five stages of ether anesthesia together with the accompanying delivery concentration schemes to reach a particular stage of anesthesia. Guedel refined John Snow’s classification of ether anesthesia stages and defined these stages by clinical signs such as pupil size, respiration characteristics, eyelid reflex, swallowing and vomiting reflexes. With volatile anesthetic agents, the concept of minimum alveolar concentration (MAC) was introduced. Because the alveolar concentration is (in steady state) in equilibrium with the plasma and brain concentration does the measured end-tidal concentration serve to give an indication of DOA. To overcome the problems with the measurement (qualitative instead of quantitative and interindividual variability for the quantitative measurements) of the clinical signs mentioned in Guedel’s scheme, the PRST score was introduced. The PRST-score is a combination of scores for heart rate, systolic blood pressure and tear production. With the Isolated Forearm Technique (IFT) an inflatable cuff on one arm of the patient prevents muscle relaxants to reach the circulation in this arm. Verbal commands to the patient asking to squeeze the experimenter’s hand verified suppression of consciousness. Main drawbacks of this technique is the difficulty to distinguish purposeful arm movements from reflex movements and the limited time that it can be applied because of ischemic risks. Lower oesophageal contractility (LOC) measures the contractions of the muscles (smooth muscles less affected by muscle relaxants) in the lower part of the oesophagus. Oesophageal contractions originate partly from the autonomous nervous system. A relationship between LOC and halothane concentration was shown during general anesthesia. For LOC as a measure of DOA positive results were reported. However, also negative results were reported. Heart rate variability measures the variation in the beat to beat time differences. This variability was shown to decrease with deeper levels of anesthesia.

At present, the non-EEG approach doesn’t provide a single monitoring variable that sufficiently fulfills the requirements of a suitable monitor for DOA. Therefore, the search for new variables extended towards measures extracted from the EEG. Expectations of these new measures were high as the EEG presumably more directly reflects the effects of administered anesthetic drugs.
1.3.2 Linear approach applied to the EEG

Until the arise of the nonlinear approach, the concept of modeling dynamical systems or time-series by linear differential equations was common practice. The basic approach to EEG analysis involved the assumption that the EEG is stochastic. Consequently, statistical pattern recognition techniques, segmentation procedures, syntactic methods, knowledge-based approaches have been developed with different levels of success. A very well known example of the linear approach to time-series analysis is spectral analysis. The spectrum is obtained by a Fourier transform and is a linear combination of sinusoidal signals with different frequencies, phase and magnitude. A short overview of linear measures applied to the EEG to measure DOA is discussed in the next paragraph.

Power spectrum measures:

Two variables that are frequently examined as a measure of DOA, are the spectral edge frequency (SEF) and the power in the delta band (δ-band). The spectral edge is the frequency where below of which 90% (SEF90) or 95% (SEF95) of the total signal power is concentrated. The power in the δ-band is defined as the power content within the frequency range: 0-4 Hz. The nomenclature and definitions for other frequency bands are: θ-band: 4-8 Hz, α-band: 8-12 Hz, and β-band: 12-30 Hz. SEF95 studies show different outcomes concerning its suitability as an indicator of DOA. During combinations of isoflurane, 70% N₂O and fentanyl, SEF95 predicted movement response to surgical stimuli. Preliminary results of a multicenter study designed to determine the utility of SEF in combination with heart rate and blood pressure for estimating DOA indicate that this procedure may provide better control of DOA. Another study concludes that using SEF to estimate DOA during induction and laryngoscopy may increase safety in high-risk patients undergoing cardiac surgery. However, other studies concluded that SEF is an unreliable indicator of DOA. Other authors claim that the median frequency (MEF or SEF50) should be kept below 6 Hz to prevent awareness during anesthesia and can be utilized as a quantitative EEG parameter for closed-loop feedback control of methohexital anesthesia. A study performed at our department showed the mean EEG frequency of the 0-24 Hz spectrum to reduce with the same time course as propofol plasma concentration. However, higher values for the mean frequency (indicating wakeup) were estimated not before the change of other clinical variables. A study comparing the anesthetic effects of desflurane and isoflurane showed that patients with baseline δ-band power < 80% of the total power showed increases in δ-band power and patients with baseline δ-band power > 80% of the total power produced no change in EEG frequency with deepening of anesthesia. Also, changes in the δ-band power were found during anesthetic induction with enflurane.
Compressed spectral array:
The compressed spectral array (CSA) is a three dimensional image created by displaying the subsequent frequency distributions in shifted positions behind each other. Some studies used the CSA as a monitor of EEG drug effects, however, quantitative information about DOA were not reported.

Aperiodic waveform analysis:
Aperiodic waveform analysis maps each waveform in relation to its frequency, amplitude, and time of occurrence rather than averaging a large number of waveforms over a given period. Aperiodic waveform analysis was used as a measure of thiopental's CNS drug effect and served to steer a computer-controlled infusion pump. When the constant serum thiopental concentration was plotted against the number of waves per second for each subject, a biphasic serum concentration versus EEG effect relationship was seen. The effect of intravenous flumazenil (10 mg) on the EEG (using aperiodic analysis) was investigated in 7 volunteers. The authors conclude that flumazenil had no significant EEG effects. Aperiodic analysis was used to monitor cerebral activity prospectively in twenty-one patients undergoing carotid artery surgery under general anesthesia. Aperiodic analysis was used to evaluate adequacy of the anesthetic level with rapid-sequence induction of anesthesia. The concentration-effect relationship of etomidate can be characterized in individual rats using aperiodic analysis in the 2.5-7.5 Hz frequency band of the EEG.

Autoregressive modeling:
Autoregressive (AR) modeling of a time series involves the prediction of the next value of this time series based on a linear combination of a number of earlier values. The coefficients used in this linear combination are called AR-coefficients. For stationary time series the averaged accuracy of this prediction (with fixed coefficients) should not change. It is just this property that is being conducted if the EEG signal becomes non-stationary (for example induced by administrated anesthetics) and this change is reflected in the AR coefficients. It was shown that changes in these AR coefficients of the EEG correlated with changes in the level of anesthesia. Using AR coefficients as an input to a neural network, in 85% of the cases the network predicted movement during anesthesia correctly compared to 65% when only hemodynamic parameters were used as input to the network. Changes in brain activity were studied at different depths of isoflurane anesthesia. Using autoregressive modeling and clustering analysis a set of basic patterns was defined to classify the EEG. These patterns were then related to the clinical DOA. The authors conclude that the EEG pattern might be a sensitive tool for decision making during administration of general anesthetics. Using a technique called semilinear canonical correlation (SCC) it is possible to extract a parameter from the EEG that is statistically optimally correlated with the apparent concentration of the benzodiazepine in the effect site. SCC was used to extract a canonical
univariate parameter (CUP\textsubscript{B}) of the EEG effect by weighing different frequency bands of the EEG power spectrum. With SCC the accompanying weights are optimized using a sigmoid-$E_{\text{max}}$ model relating effect site concentration to drug effect. The authors conclude that CUP\textsubscript{B} correlates more accurately and consistently with the predicted EEG effect than previously (at that time) reported EEG measures of benzodiazepine effect.

**Evoked potentials:**
An Evoked Potential (EP) is the response to an applied sensory stimulus to a sensory pathway. There are different ways to provoke an EP, i.e. by means of electrical (SEP), visual (VEP), or auditory (AEP) stimulation. In either way, the purpose of the stimulation is to test the reactivity of the CNS. The AEP component in the range from 10 ms to 50 ms after the stimulus is the middle latency auditory evoked potential (MLAEP). Amplitudes and latencies of peaks identified in the MLAEP relate to anesthetic effects.\textsuperscript{23,28,29,85,176,205} The AEP was found to be able to detect the transition from unconsciousness to consciousness during propofol anesthesia.\textsuperscript{57,58} Loss of consciousness after a bolus dose of midazolam was associated with an increased mean value of one of the defined latencies (Nb).\textsuperscript{17} Changes in spontaneous or auditory evoked brain activity after a brief electrical stimulus at the wrist could not be used to predict whether anesthetized patients would subsequently move at the time of surgical incision.\textsuperscript{99} Although results seem to be very promising, AEP measurement has one major problem. To obtain one single AEP, numerous auditory stimuli must be applied and the accompanying responses averaged. This puts some restrictions to the ability to detect fast changes in anesthetic condition and results are sensitive to artifacts. However, recently an AEP-index was introduced that measures the level of consciousness during general anesthesia.\textsuperscript{79} Anesthetic drug induced decreasement of peak amplitudes and increasement of peak latencies are mapped into this index, termed the AAI-index. An AEP monitor utilizing this index was introduced by A-line\textsuperscript{TM}.

**Blink-reflex:**
The blink reflex is a SEP elicited by an electrical stimulus in the vicinity of the eye. Studies performed at our department show that latency of defined components (R1 and R2) increase whereas duration and area decrease with increasing depth of sedation and anesthesia.\textsuperscript{133,134} However, utilization is restricted to the lighter and medium anesthesia levels as the components R1 and R2 disappear at the deeper levels of anesthesia.

**Burst suppression:**
During moderate and deep anesthesia, the EEG shows a burst suppression pattern (BSP), consisting of abruptly occurring high amplitude bursts alternating with periods of relative silence (suppression). The Burst Suppression Ratio (BSR) is defined as the ratio of the
Introduction

summation of the suppression parts in a certain epoch and the total length of that epoch. Devices designed for EEG trend monitoring during anesthesia should be aware of the non-stationarity of the BSP and allow for burst suppression recognition before spectral analysis. The presence of BSP did not predict lack of response to a noxious stimulation in isoflurane anesthetized rats. Some studies use the onset of the BSP to titrate the administered anesthetic drug. The coefficients of variability of the segment lengths were similar for the two anesthetics. A system for monitoring and controlling i.v. anesthesia in rats used the BSR as the control variable. A closed-loop infusion system maintained BSR accurately at targets of 30%, 50%, 70% or 90% for 60 minutes with propofol or etomidate. The authors conclude that differences between i.v. anesthetics (revealed during the maintenance of the target BSR) may be useful in screening new compounds in preclinical development. Isoflurane and desflurane produced equivalent degrees of burst suppression at similar MAC levels, however, age and δ-activity were important variables affecting this response. The degree of interrelations between EEG frequency components during burst suppression was found to depend on the sedation depth induced by hypnotic drugs.

1.3.3 Incidences at the operating room

In 1972, with the inaugural speech “De dood op tafel” (Death on the table), anesthesiologist Prof. Dr. Smalhout assumed that every year mistakes made by the anesthesiologist caused the death of approximately 200 patients. Although his colleagues were not amused about this coming out, it started a discussion and members of the Upper House of the States General asked the Ministers of Education and Science and of Health and Environment Protection questions connected with this inaugural speech. Although the answers to the questions mainly denied the existence of serious shortcomings one year later the chairman of the Health Council was asked by the then Minister of Health and Environmental Protection to set up a commission to compile an advisory report to inform about recent developments in the field of anesthesiology. As a result, in 1978, the commission advised sixteen recommendations concerning the safety of patients subjected to anesthesia. The Dutch Health Council suggested that basic intra-operative monitoring should at least involve the continuous evaluation of the patient’s oxygenation, ventilation, circulation and temperature and defined a minimal package of monitoring equipment. Several western countries followed this Dutch initiative and it is remarkable that the American Society of Anesthesiology waited until 1986 to do so.

An impression of currently demanded monitored variables, divided into different categories, is listed below. Some of these variables are routinely requested in every operation whereas others are demanded in particular situation.
**Oxygenation**: to ensure adequate oxygen concentration in the inspired gas and the blood.  
**Monitored variables**: the inspired oxygen concentration in the patient’s breathing system and the blood oxygenation (SaO₂) measured by pulse oximetry.

**Ventilation**: to ensure adequate ventilation of the patient.  
**Monitored variables**: the end-tidal CO₂ concentration, expired oxygen, nitrous oxide, inhalation anesthetic gases and vapors and airway pressure. Respiration rate and tidal volume.

**Circulation**: to ensure the adequacy of the patient’s circulatory function.  
**Monitored variables**: the electrocardiogram, arterial blood pressure, cardiac output and heart rate.

**Body temperature**: to maintain an appropriate body temperature.

The experience of the anesthesiologist together with information of indirect measures like heart rate, blood pressure, oxygen saturation etc. provides an indication of the patient’s condition or anesthetic depth. The inaugural speech of Prof. Smalhout, however, indicated the risk of human mistakes to the safety of anesthetic practice and therefore, if new monitoring variables can provide additional information concerning DOA, it will hopefully assist the anesthesiologist to better judge DOA. Conventional linear analyses of the EEG did not provide valid variables that (independent of the utilized anesthesia technique) predict and reproducibly reflect the reactions of the patient during anesthetic practice. Perhaps, the nonlinear approach can provide new variables to analyze the EEG to judge DOA.

### 1.4 Nonlinear approach

#### 1.4.1 Introduction

The nonlinear approach became important as it turned out that simple deterministic nonlinear mathematical and physical systems can generate irregular (time-)series that can not be subscribed to sources of randomness. The irregular, but not random, behavior brought the term chaos in life for this category of dynamical systems. In the following we assume that the values of the time series of these systems always stay in a bounded interval.

#### 1.4.2 Chaos theory

Before the elaboration of chaos theory, two groups with different behavior categorized dynamical systems: random behavior of stochastic systems or predictable behavior of deterministic systems. Observed irregular behavior was often subscribed to assumed stochastic properties of the examined system. Although a chaotic system must be categorized as a deterministic system, the uncommon behavior of these systems justifies a special treatment of these systems. It is the dependence of initial conditions and exponential...
divergence that causes a system's behavior to change dramatically with infinitesimal changed initial conditions.

A difficult matter in the theory of nonlinear dynamics is to distinguish nonlinear deterministic chaotic behavior from stochastic behavior. In other words: can it be demonstrated that observed irregular behavior originates from a nonlinear dynamical (chaotic) system or from a stochastic system. In the time domain the rate of decay of autocorrelation functions fails to discriminate between both options since the autocorrelation of colored noise can be similar to that of a chaotic signal. In the frequency domain the power spectrum also fails to determine the origin of the system's dynamics. To obtain more information about the system's dynamics a two-dimensional phase plot may already reveal structure that is hidden in the dynamics. With this concept of phase space reconstruction it may be possible to determine nonlinear correlations in a single measured time-series of a particular system under study.

1.4.3 Phase space representation

The behavior of a deterministic dynamical system can be exactly observed if its state and dynamics are known. The state is an instantaneous snapshot of the system and is expressed as the current values of all the variables necessary to characterize the system at a given instant in time. This set of variables is referred to as the state vector. The system's dynamics characterize the change of the system's state as a function of time and can be described by a mathematical model or a set of differential equations. The sequence of subsequent state vectors plotted in phase space fill out a trajectory that characterizes the system's time evolution or dynamics. If we delete a possible first segment of the trajectory, influenced by an artificial initial state, we find an attractor of the system.

In general, the underlying dynamics of biological measured time series are unknown. The number of variables that determine the system's behavior are unknown and are in general not measurable. Now it seems that with biological time series the concept of plotting state vectors in phase space turns out to be worthless. However, a solution to this problem came with the embedding theorem of Takens, which suggests that if only one variable of the system can be measured, it is still possible to reconstruct the underlying dynamics of the system. He proved that the method of delays provides a way to reconstruct the trajectory. Suppose the measured discrete time series:

\[ v: v[1], v[2], ..., v[N] \]

Reconstruction vectors \( V_k \) are subsequences of the form:

\[ V_k=(v[k], v[k+r], ..., v[k+(m-1)r]) \]
where \( \tau \Delta t \) (\( \Delta t = \text{sampling interval} \)) is the delay time and \( \tau \) defines the number of digitized samples between the \( m \) different coordinates of the reconstruction vector. From the time series \( v \) a total of \( k_{\max} = N - (m-1) \tau \) \( m \)-dimensional reconstruction vectors can be created. By varying \( k \) from 1 to \( k_{\max} \) a sequence of reconstruction vectors is formed that fill out the trajectory or attractor (if bounded) in phase space.

### 1.4.4 Attractor related measures

Takens embedding theorem defines a procedure to obtain a trajectory or attractor in phase space that characterizes the system’s time evolution or dynamics. This transition from analyzing properties of the time series towards analyzing properties of the attractor gives rise to a totally different way of thinking. Instead of concentrating on 1-dimensional time series, one has to deal with numerous connected points in a higher dimensional phase space. Phase space filling properties, self-similarity properties, spatial correlation between points, divergence of initial nearby points, and predictability of points serve to define various new attractor related measures.

**Correlation dimension (\( D_2 \)):**

\( D_2 \) is extracted from the correlation integral, which can be calculated by evaluating the statistics of distances between reconstruction vectors (points on the attractor). Consider the set of points \( \{ V_k: k=1...k_{\max} \} \) on the attractor. The correlation integral \( C(r) \) is defined according to:

\[
C(r) = \frac{1}{k_{\max} (k_{\max} - 1)} \sum_{k,l=1}^{k_{\max}} \Theta(r - \| V_k - V_l \|)
\]

\[D_2 = \lim_{r \to 0} \frac{\ln C(r)}{\ln r}\]

Where \( \Theta \) is the Heaviside function (\( \Theta(x)=1 \) for \( x>0 \) and \( \Theta(x)=0 \) else), \( \|...\| \) means the Euclidean distance and \( k_{\max} \) equals the number of points on the attractor. Note that \( C(r) \in [0,1] \) and is an estimate of the probability that two reconstruction vectors are within distance \( r \). In theory \( C(r) \) must be estimated for \( N \) going to infinity (\( N \to \infty \)) and for the limit of \( r \) going to zero (\( r \to 0 \)), but in practice this is not possible. In formula 1.4 where \( D_2 \) is defined, the limit of \( r \) going to zero (\( r \to 0 \)) cannot be realized because \( N \) is finite. Instead the slope of \( \ln C(r) \) as a function of \( \ln r \) is used. In fact \( D_2 \) is extracted from \( C(r) \) at the so-called scaling region where a power relationship exists between \( r \) and \( C(r) \) in the sense that for constants \( c \) and \( d \)

\[C(r) \sim c r^d\]

Then, according to 1.4, \( d \) has to be equal to \( D_2 \). This value of \( D_2 \) is estimated as the average slope of \( \ln C(r) \) as function of \( \ln r \) in the scaling region. In practice, this definition of the scaling region appears to be rather vague. More specifically, the slope of \( \ln C(r) \) as
function of \( \ln r \) is in general not exactly constant even not in the scaling region. Casaleggio and coworkers proposed a method for the automatic estimation of the scaling region and proposed an index that quantifies the variations of this slope in the scaling region.\(^{20,21}\) However, many articles don’t mention the criterion used to define this scaling region. The correlation dimension quantifies the self-similarity of the attractor that is expressed by the scaling region in the \( \ln(C'(r)) \) against \( \ln r \) plot. The latter is true only when it is known to be present. If it is not certain whether the underlying dynamics are from a low-dimensional deterministic origin, the results of the correlation dimension should be interpreted with care. Many articles characterize the correlation dimension as a measure related to the number of underlying processes responsible for the dynamic behavior of the system under study.

**Lyapunov exponents:**
The Lyapunov exponents contain information about the exponential increase of small difference in initial state due to the time evolution of the system. It depends strongly on the direction of the difference vector between these initial states. The exponents can be estimated by measuring the growth rate of the differences for nearby states.\(^{217}\) Another method uses estimates of the derivatives of the time evolution maps.\(^{42}\)

**Entropy:**
Entropy is a thermodynamic quantity for systems in equilibrium describing the amount of molecular disorder in the system.\(^{90}\) For dynamical systems the notion is used in a different way, though there is an analogy in the mathematical details. A system’s measured time series can be regarded as a stream of numbers. The entropy is a measure for the uncertainty of prediction of a future value on the basis of previous values. The time series then can be analyzed in terms of “How much do I learn of the system’s state when I perform exactly one more measurement?” or “When I observed the entire past how far can future behavior of the system be predicted?” For example, for a system at rest and a periodic system, a single observation respectively the observation of a single period suffices to determine the whole future. With a sequence of random numbers the knowledge of previous numbers provides no information about the next number. The inverse value of the entropy is the time scale relevant for the predictability of the system. There are different entropy definitions: the order-\( q \) Renyi entropies and the Kolmogorov-Sinai entropy are commonly mentioned in literature but unfortunately are difficult to extract from measured time series. However, in 1983, Grassberger and Procaccia developed a formula, based on the K-S entropy, to measure entropy of a time series.\(^{64}\) For two practical implementations of this formula, see Pincus et al.\(^{139}\), and Schouten et al.\(^{164}\)
Dimensions:
Often attractors of deterministic dynamical systems are very complicated sets. The complexity of the structure increases if one considers details of smaller length scale. In order to quantify the complexity of those, so called fractal sets, various dimensions have been introduced. All these dimensions measure in some way how the information (in bits), needed to specify the state of the system within accuracy $r$, increases with $\ln r$.

For numerical estimation the most practical one is the $D_2$ dimension, based on the probability $C(r)$ that two randomly chosen points on the attractor are within distance $r$. This dimension equals $D_2 = \lim_{r \to 0} \frac{\ln C(r)}{\ln r}$, see 1.4.

Other such dimensions are the information dimension, the pointwise scaling dimension ($D_{21}$), the point correlation dimension ($PD_2$), the coarse-grained correlation dimension ($D_{cg}$), and the correlation index ($D^*$).

1.4.5 Embedding parameters
The embedding theorem requires the choice of the parameters embedding dimension ($m$), delay time ($\tau \Delta t$), and the number of samples ($N$), i.e., length of the segment of the time series under study. The three parameters, each of them separately, have direct influence on the reconstructed attractor, which serves to facilitate the extraction of nonlinear dynamical properties of the studied system. Therefore, it is important to choose appropriate parameters. Moreover, if the extracted nonlinear properties are intended to be used in a system control environment (e.g., for the purpose of monitoring DOA), wrong parameters will obscure the required system information and hinder a successful application of the nonlinear approach.

Delay time ($\tau \Delta t$):
If the measured time series has no noise component and is of infinit length ($N \to \infty$), $\tau$ would have no influence on the reconstructed attractor. In practice, however, this is never the case and the choice of $\tau$ has considerable influence. If $\tau$ is chosen too small the coordinates of the reconstruction vector are highly autocorrelated. On the other hand if $\tau$ is chosen too high the structure of the trajectory is lost (coordinates of the reconstruction vector are not related and the result is ‘acting’ like noise). Many solutions to the ‘lag’ problem have been proposed to obtain an optimal value for $\tau$. Often the first zero crossing of the autocorrelation function is used to measure the shift from redundancy to irrelevance with nonlinear systems. In contrast to the linear dependence measured by autocorrelation, mutual information supplies a measure of general dependence and better values for $\tau$ would be obtained with the first local minimum of the mutual information between reconstructed coordinates. Given the first coordinate $v[k]$ of $V_k$, the mutual information can be obtained by estimating how many bits on the average can be predicted about the coordinates $v[k+\tau]$, $v[k+2\tau]$, etc. Later, this concept of mutual
information was applied to the correlation integral. This proposition provided a practical and easy to calculate criterion for the best choice of $t$. As a guideline to chose $t$, a new computational efficient approach used the reconstruction expansion from the identity line of the embedding space. Hereby, expansion from the main diagonal was quantified by measuring the average displacement of the embedding vectors from their original locations on the line of identity. The delay time $T \Delta t$ should not be chosen independently of $m$, but one should choose an appropriate value for the delay time window $T_w = (m-1)T \Delta t$, which is the total time spanned by the components of each reconstruction vector. The time lag dependence of a statistic based on correlation integrals was used to find a value for this delay time window $T_w$. By analyzing the effective scaling regime used to compute the correlation dimension using the Grassberger-Proccacia algorithm, an inequality relating the maximum allowed $T$ to quantities such as the embedding dimension, the length of the time series, and entropy was derived. An upper bound for the proper $T$ was obtained by solving this inequality. Furthermore, they conclude that with respect to the delay time window $T_w$, $T$ has more influence on results than $m$. With fixed $T_w$, lower values for $T$ are preferred and $m$ should accordingly be adapted to conform $T_w$. Another method to obtain an estimate for the delay time window used the time series average and its accompanying average-crossings to deduce a value called the characteristic time. A formula using this characteristic time was presented to provide the estimate.

**Embedding dimension ($m$):**

If the dynamics of a measured signal (e.g., brain activity as reflected in the EEG signal) are unknown, the number of variables that determine the system’s behavior is also unknown. The question arises what to choose for the embedding dimension. If the embedding dimension $m$ is too small, the full complexity of the state-space trajectory will not be recovered. If the trajectory serves to estimate one of the many nonlinear measures, the usual procedure is to start with a low $m$ and stepwise increase $m$ until the measure under study just saturates to some specific value. This procedure, however, requires a considerable amount of computer time as the nonlinear measure must be calculated for several embeddings. Guided by topological considerations, to determine the minimal necessary $m$, the method of false nearest neighbors was introduced. It is based on the idea that in consecutive reconstruction embeddings from $m$ to $m+1$, one can differentiate between points on the trajectory that are ‘true’ neighbors and those which are ‘false’ neighbors. A neighbor is defined as false if it is only nearby because the trajectory is viewed in too small an embedding space. In a large enough embedding space all neighbors will be ‘true’ neighbors. The first $m$ that satisfies this criterion defines the minimal necessary $m$. 

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*Chapter 1*
**Number of points (N):**

Besides the problem of choosing a proper $\tau$ and $m$, a reliable calculation of nonlinear measures extracted from the attractor depends on the available length of the original time-series ($N$) under study. The time-series must be long enough to embody all relevant dynamical structure but not too long for stationary reasons. In the case of an insufficient number of points, an overestimation of the attractor dimension would be obtained. Several articles describe simple relations that define the minimal required number of points for a reliable calculation of the correlation dimension. Examples are: $N=2^{bD_c}$, where $b$ is the number of significant binary digits in the data representation and $D_c$ is the correlation dimension, or $N=4^{1^M}$, where $M$ is the greatest integer less than the dimension of the attractor in Albano et al., or $N=10^{D_c}$ in Kantz & Schreiber. Albano et al., reports empirical results of different authors. They found that far less data was needed for a consistent correlation dimension estimate compared to the required number of points described by the former equations.

**Other influences:**

The embedding dimension $m$ and delay time $\tau$ have the most direct visible influence on the attractor itself and as a consequence on attractor derived measures. However, there are other 'problems' such as the choice of the sample frequency, non-stationarity, deterministic, or stochastic origin of the data, the precision of the AD-converter, the filters used, artifacts and different sources of noise. Random noise added to the data caused overestimates. Also, overestimates were obtained after filtering the data. However, digitizing (quantizing) the data caused underestimates. For a proper attractor related estimate a noise level of the data of at most 2% should be tolerated.

**Structural or dynamical correlation:**

With the reconstruction theorem of Takens using the method of delays, it is possible that nearby points on the attractor are dynamically correlated. They are close together because they lie on the same trajectory that originates from the same epoch in the time series. If a statistic derived from the attractor is based on the evaluation of the dynamics of nearby points, dynamic correlation can be prevented by the Theiler correction. The Theiler correction states that the time difference of these points (e.g. $V_i, V_l$) in the original time series ($k-l$) should be chosen higher than some minimal value, i.e., high enough to prevent dynamic correlation.

**Empirical approach:**

Instead of trying to choose parameters based on theoretical considerations, another approach is to find optimal embedding parameters for a particular purpose or application. A study following this approach evaluated the effect of $m$, $\tau$, low and high frequency cutoff filter
settings, analog to digital converter (ADC) resolution, and sample length on the calculation of the correlation dimension.\textsuperscript{13}

1.4.6 Testing for nonlinearity and determinism

At the start the basic idea behind the application of the nonlinear approach to EEG signals was to view an EEG as the output of a deterministic system of relatively simple complexity, but containing nonlinearities. As turned out later, this topic became a single point of interest: is there evidence for the assumption that an EEG signal originates from a deterministic nonlinear dynamical system. In the formal mathematically sense, dynamical systems are nonlinear if the differential equations that describe the system contain higher order components or terms like sine, cosine etc. Unfortunately, with measured time series of physiological origin, the differential equations are generally not known and thus cannot provide evidence for this assumption. Two linear methods one would probably first think of as suitable measures to distinguish randomism from determinism are the autocorrelation function and the Fourier transform. Stochastic systems have decaying autocorrelation functions with rate of decay depending on properties of the process. Autocorrelation functions of signals from deterministic chaotic systems decay exponentially with increasing lag. The autocorrelation functions, however, are not characteristic enough to distinguish the rate of decay of stochastic systems from deterministic chaotic signals. Using the power spectrum for this purpose originates from the idea that purely periodic or quasi-periodic signals show sharp spectral lines, whereas noise adds a continuous floor to the spectrum. However, deterministic chaotic signals may also have sharp spectral lines and even in the absence of noise there will be a continuous part of the spectrum. This latter being a consequence of the exponentially decaying autocorrelation function. Without additional information it is impossible to infer from the spectrum whether the continuous part is due to noise or to chaotic dynamics.\textsuperscript{89}

At present different methods are proposed to give an answer to the nonlinearity or determinism question. Most of them are based upon the concept of creating surrogate data sets and a predefined null hypothesis. The null hypothesis in most cases is that all the structure or dynamics in the data originate from a linear stochastic Gaussian process. Surrogate data sets are then created according to the null hypothesis. If the attractor derived statistic computed for the original data is significantly different from the ensemble of values computed for the surrogate data, the null hypothesis is rejected and nonlinearity is detected.

Three examples of algorithms for generating surrogate data are: the Unwindowed Fourier Transform (FT) algorithm, the Windowed Fourier Transform (WFT) algorithm, and the Amplitude Adjusted Fourier Transform (AAFT) algorithm.\textsuperscript{198,199} All of these algorithms are based on randomizing the phase information of the time series. Each complex amplitude of
the Fourier spectrum is then multiplied by $e^{i\phi}$, where $\phi$ is randomly chosen from the interval $[0,2\pi]$. Note that the power spectrum remains unchanged. The FT-algorithm and WFT-algorithm only differ in the applied windowing technique in the latter case. This technique is commonly used in Fourier analysis to suppress the jump discontinuity from the last to the first point of the analyzed interval. The AAFT-algorithm first rescales the values in the original time series so they are Gaussian. Then the FT- or WFT-algorithm can be used to generate surrogate data with the same Fourier spectrum as the rescaled data. Finally, the Gaussian surrogate is then rescaled back to have the same amplitude distribution as the original time series. Schreiber & Schmitz proposed an improved AAFT-algorithm.\(^{166}\) The nonlinear rescaling step of the AAFT-algorithm was shown to conduct spurious detection of nonlinearity. An iterative algorithm (IAAFT) was proposed to make appropriate surrogates, which have the same autocorrelations as the data and the same probability distribution. In a different fashion, deterministic dynamics can be established by measurement of average directional vectors in a coarse-grained d-dimensional embedding.\(^{91}\) The method determines the average direction of numerous passes of the trajectory through a specific hypercube in phase space. For a stochastic system the length of the vector in the average direction will tend towards zero, whereas for a deterministic system this length will be substantially nonzero. Another approach is to test whether the time series is a realization of a linear random process with independent identically distributed Gaussian noise. In conjunction with this approach, a test was proposed for the null hypothesis that a time series is reversible. A time series is said to be reversible if its probabilistic properties are invariant with respect to time reversal. The rejection of the null hypothesis implies that a linear Gaussian random process can be excluded as the generating mechanism.\(^{33}\) Note that rejection of the null hypothesis does not automatically imply that the opposite is true, i.e., that nonlinearity exists in the data. A recent review paper on this field has been written by Thomas Schreiber that describes recent efforts to understand the caveats, avoid the pitfalls, and to overcome some of the limitations concerning creating and interpretation of surrogate data.\(^{167}\) Recently, Kugiumtzis examined two schemes for the generation of surrogate data, the AAFT and IAAFT algorithms.\(^{104}\) Several nonlinear discriminating statistics and simulated data as well as real data were used for testing. The results suggest that the test depends on the method and its parameters, the algorithm generating the surrogate data and the observational data of the examined process. Therefore, evidence for nonlinearity from a single surrogate data test is insufficient and the test should be conducted using several methods, monitoring their parameters, and employing a number of time series from the examined process.
1.5 Use of the nonlinear approach in biologic measured time-series

1.5.1 Introduction
In 1990, Goldberger et al. demonstrated fractal properties of the small intestine, the heart rate, blood vessels of the heart, and the neuron with its dendrites. They speculate on how to make a connection between the fractal geometric properties of human physiologic systems and their corresponding nonlinear dynamics. Furthermore, they hypothesize that chaotic systems have the advantage to operate under a wide range of conditions and are therefore adaptable and flexible. As many pathologies exhibit increasingly periodic behavior and a loss of variability, they conclude that studies of fractals and chaos in physiology may provide more sensitive ways to characterize dysfunction resulting from aging, disease and drug toxicity. With this view in mind, as already mentioned in paragraph 1.3.3, nonlinear measures extracted from the EEG perhaps provide a variable that predicts and reproducibly reflects the reactions of the patient during anesthetic practice. Also many other researchers explore the nonlinear approach for its benefits on their own specific research topic. As nonlinear analysis is evolved into many different disciplines, a review is given concerning its application to biologic measured time-series with emphasis on signals retrieved from a medical environment starting with applications concerning the monitoring of DOA.

1.5.2 Use of the nonlinear approach for measuring anesthetic depth
In 1987, Mayer-Kress and Layne published one of the first articles that describe the application of nonlinear dynamics to determine anesthetic drug effect. In the occipital, not the parietal, leads they found an increase of the correlation dimension of the EEG with fluroxene (an inhalation anesthetic) anesthesia. Although this result was in contradiction with at forehand-expected behavior, the increase was consistent with the excitatory action of fluroxene. One year later Watt & Hameroff demonstrated changes of phase space trajectories and dimensionality as a result of changed DOA. They conclude that these changes confirm that the EEG becomes more synchronized (less chaotic) as DOA increases. Lee et al., studied the efficacy of D2 to estimate the depth of halothane (another inhalation anesthetic) anesthesia in the rat as defined by the presence of body movement in response to a tail clamp. The correlation dimension was found to serve as a better index for the depth of halothane anesthesia compared to β-power and median power frequency (SEF50). Widman et al., investigated several quantifiers of the EEG signal with respect to their ability to indicate depth of sevoflurane anesthesia in patients. One of the quantifiers was a modified version of D2 and therefore called the nonlinear correlation index D*. In contrast to spectral measures, D* was found to decrease monotonically with increasing (estimated) DOA. They conclude that D* seems to be able to improve the quantification of DOA from brain electrical activity, at least when sevoflurane is used. Bruhn et al., hypothesized that the EEG during higher anesthetic concentrations would show more “order” and less “randomness” than at lower
anesthetic concentrations. They used a statistical parameter *Approximate Entropy* (ApEn) derived from the Kolmogorov-Sinai entropy formula which quantifies the amount of unpredictability in the data. The dose-response relation of the EEG approximate entropy during desflurane (an inhalation anesthetic) anesthesia was investigated and compared with SEF95, SEF50, and bispectral index (as declared later). The performance of ApEn as an indicator for desflurane concentrations was similar to SEF95 and bispectral index. They conclude that the amount of regularity in the EEG increases with increasing desflurane concentrations and could be a useful EEG measure of anesthetic drug effect.

Recently, the search for a reliable estimator of DOA has moved towards a multimethodological approach. Instead of focusing on one nonlinear measure, multiple nonlinear measures are utilized. Artificial neural networks (ANN) are then used to decide on which input variable has the most weight at a certain condition. Even in some cases fuzzy logic is applied to generalize output results. Also preprocessing of the data by wavelet transform was reported. Together with this multimethodological approach a complexity index, $c(n)$, was introduced that quantifies the degree of complexity. By comparison of the raw EEG signal with its own sample mean, the signal is transformed into a sequence of ones (≥mean) and zeros (<mean). This $c(n)$ reflects the rate of distinct patterns that arise with the increase of the length of this sequence.

Significant differences in $c(n)$ of the rat EEG were found among awake, asleep, and anesthetized states. They conclude that this simple dynamic complexity index, $c(n)$, can be used to quantitatively analyze the cortical functions of rats. Another study, using $c(n)$, reported the ability to measure the hypnotic component of anesthesia by analyzing the following characteristics of the EEG: standard power spectral measures, bispectrum, fractal spectrum, Lempel-Ziv complexity, approximate entropy, and spectral entropy. Based on these analyses they developed an index which consistently described the depth of hypnosis. Complexity analysis was applied to a decomposition of the EEG signal (separated into six consecutive scaling components by wavelet transform) and the original EEG signal itself. A four-layer ANN then made prediction of movement during anesthesia. The $c(n)s$ of the former EEG decomposition and original EEG signal were fed as input to this ANN. The authors propose that movement during anesthesia can be predicted using complexity analysis of the EEG. They furthermore state that the better sensitivity and specificity of their designed system compared with other schemes (spectral analysis, principal component analysis, and bispectral index) suggest that complexity is more useful in the assessment of anesthetic adequacy. In a follow up study of the same authors the neural network approach was extended by the addition of a fuzzy knowledge model. Based on adaptive network-based fuzzy inference system (ANFIS) modeling, a derived fuzzy knowledge model is proposed for
quantitatively estimating the DOA. Three electroencephalographic derived parameters were used as input to the ANN: the complexity \( c(n) \), regularity or approximate entropy (ApEn), and the spectral entropy (SE). The latter being a parameter extracted from the power spectral density: 
\[
H = \Sigma \left[ p_f \ln \left( \frac{1}{p_f} \right) \right]
\]
where \( p_f \) is the normalized density function value at frequency \( f \). SE can heuristically be interpreted as a measure of uncertainty about the event at \( f \). The combination of the ANN and fuzzy rules map \( c(n) \), ApEn, and SE to a DOA index between 0 (awake) and 1 (asleep). The model was validated by experiments using dogs undergoing anesthesia with three different anesthetic regimens. The model demonstrated good performance in discriminating awake and asleep states and was better than SEF, MF, and BIS. They state that the proposed fuzzy knowledge model is a promising candidate as an effective tool for continuous assessment of the DOA. A similar approach was applied in another study, where EEG-derived autoregressive (AR) parameters, hemodynamic parameters, and the alveolar anesthetic concentration (MAC) were used as inputs to four ANNs. Each of the four individual ANN outputs and the integrated output were fuzzified. Dogs were anesthetized with the inhalation anesthetics nitrous oxide (concentration maintained between 40%-50%) and isoflurane (0.1% or 0.2% stepwise increment). The depth of isoflurane anesthesia was graded based on the response of the dog to a tail clamp. A gross purposeful movement of the extremities of the limbs indicated awake state, no movement together with no hemodynamic response indicated sleep, and no movement together with hemodynamic response was indicated as an intermediate state. From 43 testpoints the fuzzified output of the multiple ANN-design was able to correctly classify all awake states, 8 out of 9 intermediate states, and 21 out of 22 sleep states. In a preliminary study, the Nb latency of the auditory evoked potential was used as a feedback signal for the automatic closed-loop control of general anesthesia using ANN and fuzzy logic. They showed results of one trial, which is a poor basis to draw conclusions. A practical problem seems to be the acquisition of signals of sufficient quality.

In 1994, Sigl & Chamoun, introduced the concept of a bispectral index, (BIS™)*, derived from a set of features, one of it being the bispectrum. The bispectrum of the EEG determines whether quadratic nonlinearities exist in the EEG. The presence of quadratic nonlinearity is demonstrated if besides the two frequencies \( f_1 \) and \( f_2 \), the frequencies \( f_1 + f_2 \) and \( f_1 - f_2 \) are present and both their powers are dependent of the power of \( f_1 \) and \( f_2 \). The bispectrum detects phase coupling in the signal, but does not purely quantify the degree of phase coupling. Instead, a measure called bicoherence is used for this purpose. This bicoherence essentially normalizes the bispectrum ranging from 0 to 100%. The BIS is a univariate descriptor (scaled from 100-0, i.e., from awake to deeper anesthesia levels) derived from a set of features.

* BIS: trademark of Aspect Medical Systems, Newton, MA
including the bispectrum, the bicoherence, and time-domain features such as the level of burst suppression. The information of a variety of anesthesia techniques collected in an extensive database together with regression and discriminant analysis was used to identify features that were significant in predicting response to surgical stimulation. The selected features were then combined into the bispectral index.

Several studies evaluated the efficacy or accuracy of the BIS in predicting movement as response to an incision under a variety of anesthetic techniques. The outcomes of these studies all agreed in their conclusions that the BIS may be useful as a measure of DOA. Also, the relationship between the BIS value and the probability of response to command and recall was evaluated. Other studies focused on beneficial use of BIS in terms of reduction of the amount of anesthetic agents used, and faster post-anesthetic-care-unit discharge. Since 1991, many studies evaluated the potency of the BIS on various aspects related to DOA. As a result, without doubt at present, the BIS has reached a high acceptance level as a useful EEG measure of DOA. However, also the BIS has its shortcomings. In studies where a strong analgesic component was administered, BIS and traditional EEG measures failed to predict movement in response to incision. Vernon et al., studied the capability of the BIS to predict movement during propofol/alfentanil or isoflurane/alfentanil anesthesia. Although they found a significant difference between the BIS for movers versus nonmovers within each of the treatment groups, isoflurane/alfentanil nonmovers could not be distinguished from propofol/alfentanil movers. The authors suggest the possibility that different anesthetics have different effects on BIS, and thus BIS may not be independent of the anesthetic. Also Sebel et al., report the results of a multicenter study that was designed to evaluate the real-time utility of BIS in predicting movement response to skin incision using a variety of general anesthetic techniques. They found that BIS is a significant predictor of patient response to incision, but the utility of the BIS depends on the anesthetic technique being used. For example, the adjunctive use of opioid analgesics confounds the use of BIS as a measure of anesthetic adequacy when movement response to skin incision is used as the primary end point. Doyle, in an article devoted to the - at that time - position of the BIS in the operating room, paid attention to this dependency by putting the question whether a BIS of 50 under isoflurane anesthesia is the same as a BIS of 50 under propofol anesthesia. Further remarks were placed concerning studies performed to evaluate the potency of the BIS to prevent awareness. The statement was made that such studies would require very large study sizes to compare the frequency of unintended intraoperative awareness in patients randomized to be equipped with or without the use of BIS monitoring. Detsch et al., report paradoxical increases of BIS with increased isoflurane concentration. They conclude that the use of BIS as a guide for isoflurane administration may be misleading in some patients undergoing surgical procedures. Case reports of G.D. Puri, describe paradoxical changes in the BIS during nitrous oxide administration. In two patients
undergoing open-heart surgery, with nitrous oxide and isoflurane anesthesia, BIS decreased immediately after nitrous oxide was stopped and increased again after nitrous oxide was restarted. Mi, et al., evaluated the haemodynamic and electroencephalographic response to intubation during induction with propofol or propofol/fentanyl. The obtained results suggest that BIS and SEF are not able to predict the haemodynamic responses to intubation during anesthesia induction with propofol and fentanyl. Similar results were established at our department by Driessen et al. They evaluated the bispectral index during midazolam-fentanyl anesthesia for cardiac surgery for its possible role as a predictor of increases in systolic blood pressure during endotracheal intubation and sternotomy. There was no significant correlation between the bispectral index values in the pre-intubation and pre-incision period and the changes in systolic blood pressure during endotracheal intubation and sternotomy, respectively. They conclude that the lack of significant correlation between the bispectral index values and the haemodynamic responses suggest that the bispectral index is not a very reliable monitor of global anaesthetic adequacy during total intravenous anesthesia with a combination of midazolam and fentanyl in cardiac surgical patients. Katoh et al., evaluated the accuracy of three EEG parameters (BIS, SEF95, and SEF50) and anesthetic concentration for predicting depth of sedation and anesthesia during sevoflurane anesthesia. The prediction probability values for BIS and sevoflurane concentration indicated a high predictive performance for depth of sedation. They conclude that BIS and SEF95 are reliable guides to the depth of sedation, but not to the adequacy of anesthesia level for preventing movement during sevoflurane anesthesia. A case report of Mychaskiw et al., notifies a falsely elevated BIS during deep hypothermic circulatory arrest. They warn for erroneous readings from the BIS monitor that can lead to a potentially dangerous alteration in surgical and anesthetic management. In a letter to the editor, I. Rampil, puts some skepticism on the reliability of the results and conclusion of the previous case report, but in a response, Mychaskiw is tenacious of his conclusion. Barr et al., investigated the BIS at alternating periods of wakefulness and unconsciousness during propofol-induced hypnosis. Median BIS-index for the transition between awake and asleep and vice versa differed significantly. It was not possible, however, to establish any threshold value or zone for discriminating between wakefulness and loss of response to verbal command due to the large inter-individual variations in BIS-index. They conclude that the real-time BIS for the individual subject cannot reliably discriminate wakefulness from unconsciousness during propofol infusion.

Besides the BIS, other methodologies are developed that utilize information extracted from inter-frequency phase relationships. Two recent articles describe the characterization and quantification of the nonlinear interrelations between distinct frequency components in the EEG during basic sedation and during burst suppression patterns at the deeper levels of sedation. At sedation there is a decrease in cognitive functions without loss of consciousness. In anesthesia patients lose their consciousness. They present a method of
bispectral parameter estimation with high time resolution that allows the analysis of transient phase-coupling events, which appear during the burst pattern. The developed approach increases the sensibility of bispectral analysis and allows for third order instantaneous estimates of the bispectrum, the biamplitude, the bicoherence, and the phase bicoherence. It was demonstrated that the degree of interrelation (attributed to amplitude modulation) between a low frequency component (0-2.5 Hz) and oscillations with higher frequency (3-7.5 Hz and 8-12 Hz) was increased during BSP compared with the EEG during basic sedation. They conclude that the degree of interrelations depends on the sedation depth induced by hypnotic drugs. Another study proposed to combine frequency regions to reduce the bispectral information. With factor analysis, seven relevant regions in the bispectrum and corresponding bicoherence factors (BCF) between them were defined. An automated feature extraction based on fuzzy decision trees provided a good match with the BCF’s. These 7 BCF’s, 2 parameters from the time signal, and 7 parameters from the power spectrum were chosen to predict inadequacy of anesthesia with respect to movement in response to skin incision. Discriminant analysis applied to the selected set of parameters provided a probability value for a given patient to fall into one of the two classes, adequate or inadequate. Correct re-classification was achieved in 74% of the cases. Instead of discriminant analysis, a trained Kohonen neural net was used for classification which gave comparable results. Their main conclusion concerns the possible application of fuzzy decision trees and Kohonen nets for an efficient feature extraction as a fundamental component of an intelligent anesthesia monitor concept. The function of this component would be the selection and combination of relevant parameters together with the determination of the accompanying rules for the connections between them.

1.5.3 Nonlinear measures applied in other medical disciplines
Medical interest for nonlinear analysis comes from physicians that hope to improve the treatment of physical impairments of cardiovascular, respiratory, or neurologic origin. Their aim is to diagnose diseases like for example Parkinson, dementia, schizophrenia, depression, and epilepsy in an earlier stage or to localize the specific area in the brain that causes the illness. In general, one is hoping that diseases originating from brain failure can benefit from the variables out of the field of nonlinear dynamics. Another scientific area with gained interest for the nonlinear approach is psychology with emphasis on the search for a measure that is able to differentiate between different mental tasks or between different sleep stages. To give an impression of ongoing research in these related areas, a short survey is given in the next paragraph.

Sleep:
Among the diverse topics of interest concerning the analysis of brain activity, the application of nonlinear analysis to sleep data seems to be very straightforward. One of the aims of sleep
analysis is to unravel the neuronal mechanisms responsible for the transitions between the different sleep stages entered during the course of the night. Because of the difficulty to give evidence for the presumption that the underlying dynamics originate from nonlinear dynamics, results of nonlinear variables are interpreted as to inform about changing complexity. At forehand, one would expect the largest Lyapunov exponent, the entropy, and the correlation dimension to decrease, when calculated from EEG episodes running through the sleep stages I, II, III, and IV. This conjecture was indeed confirmed by different studies. A special sleep stage is rapid-eye-movement (REM) sleep, characterized by a totally different EEG compared to the other sleep stages I-IV. This was also reflected in the correlation dimension and Lyapunov exponent. In classifying the different sleep stages, the absolute results of the nonlinear measures among the studies are not the same. This indicates that results should be interpreted as relative changes compared to a predefined baseline condition. Application of nonlinear analysis to patients suffering from migraine, provided evidence of a global dimension decrease that is related to cortical network changes during a migraine attack. The effect of total sleep deprivation (TSD) on nonlinear dynamics of the waking EEG was examined. TSD resulted in the decrease of complexity in the brain. The authors suggested that the investigation of the relation between nonlinear dynamics of the waking EEG induced by TSD and cognitive performance may offer fruitful clues for understanding the role of sleep and the effects of sleep deprivation on brain function.

Mental activity:
Other studies related to altered brain activation try to investigate whether variations in mental task load are reflected in the correlation dimension of the EEG. A higher correlation dimension during the arithmic task (two-digit addition) was found compared to the following rest period. Comparable results were obtained in a study evaluating the correlation dimension of the EEG during an arithmic task, a time estimation task, and the corresponding resting period. In another study, subjects were presented a variety of tasks classified as imagery, sensory, and observational tasks. The pointwise dimension was the lowest for the observational tasks and the highest for the imagery tasks.

Mental illness:
Mental illness is one of the major personality destructive diseases (epilepsy, Alzheimer, Parkinsonia, schizophrenia, dementia) people can suffer from. For a better future treatment of patients, it is important to improve understanding of the cause, the progress, and the brain localization of these diseases. In this light, nonlinear analysis is mainly applied in an effort to diagnostic diseases in an early stage. Lower values for $D_2$ were found for patients suffering from Parkinson and dementia compared to the controls. The authors hypothesize that the decrease of $D_2$ reflects, at least
partially, a loss of "dynamical complexity" in the cortex due to diminished activity in the activating cholinergic system. Another study from the same group evaluated the capability of $D_2$ to discriminate between control subjects and Alzheimer (AD) subjects. Results of the nonlinear analysis were compared with linear spectral analysis. They found no overall difference in $D_2$ between AD patients and control subjects. However, a slightly lower $D_2$ reactivity, as defined by the difference in $D_2$ between eyes-open and eyes-closed, was found for the AD subjects. Used in isolation, linear analysis was superior in differentiating AD patients from controls. The best results were obtained by combining linear with nonlinear measures. They conclude that the nonlinear approach does not seem practical yet, but deserves further study. More recently, results of the same group confirm the lower values for $D_2$ in demented subjects. Surrogate data sets were generated in order to investigate the presence of nonlinear dynamics. From the results of the surrogate analysis, they conclude that linear dynamics change first in the course of AD, followed by changes in nonlinear dynamics. Lower values for the dimensional complexity were found in a study that compared the dimensional complexity of 50 AD patients with 42 normal controls. Comparable results were found by Jeong et al., where AD patients had significantly lower values for $D_2$ and the first positive Lyapunov exponent than control subjects. Schizophrenic patients had a lower correlation dimension in the left inferior frontal and anterior temporal regions compared with controls. Also, in schizophrenic patients, a lower first positive Lyapunov exponent was found. The finding of decreased left frontal and temporal chaotic activity in schizophrenics is in line with the findings of a hypofrontality and hypotemporality reported in previous EEG, blood flow, brain MRI and positron emission tomography studies in schizophrenia. In another study, a decrease of dimension complexity was found in the EEG of schizophrenia compared with controls. They interpreted it as the result of the psychopath's dysfunction of the overall brain. Woyshville et al., quantified occipital EEG changes in AD subjects using the fractal dimension. Compared to the control subjects, the fractal dimension was lower in the AD group. Pritchard et al., used an artificial neural network (ANN) to classify AD subjects versus controls. The addition of a dimensional complexity measure as input to the ANN improved the classification accuracy. Molnár et al., studied the usefulness of nonlinear analysis for the purpose of localizing brain pathology. The scalp distribution of the point correlation dimension, PD2, was calculated from patients with unilateral stroke. Compared to normal controls, an asymmetrical PD2 distribution was observed with low values on the side of the stroke. Röschke et al., report on findings concerning altered nonlinear brain dynamics mainly during slow wave sleep in depression and during REM sleep in schizophrenia. Magnetoencephalogram (MEG) recordings were obtained from the brain of patients suffering from Parkinson's disease (PD). The estimated values of $D_2$, in conjunction with the results derived from other data analysis methods, strongly support the existence of low dimension chaotic structures in the dynamics of cortical activity of PD patients. EEGs were recorded from patients in early stages of Parkinson's disease and healthy controls during rest and during
In the resting state, analysis of correlation dimension of EEG time series revealed only slight topographical differences between the groups. During performance of a complex motor task, however, data from PD patients showed higher dimensionality than data from controls, indicating more complex EEG time series.

Epilepsy:
In epileptology extraction of nonlinear measures from the recorded EEG seems to be very promising for clinical practice. Main aims of interest are localization of the primary epileptogenic area, investigation of antiepileptic drug effects, analysis of interactions between epileptogenic zone and other brain areas, and detection of features predictive of seizure activity. In 1986, Babloyantz et al., showed the existence of a chaotic attractor during a human epileptic seizure as indicated by its very low dimensionality. In a speculative explanation the authors suggest that the underlying mechanism that produces the examined type of petit mal epileptic seizure drives the brain activity towards a stable periodic motion. In this state, information processing would be impossible and recovery very difficult. However, the brain manages to remain on a chaotic attractor, although one of a very low dimensionality, in order to process reflex activities. Frank et al., studied a markedly different seizure event from that described in the previous study (a longer seizure episode indicating a more complex state). They found partially evidence for chaos as confirmed by calculation of the Lyapunov exponent and correlation dimension. The correlation dimension of the seizure was considerably larger than that found by Babloyantz et al. The difference was attributed to the different seizure composition. Iasemidis et al., analyzed the electrocorticograms from 16 chronically implanted subdural electrodes, placed over the right temporal cortex in a patient with a right medial temporal focus. For every electrode, they calculated the largest positive Lyapunov exponent before, in and after the epileptic seizure for three seizures of the same patient. The results indicate that the largest average Lyapunov exponent can be useful in seizure detection as well as focus localization in multielectrode analysis. In a preliminary study of Arle et al., it was shown that fractal dimension changes as a response to transients in the EEG. They consider detection of early transients to be useful as a precursor of seizure activity. Another study of Bullmore et al., applied a modified fractal analysis to human, intracerebrally recorded, ictal EEG signals. They report relative increased fractal dimensions during arrhythmic EEG events and relative decreased fractal dimensions during rhythmic EEG events. A color-coded display of deviations from mean fractal dimension in data recorded from all electrodes was proposed as probably diagnostically useful for clinical visualization of long periods of EEG data. Lehnertz et al., evaluated the capability of nonlinear time series analysis to extract features from the EEG predictive of epileptic seizures. They recorded brain electrical activity directly from the cortex and from within relevant structures using up to 128 implanted electrodes in 16 patients with pharmaco-
resistant epilepsy. Analyzed EEG data originating from the seizure-generating brain area indicated marked changes in $D^*$ for up to several minutes prior to seizures as compared to other states or recording sites. They conclude that the results are possibly useful for future interventions in the preseizure period. Widman et al., tested whether different outcomes of studies concerning predictive power of nonlinear analysis to detect and identify an unequivocal pre-ictal phase, could be subscribed to dependence of the type of elementary mechanisms underlying epileptic processes. The transition from normal to pharmacologically induced epileptiform activity was analyzed in four models of epilepsy using the effective correlation dimension ($D^*$). In two out of four models signal complexity in intracellular recordings (guinea pig) was reduced before manifestation of paroxysmal depolarization shifts. The predictive inability of $D^*$ in the two models was attributed to a probably faster arising epileptic activity. Van der Heyden et al., used the coarse-grained correlation dimension ($D_{cg}$) and entropy to characterize the EEG epochs recorded before and during a seizure from patients suffering from temporal lobe epilepsy. They conclude that ictal and non-ictal EEG can be well distinguished on the basis of nonlinear analysis. Furthermore, they speculate on how to interpret the results. In their opinion, changed nonlinear measures of the EEG during the ictal state might be subscribed to synchronized, correlated activity of the neurons in the ictally active brain structures. Recently, various groups reported their advances on the use of nonlinear analysis for early seizure detection. Le Van Quyen et al., proposed a nonlinear strategy adapted to track dynamic changes in brain signals. To classify an epoch as a seizure precursor, a statistical measure of similarity based on the cross-correlation integral between the pre-ictal and ictal state should decrease below a critical level, a value lower than one, for a certain period of time. From a homogeneous group of 13 patients with temporal lobe epilepsy, in most cases, the similarity index allows seizure anticipation several minutes in advance (mean 5.5 minutes). Jerger et al., compared the results of seven linear and nonlinear methods in detecting the earliest dynamical changes preceding 12 intracranially recorded seizures from 4 patients. All the methods were successful in detecting changes leading to a seizure between one and two minutes before the first EEG change noticed by the neurologist, although analysis of phase correlation proved to be the most robust. Savit et al., introduced a measure that is sensitive to the extent to which two temporal windows of a time series are dynamically similar. This measure compares the reconstructed dynamics among windows and measures the extent to which those reconstructed dynamics differ from window to window. Dynamic differences among windows are quantified by a distance measure and visualized in a meta-phase space (MPS). The points in the MPS plots reveal structures that change in the preictal epochs. Protopopescu et al., introduced four new measures of dissimilarity that capture more details about the dynamics than traditional nonlinear measures, such as correlation dimension, Lyapunov exponents, and so forth. Changes in these measures signify departure from prevailing dynamics and can be interpreted as a forewarning of an impending epileptic event. They
showed that the dissimilarity measures seem to be superior to traditional nonlinear measures for detection of conditional change. Lehnertz et al., introduced the neuronal complexity loss $L^*$ as an integral measure for temporal changes of $D^*$ (see paragraph 1.4.4). Maximum $L^*$ values were found in the neighborhood of the focal area and decreased gradually with increased distance from this focal area. In patients where the lesion is removed, a high conformity between maximum values of $L^*$ and the area of resection was observed.

Univariate nonlinear EEG analysis allows for classification of temporal aspects and relative spatial distribution (with multichannel recordings) of the epileptogenic process. However, it does not reveal information connected with spatial synchronization phenomena. The authors also evaluated two bivariate analysis techniques: the nonlinear interdependence measure $S$ which attempts to characterize statistical relationships between two time series and the mean phase coherence $R$ as a statistical measure for phase synchronization. The results of the bivariate measures indicate that a pathologically increased level of interdependence or synchronization characterizes the epileptogenic focus. They conclude that the nonlinear EEG analysis techniques allow one to define a preictal phase and to characterize different temporal and spatial aspects of this phase. Sarbadhikari et al., and Lehnertz published a short overview and review alluding to epilepsy.113,153

Cardiovascular and respiratory system:
Other medical disciplines are interested in the application of nonlinear analysis techniques to physical signals derived from the cardiovascular and respiratory system. Skinner et al., demonstrated reduced values for PD2 of R-R heart beat intervals in subjects with pre-existing coronary heart disease who experienced ventricular fibrillation.184 These low values were not found in control subjects, who had severe arrhythmias but no history of ventricular fibrillation. Fleisher et al., calculated ApEn of R-R intervals retrieved in twenty-three high-risk noncardiac patients from the evening before surgery up to 80 hours during the postoperative period.54 For the majority of patients, a decrease in ApEn occurred before ventricular dysfunction or coincidented with it. They conclude that ApEn indicates there is a difference between good and poor left ventricular function, based on heart rate data, without indicating the cause of the difference. B.P.T. Hoekstra, explored methods from nonlinear time series analysis to probe the dynamics of atrial fibrillation.71 One of the results presented in this thesis and published elsewhere was the finding that nonlinear analysis discriminates between different types of atrial fibrillation in humans.72 Almog et al., investigated the potency of the correlation dimension of the blood pressure time series to evaluate cardiovascular control.5 They conclude that nonlinear modeling is an important approach providing additional insight into the cardiovascular control system.
Synchronization between cardiac and respiratory rhythms:
Schäfer et al., studied the heartbeat synchronization with ventilation.\textsuperscript{159} They used a newly developed data analysis technique that allows the observation of interactions that occur even in weakly coupled complex systems. With this technique they found long periods of hidden cardiorespiratory synchronization in humans during spontaneous breathing at rest. In another article of the same authors, phase analysis of the cardiovascular and respiratory rhythms, retrieved from healthy humans under free running conditions, reveals synchronous regimes of different orders $n:m$ and transitions between them.\textsuperscript{158} Stefanovska et al., also investigated phase synchronization between cardiac and respiratory oscillations during anesthesia in rats.\textsuperscript{191} They showed that the cardiac and respiratory systems possess dynamical properties and couplings that can synchronize their oscillations in a hierarchy of different phase-locked states. During the course of anesthesia, different phase-locked states occurred in a reproducible sequence. They suggest that the state of synchronization between the cardiac and respiratory system may provide a potentially useful measure of DOA at any moment.
Kanters et al., tested whether nonlinear input from spontaneous respiration is a source for the nonlinearities in heart rate variability.\textsuperscript{87} Nonlinear dynamics were measured as the correlation dimension and the nonlinear prediction error. They conclude that nonlinear dynamics in heart rate variability do not originate from respiratory nonlinear input.

1.6 Considerations and developments important to the study setup
The above introduction indicates there are many obstacles regarding monitoring DOA. Potency and problems encountered with traditional methods or variables such as Guedel’s scheme, PRST-score, IFT, and LOC are briefly described in section 1.3.1: non-EEG approach. In summary, the shortcomings of these traditional variables are manifested by problems due to interindividual variability, obscuring effects of muscle relaxants, limited time of utilization, and contradictory results concerning descriptiveness of DOA. As the capability of the traditional variables to monitor DOA was unsatisfactory, research moved towards a direction of analyzing variables extracted from the EEG assuming this would perhaps provide better information related to DOA. In section: 1.3.2 linear approach applied to the EEG a short review is presented of variables deduced from the EEG by use of linear analysis methods. Results are sometimes promising, but none of the variables or methods is applicable as a universal measure of DOA. SEF is found to be an unreliable indicator of DOA. Mean frequency did not change before the change of other traditional clinical variables. Aperiodic waveform analysis showed a biphasic relationship between EEG effect and anesthetic drug concentration. The averaging process and sensitivity to artifacts are main drawbacks of AEP measurement. The blink reflex seems to be restricted to the lighter and medium levels of anesthesia and the presence of BSP did not predict lack of response to a noxious stimulation in rats. In summary, the shortcomings of these linear EEG measures are manifested by
problems due to unreliability, non-improvement, biphasic response, non-practical methodology, non-predictive for presence of response to noxious stimuli, and non-covering of the total anesthetic trajectory.

Former studies at our department concerning monitoring DOA, were focused on existing non-EEG measures and/or linear EEG measures.\textsuperscript{147,160,161,207} Although the results of these studies – just as results reported in literature - were sometimes encouraging, we faced the same problems as described above. The failure of traditional and linear EEG measures to provide a variable that universally informs about DOA, and the - at that time - preliminary results of the BIS, strengthened our opinion that nonlinear EEG analysis perhaps uncovers information not available to linear analysis. The decision was made to move research of monitoring DOA towards a new direction by starting this thesis study with the intention to evaluate other EEG variables provided by methods of nonlinear analysis.

The review of international literature subjected to the application of nonlinear analysis for the purpose of DOA (section 1.5.2) and to applications in other related medical disciplines (section 1.5.3), revealed possible utilization of a variety of measures. The two variables most often object of investigation were dimensionality and Lyapunov exponents (the latter mainly in studies exploring personality destructive diseases). Note that at the start of this thesis study there was barely literature devoted to the evaluation of usefulness of nonlinear analysis for monitoring DOA. The two articles, as mentioned in section 1.5.2, that pay attention to this subject, both use $D_2$.\textsuperscript{126,213} A comparison of the expected implementational problems of algorithms to calculate $D_2$ and Lyapunov exponents, revealed that the pitfalls of the latter algorithm were expected to be of higher order compared to the algorithm of $D_2$.\textsuperscript{65} Therefore, we decided to keep Lyapunov exponents in mind for future study and to focus research efforts on $D_2$ alone. Also, literature study brought to light several pitfalls connected with the implementation of the algorithm to calculate $D_2$. One of which was the enormous required computer time per estimate.\textsuperscript{27} Other pitfalls concerned the influence of delay time $\tau$, embedding dimension $m$, and definition of the scaling region on $D_2$ (see section 1.4.5). For a practical implementation – the ultimate goal – we decided to investigate whether any changes could be made to the algorithm in order to reduce the negative effects of aforementioned pitfalls.

To test the performance of possible changed algorithms as an indicator of DOA, we planned three rat studies with different anesthetic drugs. Two anesthetic drugs were chosen: the intravenous anesthetic propofol and the volatile anesthetic sevoflurane (chapter 3,4,5). In the experimental setup, the noxious induced withdrawal reflex (NIWR) was selected to inform about DOA. The NIWR is in fact the force of the reflex of the hind paw of the rat as a
response to a painful electrical stimulus. Measurement of the NIWR demands an advanced measurement set up for which, in the past, developments were made at our department.\textsuperscript{35} We intended to make some refinements to this setup with the aim to create an environment well suited to guarantee as far as possible a stable condition of the rat during the whole experiment.

At the end a clinical study was designed to test performance of possible changed $D_2$ algorithms as a measure of DOA in patients. In this study, we planned to measure the EEG of patients during different defined steady state levels (as indicated by a computer model) of propofol anesthesia. At every stage, an adapted version of the observer's assessment of alertness and sedation (OAA/S) scale should define DOA. Finally, to evaluate changed algorithms in clinical practice, we had in mind to collect EEG data of some patients recorded during the induction of anesthesia and during the entire surgery.

The objective of the studies described in this thesis was to find answers to the following questions: can the $D_2$ algorithm be optimized for improvement of its sensitivity to anesthetic effects and for feasibility of real time estimates? Is this altered algorithm (if applied to the EEG) then related to DOA and can it provide relevant information to the anesthesiologist (practical evaluation)? These questions can be adapted to the next four conjectures.

$H_A$: Appropriate algorithm parameter choices enhance sensitivity of dimensional analysis for the purpose of monitoring DOA.

$H_B$: The $D_2$ algorithm can be adapted to enable real time estimates.

$H_C$: The changed $D_2$ algorithm is related to DOA.

$H_D$: The changed $D_2$ algorithm can predict forthcoming changes in DOA.
2 Correlation dimension applied to the EEG: evaluation of the effect of a distance reduction scheme, definition of the scaling region, and choice of embedding parameters on results

2.1 Abstract

Background: The aim of this study was to find out how to choose embedding parameters, how to define the scaling region, and to find out whether a reduction of computer run time could be realized with the intention to achieve optimal results for the correlation dimension as a measure of depth of anesthesia (DOA).

Methods: An effective correlation dimension (CD) was computed following a modified Grassberger/Procaccia/Takens approach (the abbreviation ‘CD’ is used to pronounce the difference with $D_2$). Influence of parameter settings on the sensitivity of CD to anesthetic drug changes and computer run time were evaluated. A definition of the scaling region based on the distribution of distances is proposed. For the calculation of the correlation integral, it was investigated to what extent the number of distances between points on the attractor could be reduced, without having adverse effects on capability of CD to inform about DOA. Three rats were anesthetized with a baseline infusion of propofol with superimposed episodic boluses. The CD of the EEG acquired during these experiments was used to test its performance as a measure of DOA.

Results: By taking a subset (0.33%) of the maximum possible number of distances, computation time could be reduced without loss of performance for CD as a measure of DOA (parameters $p$ and $s$). A semi-fixed scaling region, optimal embedding dimension ($m=20$) and delay time ($\tau \Delta t=8$ ms) were assessed. These settings yielded an optimal ratio between sensitivity to drug changes and short-term fluctuations (S/N-ratio) not related to anesthesia and enabled on-line estimation of CD with a standard Pentium based personal computer. The rat experiments demonstrated a decrease of CD with increasing propofol concentrations and vice versa.

Conclusions: A carefully, although empirical choice of embedding dimension and delay time may optimize results of CD for this particular application. Also, in a practical setting, apparently a large number of distances can be omitted without having negative effects on the capability of CD to inform about the specific topic of interest. The accompanying reduced computer run time per CD estimate enables use of CD in these practical applications.

Keywords: Nonlinear; EEG; Chaos; Monitoring; Anesthetic-depth; Time-series analysis
2.2 Introduction

Takens’ embedding theorem defines a procedure to obtain a trajectory or attractor in phase space that characterizes the system’s time evolution or dynamics. By evaluating the statistics of distances between points on this attractor, the correlation integral can be calculated. $D_2$ is extracted from this correlation integral. The embedding theorem requires the choice of some parameters. These parameters are the embedding dimension ($m$), delay time ($\tau$), and the number of samples ($N$), i.e., length of the segment of the time series under study. The three parameters have direct influence on the reconstructed attractor, which serves to facilitate the extraction of nonlinear dynamical properties of the system under consideration. Therefore, it is important to choose appropriate parameters. Moreover, if the extracted nonlinear properties are intended to be used in a system control environment (e.g., for the purpose of monitoring depth of anesthesia), wrong parameters will obscure the required system information and hinder a successful application of the nonlinear approach.

If the measured time series has no noise component and is of infinite length, $\tau$ would have no influence on the reconstructed attractor. In practice, however, this is never the case and the choice of $\tau$ has considerable influence on the results. Many solutions to the ‘lag’ problem have been proposed to obtain an optimal value for $\tau$. If the dynamics of a measured signal (e.g., brain activity) are unknown, the number of variables that determine the system’s state is also unknown. The question arises what to choose for the embedding dimension. Guided by topological considerations, to determine the minimal necessary $m$, the method of false nearest neighbors was introduced. A reliable calculation of nonlinear measures extracted from the attractor also depends on the available length of the original time-series ($N$) under study. The time-series must be long enough to embody all relevant dynamical structure but not too long for reasons of stationarity. Several articles describe simple relations that define the minimal required number of samples for a reliable calculation of the correlation dimension. Albano et al., reports empirical results of different authors. They found that far less data were needed for a consistent correlation dimension estimate than the numbers suggested in the foregoing references. $D_2$ is extracted from the correlation integral at the so-called scaling region. In practice, the definition of the scaling region appears to be rather vague. It is often difficult to establish this scaling region especially with measured time-series. There are some articles devoted to this subject. However, many articles don’t mention the criterion used to define this scaling region. Two $D_2$-derived measures that use specific definitions of the scaling region are $D_{cg}$ and $D^*$. In the case of $D_{cg}$ the scaling region is defined at a distance $r=r_{cg}$, where $r_{cg}$ is defined by the standard deviation of the time series. For $D^*$ the scaling region is defined by a lower bound $r_l$ and upper bound $r_u$. Both bounds $r_l$ and $r_u$ are calculated based on the histogram of sample values. $D^*$ is then obtained from the scaling region at higher embedding ($m=25$) between $r_l$ and $r_u$. 

Chapter 2
The embedding dimension $m$ and delay time $\tau$ have the most direct visible influence on the attractor itself and as a consequence on attractor derived measures such as $D_2$. However, there are other ‘problems’ such as the choice of the sample frequency, stationarity, deterministic or stochastic origin of the data, the precision of the AD-converter, the filters, artifacts and different sources of noise.\textsuperscript{3,10,40,88,101,130,131,163,165}

In summary, there are many obstacles that must be handled with care for a reliable calculation of $D_2$, especially if applied to measured time series. Instead of trying to choose parameters based on theoretical considerations, another approach is to find optimal embedding parameters for a particular purpose or application.\textsuperscript{13,69} In the present study, this approach was followed. Parameters were chosen based on the evaluation of their effects on $CD$ using experimental time series and a composite time series, the latter being a combination of two mathematically defined differential equations (Lorenz- and Rössler-attractor).\textsuperscript{122,151} As proposed by Widman et al. for $D^*$, the modified algorithm utilized to calculate $CD$ – the abbreviation $CD$ is introduced to pronounce the difference with the proper $D_2$ - precludes any interpretation in terms of fractal dimension, number of degrees of freedom, etcetera.\textsuperscript{115,215}

Therefore, $CD$ should be interpreted as an operational measure of EEG complexity.

Using general anesthesia, the anesthesiologist tries to suppress the physiologic responses of the patient to external noxious stimuli e.g., surgery. The administration of anesthetics also results in depression of the activity of the central nervous system (CNS) and thus to changes in the electroencephalogram (EEG). The depth of anesthesia (DOA) not only depends on the pharmacological effects of the anesthetics, but also on the amount of surgical stimulation. It is desired, however, that DOA throughout the procedure remains at a safe level. If the anesthesiologist can obtain relevant information from the EEG, a more balanced anesthesia might be possible. In an effort to quantify the effects of anesthetics during surgery, several reports have studied EEG measures derived from the power spectrum of the EEG (linear approach) with different levels of success. Positive results were reported\textsuperscript{39}, however, also negative ones.\textsuperscript{157,162,179,41,61,144,203}

In 1987, Mayer-Kress and Layne published one of the first articles that describe the application of $D_2$ to determine anesthetic drug effects.\textsuperscript{126} One year later Watt & Hameroff demonstrated changes of phase space trajectories and dimensionality as a result of changed DOA.\textsuperscript{213} They conclude that these changes confirm that the EEG becomes more synchronized (less chaotic) as DOA increases. This conclusion was confirmed by Bruhn et al., using an estimate of entropy, a measure that quantifies the amount of unpredictability in the data.\textsuperscript{16} Widman et al. investigated a modified version of $D_2$, the nonlinear correlation index $D^*$, as a measure of depth of sevoflurane anesthesia.\textsuperscript{215} In contrast to spectral measures, $D^*$ was found to decrease monotonically with increasing (estimated) DOA. Lee et al., found $D_2$ to serve as a better index for the depth of halothane anesthesia in the rat compared to $\beta$-power or median power frequency.\textsuperscript{110} Previously mentioned studies report encouraging results for $CD$ as a
measure of DOA, but none of the variables or methods is unambiguous in all possible anesthesia regimes. Therefore, further investigations to improve DOA monitoring are still beneficial. In this light, with having in mind the demonstrated potency of the correlation dimension and derived measures to inform about DOA, the objective of this article is threefold.

1) To eliminate the effect of changing parameters on results, it is proposed to fix them to a carefully selected value. Embedding dimension and delay time are chosen in order to maximize sensitivity to anesthetic drug concentration changes and a definition of the scaling region is proposed based on the distribution of distances between points on the attractor.

2) Also, the effect of parameter choices on required computation time and results are evaluated in order to minimize the computational effort for on-line measurement purposes, but without significant reduction of the performance of CD as a measure of DOA. Instead of taking a random subset of distances between points on the attractor, a reduction scheme is introduced that can be implemented more efficiently in computer code.

3) Finally, the hypothesis that CD of the EEG relates to DOA, is evaluated.

2.3 Materials and Methods

2.3.1 Experiment

After approval of the University Committee on Ethics in Animal Experiments adult male Wistar rats are anesthetized with pentobarbital (60 mg.kg\(^{-1}\) ip.). One tripolar electrode (Plastic Products Company, MS 333/2A) is implanted under stereotactic conditions for the purpose of long-term recording of the cortical EEG. The coordinates related to the bregma are: A 2.0, L 2.0; A -3.7, L 9.0. A ground electrode is placed above the cerebellum. Experiments are performed after a recovery period of at least two weeks. The studies are performed to quantify EEG changes due to anesthesia induced by propofol infusion (30-40 mg.kg\(^{-1}\).h\(^{-1}\)) with repeated bolus injections of 3 mg to induce periods of more profound anesthesia.

2.3.2 EEG: registration and analysis

The EEG is recorded continuously. The raw signal is filtered between 1 and 100 Hz, digitized at a rate of 250 Hz and stored to disk for “off-line” analysis. The CD of the EEG is computed every epoch of 65.536 s duration (16384 samples) and repeated every 8.192 s (7/8 overlap with previous estimate). At the deepest anesthetic depths, burst suppression patterns appear in the EEG signal. Short periods with low frequency and high amplitudes (bursts) alternate with longer periods with high frequency and low amplitudes (suppression). Suppression periods are defined as those periods of at least 0.3 s duration where the absolute amplitude of the EEG remains below a threshold value. The threshold values are manually estimated.
the burst suppression pattern is highly non-stationary, the suppression periods are omitted for
the calculation of CD. During burst suppression patterns the number of EEG samples is
maintained at 16384 by increasing the epoch length. It is important to note that transitions
from burst epochs to suppression epochs and vice-versa are avoided within the time span of
the reconstruction vectors (see later).

2.3.3 Correlation dimension
Introduction
The CD was calculated off-line. To calculate CD, the system dynamics that describe the EEG
signal are required to determine the attractor. Suppose that a certain system can be exactly
described with \( m \) variables; if this system is examined by measuring all \( m \) variables every
time interval \( \Delta t \), a vector with those \( m \) variables as coordinates can be plotted as a function
of time in a \( m \)-dimensional state-space. For each interval \( \Delta t \), a vector is plotted in state-space and
together they form a trajectory that is filling out the attractor of the system. The attractor in
fact embodies the dynamic structural information of the original time series. In practice,
however, the dynamics generating the EEG are unknown. Also, instead of measuring all \( m \)
variables only one variable is measured. Using the embedding theorem the complete
dynamics can be reconstructed from the time series of one variable.\(^{196}\) Strictly speaking this
theorem requires the dynamics to be deterministic, but the embedding and reconstruction
method has also been widely used for stochastic systems. From a time discrete sampled signal
\( v: v[1], v[2], v[3], \ldots, v[N] \), a total of \( k_{\text{max}} = N - (m - 1) \tau \) \( m \)-dimensional reconstruction vectors
can be formed using the method of delays.\(^{196}\) Reconstruction vectors \( V_k \) are subsequences of
the form:

\[
V_k = (v[k], v[k + \tau], \ldots, v[k + (m - 1) \tau])
\]

where \( \tau \Delta t \) is the delay time and \( \tau \) defines the number of digitized samples between the \( m \)
different coordinates of the reconstruction vector. For every combination of the parameters \( m \)
and \( \tau \), a cloud of points in \( \mathbb{R}^m \) is obtained by choosing all possible starting points \( k \). The CD is
extracted from the correlation integral, which can be calculated by evaluating the statistics of
distances between reconstruction vectors (points on the attractor). Consider the set of points
\( \{V_k: k=1...k_{\text{max}}\} \) on the attractor. The correlation integral \( C(r) \) is defined according to:\(^{65}\)

\[
C(r) = \frac{2}{k_{\text{max}}(k_{\text{max}} - 1)} \sum_{k,l=1}^{k_{\text{max}}} \Theta(r - \| V_k - V_l \|)
\]

\[
D_2 = \lim_{r \to 0} \frac{\ln C(r)}{\ln r^{-1}}
\]
Where $\Theta$ is the Heaviside function ($\Theta(x) = 1$ for $x > 0$ and $\Theta(x) = 0$ else), $||...||$ means the Euclidean distance and $k_{max}$ equals the number of points on the attractor. Note that $C(r) \in [0,1]$ and is an estimate of the probability that two reconstruction vectors are within distance $r$. In theory $C(r)$ must be estimated for $N$ going to infinity ($N \to \infty$) and for the limit of $r$ going to zero ($r \to 0$), but in practice this is not possible. In formula 2.2 where $D_2$ is defined, the limit of $r$ going to zero ($r \to 0$) cannot be realized because $N$ is finite. Instead the slope of $\ln C(r)$ as a function of $\ln r$ is used. $D_2$ is extracted from $C(r)$ at the so-called “scaling region” where an exponential relationship exists between $r$ and $C(r)$ and the slope of $\ln C(r)$ as a function of $\ln r$ is constant. $D_2$ is then obtained by regression analysis applied to the scaling region. The human eye can easily find this scaling region but is not objective and cannot be used for online monitoring.

**Determination of scaling region or fitting interval**

In this study, an effective dimension $CD$ was extracted from $C(r)$ at some intermediate region. Five possible regions were evaluated defined by the distribution of distances that define $C(r)$. The following intervals were defined: $[r_0,r_1]$, $[r_1,r_2]$, $[r_2,r_3]$, $[r_3,r_4]$, $[r_4,r_5]$ where $r_0$, $r_1$, $r_2$, $r_3$, $r_4$ and $r_5$ were defined by respectively: $\ln C(r_0) = -C_{max}$, $\ln C(r_1) = -0.8C_{max}$, $\ln C(r_2) = -0.6C_{max}$, $\ln C(r_3) = -0.4C_{max}$, $\ln C(r_4) = -0.2C_{max}$, and $\ln C(r_5) = 0$ and $C_{max} = \ln (1/k_{max}(k_{max}-1))$. A sinusoidal combination of the Lorenz-122 and Rössler-attractor is used to find out which region can best be used to compute $CD$. The Lorenz- and Rössler-attractor were computed from the following (differential) equations using Fixed RK4 integration:

Lorenz $L(t)$:

\[
\begin{align*}
\dot{x} &= \sigma(y-x); \\
\dot{y} &= r \cdot x - y - x \cdot z; \\
\dot{z} &= x \cdot y - b \cdot z,
\end{align*}
\]

$x_0 = 0; y_0 = 1; z_0 = 0; \quad \sigma = 10; \quad b = \frac{8}{3}; \quad r = 28.00; \quad \Delta t = 0.05$  \quad 2.3

Rössler $R(t)$:

\[
\begin{align*}
\dot{x} &= -z - y; \\
\dot{y} &= x + a \cdot y; \\
\dot{z} &= b + z(x-c),
\end{align*}
\]

$a = 0.20; \quad b = 0.20; \quad c = 5.70 \quad \Delta t = 0.05$  \quad 2.4

From both signals the first 2000 iterations are omitted.

Both numerically calculated $x$-components of the $L(t)$ and $R(t)$ time series are transformed to integers with 12-bit resolution. The combination signal $c(n)$ is made as follows:

\[
c(n) = \frac{1}{2} \left( 1 + \sin (\omega t) \right) L(t) + \frac{1}{2} \left( 1 - \sin (\omega t) \right) R(t)
\]

where: $t = n \cdot \Delta t$, $\Delta t = 0.05$, $\omega = 2\pi / 5000$, $n = 0..200000$  \quad 2.5
At \( t=0 \), \( c(n) \) is a mix of the two attractors both with equivalent weight. With increasing \( t \) in following order \( c(n) \) moves from a mixed attractor to a pure Lorenz-attractor, to a mixed attractor, to a pure Rössler-attractor, and again back to the mixed variant. In the signal \( c(n) \) this sequence is repeated twice (two full periods of the sinus). If the CD of \( c(n) \) is computed (with: \( \tau=1 \), \( m=15 \) and \( N=16384 \)) one expects to find higher values (higher than the CD of both the pure attractors, but lower than or equal to the sum of both) if in an epoch both attractors are evidently visible.

**Reduction of distances**

The maximum number of distances between different points \((k<l)\) on the attractor is equal to \( \frac{1}{2}k_{\text{max}}(k_{\text{max}}-1) \). The amount of computational effort to calculate CD is mainly determined by the process of estimating these distances. With fixed \( N \), reduction of distances is possible by choosing a carefully selected subset of the \( \frac{1}{2}k_{\text{max}}(k_{\text{max}}-1) \) pairs of points. Often this is achieved by taking distances between reconstruction vectors \( (V_i,V_k) \) with random starting points \( l,k \). A main drawback of this approach is the inability to use already computed distance information for the next distance estimation. Two points (reconstruction vectors) on the attractor can be characterized with the two indices \( l \) and \( k \) (the index of the samples in the time series that corresponds to the first coordinate). A straightforward approach to compute all distances between points on the attractor would be to take the following sequence of pair of points:

\[
\sum_{k=1}^{k_{\text{max}}-TC} \sum_{l=k+TC}^{k_{\text{max}}} (V_k, V_l) \quad \text{2.6}
\]

The Theiler correction (TC) guarantees sufficient time separation between the two reconstruction vectors, thus preventing spurious results caused by undesired temporal correlation. By the Theiler correction only a minor part of all distances are discarded. The sequence of formula 2.6 is visualized in Fig. 2.1. The order in which the distances are calculated for the filled dots (gray and black) of the lower triangle are horizontal lines from left to right going upward. In fact one point is fixed while the other is being varied along the remaining total range. This approach has the disadvantage that all coordinate differences that make up the distance between the two reconstruction vectors change with every estimate. The following order, as indicated by formula 2.7, however, does not have this drawback and already computed distance information is preserved for the next estimate:

\[
\sum_{n=1}^{k_{\text{max}}-TC-n+1} \sum_{k=1}^{k_{\text{max}}-TC} (V_k, V_{l=k+TC+n-1}) \quad \text{2.7}
\]

With this order the lower triangle with the filled dots (black and gray) is filled out following the diagonals as indicated with the arrows in the figure. As a consequence, the index difference \((l-k=TC+n-1)\) between both reconstruction vector indices remains constant. In this case the succeeding pairs of reconstruction vectors only differ at the beginning and end. The
The idea is that both summations in formula 2.7 can be stepped through with values higher than one. The summation over $n$ is stepped through with $s$ and the summation over $k$ is stepped through with $p$. Fig. 2.1 visualizes how a subset of distances is chosen with the parameters $p$ and $s$. Both the vertical and horizontal axes symbolize all possible $k_{\text{max}}$ reconstruction vectors denoted with the indices $l$ and $k$. The intersections of the block pattern represent the pairs of reconstruction vectors or even the distances between the reconstruction vectors of such pairs. The intersections occupied by the open circles are omitted due to the Theiler correction (TC=1s). The filled dots (gray and black) represent all remaining unique distances with $p=1$ and $s=1$. The black dots represent an example of a subset of distances that is obtained with $p=2$ and $s=3$. Parameters $p$ and $s$ should not be chosen arbitrarily. They cannot, for example, be even numbers in order to prevent the loss of a great deal of
information during the process of distance determination (all even samples of the time series would be omitted in the reconstruction vectors). A well-chosen combination of $p$ and $s$ combines the advantage of reduced needs for computer time and a homogeneous usage of the available information from the original time series. Note that reuse of distance information is only beneficial as long as $p < \sqrt{2m}$.

**Determination of $m$ and $\tau$**

Many articles speculate on how to estimate the delay time $\tau \Delta t$ and the proper embedding dimension $m$.\textsuperscript{3,5,119,120,150} In the present article a lower bound for the embedding dimension is initially estimated using the method of false nearest neighbors (FNN).\textsuperscript{94} The FNN are computed using software from the Non-linear Dynamics Toolbox (NDT-0.9; ©Applied Chaos Lab) written by Josh Reiss and is applied to the EEG of the rat measured during varying levels of vigilance (awake, eating and sleep). Following this procedure a lower bound for $m$ is obtained and subsequently the effects of different combinations of $\tau$ and $m$ on the results of CD are evaluated. For each combination of $\tau$ and $m$, the CD of the total EEG time series of three rats is computed. During the experiments a bolus of propofol is administered several times to induce a dynamic anesthetic response. Immediately after the boluses, CD decreases and returns to its pre-bolus value after the wash out of propofol (Fig. 2.2). It is assumed that during the time course of the dynamic anesthetic response, the difference between the minimum and maximum CD should be maximized to achieve maximum sensitivity to changes in anesthetic drug levels. The performance of each combination is defined by a “signal” to “noise” ratio (S/N-ratio). The “signal” part is defined as the averaged absolute difference between the measured CD-curve and the linear regression line (trend) of this curve. The “noise” part is defined as the root mean squared difference between the measured CD-curve and a (first order 11-points convolution) smoothed line of this curve.\textsuperscript{155,193} With this definition higher S/N-ratios indicate better performance. It is important to note that the S/N-ratio can only be compared within the subject and within the same experiment. The nomenclature and meaning of the “S/N-ratio” used here must be regarded as described above and may not be confused with the definition most commonly assigned to it.

An equivalent procedure is followed with combinations of the parameters $p$ and $s$ in order to find out how many distances during the correlation integral estimate can be skipped without loss of performance for CD as a measure of DOA. Again the S/N-ratio is used to check this performance. The aim of this reduction-scheme is to minimize the computational effort needed to compute the CD and by doing this to increase the feasibility of on-line CD monitoring.
2.3.4 Statistical analysis
Averaged and normalized results of the S/N-ratios (as defined earlier) are used to determine the change of performance of the CD algorithm as the accompanying parameters $m$, $\tau$, $p$ and $s$ are varied.

2.4 Results

2.4.1 Experiments in rats
Three experiments were performed (mean rat weight: 426 g, $\sigma=36$ g). A strong correlation was found between CD and propofol dose (Fig. 2.2 depicts a typical example). The arrows on the time-axis indicate the time points where a bolus of propofol was given. As a response to the administered bolus, CD immediately decreased and in the course of the presumed elimination of propofol, returned to its pre-bolus value. Similar results were found for the other two measured experiments. The increase of CD after approximately 50 minutes can be subscribed to adjustments of the propofol infusion rate. The threshold values that define the suppression periods during burst-suppression patterns were manually estimated for each rat individually and varied between 0.1 and 0.3 mV.

![Fig. 2.2 Variation of CD by propofol. Typical example of the response of CD ($\tau$) to changing propofol levels. A safe level of DOA was achieved by propofol, whose infusion rate is shown below. A deep level of DOA was achieved by an extra propofol bolus (3 mg). Every extra administrated bolus of propofol is marked with an arrow and a dashed line on the time axis.](image)

2.4.2 Determination of fitting interval
Fig. 2.3 shows the CD results for the Lorenz- and Rössler time series separately and the sinusoidal combination of the two, for three different intervals. The results of the first two
intervals \([r_0-r_1]\) and \([r_1-r_2]\) are not shown because they were obviously corrupted by fluctuations. The sinusoidal pattern of the combination signal is at best visible in the CD results of the interval \([r_3-r_4]\). The averaged results of CD (n=88) for the separately calculated time series for the three intervals \([r_2-r_3]\), \([r_3-r_4]\), \([r_4-r_5]\) were respectively: 2.088 (\(\sigma=0.080\)), 2.012 (\(\sigma=0.012\)), 1.679 (\(\sigma=0.007\)) for the Lorenz time series and 1.800 (\(\sigma=0.194\)), 1.82 (\(\sigma=0.043\)), 1.18 (\(\sigma=0.002\)) for the Rössler time series. The results of interval \([r_3-r_4]\) provide the most stable results close to the theoretical values of 2.06 and 2.01.\(^{152}\) It also agrees with the criterion that the mixed signals produce higher CD’s, lower than or equal to the sum of both separate results.

Fig. 2.3 Selection of interval. Results of CD for the Lorenz-attractor (0), Rössler-attractor (+) and the sinusoidal combination of the two (■). From top to bottom the CD results of three different intervals (top: \([r_2-r_3]\), middle: \([r_3-r_4]\) and bottom: \([r_4-r_5]\)) are displayed.
2.4.3 Determination of \( m \) and \( \tau \)

To reduce the percentage of False Nearest Neighbors below 1%, attractor reconstruction should be performed using an embedding dimension above \( m=20 \). This result is based on attractor reconstruction of rat EEG under varying levels of vigilance (eating, passiveness and sleep).

The results of the three rats were used to optimize the parameters \( m, \tau, p \) and \( s \). To enable a true comparison of the S/N-ratios between the three subjects, the S/N-ratios of each subject were normalized with respect to the maximum estimated S/N-ratio of the specific subject. For each \((m, \tau)\)-combination the average of these three normalized S/N-ratios is presented in Table 2.1. Fig. 2.4 illustrates the influence of \( \tau \) and \( m \) on CD as applied to EEG data acquired from one single rat experiment (see Fig. 2.2). Differences between the tracings can be subscribed to the varied parameters \( \tau \) (Fig. 2.4; left; \( m=20 \)), and \( m \) (Fig. 2.4; right; \( \tau=8ms \)).

A high value of \( \tau \) (20 ms) seems to have a leveling off effect on CD. This is expressed by the tendency of the CD tracing to turn into a flat line just before the administration of a new bolus at the end of the propofol washout. In general, increase of \( \tau \) and \( m \) lead to higher values for CD (lift-up of the entire tracing). Further examination of Table 2.1 shows that the product of \( m \) and \( \tau \Delta t \) is related to the S/N-ratio, i.e. a maximum for the S/N-ratios can be found if \( m \cdot \tau \Delta t \) lies between 0.16s and 0.24s (sampling interval \( \Delta t=4 \) ms). If translated towards the original EEG time series, the time coverage of the reconstruction vectors should be about 0.2 s. From Fig. 2.4 it can be seen that approximately equal S/N-ratios (0.73: \( \tau=8ms, m=50 \) and 0.79: \( \tau=20ms, m=20 \)) do not necessarily imply similar CD tracings (see both upper tracings, left and right in Fig. 2.4).
Correlation dimension applied to the EEG: evaluation of the effect of a distance reduction scheme, definition of the scaling region, and choice of embedding parameters on results

### Table 2.1
Normalized and averaged (3 subjects) S/N-ratios for different values of embedding dimension (m) and delay time (r-Δt).

<table>
<thead>
<tr>
<th>r-Δt [ms]</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
</tr>
</thead>
<tbody>
<tr>
<td>m=15</td>
<td>0.77</td>
<td>0.86</td>
<td>0.97</td>
<td>0.96</td>
<td>x</td>
</tr>
<tr>
<td>m=20</td>
<td>0.81</td>
<td>0.96</td>
<td>0.92</td>
<td>0.81</td>
<td>0.79</td>
</tr>
<tr>
<td>m=25</td>
<td>0.82</td>
<td>0.96</td>
<td>0.81</td>
<td>0.78</td>
<td>x</td>
</tr>
<tr>
<td>m=33</td>
<td>0.90</td>
<td>0.84</td>
<td>0.76</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>m=50</td>
<td>0.95</td>
<td>0.73</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

#### 2.4.4 Reduction of distances with p and s

The S/N-ratios estimated with varying parameters p and s, were also individually normalized with respect to the corresponding maximum S/N-ratio and averaged over the three subjects. Three gray-scaled surface-plots (Fig. 2.7) display the S/N-ratios and the separate results for the signal and noise components with decreasing values going from black to white. The results presented are based on the average of the three subjects. Both separate results for the signal and noise components (Fig. 2.7, left and right) decrease steadily with increasing p and/or s. However, maximum S/N-ratios (Fig. 2.7, bottom/left) can be found around p=15 and s=20. The individual results showed that the spread and decay of the S/N-ratios differ per subject. It is important to note that the condition (p,s)=(1,1), where all distances are included, does not correspond to the highest S/N-ratio.

With a window length of 16384 samples (approximately 1 minute EEG), embedding dimension m=20, delay time r-Δt=8 ms (2 sampling intervals), Fig. 2.5 demonstrates the influence of parameters p and s on computer run time. Also, the figure demonstrates run time benefits of applied overlapping intervals with saving of previous results of squared coordinate differences.
Fig. 2.5 Effect of different parameters on run time per CD estimate using 16384 points, embedding dimension $m=20$, delay time $\tau \Delta t=8$ ms. Both y-axes show fraction of required computer time compared to the situation where all distances are taken into account $(p,s)=(1,1)$. The left y-axis for the first estimate and the right y-axis for the second and subsequent estimates with $7/8$ overlapping (shift 2048 points) intervals. Influence of parameter $p$ on run time can be divided into two segments: with reuse of information of squared coordinate differences from the previous estimate (curve II) and recomputation of all squared coordinate differences (curve III). The crossing of curve I and curve II occurs at $p=0.5m$ and is indicated by a dashed line. Curve III shows the influence of parameter $s$. The different curves are described by the equations shown in the figure (eq. 2.8, 2.9, 2.10). Both figures (left, right) are identical, except for the logarithmic (left) and linear axes (right) and the range of the y-axes.

For both parameters $p$ and $s$, the equation to describe the relationship with achieved relative run time reduction, should be proportional to the number of omitted distances: $1/p$ respectively $1/s$. For $s$ this is true (Fig. 2.5: curve III; eq. 2.10), but since extra run time reduction is achieved by reuse of already calculated squared coordinate differences during the previous estimate, a different relationship is found for $p$. As long as $p < 0.5m$ ($m$=embedding dimension), the relative run time reduction ($T_{f^p}$) is described by curve I_A (Fig. 2.5; eq. 2.8).

\[
I_A: \quad T_{f^p} = \frac{1+ \alpha (p - 1)}{p} \quad p < \frac{1}{2} m
\]

\[
I_B: \quad T_{f^p} = \frac{1+ \alpha (0.5m - 1)}{p} \quad p \geq \frac{1}{2} m
\]

\[
\alpha = 0.3262; m \geq 2
\]

\[
III: \quad T_{f^s} = \frac{1}{s} \quad s \geq 1
\]

For higher values of $p$, there is no longer computational benefit of the reuse of previous calculated squared coordinate differences and distances between points are just calculated by recalculation of all $m$ squared coordinate differences. The latter situation is described by curve...
II \_B (T_{f_{pp}}, \text{eq. 2.9}). Parameter \( \alpha \) is directly related to the relative extra time necessary for each additional subtraction and summation of squared coordinate differences as \( p \) is increased. If \( p \gtrsim \frac{1}{2} m \), the extra time exceeds the time necessary for a total recalculation and summation of all \( m \) squared coordinate differences. Therefore, from this point, run time reduction is described by curve II (Fig. 2.5, eq. 2.9). The value of \( \alpha \) was found by fitting equation 2.8 through measured reduced run time estimates for \( p \) varied between 1 and 50.

![Diagram](image)

**Fig. 2.6** Visualisation of how a pair of points can be categorized by \( \lambda \) different subsegments for computational benefits. The \( \lambda \) sub-segments together produce the epoch window that is object of study to obtain an estimate for CD. Each square or triangle represents all possible pair of points between accompanying sub-segments. The pair of points of the squares and triangles within the large square (thick solid line), all together represent all possible pairs of points \((V_0, V_1)\) in the epoch window. The upper square (thick dashed line) represents the pair of points that need to be evaluated for the next CD estimate. The shaded area at the right, represents the extra pair of points to be evaluated compared to the first estimate. The ratio of the dashed area and half of the area of the large square express computational benefit (see also eq. 2.11).

### 2.4.5 Trend analysis

For trend analysis purposes, subsequent estimates overlap with foregoing estimates. By storing distance information gathered during previous estimates, a considerable run time reduction can be achieved (see Fig. 2.6). This is expressed by the difference between the scale of the left y-axis for the first estimate and the right y-axis for the second and subsequent estimates (Fig. 2.5). The number of data samples that are common between two subsequent estimates define the overlap between estimates. To enable implementation of time reduction, the number of samples between windows divided by the number of samples in each window,
must be an integer larger than one. If the result of this division, the number of defined sub-segments is called \( \lambda \), the following equation for the achieved time reduction \( T_{f0} \) can be derived.

\[
T_{f0} = \frac{2^{\lambda - 1}}{\lambda^2} \quad (\lambda > 1)
\]  

If the indices \( k \) and \( l \) of reconstruction vectors \( V_k \) and \( V_l \) are in different sub-segments, the distance between these vectors is denoted to origin from \( A_{ij} \) \((i \neq j)\), where \( i, j \) indicate the sub-segments where \( V_k \) respectively \( V_l \) origin from.

\[
\sum_{i=1}^{\lambda} \sum_{j=i}^{\lambda} A_{i,j} \quad 2.12
\]

By calculating all possible distances between vectors with indices (start point of reconstruction vector in the time series) in the sub-segments described by eq. 2.12, all distances that contribute to the correlation integral \( C(r) \) are calculated (lower triangle of the large square in Fig. 2.6). This is required for the first estimate. For the next estimate, it is only necessary to calculate distances between vectors originating from the sub-segments described by eq. 2.13.

\[
\sum_{i=2}^{\lambda+1} A_{i,i=1} \quad 2.13
\]

In case of \( i=j \) only half of the distances within the single sub-segment need to be calculated because of the equivalence of distances between \( (V_k, V_j) \) and \( (V_l, V_k) \). If the demanded computer run time to estimate distances between vectors in \( A_{ij} \) \((i \neq j)\) is defined by \( t_0 \), the demanded computer run time for \( A_{ij} \) \((i=j)\) is defined by \( \frac{1}{2}t_0 \). The total computer time required for the first estimate is \( \frac{1}{2}\lambda(\lambda-1)t_0 + \lambda(\frac{1}{2}t_0) = \frac{1}{2}\lambda^2t_0 \). The total computer time required for the second and subsequent estimates adds to \( \frac{1}{2}t_0 + (\lambda-1)t_0 \) and is displayed in Fig. 2.6 by the shaded area. The ratio of the required computer time for the second or subsequent estimates and the first estimate yields equation 2.11.

For trend monitoring the total potential computer time reduction for the second and subsequent estimates can be derived from equations 2.8 to 2.11 and is described by:"
Correlation dimension applied to the EEG: evaluation of the effect of a distance reduction scheme, definition of the scaling region, and choice of embedding parameters on results

\[ T_{f_{\text{Hi}}} \cdot T_{f_s} \cdot T_{f_o} = \begin{cases} \frac{1 + \alpha(p - 1)}{p} \cdot \frac{1}{s} \cdot \frac{2 \lambda^2}{\lambda^2} & \text{if } p \leq \frac{1}{2}m \\ \frac{1 + \alpha(0.5m - 1)}{p} \cdot \frac{1}{s} \cdot \frac{2 \lambda^2}{\lambda^2} & \text{if } p \geq \frac{1}{2}m \end{cases} \]

\[ \alpha = 0.3262; m \geq 2 \]

As an illustrative example, for \( m = 20, r = 8\text{ms}, \alpha = 0.3262, p = 15, s = 20, \) and \( \lambda = 8, \) equation 2.14 yields \( 3.07 \times 10^{-3}, \) which means that the required computer time for the situation where all distances are recalculated for every subsequent overlapping estimate, is 325 times reduced. On a PC with dual-pentium 233MHz microprocessor, with a 1 minute EEG epoch length (16384 samples) the according absolute computer run time reduces from 205s to 0.6s.

![Fig. 2.7 S/N-ratio as a function of skipping distances by changing parameters p and s. Three surface-plots with the averaged (three subjects) normalized (to maximum of corresponding data) results of the signal (top, left), noise (top, right) and S/N-ratio (bottom, left) for different combinations of parameters p and s. The effect of p and s (three combinations) on the tracing of one subject (see Fig. 2.2) is also demonstrated (bottom, right).](image)

The accompanying effect of these settings on results (number of distances are \( p \cdot s \) times reduced), is demonstrated in Fig. 2.7. The surface plots show the effect of the distance
reduction scheme on sensitivity to anesthetic drug changes as expressed by the S/N-ratio. The lower right plot, shows the effect of the reduction scheme on the tracing of one subject. From this tracing it can be seen that as more distances are omitted, results for CD are decreased.

In summary, the proposed parameter settings are embedding dimension \( m = 20 \), delay time \( \tau \Delta t = 8 \) ms (2 sampling intervals), extraction of CD from \( C(r) \) at interval \([r_3-r_4]\), reduction of the number of distances with \( p = 15 \) and \( s = 20 \).

2.5 Discussion

2.5.1 Introduction

The method of surrogate analysis was not applied.\(^{199}\) Regardless of the outcome of the surrogate test (i.e. the signal is Gaussian or not), the found relationship between propofol concentrations and CD remains identical. Even if the signal was Gaussian it is still unclear how to obtain the same information from the power spectrum.

2.5.2 Determination of fitting interval

The intervals (adjacent and equal in size on the C-axis, but in general not on the \( r \)-axis) were arbitrarily chosen, but it is clear that an optimal interval range should be chosen in the neighborhood of interval \([r_3-r_4]\). The aim was to utilize as much as possible an objective definition minimally disturbed by environmental influences. The advantage of this approach perhaps is the independency of this interval of the amplitude of the measured time series, its assumed relative robustness against amplitude artifacts and hopefully reduced variability in final results obtained for CD. However, this remains speculative as no specific tests were performed to confirm these statements.

2.5.3 Determination of \( m \) and \( \tau \)

The compressing effect of low a value of \( \tau \) on the CD tracing (Fig. 2.4), perhaps can be subscribed to autocorrelation between coordinates of the reconstruction vector. The effect of which is a reconstructed attractor that moves towards a line of unity and as a consequence CD is decreased. The lift-up effect with increased \( \tau \), perhaps moves results of CD towards an upper limit. A fixed \( m \) limits the theoretical obtainable CD to \( m \). However, in practice this upper limit is far below this value. Perhaps this explains the leveling off effect visible in the tracing retrieved with \( \tau \Delta t = 20 \) ms. The increase of CD with increased \( m \) is most probably the effect of noise, which effect is unavoidable with measured time series.

The delay time \( \tau \Delta t \) should not be chosen independently of \( m \), but one should choose an appropriate value for the delay time window \( \tau_w \).\(^{36,105,150,163}\) The results of this study confirm the \( m \cdot \tau \Delta t \)-dependency by the optimal S/N-ratios found for \( m \cdot \tau \Delta t \approx 0.2 \)s. However, note that
other parameter choices still inform about DOA. Lai et al., suggested that with fixed $\tau_w$, lower values for $\tau$ are preferred and $m$ should accordingly be adapted to conform $\tau_w$. The embedding dimension, $m=20$, was chosen based on the FNN-search criterion ($m \geq 20$) and as a consequence the delay time, $\tau \Delta t=8$ ms, was chosen generating the highest S/N-ratio (see Table 2.1). Besthorn et al., followed a similar approach by evaluating influence of parameters on estimated dimensional complexity in Alzheimer diseased patients. As a result, they proposed to use $\tau \Delta t=20$ ms and $m=30$. However, they noticed that their main result (dimensional complexity of AD patients is lower than controls) was robust from $m=5$ to $m=85$, and from $\tau \Delta t=5$ ms to $\tau \Delta t=70$ ms. Here, parameters were chosen based on the performance criterion as defined by the S/N ratio and both turn out to be within these robust ranges.

### 2.5.4 Reduction of distances with $p$ and $s$

Examining the results of the S/N-ratios with varying parameters $p$ and $s$, it is remarkable that the situation ($p=1$, $s=1$) where all distances are included, does not result in the highest S/N-ratio. This remains an open question. Note that the combinations of $p$ and $s$ with the worst S/N-ratios still reach values up to a fraction of 75% of the optimal S/N-ratio. Also, note that at the situation ($p=15$, $s=20$) where the highest S/N-ratio was found, the ‘signal’ component is only decreased to 85% of its maximum value. The number of distances, however, is then reduced by 300 and the computer run time by 325. The calculation of $C(r)$ with $p=s=1$ is based on distance information retrieved from $\frac{1}{2}N^2$ pairs of points. Note that these pairs of points are derived from $N$ samples of the original (EEG) time series, which subsequent samples also are not independent. Therefore, in this case, it is amenable that there is a large amount of redundant information, which can be omitted by choosing $p$ and $s$ higher than one. When both parameters $p$ and $s$ are even numbers, the information of half of the digitized samples of the original time series are omitted during the calculation of CD. It was expected to see this effect in Fig. 2.7, but this is not the case. This may be explained by the used sample frequency of 250 Hz. Perhaps the contribution of the highest frequencies (above 64 Hz) is of less importance in the calculation of CD or the power content is too low to contribute significantly to CD. This effect can also be utilized in an advantageous way if oversampled data is to be analyzed. By increasing $p$ and/or $s$, redundant distances can easily be omitted.

### 2.6 Conclusions

The correlation between propofol dose and CD indicates that CD can probably give valuable information about anesthetic effects of propofol on the rat EEG. CD, calculated with the proposed modifications and settings, may provide relevant and valuable information to the anesthesiologist and may help in detecting changes in the EEG induced by anesthetics.
carefully, although empirical based, choice of embedding dimension and delay time optimize results for CD as a measure of DOA. Also, in a practical setting, apparently a large number of distances can be omitted without having negative effects on capability of CD to inform about DOA. The accompanying reduced computer run time per CD estimate enables use of CD in practical applications.

2.7 Acknowledgements

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3 Correlation Dimension and Burst Suppression Ratio of the EEG Correlate with Sevoflurane Concentration in Rat

3.1 Abstract

Background: Anesthesiologists have searched for many years to identify a parameter that measures depth of anesthesia (DOA). In the context of this search, the aim of the present study is to investigate how the correlation dimension (CD) and Burst Suppression Ratio (BSR) correlate with the concentrations of sevoflurane.

Methods: The CD and BSR of the EEG of eight rats were recorded during sevoflurane anesthesia. Experiments were performed in a box placed on a swing to keep the rat in an alert state preventing it from falling spontaneously asleep rather than from the supplied sevoflurane. In the box, the rat could move freely while the EEG was continuously measured. Sevoflurane concentration in the box varied between 0.0 and 6.4%. The CD was computed following the Grassberger/Procaccia/Takens approach with optimized parameter settings to achieve maximum sensitivity to anesthetic drug effects. The BSR was calculated based on manually estimated individual threshold values. The Hill equation was fitted to the data.

Results: Both the CD and BSR showed a strong correlation with the administered sevoflurane concentration with slope factors: \( \gamma_{\text{CD}} = -1.8 \) and \( \gamma_{\text{BSR}} = 5.4 \). The sevoflurane concentration associated with 50% of the maximum effect (C50) was lower for CD (C50,CD = 0.60%) than for BSR (C50,BSR = 1.72%). The CD varied between 9 and 4 and the BSR between 0 and 0.9.

Conclusions: Both CD and BSR are related to sevoflurane concentrations and may be useful EEG measures of anesthetic drug effect or depth. The sharp transition of BSR from 0 to 0.9 between sevoflurane concentrations 1.5% and 2.0% make it less suitable than CD for monitoring during varying anesthetic drug dosage. A more potent anesthetic drug effect measure is available when both the results of CD and BSR can be combined.

3.2 Introduction

One of the main purposes of anesthesia is the suppression of physiologic responses to external noxious influences. Pharmaceutical companies have developed anesthetics that have specific effects on different physiological subsystems. This gives the anesthesiologist more possibilities to control anesthetic effects. To benefit from these advances, it is useful to know the physiological condition of the patient. At present, the anesthesiologist obtains this information by measuring physiological variables such as arterial pressure, heart frequency, respiration, and oxygen saturation. Based on these variables, the anesthetic depth is varied as necessary.
Anesthetics result in changes in the activity of the central nervous system (CNS). These changes might be reflected in the electroencephalogram (EEG). If the anesthesiologist can obtain relevant information from the EEG, a more balanced anesthetic might be possible. In an effort to quantify the effects of anesthetics during surgery, several reports have studied relevant EEG measures from the power spectrum of the EEG (linear approach) with different levels of success. Positive results were reported \cite{39,157,162,179} But also negative results.\cite{41,61,144,203}

At present many researchers, with different scientific backgrounds, investigate the potential of the non-linear approach. A quantitative measure that has been developed to characterize non-linear dynamics is $D_2$, the correlation dimension.\cite{65,196} In this study an adapted algorithm was used to compute $D_2$, to pronounce the difference another abbreviation: CD was introduced (see chapter 2). In another study, performed by the authors, a close relationship between CD and anesthetic effects induced by propofol was demonstrated (see chapter 5). In 1987, Mayer-Kress and Layne published one of the first articles that describe the application of $D_2$ to determine anesthetic drug effect.\cite{126} One year later Watt & Hameroff demonstrated changes of phase space trajectories and dimensionality as a result of changed DOA.\cite{213} Widman et al., investigated a modified version of $D_2$, the nonlinear correlation index $D^*$, as a measure of depth of sevoflurane anesthesia.\cite{215} Lee et al., found $D_2$ to serve as a better index for the depth of halothane anesthesia in the rat compared to $\beta$-power and median power frequency.\cite{110}

Recently, the search for a reliable estimator of DOA has moved towards a multimethodological approach. Instead of focusing on one nonlinear measure, multiple nonlinear measures and discriminating methods are utilized.\cite{136,177,211,220,221} The results of these articles show the potency of $D_2$ or derived measures to inform about DOA.

Another processed EEG variable, the Burst Suppression Ratio (BSR) was also calculated.\cite{74,168} At the deepest anesthetic levels, the EEG pattern changes, i.e. EEG epochs with high frequencies and low amplitudes (suppression) are alternated with epochs with low frequencies and high amplitudes (bursts), see Fig. 3.1. The Burst Suppression Ratio (BSR) is defined as the ratio of the summation of the suppression parts in a certain epoch and the total length of that epoch. Several studies evaluated the BSR, the burst suppression pattern (BSP), and the onset of BSP as possible informatives of anesthesia related phenomena. Some studies used the onset of the BSP to titrate the administered anesthetic drug.\cite{45,103,128} The presence of BSP did not predict lack of response to a noxious stimulation in isoflurane anesthetized rats.\cite{144} Differences were found between BSP’s retrieved during isoflurane and enfurane anesthesia.\cite{121} Also BSR was used as the control variable in a closed-loop infusion system for monitoring and controlling i.v. anesthesia in rats.\cite{212}
In the presented study, eight rats were individually exposed to an increasing sevoflurane concentration that reached a maximum of approximately 6.3% and thereafter exponentially decreased towards zero. This caused the level of vigilance of the rats to change from awake to deep anesthesia and vice versa in about 60 minutes. During this forced awake-anesthesia-awake sequence the EEG of the rat was continuously recorded and afterwards the CD and BSR of the EEG were calculated and related to the applied sevoflurane concentration. The assumption was made that anesthetic depth relates to the sevoflurane concentration, without knowing the exact relationship. Object of this study was to investigate how the CD and BSR correlate with the sevoflurane concentration.

3.3 Materials and methods

3.3.1 Experiment

After approval of the University Committee on Ethics in Animal Research eight adult male Wistar rats (mean weight: 426 g, SD=36 g) were used. A tripolar and a bipolar electrode (Plastic Products Company, MS 333/2A) were implanted under Narcovet anesthesia (60 mg.kg$^{-1}$ ip.) to enable long-term recording of two bipolar leads of the cortical EEG. For the data presented in the present paper only one lead was used. The coordinates of the electrodes used were: A 2.0, L 3.5; A -6.0, L 4.0 related to the bregma. The ground electrode was placed above the cerebellum. Experiments were performed after a recovery period of at least two weeks. The rats were placed in a box with heated bottom to keep the rat at appropriate temperature and a ventilator contributed to even mixing of the sevoflurane in the box. The box was placed on a swing that moved with a period of 40 s and an angle deviation of 20 degrees (both directions). The swinging prevented spontaneous sleep enabling the
measurement of the transition from the awake state to the anesthetic state induced by sevoflurane. Sevoflurane was delivered to the box by a mixed gas flow of 100 ml min\(^{-1}\) oxygen and 300 ml min\(^{-1}\) air, passing through a sevoflurane vaporizer. Four sevoflurane concentrations (manually adjusted with the vaporizer) were delivered to the box: 0.0% (at least 10 minutes), 3.0% (10 minutes), 5.5% (10 minutes), 8.0% (15 minutes) and finally again 0.0% until awakening of the rat and thereafter at least 15 minutes more. Prior to the start of the experiments, the change of the sevoflurane concentration as a function of time (without rat), was measured three times in different experiments (Mass Spectrometer: QP 9000; Case Ltd. England). Fig. 3.2 describes the averaged curve of the sevoflurane concentration in the box as a function of time.

During the experiments the rats were isolated in the box and a video camera allowed observation of the rat’s behavior. The vaporizer delivering sevoflurane was placed outside the box enabling adjustments without disturbing the rat.

![Graph](image)

**Fig. 3.2** Sevoflurane concentration in the box exposed to the rat. In the figure, near the curve the percentages of the sevoflurane delivery to the box are specified.

### 3.3.2 EEG registration

The EEG was recorded continuously. The raw signal was filtered between 1 and 100 Hz, digitized at a rate of 256 Hz and stored to disk for “off-line” analysis. The CD of the EEG of the rat was computed every epoch of 64s (16384 samples) and repeated every 8s (7/8 overlap with previous estimate).

### 3.3.3 EEG analysis

**CD**

The CD was computed following the Grassberger\Procaccia\Takens algorithm\(^{65,196}\) with alterations to maximize the sensitivity to anesthetic effects (see chapter 2). Attractor reconstruction was performed with 16384 samples, embedding dimension=20, delay
time=8.0 ms and 1 second Theiler correction.\textsuperscript{200} To speed up computation time, the correlation integral was estimated using only a subset of all possible distances between points on the attractor. The CD was extracted from the correlation integral at a fixed interval defined by the distribution of distances in the correlation integral. Since the burst suppression pattern was highly non-stationary, the suppression periods were omitted in the calculation of CD. During burst suppression patterns the number of EEG-samples was maintained at 16384 by increasing the epoch length. Transitions from burst epochs to suppression epochs and vice-versa were avoided within the time span of the reconstruction vectors.

**BSR**
At the deepest anesthetic depths burst suppression appeared in the EEG signal.\textsuperscript{74,168} Suppression periods were defined as periods of at least 0.3s duration where the absolute amplitude of the EEG remained below some threshold value. The threshold values were manually estimated for all eight rats individually and were 0.2 or 0.3 mV. The Burst Suppression Ratio (BSR) was defined as the ratio of the summation of the suppression parts in 64s epochs and the total length of that epoch (i.e. 64s).

### 3.3.4 Pharmacokinetic/dynamic Analysis
A first order model as introduced by Sheiner et al. (equation 3.1), was used to describe the relation between inspiratory concentration and effect-compartment concentration.\textsuperscript{178} The relation between effect compartment sevoflurane concentration and effect (i.e., CD or BSR) was described by the Hill-equation\textsuperscript{70}, equation 3.2:

\[
\frac{dC_{\text{eff}}}{dt} = (C_{\text{in}} - C_{\text{eff}})k_{e0}
\]

\[E = E_{\text{begin}} - \left( E_{\text{begin}} - E_{\text{end}} \right) \left( \frac{C_{\text{eff}}'}{C_{\text{50}}' + C_{\text{eff}}'} \right)\]

where, \(E_{\text{begin}}\) = baseline, at awake condition, \(E_{\text{end}}\) = end value at infinite sevoflurane concentration, \(C_{\text{50}}\) = concentration associated with 50% of the maximum effect, \(\gamma\) = steepness factor determining the slope of the concentration-response relation, \(C_{\text{eff}}\) = concentration in the effect compartment, \(C_{\text{in}}\) = inspiratory concentration of sevoflurane, and \(k_{e0}^{-1}\) = time constant determining the influx to and efflux from the effect compartment via the central compartment. The parameters were determined for each rat individually. The parameters were optimized using the Solver tool within Excel (Microsoft, Redmond, WA) using nonlinear regression with least-squares. This was performed only for the relation between sevoflurane concentration and CD and the resulting effect compartment concentrations (\(C_{\text{eff}}\)) were also utilized to determine the relation between sevoflurane concentration and BSR. After transformation of the inspired sevoflurane concentrations into \(C_{\text{eff}}\) (hysteresis elimination), the
pharmacokinetic/dynamic parameters of CD and BSR were obtained for the seven rats grouped together using a subset of the data as explained later.

3.4 Results

3.4.1 EEG analysis

The CD and BSR of the EEG of all eight subjects are displayed in Fig. 3.3. At time point zero the delivery of the sevoflurane was started. The changes of the sevoflurane concentration in the box are shown in Fig. 3.2 and are assumed to be the same for all subjects. All subjects show a decrease of CD in response to the increased sevoflurane concentration. When the sevoflurane concentration in the box decreases, CD increases and returns to its baseline values. Some peaks emerged in the CD curve some minutes after the start of sevoflurane delivery. This coincided with an excitation period that was observed, characterized by attempts to stand up and by ataxic walking. The awakening of the rat approximately 25 minutes after stopping the sevoflurane coincides in most cases with a sudden increase of CD. The BSR starts to increase at the higher sevoflurane concentrations and reaches its maximum at the highest sevoflurane concentration. During wash out of the sevoflurane, BSR decreases towards zero. In awake conditions no burst suppression patterns were observed in the EEG and therefore BSR should be zero. The BSR results higher than zero at awake conditions of the rat must be ascribed to methodological artifacts in the BSR algorithm (EEG-patterns during awake conditions were confused with burst-suppression patterns).

![Figure 3.3](image1.png)

Fig. 3.3 Results of CD (open circles) and BSR (solid line) as a function of time of all eight experiments. At time point zero the delivery of the sevoflurane was started. At time point 35 minutes, the delivery of sevoflurane was stopped (see also Fig. 3.2).

3.4.2 Relation between CD, BSR and $C_{\text{et}}$

A typical example (subject 5) of a plot of CD and BSR versus the inspired sevoflurane concentration is presented in Fig. 3.4 (left). Variation of CD and BSR during the induction
and wash-out of sevoflurane, take place at different ranges of sevoflurane concentration intervals. This hysteresis can be eliminated by the introduction of an effect compartment (Fig. 3.4, right).  

A Hill-equation describes the relation between CD, BSR and effect compartment concentration. The pharmacokinetic/dynamic parameters (CD only) were determined for each rat individually ($k_{e0}=0.25 \text{ min}^{-1}$, SD=0.05) and for the seven rats grouped together (CD and BSR, see Table 3.1 and Fig. 3.5). Averaged results of the seven rats were obtained per 0.1 division on a logarithmic sevoflurane concentration scale. One rat (rat 3, see Fig. 3.3) was excluded because of atypical results at the highest sevoflurane concentrations. The fits were restricted to the results obtained from the moment that $C_{eff}$ reached it’s maximum until the rat awoke, thereby omitting the periods of excitation.

**Fig. 3.4** Relation between both CD (solid line), BSR (dashed line) and end-tidal sevoflurane concentrations (left subplot) or effect compartment sevoflurane concentrations (right subplot) as obtained by the Sheiner algorithm. Time course is indicated by arrows.

**Fig. 3.5** Relation between CD (○), BSR (◆) and effect compartment sevoflurane concentration restricted to the reverse sevoflurane trajectory (from maximum sevoflurane concentration until awakening of the rat). The figure displays the combined results of seven subjects. Results were pooled per 0.1 division on a logarithmic sevoflurane concentration scale. Error bars represent SEM values. The accompanying pharmacokinetic/dynamic parameters are displayed in Table 3.1.
Comparable results were found for all eight subjects (Fig. 3.6). The peaks in the curve of CD versus sevoflurane concentration (mainly between 1% and 3%) are related to the excitation phases as described before.

![Graph showing the relation between CD, BSR, and sevoflurane concentration](image)

**Fig. 3.6** Relation between CD (solid line), BSR (dashed line) and effect compartment sevoflurane concentration of all measured subjects. Hysteresis was eliminated by applied Sheiner algorithm (see Fig. 3.4).

A sigmoidal relation between CD, BSR and $C_{\text{eff}}$ can be observed. The highest steepness factor, determining the slope of the concentration-response relation, and $C_{50}$, determining the concentration associated with 50% of the effect, were found for BSR. The absolute values of CD varied between approximately 9 and 4 and the BSR varied between 0 and 0.9 for the lowest and highest administered sevoflurane concentrations respectively.

**Table 3.1: Pharmacodynamic parameters.** Averaged results (seven subjects, rat 3 is deleted from the fit) of the pharmacokinetic/dynamic parameters that describe the relation between CD and BSR and the effect compartment concentration $C_{\text{eff}}$, see eq. 3.2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CD mean (95% CI)</th>
<th>BSR mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{\text{beg}}$</td>
<td>9.46 (9.10 / 9.82)</td>
<td>0.0 (constant)</td>
</tr>
<tr>
<td>$E_{\text{end}}$</td>
<td>4.09 (3.53 / 4.64)</td>
<td>0.90 (0.86 / 0.93)</td>
</tr>
<tr>
<td>$C_{50}$ (%)</td>
<td>0.60 (0.48 / 0.75)</td>
<td>1.72 (1.65 / 1.79)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>-1.80 (-2.45 / -1.14)</td>
<td>5.36 (4.38 / 6.35)</td>
</tr>
</tbody>
</table>

### 3.5 Discussion

In the present experiment, the relation was investigated between sevoflurane concentration and the EEG parameters CD and BSR. Due to the setup of the experiment with the aim to
Correlation Dimension and Burst Suppression Ratio of the EEG Correlate with Sevoflurane Concentration in Rat

measure transitions from awake to sleep, end-tidal sevoflurane concentrations could not be measured. Animals were allowed to breathe freely and therefore concentration-effect relations between CD and sevoflurane were estimated using inspiratory sevoflurane concentrations. The assumption was made that sevoflurane concentration is related to DOA. A clear relation between CD and BSR with sevoflurane concentration ($C_{eff}$) was demonstrated. The relation between BSR and $C_{eff}$, however, was restricted to higher concentrations and not wakefulness. The time needed for the sevoflurane concentration in the brain to equilibrate to the inspired sevoflurane is 4 minutes (time constant: $k_{e0^{-1}}$). The induction of sevoflurane induced a period of excitatory behavior. The increased level of CD coinciding with these periods seems reasonable since the rat becomes more active. This suggests that the CD of the EEG is not only related to $C_{eff}$, but also to the brain state. During the wakening phase when sevoflurane concentrations are decreasing, no excitatory behavior was observed. Excitation is also seen clinically, when sevoflurane is administered to the patient with slowly increasing concentrations. Concentration-response relations between CD, BSR and $C_{eff}$ were found. These relations were confirmed by the observation that forward and reverse trajectories (falling asleep and wakening) overlapped and that CD and BSR returned to baseline levels at the end of each study.

### 3.6 Conclusions

The CD should be interpreted as a relative measure. The absolute values of CD are unimportant, but the change (maximally approximately 57%) of CD as a response to the administered anesthetic is important. Both CD and BSR vary with sevoflurane concentrations and may therefore be useful EEG measures of anesthetic drug effect. The steep transition of BSR from 0 to 0.9 ($\gamma=5.4$) makes BSR less suitable than CD ($\gamma=-1.8$) for the monitoring of DOA. However, if the results of CD and BSR can be combined, a more reliable and accurate measure of DOA is feasible.

### 3.7 Acknowledgements

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4 Correlation dimension and burst suppression ratio of the EEG correlate with sevoflurane induced anesthetic depth in the rat

4.1 Abstract

Background: The hypothesis that correlation dimension (CD) and Burst Suppression Ratio (BSR) of the electroencephalogram (EEG) both relate to depth of anesthesia (DOA), is object of the present study. The CD and BSR of the EEG of eight rats were estimated during sevoflurane anesthesia and the effect of arousal on CD and BSR was examined.

Methods: Experiments were performed under sevoflurane anesthesia and changing the amount of sevoflurane mixed to the administered gas flow varied anesthetic depth. To get informed about the anesthetic state, the noxious induced withdrawal reflex (NIWR) was measured, i.e. the withdrawal force elicited by transcutaneous electrical stimulation of the hind paw. The EEG was continuously recorded. The CD was computed following the Grassberger-Procaccia-Takens approach with optimized parameter settings to achieve maximum sensitivity to anesthetic drug effects. The CD, BSR and sevoflurane concentrations were correlated with the NIWR responses.

Results: CD and BSR both correlate to the NIWR, i.e. to DOA. However, BSR informs about anesthetic depth only beyond a sevoflurane percentage of 3% or an NIWR below 75 g. When the NIWR stimulus arouses the rat, CD increases and BSR decreases.

Conclusions: Both CD and BSR can be useful EEG measures of DOA. A more potent anesthetic drug effect measure is imaginable if both the results of CD and BSR can be combined. The arousal effect on CD and BSR might be an extra indication that both variables are related to DOA.

4.2 Introduction

One of the main purposes of anesthesia is the suppression of physiologic responses to external noxious influences. During the recent past, pharmaceutical industries developed anesthetics that have specific effects on different physiological subsystems. It gives the anesthesiologist more instruments to control the anesthetic effects. To profit from these instruments, it is desirable to be informed at best about the physiological condition of the patient. At present, the anesthesiologist obtains this information by measuring physiological variables such as blood pressure, heart frequency, respiration, blood saturation and the variability of these variables. Based on these measures, he/she decides to increase or decrease the dose of the anesthetic.

Administration of anesthetics results in changes in the activity of the central nervous system (CNS). These changes might be reflected in the electroencephalogram (EEG). If the anesthesiologist can obtain relevant information from the EEG, a more balanced anesthetic
Correlation dimension and burst suppression ratio of the EEG correlate with sevoflurane induced anesthetic depth in the rat

might be possible. In an effort to quantify the effects of anesthetics during surgery, several reports have studied relevant EEG measures from the power spectrum of the EEG (linear approach) with different levels of success. Positive results were reported. But also negative results.

At present many researchers, with different scientific backgrounds, investigate the potential of the non-linear approach. A quantitative measure that has been developed to characterize non-linear dynamics is $D_2$, the correlation dimension. In this study an adapted algorithm was used to compute $D_2$, to pronounce the difference another abbreviation: CD was introduced (see chapter 2). In 1987, Mayer-Kress and Layne published one of the first articles that describe the application of $D_2$ to determine anesthetic drug effect. One year later Watt & Hameroff demonstrated changes of phase space trajectories and dimensionality as a result of changed DOA. Widman et al., investigated a modified version of $D_2$, the nonlinear correlation index $D^*$, as a measure of depth of sevoflurane anesthesia. Lee et al., found $D_2$ to serve as a better index for the depth of halothane anesthesia in the rat compared to $\beta$-power and median power frequency. Recently, the search for a reliable estimator of DOA has moved towards a multimethodological approach. Instead of focusing on one nonlinear measure, multiple nonlinear measures and discriminating methods are utilized. The results of these articles show the potency of $D_2$ or derived measures to inform about DOA.

Another processed EEG variable, the Burst Suppression Ratio (BSR) was also calculated. At the deepest anesthetic levels, the EEG pattern changes, i.e. EEG epochs with high frequencies and low amplitudes (suppression) are alternated with epochs with low frequencies and high amplitudes (bursts), see Fig. 4.1. The ratio of the summation of the suppression parts in a certain epoch and the total length of that epoch defines BSR. Several studies evaluated the BSR, the burst suppression pattern (BSP), and the onset of BSP as possible informatives of anesthesia related phenomena. Some studies used the onset of the BSP to titrate the administered anesthetic drug. The presence of BSP did not predict lack of response to a noxious stimulation in isoflurane anesthetized rats. Differences were found between BSP’s retrieved during isoflurane and enflurane anesthesia. Also BSR was used as the control variable in a closed-loop infusion system for monitoring and controlling i.v. anesthesia in rats.

Two previous studies of the authors showed a strong relationship between CD and anesthetic effects induced by propofol (see chapter 5) and showed that increasing percentages of sevoflurane decreased CD and increased BSR (see chapter 3). The former sevoflurane study measured the EEG of the rat going from awake condition to deep anesthetic condition and vice versa; however, information about DOA was not available. To get informed about DOA, in a follow up experiment with the same rats, the noxious induced withdrawal reflex (NIWR) was measured. Measurements were only performed during anesthetic conditions. As the
same rats were used within the two experiments, comparisons between the two studies could be made. Both the results of the CD and BSR were correlated with the NIWR and sevoflurane concentrations.

4.3 Material and methods
4.3.1 Experiment
After approval of the local Animal Care Committee eight adult male Wistar rats (averaged rat weight: 426 g, SD=36 g) were anesthetized with Narcovet (60 mg kg\(^{-1}\) ip.) and one tripolar electrode (Plastic Products Company, MS 333/2A) was implanted for long-term recording of the cortical EEG. The coordinates related to the bregma were: A 2.0, L 3.5; A −6.0, L 4.0. A ground electrode was placed above the cerebellum. Experiments were performed after a recovery period of at least two weeks. Just before the start of the experiments the rats were anesthetized with sevoflurane and prepared with an arterial line, infusion line (Ringers/glucose, 2ml h\(^{-1}\)) and trachea canula. The force of the noxious induced withdrawal reflex (NIWR) was used to quantify the anesthetic effect.\(^{35}\) The stimulus consists of a 500 ms pulse train duration, 4 ms pulse width, 100 Hz pulse frequency and 7.5 mA pulse amplitude. The EEG and NIWR were continuously recorded. Every 80 seconds the NIWR was determined for quantification of DOA. At the start of the experiment the administered sevoflurane concentration to the rat was maintained at 4% to assure a sufficient level of anesthesia during the first painful stimulus (NIWR). By changing the amount of administered sevoflurane to the rat the level of anesthesia was regulated (manually) in such way that NIWR varied several times between 0 and 125 g. The total recording time for each experiment was approximately 3 hours.

4.3.2 EEG registration
The raw EEG-signal was filtered between 1 and 100 Hz, digitized at a rate of 256 Hz and stored to disk for “off-line” analysis. The CD and BSR of the EEG of the rat were computed every epoch of 64s (2\(^{14}\)=16384 samples) duration and repeated every 8s (7/8 overlap with previous estimate). The number of CD and BSR estimates (every 8s) was very large compared to the number of NIWR estimates (every 80s).

4.3.3 EEG analysis
CD
The correlation dimension was computed following the Grassberger\Procaccia\Takens algorithm\(^{65,196}\) with alterations to maximize the sensitivity to anesthetic effects (see chapter 2). Attractor reconstruction was performed with 16384 samples, embedding dimension=20, delay time=8 ms and 1 second Theiler correction.\(^{200}\) To speed up computation time, the correlation integral was estimated using a subset of all possible distances between points on
Correlation dimension and burst suppression ratio of the EEG correlate with sevoflurane induced anesthetic depth in the rat

the attractor. The CD was extracted from the correlation integral at a fixed interval defined by the distribution of distances in the correlation integral (see chapter 2).

BSR
At the deepest anesthetic depths burst suppression appeared in the EEG signal.\(^\text{74,168}\) Suppression periods were defined as periods of at least 0.3s duration where the absolute amplitude of the EEG remained below some threshold value. The threshold values were manually estimated for all eight rats individually and were 0.2 or 0.3 mV. The Burst Suppression Ratio (BSR) was defined by the ratio of suppression epochs during fixed intervals of 64s and the length of this interval (64s).

4.3.4 Pharmacokinetic/dynamic Analysis
A first order model, equation 4.1, was used to describe the relation between inspiratory concentration and effect-compartment concentration.\(^\text{178}\) The relation between effect compartment sevoflurane concentration and effect (i.e., NIWR, CD or BSR) was described by the Hill-equation\(^\text{70}\), equation 4.2:

\[
\frac{dC_{\text{eff}}}{dt} = (C_{\text{in}} - C_{\text{eff}})K_{e0}
\]

\[
E = E_{\text{begin}} - \left( \frac{E_{\text{begin}} - E_{\text{end}}}{C_{50} + C_{\text{eff}}} \right) \left( \frac{C_{\text{eff}}}{C_{50} + C_{\text{eff}}} \right)
\]

where, \(E_{\text{begin}}\) = baseline, at awake condition, \(E_{\text{end}}\) = end value at infinite sevoflurane concentration, \(C_{50}\) = concentration associated with 50% of the maximum effect, \(\gamma\) = steepness factor determining the slope of the concentration-response relation, \(C_{\text{eff}}\) = concentration in the effect compartment, \(C_{\text{in}}\) = inspiratory concentration of sevoflurane, and \(K_{e0}\)\(^{-1}\) = time constant determining the influx to and efflux from the effect compartment via the central compartment. In an earlier study (see chapter 3, the same rats were used here) \(K_{e0}\) was already determined for each rat individually. The same \(K_{e0}\) was used in this study to transform the inspired sevoflurane concentrations into \(C_{\text{eff}}\) (hysteresis elimination). The pharmacokinetic/dynamic parameters of NIWR, CD and BSR were obtained for the eight rats grouped together.
Correlation dimension and burst suppression ratio of the EEG correlate with sevoflurane induced anesthetic depth in the rat

4.4 Results

Fig. 4.1 displays the results of a typical example of one rat and shows that an increase or decrease of the inspired sevoflurane decreases respectively increases NIWR and in this way varies DOA. A correlation between CD, BSR and NIWR is demonstrated by the decrease of CD and increase of BSR as NIWR decreases and vice versa.

Fig. 4.2 (left) shows the dose-response curves of NIWR, CD and BSR versus $C_{eff}$. Averaged results of the eight rats (for each variable) were obtained per 0.2 division on a logarithmic sevoflurane concentration scale. Apparently, on average $C_{eff}$ must be higher than approximately 2.5% to maintain a sufficient level of anesthesia during NIWR measurement. If $C_{eff}$ increases beyond 4.5% no information about changes in DOA are available as NIWR reaches its measurable minimum. At this point the results of CD and BSR suggest that they did not reach their maximum measurable ranges and still can be varied. The start value of CD around 6 (rat is already in anesthetic condition) is conceivable as the previous study (see chapter 3) revealed values of approximately 9 for CD in an awake condition. A Hill-equation\textsuperscript{70}, see equation 4.2, describes the relation between CD, BSR, NIWR and $C_{eff}$.
Table 4.1 shows the averaged results of the accompanying pharmacokinetic/dynamic parameters. The highest steepness factor, determining the slope of the concentration-response relation, and $C_{50}$, determining the concentration associated with 50% of the effect, were found for BSR. Based on the results of a previous study (see chapter 3, Table 3.1) of the authors, the begin value ($E_{\text{begin,CD}}$) of CD was set to 9.5 and the end value ($E_{\text{end,BSR}}$) of BSR was set to 0.9. The settings of $E_{\text{begin,BSR}}=0$, and $E_{\text{end,CD}}=1$ were based on theoretical limiting end or start points. Fig. 4.2 (right) shows the effect-response curves of CD and BSR versus NIWR. For a complete visualization of the dependencies between all the variables $C_{\text{eff}}$ is also included in the figure. Averaged results of the eight rats (for each variable) were obtained for every NIWR-subsection of 10 g. Regression lines through the curves of CD (correlation coefficient $r=0.46$; $p<0.001$) and BSR ($r=0.66$; $p<0.001$) show their relation to NIWR i.e. to DOA.

The results of the previous study (without NIWR) and current study (with NIWR) are combined in one figure (Fig. 4.3). Examining the results of both studies at the same sevoflurane concentrations, one can observe that compared to the study without administered NIWR, CD is increased and BSR is decreased by the arousal effect of the noxious stimulus of the NIWR.
Table 4.1: Averaged results (eight subjects) of the pharmacokinetic/dynamic parameters that describe the relation between NIWR, CD, BSR and the effect-compartment concentration $C_{eff}$ see eq. 4.2.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>NIWR mean (95% CI)</th>
<th>CD mean (95% CI)</th>
<th>BSR mean (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_{begin}$</td>
<td>190 (constant)</td>
<td>9.5 (constant)</td>
<td>0.0 (constant)</td>
</tr>
<tr>
<td>$E_{end}$</td>
<td>0.0 (constant)</td>
<td>1.0 (constant)</td>
<td>0.9 (constant)</td>
</tr>
<tr>
<td>$C_{50}$ (%)</td>
<td>2.13 (1.92 / 2.37)</td>
<td>2.93 (2.87 / 3.00)</td>
<td>3.20 (3.12 / 3.28)</td>
</tr>
<tr>
<td>$\gamma$</td>
<td>-3.11 (-3.92 / -2.31)</td>
<td>-1.76 (-1.92 / -1.60)</td>
<td>4.66 (3.78 / 5.54)</td>
</tr>
</tbody>
</table>

Fig. 4.3 Effect of the stimulus of the NIWR on measured variables. The effects are illustrated by the differences in CD (left) and BSR (right) between aroused (□) and non-aroused (O) subjects. Error bars represent SD values.

4.5 Discussion

In a previous study (see chapter 3) of the authors it was demonstrated that CD and BSR relate to the effect compartment sevoflurane concentration ($C_{eff}$). The present study demonstrates that both CD and BSR relate to the NIWR and thus to DOA. Another study of the authors showed that CD also correlates with propofol induced DOA (see chapter 5). The results of these three studies together indicate that CD and BSR can be useful measures to monitor DOA. For values of $C_{eff}$ above 4.5%, contrary to the NIWR and CD, BSR is able to inform about DOA. However, CD can be measured from awake vigilance levels to deep levels of anesthesia where BSR can only be measured starting at the deeper levels of anesthesia. This makes CD more suitable for steering purposes than BSR during anesthesia control. However, a more potent anesthetic drug effect measure is imaginable if both CD and BSR are combined. If the rat is stimulated, it is conceivable that the NIWR increases the level of vigilance as the painful stimulus arouses the rat. The differences in the results (shifted curves) between the present study (with NIWR) and the previous study (without NIWR) show that the
effects of this arousal on the rat are reflected in CD and BSR. This result is an extra indication that CD and BSR are related to DOA. Besides the shifted curves one can observe a crossing of the two curves (Fig. 4.3, top) of CD measured with and without stimulation. A speculative explanation for this crossing is given next. The effect of arousal on BSR was confirmed by the fact that each NIWR stimulus initiated a period of burst pattern EEG if it was given during a period of suppressed EEG. It is just this phenomenon that plays an important role in the explanation. As stated before arousal increases CD, however, the crossing of the two curves is not in agreement with this statement. If anesthetic depth increases, BSR increases. As a result the periods of suppressed EEG increase. CD is calculated using 16384 points. During burst suppression patterns, the suppression periods are omitted and to keep the number of points at 16384 the calculation time period is increased. As the calculation time period increases, the ratio of the number of stimulus-initiated bursts and the number of spontaneous bursts increases. With the assumption that differences between stimulus initiated bursts (by NIWR) are smaller than differences between spontaneous initiated bursts, CD is lower in the first case (decreased complexity) and might explain the crossing of the two curves.

4.6 Acknowledgements

Contributions to this chapter from:

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5 Correlation dimension of the EEG correlates with propofol induced anesthetic depth in the rat

5.1 Abstract

Background: The correlation dimension (CD) and burst suppression ratio (BSR) were estimated from EEG measured at different levels of depth of anesthesia (DOA) during propofol induced anesthesia in rat. CD and BSR were compared to the Spectral Edge Frequency (SEF), a linear measure extracted from the power spectrum, in their correlation with anesthetic effects due to propofol.

Methods: Experiments were performed under continually propofol infusion (30 \(\text{a} 40 \text{mg.kg}^{-1}.\text{h}^{-1}\)), with repeated bolus injections (3 mg) to induce periods of deeper anesthesia. To get informed about the anesthetic effect, the noxious induced withdrawal reflex (NIWR) was measured, i.e. the withdrawal force elicited by transcutaneous electrical stimulation of the hind paw. The EEG was continuously recorded. The CD was computed following the Grassberger-Proccacia-Takens approach with optimized parameter settings to achieve maximum sensitivity to anesthetic drug effects. CD, BSR, and SEF were all correlated with the NIWR responses.

Results: CD and BSR both correlate to the NIWR, i.e. to DOA. However, BSR varies with DOA only below an NIWR of 50 g. The CD showed higher and more consistent correlations with the NIWR than the SEF. Correlation coefficients of NIWR and CD mainly varied between 0.6 and 0.8.

Conclusions: Both CD and BSR can be useful EEG measures of DOA. A more potent anesthetic drug effect measure is imaginable if both the results of CD and BSR can be combined. Non-linear measures reveal additional information from the EEG that is not accessible to linear measures such as the SEF.

5.2 Introduction

One of the main purposes of anesthesia is the suppression of physiologic responses to external noxious stimuli. During the recent past, pharmaceutical industries developed anesthetics that have specific effects on different physiologic subsystems. It gives the anesthesiologist different instruments to control DOA. To profit from these instruments, it is desirable to be informed at best about the physiologic condition of the patient. At the moment, the anesthesiologist obtains this information by measuring physiologic responses such as (changes of) blood pressure, heart frequency, respiration and blood saturation with oxygen. Based on these measures, he/she decides to increase or decrease the anesthetic dose. However, these are indirect measures that respond to changes in the activity of the central nervous system (CNS). Perhaps a more direct reflection of these changes is measurable with the electroencephalogram (EEG). If the anesthesiologist can obtain relevant information from
the EEG a more balanced anesthetic might be possible. Several reports have studied the EEG in an effort to quantify the effects of anesthetics during surgery.\textsuperscript{145}-\textsuperscript{172} Research has been mainly focused on measures extracted from the EEG’s power spectrum thereby following a linear approach. One example is the Spectral Edge Frequency (SEF) that estimates the frequency below which 90 percent of the signal power is concentrated.\textsuperscript{145} At present many researchers, with different scientific backgrounds, investigate the potential of the non-linear approach. A quantitative measure that has been developed to characterize non-linear dynamics is $D_2$, the correlation dimension.\textsuperscript{65,196} In this study an adapted algorithm was used to compute $D_2$, to pronounce the difference another abbreviation: CD was introduced (see chapter 2). In 1987, Mayer-Kress and Layne published one of the first articles that describe the application of $D_2$ to determine anesthetic drug effect.\textsuperscript{126} One year later Watt & Hameroff demonstrated changes of phase space trajectories and dimensionality as a result of changed DOA.\textsuperscript{213} Widman et al., investigated a modified version of $D_2$, the nonlinear correlation index $D^*$, as a measure of depth of sevoflurane anesthesia.\textsuperscript{215} Lee et al., found $D_2$ to serve as a better index for the depth of halothane anesthesia in the rat compared to $\beta$-power and median power frequency.\textsuperscript{110} Recently, the search for a reliable estimator of DOA has moved towards a multimethodological approach. Instead of focusing on one nonlinear measure, multiple nonlinear measures and discriminating methods are utilized.\textsuperscript{136,177,211,220,221} The results of these articles show the potency of $D_2$ or derived measures to inform about DOA.

Another processed EEG variable, the Burst Suppression Ratio (BSR) was also calculated.\textsuperscript{74,168} At the deepest anesthetic levels, the EEG pattern changes, i.e. EEG epochs with high frequencies and low amplitudes (suppression) are alternated with epochs with low frequencies and high amplitudes (bursts), see Fig. 4.1. The ratio of the summation of the suppression parts in a certain epoch and the total length of that epoch defines BSR. Several studies evaluated the BSR, the burst suppression pattern (BSP), and the onset of BSP as possible informatics of anesthesia related phenomena. Some studies used the onset of the BSP to titrate the administered anesthetic drug.\textsuperscript{45,103,126} The presence of BSP did not predict lack of response to a noxious stimulation in isoflurane anesthetized rats.\textsuperscript{144} Differences were found between BSP’s retrieved during isoflurane and enflurane anesthesia.\textsuperscript{121} Also BSR was used as the control variable in a closed-loop infusion system for monitoring and controlling i.v. anesthesia in rats.\textsuperscript{212} Two previous studies of the authors showed strong relationships of CD and BSR with anesthetic effects induced by sevoflurane (see chapters 3 and 4).

This paper compares under mono-anesthetic conditions CD and the SEF of the EEG. To get informed about the anesthetic effects, the noxious induced withdrawal reflex (NIWR) was measured, i.e. the force elicited by transcutaneous electrical stimulation of the hind paw.\textsuperscript{35} The results of the CD, BSR, and SEF were correlated with the NIWR.
5.3 Material and methods

5.3.1 Experiment

After approval of the local University Committee on Ethics in Animal Research, eight adult male Wistar rats are anesthetized with Narcovet (60 mg.kg\(^{-1}\) ip.). One tripolar electrode (Plastic Products Company, MS 333/2A) is implanted for long-term recording of the cortical EEG using a stereotactic approach. The coordinates related to the bregma are: A 2.0, L 3.5; A –6.0, L 4.0. A ground electrode is placed above the cerebellum. Experiments are performed after a recovery period of at least two weeks. Basis anesthesia is then induced by propofol infusion (30 \(\pm\) 40 mg.kg\(^{-1}\).h\(^{-1}\)). Repeated bolus injections (3 mg) induce periods of more profound anesthesia. The force of the noxious induced withdrawal reflex (NIWR) is used to quantify the anesthetic effect.\(^{35}\) The stimulus consists of a 500 ms pulse train duration, 4 ms pulse width, 100 Hz pulse frequency and 7.5 mA pulse amplitude. The EEG and hind paw force are continuously recorded. Every 80 seconds the NIWR is determined for quantification of anesthetic effects.

5.3.2 EEG registration

The raw EEG signal is filtered between 1 and 100 Hz, digitized at a rate of 250 Hz and stored to disk for “off-line” analysis. The CD of the EEG is computed every epoch of 16384 samples (65.536 s) duration and repeated every 2048 samples (7/8 overlap with previous estimate). The SEF of the power spectrum is computed every epoch of 2.048 second (512 points FFT) and subsequently averaged over 4 epochs. The number of CD and SEF estimates (every 8.192 s.) are very large compared to the number of NIWR estimates (every 80 s). To make a one on one comparison between CD, SEF and NIWR possible, the calculations of CD and SEF are averaged.

5.3.3 EEG analysis

CD

The correlation dimension is computed following the Grassberger\Procaccia\Takens algorithm\(^{65,196}\) with alterations to maximize the sensitivity to anesthetic effects. Attractor reconstruction is performed with 16384 samples, embedding imension=20, delay time=8 ms and 1 second Theiler correction.\(^{200}\) To speed up computation time, the correlation integral is estimated using only a subset of all possible distances between points on the attractor. The CD is extracted from the correlation integral at a fixed interval defined by the distribution of distances in the correlation integral (see chapter 2).

BSR

At the deepest anesthetic depths burst suppression patterns appear in the EEG signal (see Fig. 5.3, top).\(^{74,168}\) Short periods with low frequency and high amplitudes (bursts) alternate with...
longer periods with high frequency and low amplitudes (suppression). Suppression periods are defined as those periods of at least 0.3 s duration where the absolute amplitude of the EEG remains below some threshold value. The threshold values are manually estimated for each rat individually. BSR was defined by the ratio of the suppression epochs during fixed intervals of 64s and the interval length (i.e. 64s). Since the burst suppression pattern is highly non-stationary, the suppression periods are omitted during the calculation of CD. During burst suppression patterns the number of EEG-samples are maintained at 16384 by increasing the epoch length. The transitions from burst epochs to suppression epochs and vice-versa are avoided within the time span of the reconstruction vectors.

Statistical Analysis
Pearson correlation coefficients are calculated to determine the fraction of the variance that is shared between NIWR and CD and between NIWR and SEF.

![Graph showing the relationship between NIWR, SEF, and CD during propofol anesthesia.](image)

**Fig. 5.1** Typical example (rat 5) of the relationship between the measured variables NIWR (□), SEF (X) and CD (○) during propofol anesthesia. The continuous line in the lowest portion shows the propofol infusion rate (expressed in mg.kg\(^{-1}\).h\(^{-1}\)) during the experiment. The bolus (3 mg) administrations are marked with arrows on the time axis.
5.4 Results

Fig. 5.1 shows a typical example of the results of one rat out of the eight rats (averaged rat weight: 426 g, SD=36 g) measured. Arrows on the time axis mark the time points when bolus injections of propofol were administered. After the bolus the NIWR almost immediately decreases towards zero indicating a condition where motor responses to painful stimuli are absent. In the course of the elimination of propofol, the NIWR returns to its pre-bolus value. The results for CD and SEF are similar: decreasing values immediately after administration of the bolus and increasing values during the washout of propofol.

CD and BSR correlate with the NIWR (Fig. 5.2), although for BSR a clearly correlation only exists below NIWR values of 50 g. The relationship between SEF and NIWR is ambiguous and therefore no line was fitted through the curve. SEF does not correlate consistently with the NIWR, i.e. negative as well as positive correlation coefficients are found. The correlation coefficients of the NIWR,CD and NIWR,SEF relationships per rat and for the combination of all rats are shown in Table 5.1. SEF correlates less to the NIWR than the CD to the NIWR. The sensitivity of CD and SEF to changes of NIWR and the variability differ per subject. The CD varies between 4 for deep levels of anesthesia and 9 for lower levels of anesthesia. Until NIWR decreases below 50 g, BSR approximately remains constant at an average value of 0.1. Below 50 g, BSR increases to an averaged maximum value of 0.5.
Correlation dimension of the EEG correlates with propofol induced anesthetic depth in the rat

The influence of the administered propofol anesthesia on the EEG-signal is shown in Fig. 5.3. The threshold values that define the suppression periods during burst-suppression patterns (Fig. 5.3, top) were manually estimated for each rat individually and varied between 0.08 and 0.30 mV.

Table 5.1 Pearson correlation coefficients (R) of NIWR with CD and NIWR with SEF per rat and for the combination of all rats (last row). The first column shows the rat subject number and the second column the number of observations (N). All coefficients are significant with P-values < 0.05 except for the values marked with an asterisk.

<table>
<thead>
<tr>
<th>Rat</th>
<th>N</th>
<th>R=</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CD</td>
</tr>
<tr>
<td>1</td>
<td>97</td>
<td>0.60</td>
</tr>
<tr>
<td>2</td>
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<tr>
<td>All</td>
<td>822</td>
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</tr>
</tbody>
</table>

5.5 Discussion

The results of this study show a correlation between DOA as quantified by the NIWR and the CD of the EEG. At the deeper levels of DOA, this is also true for BSR. A lesser correlation was found between NIWR and SEF. The dose-response relationship between propofol and NIWR shows individual variability between subjects and therefore CD and SEF instead of the propofol dose were compared with NIWR. The correlation between NIWR and CD indicates that CD gives valuable information about anesthetic effects of propofol on the rat.

Chapter 5
The correlation coefficient for all rats together is much lower compared to that of the individual results. This demonstrates the existing variability and different sensitivity in responses to anesthetics between subjects and implies that the CD must be regarded as a relative measure: comparing values with the pre-anesthetic state. In the time course after the washout of the bolus propofol, the pre-bolus value of the NIWR (Fig. 5.1) slowly decreased to lower values whereas the CD kept returning to the same level. This phenomenon was also present in the other seven subjects and might be explained by muscle exhaustion. The CD was not influenced by this effect. The lower correlation coefficients found for the SEF suggest that non-linear analysis using CD reveals information from the EEG that is not obtained by linear analysis using the SEF. Therefore, we conclude that CD, as a new parameter from the field of non-linear dynamics, can be an aiding tool in detecting effectual changes in the EEG induced by anesthetics. CD can be measured from the lighter levels of DOA to deep levels of DOA where BSR can only be measured starting at the deeper levels of anesthesia (at the lighter levels there is no BSR present). This makes CD more suitable for steering purposes than BSR during anesthesia control. However, a more potent anesthetic drug effect measure is imaginable if both CD and BSR are combined.

5.6 Acknowledgements

Contributions to this chapter from:
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6 Relation between CD and anesthetic effects in human (static evaluation)

6.1 Abstract

Background: Because of the inter-individual variability in sensitivity to anesthetics and the dependence of depth of anesthesia (DOA) to the strength of surgical stimulation, the need for an individualized dosage scheme with constant readjustment of DOA is evident. The electroencephalogram (EEG) reflects the overall activity of the central nervous system (CNS) and is influenced by anesthetic drugs. At present, the usefulness of new measures originating from nonlinear dynamics to characterize the EEG are frequently studied. Here, an adapted algorithm to compute the correlation dimension (CD) was used. The hypothesis that CD of the EEG relates to DOA, is object of the present study.

Methods: One hour before elective surgery patients received propofol by target controlled infusion with a stepwise deepening of anesthesia. DOA was assessed by an extended version of the Observer’s Assessment of Alertness and Anesthesia and therefore termed Observer’s Assessment of Sedation and Anesthesia (OASA) scale to enable DOA assessment at deep anesthesia levels. With approval of the local ethics committee, twenty ASA 1,2 patients undergoing surgery (age>18 yrs) were selected for the study. The EEG was recorded continuously, filtered (analogue BP: 0.16-250 Hz and digital LP: 40 Hz) and digitized at a rate of 1000 Hz. At 5 to 7 steady state propofol levels, CD of 9 EEG-leads was computed. The results of CD were related to the OASA-score and BIS.

Results: When DOA was becoming deeper (decrease of OASA score) CD decreased. A sharp decrease of CD was found between OASA=4 and OASA=3. There were no significant differences for CD among the EEG-leads. BIS showed no sharp decrease between OASA=4 and OASA=3. However, at deeper levels of DOA (OASA<=3), BIS at OASA=0 was not significantly different from BIS at OASA=3. To compare CD and BIS as anesthetic depth indicators, the prediction probability \( P_k \) was calculated. Results showed a higher \( P_k \) for BIS (0.9) compared to CD (0.7). If \( P_k \) is calculated without the awake levels (OASA-score 7,6,5), results of \( P_k \) change to or remain at 0.7 for BIS respectively CD.

Conclusions: During propofol administration CD is especially sensitive to DOA changes at the transition from awake or light anesthesia to deep anesthesia. At the deeper DOA levels CD and BIS perform equal as indicators of anesthetic depth. Differences between CD and BIS in recorded time tracings show that CD can provide information not supplied by the BIS. As CD can be calculated online it might be useful for monitoring purposes.
6.2 Introduction

The aim of general anesthesia is to provide relief of pain and loss of consciousness for patients during surgery and to provide optimal operative conditions for surgeons, both in the safest manner possible. This task is performed by execution of the functional sequences described in control systems theory. Thus, the anesthesiologist acts as an "external control unit" for various "controlled variables" derived from the cardiovascular system, gas transport, respiration, and the sensory and motor nervous system. A variety of monitoring devices inform about the level and variability (short and long term, spontaneous and evoked) of these variables. These monitoring devices serve the same goal: the assessment of the patient’s condition with special emphasis on detection of change. The anesthesiologist modulates the patient’s condition with analgesics (pain relief), hypnotics (sleep/unconsciousness) and muscle relaxants. General anesthesia is the result of interactions of these drugs with several processes in the central nervous system (CNS). At present, monitoring of anesthetic effects is based on indirect physiologic reactions (changes in heart rate, blood pressure etc.) resulting from these interactions in the CNS. To provide a more direct image of the effects of anesthetics on the CNS an analysis of the processes in the CNS is needed. The EEG is a well-known, electrically measurable signal that is a direct result of the activities of the CNS. The interpretation of the EEG, however, is complex because it is a reflection of the state of the brain, the effects of the surgical procedure and the influence of the anesthetics. The different anesthetics prove to have different effects on the EEG. The complexity of interpretation of the unprocessed EEG makes its use for routine monitoring of the depth of anesthesia (DOA) clinically unfeasible. In 1990, Goldberger et al., demonstrated fractal properties of the anatomic structure of the small intestine, blood vessels of the heart, and the neuron with its dendrites. They speculate on how to relate the fractal geometric properties of human physiologic systems and their corresponding nonlinear dynamics. Furthermore, they hypothesize that chaotic systems have the advantage to operate under a wide range of conditions and are therefore adaptive and flexible. As many pathologies exhibit increasingly periodic behavior and a loss of variability, they conclude that studies of fractals and chaos in physiology may provide more sensitive ways to characterize dysfunction resulting from aging, disease and drug toxicity. With this view in mind nonlinear measures extracted from the EEG may provide a variable that predicts and reproducibly reflects the reactions of the patient during anesthetic practice.

In 1987, Mayer-Kress and Layne published one of the first articles that describe the application of the correlation dimension (D2) to determine anesthetic drug effect. One year later Watt & Hameroff demonstrated changes of phase space trajectories and dimensionality as a result of changed DOA. They conclude that these changes confirm that the EEG becomes more synchronized (less chaotic) as DOA increases. This conclusion was confirmed by Bruhn et al., using a different measure, approximate entropy, that quantifies the amount of...
regularity in the data. Widman et al., investigated a modified version of \( D_2 \), the nonlinear correlation index \( D^* \), as a measure of depth of sevoflurane anesthesia. In contrast to spectral measures, \( D^* \) was found to decrease monotonically with increasing (estimated) DOA. Lee et al. found \( D_2 \) to serve as a better index for the depth of halothane anesthesia in the rat compared to \( \beta \)-power and median frequency. Rat studies performed at our department also showed positive relationships between CD (a modified version of \( D_2 \)) and propofol or sevoflurane induced DOA (see chapters 3, 4, and 5). Recently, the search for a reliable estimator of DOA has moved towards a multimethodological approach. Instead of focusing on one nonlinear measure, multiple nonlinear measures are utilized. Artificial neural networks (ANN) are then used to combine the information of several variables into one DOA index. Topics of the multimethodological approach concern: cortical function of rats, measuring the hypnotic component of anesthesia, prediction of movement during anesthesia, and the continuous assessment of DOA.

In 1994, Sigl & Chamoun, introduced the concept of a bispectral index, (BIS™)*, a univariate descriptor (scaled from 100-0, i.e., from awake to deep anesthesia levels) derived from a set of features including the bispectrum, the bicoherence, and time-domain features such as the level of burst suppression. Several studies evaluated the potency of the BIS on various aspects related to DOA. The outcomes of these studies all agreed in their conclusions that the BIS may be useful as a measure of DOA. At present, the BIS has reached a high acceptance level as a useful EEG measure of DOA. However, also the BIS has its shortcomings. Problems were reported in cases where a strong analgesic component was present. Some articles report possible BIS dependency of the anesthetic used and other articles report paradoxical increases of BIS with increased anesthetic drug concentration. BIS was also criticized for not being reliable to guide the adequacy of anesthesia level for preventing movement during sevoflurane anesthesia, or to discriminate wakefulness from unconsciousness.

Just as proposed for \( D^* \) by Widman et al., the altered algorithm utilized here to calculate CD precludes any interpretation in terms of fractal dimension, number of degrees of freedom, etcetera. CD should therefore be interpreted as an operational measure of EEG complexity. The shortcomings of BIS in certain circumstances, emphasize the need for further investigations to enhance monitoring of anesthetic depth. In this light, and with in mind the demonstrated potency of the correlation dimension and derived measures to inform about depth of anesthesia, the hypothesis that CD of the EEG relates to propofol induced depth of anesthesia in human, is object of the present study.

* BIS: trademark of Aspect Medical Systems, Newton, MA
6.3 Material and methods

6.3.1 Anesthesia

After informed consent and with CWOM (Ethics Committee; institutional review board) approval, patients received propofol by target controlled infusion (TCI). Patients received no premedication. To create a stepwise deepening of sedation and anesthesia, the program Rugloop© determined a patient-dependent drug dosage delivery scheme based on the pharmacokinetic model of Marsh. The following target brain concentrations were used: 0, 0.5, 1.0, 1.5, 2.2, 3.5, 5.0 μg/ml and optional 6.0 μg/ml up to 7.0 μg/ml (see Fig. 6.1). The delivery scheme was stopped in case of hemodynamic or respiratory instability or at an anesthesia level where the patient did not respond to intubation. Depth of anesthesia was assessed by an extended version of the Alertness and Sedation (OAA/S) scale. Extensions concerned the deep levels of anesthesia and to pronounce the difference with the OAA/S scale, it is referred to as the Observer’s Assessment of Sedation and Anesthesia (OASA) scale (definition: 7 = responds readily to name spoken in normal tone; 6 = lethargic response to name spoken in normal tone; 5 = responds only after name is called loudly or repeatedly; 4 = responds only after mild prodding or shaking; 3 = responds only to tetanic stimulation (2s, 100Hz, 50mA); 2 = responds only to laryngoscopy; 1 = responds only to intubation; 0 = does not respond to intubation).

Fig. 6.1 Propofol delivery scheme as determined by the program Rugloop©. A patient dependent drug dosage delivery scheme was based on the pharmacokinetic model of Marsh using 5 to 7 target brain concentrations (in the range of 0.5 to 7.0 μg/ml). The lowest trace shows the volume propofol administered to the patient to achieve the specified target brain concentrations.
6.3.2 Patient selection
Twenty ASA 1,2 patients undergoing elective surgery (age>18 yrs) were selected for the study. Exclusion criteria were: neurologic impairment, oversensitivity to the used medicines, use of analgesics or psychopharmaca. The experiment preceded the actual surgery.

6.3.3 EEG analysis
The EEG was recorded (Neuroscan®) continuously, filtered (analogue BP: 0.05 - 200 Hz and digital LP: 40 Hz) and digitized at a rate of 1000 Hz. The CD of 9 EEG-leads (Fz, C3, Cz, C4, P3, Pz, P4, O1 and O2: according to the international 10-20 system) was computed. Selected from 2 minutes EEG recorded during steady state propofol levels (as indicated by Rugloop), non-overlapping epochs of 16 s duration were used to calculate CD. The results of EEG epochs contaminated by artifacts were rejected. The averaged CDs of the artifact-free epochs were compared to the averaged BIS (Aspect 2000, version 1.08) extracted from the same 2 minute epoch. Immediately after this epoch two additional measurements were performed: an auditory evoked potential and eye-blink reflex measurement. Results of these extra measurements are not described here. The OASA score was determined at the end of these additional measurements, just before installing a new target brain concentration. This prevented accompanying EEG artifacts disturbing CD and BIS results.

6.3.4 CD
The correlation dimension was computed following the Grassberger/Procaccia/Takens algorithm\textsuperscript{65,196} with alterations to maximize the sensitivity to anesthetic effects. Attractor reconstruction was performed using EEG epochs of 16 s duration, embedding dimension=20, delay time=8 ms and 1 second Theiler correction.\textsuperscript{200} To reduce the required computation time per calculation, the correlation integral was estimated using a subset of all possible distances between points on the attractor (\(p=40, s=30\); see paragraph 2.4.4). The parameters \(p\) and \(s\) were chosen rather high due to the high sample rate. The CD is extracted from the correlation integral at a fixed interval defined by the distribution of distances in the correlation integral (see chapter 2).

6.4 Results
Twenty patients (3 male, 17 female; mean age 40, SD=15 years) were included in this study. The first two patients were excluded from the results due to adaptation of the measurement protocol. For one patient recordings ended at 3.5 \(\mu\)g/ml since at this level the OASA score already reached a value of zero. Five patients received 5 \(\mu\)g/ml as the highest dose, due to shortage of time, since the surgeon was ready to start. For twelve patients enough time was left to perform an additional step at 6.0 \(\mu\)g/ml, and for 3 of them even an additional step at 7.0 \(\mu\)g/ml. No patient showed hemodynamic or respiratory instability.
CD and OASA-score decreased when propofol target brain concentration increased. The averaged CD results of 18 patients (EEG recordings of the first two patients were excluded) for the three leads (Fz, Cz, Pz) are shown in Fig. 6.2. The inset shows the relationship between the OASA-score and propofol brain concentration. There are no significant differences among the nine EEG leads and therefore the results of the remaining six leads are excluded from the figure.

![Fig. 6.2 Dose response relationship between CD and propofol shown for three different EEG leads (α:Fz, Δ:Cz and □:Pz). The inset shows the dose response relationship between the OASA-score and propofol. Error bars represent 95% confidence intervals.](image)

CD results were also related to DOA using the OASA-score as shown in Fig. 6.3. Results for the same three leads as in Fig. 6.2 are shown together with the results obtained for the BIS. A sharp decrease of CD is visible between OASA=4 and OASA=3. There are no significant differences for CD among the EEG-leads. BIS shows no sharp decrease between OASA=4 and OASA=3. At deep levels of DOA (OASA<=3), a nonparametric one-way ANOVA test did not reveal any significant differences of CD (all three EEG leads) and BIS between these four levels of DOA. Also, the same ANOVA test did not show any significant differences of CD at the lighter anesthesia levels (OASA=7,6,5). To measure the performance of CD and BIS as an indicator of anesthetic depth, the prediction probability $P_k$ was computed. The advantage of $P_k$ is the ability to handle ordinal scales like the OASA-score appropriately. Results of $P_k$ together with correlation coefficients are presented in Table 6.1.
Relation between CD and anesthetic effects in human (static evaluation)

Fig. 6.3 Relation of EEG leads (■) and BIS (○) with depth of anesthesia as indicated by the OASA score. Error bars represent 95% confidence intervals.

Table 6.1 Prediction probability ($P_k$) and correlation coefficient of CD (three leads) and BIS with OASA-score. The same data of Fig. 6.3 was used. All $P_k$'s are significant different from 0.5 ($p<0.001$) and correlation coefficients are significant different from zero ($p<0.001$).

<table>
<thead>
<tr>
<th></th>
<th>$P_k$ Pooled$^1$</th>
<th>SE</th>
<th>$P_k$ pooled$^2$</th>
<th>SE</th>
<th>$P_k$ Subject$^3$</th>
<th>SD</th>
<th>$R_{	ext{Spearman}}$ pooled$^4$</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD$_{Fz}$</td>
<td>0.76</td>
<td>0.05</td>
<td>0.70</td>
<td>0.11</td>
<td>0.79</td>
<td>0.16</td>
<td>0.63</td>
<td>0.06</td>
</tr>
<tr>
<td>CD$_{Cz}$</td>
<td>0.77</td>
<td>0.05</td>
<td>0.67</td>
<td>0.12</td>
<td>0.79</td>
<td>0.13</td>
<td>0.65</td>
<td>0.06</td>
</tr>
<tr>
<td>CD$_{Pz}$</td>
<td>0.73</td>
<td>0.06</td>
<td>0.69</td>
<td>0.11</td>
<td>0.77</td>
<td>0.14</td>
<td>0.56</td>
<td>0.07</td>
</tr>
<tr>
<td>BIS</td>
<td>0.91</td>
<td>0.02</td>
<td>0.73</td>
<td>0.10</td>
<td>0.97</td>
<td>0.04</td>
<td>0.90</td>
<td>0.02</td>
</tr>
</tbody>
</table>

1. Pooled: one estimate over pooled data
2. Pooled: one estimate over pooled data, excluding OASA levels 7, 6, and 5
3. Subject: average of $P_k$ calculated per subject

The $P_k$ values calculated using pooled data are slightly lower compared to the mean of $P_k$'s estimated per subject. $P_k$ of BIS is higher than $P_k$ of CD (all three leads) in case all OASA-scores are included. However, after excluding OASA-scores 7, 6, and 5 (awake levels), $P_k$ of BIS and CD are not different (all: $P_k = 0.7$, SE = 0.1).

Fig. 6.4 shows dynamic results of the OASA-score, CD and BIS as a function of time in two patients during the entire propofol delivery scheme. In this case, CD was calculated using an epoch length of 1 minute duration and repeated every 8 s. Epochs with artifacts were not rejected, except for a period containing severe artifacts around $t = 40$ min. The responses of CD to the stepwise propofol delivery are clearly visible. Differences between CD and BIS tracings in the first 10 minutes (Fig. 6.4; left) can be subscribed to movement artifacts. The overall behavior of CD is similar to the BIS. However, CD deviates from BIS in the absence of the peak around $t = 65$ min (no artifacts were visible at that point) and the flat line of BIS
during awake state (Fig. 6.4; right). An overview of results acquired from all patients is presented in Fig. 6.5.

![Image](image.png)

**Fig. 6.4 Example of results acquired from two patients with varying DOA as indicated by the OASA score (line with cubic markers). The effect of changed DOA on CD (calculated from lead Fz; solid line) and BIS (dashed line) are demonstrated. The left figure shows the similarity between CD and BIS tracing (deviations in the first 10 minutes can be subscribed to movement artifacts), however the right figure also shows a remarkable difference around t=65 min.**

### 6.5 Discussion

In a clinical study, the potency of CD as a measure of DOA was evaluated. It is found that CD relates to propofol induced DOA. This relationship is very similar for all nine measured EEG leads. The fact that there are no significant differences among these leads suggests that anesthesia has a global effect on the brain or that CD is not specific enough to reveal location dependent differences. The flat response of CD at the lighter anesthesia levels perhaps can be explained by coincidence of episodes of observed patient arousal. Perhaps, CD is more sensitive to these episodes than BIS. Also, another explanation can be the disturbing influence of eye or head movements on CD during awake conditions. Although it was tried to eliminate EEG epochs contaminated by such artifacts, it is very well possible that EEG epochs with minor artifacts were not rejected. These movements introduce low frequency components in the EEG signal (interference of eyeball electrical activity or drift due to electrode displacement) and have a lowering effect on CD. To eliminate subject related differences caused by inter-individual variability in response to administered drug doses, CD was compared to the OASA-score. The sharp decrease of CD between OASA=4 and OASA=3 does not necessarily indicate a temporarily altered relationship between CD and OASA. It can also be caused by a non-equidistant definition of the ordinal OASA scale. Perhaps the difference in intensity between the tests for OASA=3 and OASA=4 is much bigger compared to the intensity difference between other subsequent OASA scores. On the other hand, the sharp decrease just appears at the transition from awake or sedation to unconsciousness and perhaps can be interpreted as a phase of higher sensitivity of CD to changes in DOA at this
point. In the study setup the OASA-score was determined a few minutes after the recording of the 2-minute EEG epochs used to calculate CD and BIS. As long as the propofol brain concentration remains constant within the two time points, this delay has no effect on results. Rugloop concentration calculation is based on patient group kinetics. In general individual kinetics will deviate in level and dynamics from the group kinetics and Rugloop estimated brain (effector compartment) concentration estimates can not be considered to be 100% accurate. Therefore, it is amenable that this delay causes a systematic error. Although, as a consequence the absolute values may be wrong, the effect of the systematic error is only a shifted curve for the relationship between CD, BIS and the OASA-score. The doubted capability of Rugloop to determine accurate brain concentrations is also illustrated by the sharp peaks downwards of CD and BIS at the start of a new target propofol brain concentration. Although the latter remains speculative because it assumes both CD and BIS to be related to the propofol brain concentration, which just partly happens to be object of study here. The grand average of CD hinders an evaluation of CD in its performance to inform about DOA in one patient. From the individual tracings (figure Fig. 6.5; results obtained without artifact rejection) it can be seen that in general the responses of CD and BIS to propofol seem to be similar. However, precise inspection demonstrates some cases where CD can provide additional information to the BIS.

In summary, the main difference between CD and BIS concerns the ambiguous baseline level of CD at the awake condition due to contamination of the EEG by movement artifacts. Also, CD is especially sensitive to DOA changes at the transition from awake or sedation to unconsciousness. Furthermore, at the deeper DOA levels CD and BIS perform equal as indicators of anesthetic depth.

Results of CD presented here, confirm the results thusfar reported in literature for the correlation dimension and derived measures to be informative as a measure of DOA. Nevertheless, more studies are necessary to evaluate CD under different anesthetic regimes and a variety of surgeries. As CD can be calculated on line it might be useful for monitoring purposes.

6.6 Acknowledgements

Contributions to this chapter from:
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Chapter 6
Fig. 6.5 Individual tracings of all subjects. The tracings demonstrate dependencies between OASA-score (solid line), CD (solid line), and BIS (dashed line) for one EEG lead (Fz).
Evaluation of usefulness of CD in clinical practice

7.1 Abstract

Because of the inter-individual variability in sensitivity to anesthetics and the dependence of depth of anesthesia (DOA) to the intensity of surgical stimulation, the need for an individualized dosage scheme with constant readjustment of DOA is evident. The evaluation of the performance of the correlation dimension (CD) as a measure of DOA in clinical practice is object of the present study. In this retrospective evaluation patient data of two former studies performed at our department were used. One study investigated an anesthesia induction technique where patients were asked to initially inhale a single deep breath of sevoflurane until unconsciousness. The other study evaluated the BIS during fentanyl-midazolam anesthesia for cardiac surgery. The aim of the present study is to find out whether CD can provide meaningful (additional) information to the anesthesiologist in situations of daily anesthetic practice. Values of CD were compared to the BIS. Results show a strong relationship between CD and BIS. However, there are situations where CD and BIS differ. In conclusion, CD may be useful as a measure of DOA and in some cases may provide information not supplied by the BIS.

7.2 Introduction

The aim of general anesthesia is to provide relief of pain and loss of consciousness for patients during surgery and to provide optimal operative conditions for surgeons, both in the safest manner possible. A variety of monitoring devices inform about the level and variability of variables retrieved from the sensory and motor nervous system, the cardiovascular system, and respiration. These monitoring devices serve the same goal: assessment of the patient’s condition with special emphasis on detection of change. The anesthesiologist modulates the patient’s condition with analgesics (pain relief), hypnotics (sleep/unconsciousness) and muscle relaxants. At present, monitoring of anesthetic effects is based on physiologic reactions (changes in heart rate, blood pressure etc.). A quantitative measure that has been developed to characterize non-linear dynamics is $D_2$, the correlation dimension. In 1987, Mayer-Kress and Layne and one year later Watt & Hameroff published the first articles that describe the application of the correlation dimension ($D_2$) of the EEG to determine anesthetic drug effects. Widman et al., investigated a modified version of $D_2$, the nonlinear correlation index $D^*$, as a measure of depth of sevoflurane anesthesia. Lee et al., found $D_2$ to serve as a better index for the depth of halothane anesthesia in the rat compared to $\beta$-power and median frequency. Rat studies performed at our department also showed positive relationships between a modified version of $D_2$ - therefore called CD - and propofol or sevoflurane induced DOA (see chapters 3, 4, and 5). Other studies used multiple nonlinear
measures to assess DOA. In 1994, Sigl & Chamoun, introduced the concept of a bispectral index, (BIS™*, a univariate descriptor (scaled from 100-0, i.e., from awake to deep anesthesia levels) derived from a set of features. Several studies evaluated the potency of the BIS on various aspects related to DOA. At present, the BIS has reached a high acceptance level as a useful EEG measure of DOA. However, also the BIS has its shortcomings. These shortcomings, emphasize the need for further investigations to enhance monitoring of DOA. In this light, and with in mind the demonstrated potency of the correlation dimension and derived measures to inform about DOA, the hypothesis that CD of the EEG relates to DOA in human, is object of the present study. In particular, the intention was to find out whether CD can provide meaningful (additional) information to the anesthesiologist in situations of daily anesthetic practice.

7.3 Material and methods

7.3.1 Study protocols

The EEG data of two different studies performed at our department were used. The first study (referred to as A) compared two induction schemes for general anesthesia: the so called ‘single-breath’ technique using sevoflurane, versus intravenous induction using propofol. EEG data retrieved from the sevoflurane group were used to calculate CD. Patient inclusion criteria were: ASA I,II,III, age between 18 and 75 year, quetelet index below 30. No intracranial surgery was allowed. With informed consent of the local ethics committee, patients were selected from the elective surgery program. Patients got instructions to exhale to residual volume and subsequently (after placement of the ventilation mask and ensuring the ventilation circuit is filled with 8% sevoflurane) inhale maximally and keep their breath as long as possible to achieve a fast increase of alveolair sevoflurane concentration. In general, patients were unconsciousness after this single breath. After spontaneous breathing had restored, the end tidal concentration was measured. As soon as the end-tidal sevoflurane concentration reached a value of 4.5%, 1.6µg/kg fentanyl (an analgesic) was administered and three minutes later the patient was intubated. After intubation the end-tidal sevoflurane target concentration was set to 2.0%. Five minutes after intubation, the study part ended, surgery started and the patient followed normal anesthetic procedures.

The second study (referred to as B) by Driessen et al., was performed to evaluate whether BIS predicts haemodynamic responses during endotracheal intubation and sternotomy during fentanyl-midazolam anesthesia for cardiac surgery. After institutional approval and informed consent, 7 patients scheduled for cardiac surgery, were selected. All patients were premedicated with paracetamol, and either midazolam or oxazepam 1h before induction of anesthesia. Anesthesia was induced with fentanyl and midazolam. Pancuronium was given to

* BIS: trademark of Aspect Medical Systems, Newton, MA
facilitate endotracheal intubation and anesthesia was maintained with continuous infusion of fentanyl (4-6 μg kg⁻¹h⁻¹) and midazolam (0.1 mg kg⁻¹h⁻¹). A further bolus dose of fentanyl 10-12.5 μg kg⁻¹ was given before the start of incision and sternotomy. Cardiopulmonary bypass was performed using an extracorporeal roller pump and a membrane oxygenator.

7.3.2 EEG analysis
The EEG was recorded (Aspect A-1000) continuously and digitized at a rate of 256 Hz. EEG electrode positions were determined by the standard BIS bipolar frontal-temporal electrode montage (Aspect Medical, Zipprep, BIS version 3.12). Overlapping EEG epochs (overlap 8s) of 1 minute duration were used to calculate CD. No artifact rejection was applied to the raw EEG signal.

7.3.3 CD
The correlation dimension was computed following the Grassberger/Procaccia/Takens algorithm with alterations to maximize the sensitivity to anesthetic effects. Attractor reconstruction was performed using EEG epochs of 1 minute duration, embedding dimension=20, delay time=8 ms and 1 second Theiler correction. To reduce the required computation time per calculation, the correlation integral was estimated using a subset of all possible distances between points on the attractor (p=3, s=4; see paragraph 2.4.4). The CD is extracted from the correlation integral at a fixed interval defined by the distribution of distances in the correlation integral (see chapter 2).

7.4 Results
7.4.1 Study A (sevoflurane single-breath)
Fig. 7.1 shows the results of one patient. CD (thick solid line) decreases as a response to the sevoflurane (dashed line) inhalation. After intubation (marked by character I) and decrease of sevoflurane delivery, CD increases and stabilizes to a value of approximately 4. The response of BIS (thin solid line) is remarkably different from CD. An unexpected increase of BIS after administration of fentanyl (marked by character F) is found.
Fig. 7.1 Typical example of one patient. The figure demonstrates responses of CD (thick solid line) and BIS (thin solid line) to administered sevoflurane (dashed line). Time of administration of fentanyl and intubation are respectively marked by characters F and I.

Fig. 7.2 shows an overview of results of all patients. EEG measurements started just before the induction of anesthesia and CD was estimated using an EEG epoch of 1 minute. Therefore, as within this first minute the anesthetic condition of the patient rapidly changes, the first results of CD not always reflect baseline conditions. Similar responses, as shown in Fig. 7.1 for patient number 8, can be found for the patient numbers 3, 5, 7, 12, 13, and 15. During phases of burst suppression pattern CD gives erroneous results. The epochs with burst suppression are marked with a thick line on the time axis. After intubation (arousal effect) and simultaneously lowered sevoflurane concentration, CD slightly increases and stabilizes to values between 4 and 5. CD shows a reasonable response compared to administered anesthetic drugs.

Fig. 7.3 illustrates a possible different response of CD and BIS to changed anesthetic condition as measured in one particular patient. At 30 minutes, the patient started to cough. After this coughing incident, the administered sevoflurane concentration was temporarily increased to deepen anesthesia. This response seems to be better predictable by the foregoing CD increase than by the more ambivalent increase of the BIS.
Evaluation of usefulness of CD in non standard clinical practice

Fig. 7.2 Individual results for study A. Single figures show CD (thick solid line), sevoflurane concentration (dashed line), and BIS (solid thin line). Administration of fentanyl and start of intubation are respectively marked with characters F and I. In one case (patient 11, character R) also 40 mg rocuronium was given. EEG epochs with burst suppression are marked with a thick line on the time axis.

Fig. 7.3 Illustration of possible different response of CD (thick solid line) and BIS (thin solid line) to changed anesthetic condition as measured in one particular patient during sevoflurane (dashed line) anesthesia. At 30 minutes, the patient started to cough. After this coughing incident, the administered sevoflurane concentration was temporarily increased to deepen anesthesia.
Individual results (see Fig. 7.4) of the relationship between CD and BIS show inconsistent results. This inconsistency can be explained by the difference in responses to applied anesthetic drugs (see Fig. 7.1) between CD and BIS. This is illustrated by the deviation of points from the regression line (BIS values in the range of 50-80) in the grand average plot of all patients. Outside this area exists a consistent and at forehand expected relationship between CD and BIS. For example, the individual plots (see Fig. 7.4) of CD against BIS of the patients 3, 5, and 12 show a poor relationship. However, this does not automatically imply...
Evaluation of usefulness of CD in non standard clinical practice

CD to perform inferior as an indicator of anesthetic depth. A close look at the corresponding time series in Fig. 7.2 reveals anomalous changes of BIS which are not expected considering the administrated anesthetic drugs. The different changes of CD (downwards) and BIS (upwards) produce this poor relationship.

7.4.2 Study B (fentanyl-midazolam)

Fig. 7.5 shows the results of one patient measured in study B. At awake condition the calculation of CD is too much disturbed by artifacts and therefore omitted. The dashed line and arrow on the time axis mark an incidence of patient movement (cough response to sternotomy). Here, two important differences between CD and BIS can be seen. Firstly, the ability of CD to continuously produce results, even at EEG-episodes severely contaminated by electrocautery artifacts. This is possible because CD can be calculated by collecting the numerous short artifact-free EEG segments that exist between the electrocautery contaminated EEG segments. In case of the BIS, around the cough incidence BIS was not able to produce results and at the arrow values are almost 100, which is an artifactual result. Secondly, CD is able to give a prewarning of the movement incident of the patient as can be seen by the sharp increase of CD just before the cough incident. BIS fails at this point.

**Fig. 7.5** Example of tracings of CD (upper) and BIS (lower) of one patient under cardio surgery. The arrow on the time axis marks an incidence of patient movement (cough response to sternotomy). The inset shows the effect of electrocautery on the EEG time series. The time period in the region of the arrow is contaminated by electrocautery and surgeon handling (incision, sternotomy).

Fig. 7.6 demonstrates the relationship between CD and BIS for individual patients and pooled data of seven subjects. Except for patient number 7, the individual tracings reveal a consistent
response of CD and BIS to changed anesthetic conditions. Please take notion of the fact that the number of observations per estimate varies between n=10 and n=1000 for the individual plots. The averaged plot of all patients is based on mean results of the individual patients (n=7).

**Fig. 7.6** Comparison of CD and BIS for all subjects individually and average (bottom, right; different scaled y-axis) of all subjects. Error bars represent SD values.

### 7.5 Discussion

The results of both studies A and B confirm the previous (chapter 6) established relationship of CD with DOA in a practical setting. Results of CD also correspond to at forehand expected behavior: decrease of CD after increase of end tidal sevoflurane concentration and vice versa. Study A shows reproducible differences between CD and BIS just after the induction of anesthesia with sevoflurane. Where BIS increases CD decreases, which seems to be a more reasonable response to the administered anesthetic drugs. An explanation for this difference was not found. The need for artifact rejection is evident as turned out by the erroneous CD results obtained at awake conditions (movement artifacts). Also, the nonstationarity of the EEG signal during burst suppression patterns, is a point that needs to be addressed further. In general, the overall behavior of CD and BIS are comparable, however, there are situations where the two differ. Two examples demonstrated possible prewarning of CD for the patient to move, a situation that was not convinced foreseen by the BIS. The two studies and accompanying examples are not enough to justify any conclusions in the direction of statements that CD is better than BIS or the opposite. However, it at least seems that CD is capable of giving additional information and that the CD-algorithm can handle severe artifacts (such as electrocautery) better.
7.6 Conclusions

CD may be useful as a measure of DOA and in some cases may provide additional information compared to the BIS. More study is advised to investigate the potency of CD as a precursor of patient movement.

7.7 Acknowledgements

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Chapter 7
8 General discussion

The main aim of this study was to investigate whether the correlation dimension (D2) is able to inform the anesthesiologist about depth of anesthesia (DOA) and additionally the question whether the algorithm to calculate D2 could be modified in order to make online estimations feasible. Results described in this thesis are discussed here.

8.1 Methodology

Based on the evaluation of mathematically created composite time series and in-situ, real life measured time series, some modifications concerning the algorithm and parameter choices involved in the calculation of D2 were suggested in order to achieve maximum sensitivity to anesthetic effect with minimum computational effort. Subsequently, an optimal combination for the embedding dimension and delay time was found yielding an optimal ratio (S/N-ratio: signal-to-noise ratio) between sensitivity to drug changes (S) and short-term fluctuations (N) not related to changed DOA. Finally, a reduction-scheme was evaluated to find out how many distances in the correlation integral estimate could be discarded without loss of performance in order to decrease the amount of computer time needed per estimate and increase the feasibility of on-line CD calculations. Considering the differences with the D2-algorithm, the abbreviation CD is used.

8.1.1 Scaling region

In the histogram of distances between points on the attractor, \( r_3 \) is defined as the distance in the histogram at which 60% of the distances, and \( r_4 \) as the distance at which 80% of the distances can be found. Thus, instead of extracting CD from a ‘scaling region’, it is extracted from \( C(r) \) at the interval defined by \( r_3 \) and \( r_4 \). This approach was inspired by the aim to utilize an objective definition, which is minimally disturbed by environmental influences with the intention to reduce variability in CD estimates. A correct determination of the scaling region based on objective criterions is difficult. Here, solutions have been proposed with the intention to prevent dependency of visual inspection. The exact meaning of these solutions to the interpretation of the final estimate remains uncertain. If scaling properties are present in the interval defined by \( r_3 \) and \( r_4 \), results are equal to D2, but if this is not the case results should be interpreted as an operational variable related to the complexity of the time series, in our case the EEG. Perhaps the meaning of CD must be positioned somewhere in between two options: as an operational variable related to anesthetic effects or as strongly related to D2.\(^{115}\)
8.1.2 Embedding dimension \((m)\) and delay time \((\tau A)\)

The delay time \((\tau A)\) should not be chosen independently of the embedding dimension \((m)\), but one should choose an appropriate value for the delay time window \((\tau_0)\), which is the total time spanned by the components of each reconstruction vector.\(^{96,105,150,163}\) The results of this study confirm the \(\tau_0\)-dependency: equal S/N-ratios (the S/N-ratio determines the quality of CD as a measure of DOA) are found for \(m \cdot \tau A \approx 0.2s\) \((\tau =\text{sampling interval})\). Fulfilling this dependency and other criterions, the delay time, \(\tau A=8\) ms and \(m=20\), were chosen generating the highest S/N-ratio (see Table 2.1). Besthorn et al., followed a similar approach by evaluating influence of parameters on estimated dimensional complexity in patients with Alzheimer disease (AD).\(^{13}\) As a result, they proposed to use \(\tau A=20\) ms and \(m=30\). However, they noticed that their main result (dimensional complexity of AD patients is lower than controls) was robust from \(m=5\) to \(m=85\), and from \(\tau A=5\) ms to \(\tau A=70\) ms. Here, parameters were chosen based on the performance criterion as defined by the S/N ratio and demonstrate robustness for parameter choices of \(m\) and \(\tau A\) that obey the relationship \(m \cdot \tau A \approx 0.2s.\) However, other parameter choices still inform about DOA.

8.1.3 Reduction of number of distances with \(p\) and \(s\)

Examining the results of the S/N-ratios with varying parameters \(p\) and \(s\), it is remarkable that the situation where all distances are included \((p=1, s=1)\), does not result in the highest S/N-ratio. This remains an open question. At the optimum \((p=15, s=20)\), the ‘signal’ component is only decreased to 85% of its maximum value. The number of distances, however, is then reduced, leaving only 0.33% of the maximum number of possible distances. Thus, at first sight it seems that this choice discards a huge amount of information. However, in the time domain it appears that every single data point (EEG sample) is still used many times in the calculation of \(C(r)\). Even in the case of \(p=60\) and \(s=40\) (see Fig. 2.7), CD issues a faithful relationship with DOA not very different from the case \(p=15\) and \(s=20\). This is an intriguing point. Many articles make statements about the minimal number of points needed for a reliable estimate of the correlation dimension. The underlying thought is that this number is necessary for an adequate reconstruction of the attractor. In this light, more points serve to reveal more of the dynamical structure of the studied system. Discarding points produces a more course attractor. However, parameters \(p\) and \(s\) only discard some distances between the attractor points and the geometric structure is preserved. The calculation of \(C(r)\) with \(p=s=1\) is based on distance information retrieved from \(\frac{1}{2}N^2\) pairs of points. Note that these pairs of points are derived from \(N\) samples of the original (EEG) time series, which subsequent samples also are in general not independent. Therefore, in this case, it is amenable that there is a large amount of redundant information, which can be omitted by choosing \(p\) and \(s\) higher than one. This option can also be utilized in an advantageous way if
oversampled data are to be analyzed. By increasing \( p \) and/or \( s \), superfluous distances can easily be omitted.

With the parameters \( p \) and \( s \) a different approach is introduced to reduce the number of distances in the correlation integral. This reduction is not achieved by just simply omitting attractor points. Instead, reduction is achieved by omitting distances between attractor points.

Choices of \( m, \tau, p, \) and \( s \) far beyond the optimal range of values produce a CD that still informs about DOA. However, these parameter choices influence the absolute outcome of CD. Therefore, it can be concluded that not the absolute values are relevant, but the relative changes of CD compared to baseline conditions. This also implies that comparison of the absolute results of CD between studies is only sensible if in the calculation of CD equal parameter settings were chosen and measurement conditions were comparable.

### 8.2 Relationship with DOA

To evaluate the relationship of CD with DOA, one human study and three rat studies were performed. In all these studies it was found that CD decreases as DOA increases and vice versa. The CD results of the two rat studies that included NIWR measurement, were obtained using equal parameter settings and measuring equipment. At the same DOA levels, as indicated by the NIWR, CD values for the propofol study were higher and BSR results were lower than those of the sevoflurane study. This may be interpreted as evidence for CD to be dependent of the administered anesthetic drug. A speculative explanation would be the following. Since the NIWR is influenced by the level of consciousness and the level of analgesia. If two drugs have different hypnotic and analgetic effects, it is possible to obtain a different NIWR, but the level of consciousness may very well be the same.

That CD is indeed related to consciousness can also be deduced from the effect of arousal on CD. If the results of CD from the two sevoflurane studies are compared, CD is higher at the same dose in case of the study where NIWR measurement is included. In other words, the arousal effect of the NIWR stimulus causes CD to increase. This arousal effect is also confirmed by the peaks that emerged in the CD curve some minutes after the start of sevoflurane delivery as the rat fell asleep (sevoflurane rat experiment; see paragraph 3.4.1, Fig. 3.3). This coincided with an excitation period that was observed, characterized by attempts to stand up and by ataxic walking. This excitation phenomenon and accompanying increased values of dimensionality were also observed for the anesthetic drug fluroxene by Mayer-Kress and Layne.\(^{126}\)

At deep levels of DOA, the EEG shows a burst-suppression pattern. From this pattern the burst suppression ratio (BSR) is deduced. BSR also shows a relationship with DOA, albeit restricted to the deep levels of DOA. BSR increases as DOA increases and vice versa. The
combination of both CD and BSR as a descriptor of DOA probably enhances results if compared to the individual variables. Also the combination enables the monitoring of a broader anesthetic range.

8.3 Interpretation

The application of the nonlinear approach to EEG signals considers the EEG to be the output of a deterministic system of relatively simple complexity, but containing nonlinearities. This presumption became a single point of interest: is there evidence for the assumption that an EEG signal originates from a deterministic nonlinear dynamical system. At present in literature different methods or tests are proposed to give an answer to the nonlinearity or determinism question. None of these methods were applied here. Kugiumtzis suggests that these tests should be performed numerous times for different parameter combinations, which hinders a practical implementation.104 Moreover, regardless of the outcome of these tests (i.e. the signal is Gaussian or not), the observed relationship between propofol/sevoflurane concentrations or NIWR/OASA-score and CD remains identical. Even, in the worst case, if the signal was Gaussian it is still unclear how to obtain the same information from the power spectrum. However, what meaning should then be attached to CD? The most straight forward option is to regard CD as an operational measure strongly related to complexity, just as proposed for D* by Widman et al.215

8.4 Monitoring DOA

In the medical environment, in the last few years research of nonlinear variables has been expanded. Most promising seem the results achieved in epilepsy research. Indications were found for some measures able to classify EEG segments as a precursor of epileptic activity.115,208 However, a practical implementation (beyond research stadium) of these measures is still difficult.

Compared to our research activities, the group of Widman et al., follow a similar approach in the search for a descriptor of DOA. They also use a D2-derived measure, D* to inform about DOA.215 However, their algorithm demands considerably more computer run time per estimate. Therefore, a practical implementation of D* should be more difficult compared to that of CD. Another difference between the two concerns the way of handling of the nonstationarity of the burst suppression pattern. Our CD algorithm focuses its analysis solely on the burst segments, where D* claims to include both the suppression and burst pattern. The exclusion of the suppression segments in the calculation of CD very much resembles the approach of another D2-derived measure, PD2i, proposed by Skinner et al. (see paragraph 1.4.4).183
The monitoring of DOA is a very complex matter. Results presented in this thesis demonstrate that CD is an extra tool that can be utilized for this purpose. Further study is advised to investigate the role of CD as a possible predictor of patient movement. At present, BIS is widely accepted as a new DOA monitoring variable despite its shortcomings. The occasionally failure of BIS emphasize the complexity of the assessment of DOA. Therefore, the search for new variables to inform about DOA must be prolonged. This becomes even more evident by the potential enhancements that can be achieved with the multimethodological approach. At present, some research groups already combine several EEG variables from which it is known that they individually inform about DOA. This approach probably has the best chance to be successful. It remains a challenge to combine the information of these variables into an index that optimally informs about DOA. Ultimately however, the wish of every anesthesiologist presumably is to be equipped with an apparatus able to inform about the different components hypnosis, analgesia, muscle relaxation, and suppression of autonomic reflexes. Hopefully, in the future CD can contribute to this aspiration.
Summary and conclusions

There are many obstacles regarding monitoring depth of anesthesia (DOA). The shortcomings of the traditional variables are manifested by problems due to interindividual variability, obscuring effects of muscle relaxants, limited time of utilization, and contradictory results concerning their correlation with DOA. As the capability of the traditional variables to monitor DOA was unsatisfactory, research moved towards a direction of analyzing variables extracted from the EEG assuming this would perhaps provide better information related to DOA. Results were sometimes promising, but none of the variables or methods proved applicable as a universal measure of DOA.

Former studies at our department concerning monitoring DOA, were focused on existing non-EEG measures and/or linear EEG measures. Although the results of these studies were sometimes encouraging, they were not satisfactory. The failure of traditional and linear EEG measures to provide a variable that universally informs about DOA, and the - at that time - preliminary results of the BIS, strengthened our opinion that nonlinear EEG analysis perhaps uncovers information not available using linear analysis. The decision was made to move research of monitoring DOA towards a new direction by starting this thesis study with the intention to evaluate other EEG variables provided by methods of nonlinear analysis.

The review of international literature subjected to the application of nonlinear analysis for the purpose of DOA (section 1.5.2) and to applications in other related medical disciplines (section 1.5.3), revealed possible utilization of dimensionality (D2) and Lyapunov exponents. A comparison of the expected implementational problems of algorithms to calculate D2 and Lyapunov exponents revealed that the pitfalls of the latter algorithm were expected to be of higher order compared to the algorithm of D2. Therefore, we decided to keep Lyapunov exponents in mind for future study and to focus research efforts on D2 alone. Also, literature study showed several pitfalls connected with the implementation of the algorithm to calculate D2. One of which was the enormous required amount of computer time required per estimate. Other pitfalls concerned the influence of delay time, embedding dimension, and scaling region on D2 (see section 1.4.5). We decided to investigate whether any changes could be made to the algorithm in order to reduce the negative effects of aforementioned pitfalls.

The implementation of the algorithm to calculate D2 confirmed in literature reported influence of delay time $\tau$, $\Delta t$ and embedding dimension $m$ on D2 (section 1.4.5). Moreover, we found an additional source of variation to the result of D2 caused by the ambiguous definition of the scaling region, which in fact determines D2. For a practical implementation – the ultimate goal - these two problems (required computer time and sources of variation) should be encountered first. Therefore, we started to optimize software code to decrease the required calculation time per estimate. We achieved substantial time reduction by minimizing
recalculation of information already acquired at earlier phases of the algorithm (chapter 2). Although we tried different methods proposed in the literature for an appropriate estimation of the parameters involved in the D₂ algorithm, the influence of these parameters on D₂ remained. As a result, we decided to fix parameter values to rule out as much as possible variation in D₂ caused by other sources than changed DOA. Chapter 2 describes the different methods utilized to determine appropriate parameter values and the modifications made to the Grassberger/Procaccia algorithm. Also, preliminary results of the correlation dimension (CD) another abbreviation is introduced here to emphasize the difference with D₂ to inform about DOA were presented. Besides the efforts taken to write optimized computer code for the sake of a practical implementable DOA monitoring device, efforts were taken to implement this algorithm into a user-friendly program (Cordimanes©). This software package Cordimanes enabled the employment of students to aid in our research activities.

To test the performance of CD as an indicator of DOA and to optimize the sensitivity of CD to changes in DOA, three rat studies were performed. EEG signals of rats were measured at conditions with different levels of DOA. Two anesthetic drugs were tested: the intravenous anesthetic propofol (chapter 3) and the volatile anesthetic sevoflurane (chapters 4 and 5). Information concerning DOA was obtained by measurement of the force of the noxious induced withdrawal reflex (NIWR) of the hind paw of the rat as a response to an electrical stimulus. In this light, the NIWR is used as a reference measure of DOA. To measure the performance of CD as an indicator of DOA, results of CD were compared to the NIWR. Measurement of the NIWR demands an advanced measurement setup for which, in the past, developments were made at our department. We made some refinements to this setup to enable sophisticated monitoring of vital functions and enhance regulation of rat body temperature. With this measurement setup the rat was placed in an environment well suited to guarantee a stable condition of the rat during the whole experiment. For example, the new set up stabilized changes of the body temperature of the rat within the range of ±0.1 °C. As metabolism in general is affected by changes in body temperature, this will probably also influence effects on the CNS and as a consequence on the measured EEG.

After adaptation and optimization of the CD algorithm and establishment of meaningful relationships between CD and DOA in rats, we started a clinical study to test CD performance in patients. In this study, we measured the EEG of twenty patients during five to seven defined steady state levels (as indicated by a computer model) of propofol anesthesia. At every stage, the observer’s assessment of sedation and anesthesia (OASA) scale served to define DOA. To test the performance of CD as an indicator of DOA, we related CD to this score (chapter 6). The former study calculated CD of EEG epochs retrieved at steady state propofol levels. Therefore, it can be regarded as a static performance evaluation of CD.
Finally, to test the performance of CD in a dynamical environment, we used the EEG of some patients recorded during the induction of anesthesia and during the entire surgery (chapter 7).

We wrote user friendly software (Cordimanes®) that implements the described algorithm to calculate CD. It is written in C++ using the Borland C++ Builder and can be used in combination with the windows 9x, NT/2000 operating systems. For monitoring trend purposes, it is desirable to calculate CD using overlapping intervals. In Cordimanes the algorithms are optimized in such a way that information from previous overlapping intervals is maintained for the next estimate. This reduces the amount of computer time needed per estimate (see paragraph 2.4.4). All parameters used in the described CD-algorithm are adjustable. Time series that contain up to sixteen channels can be analyzed. Cordimanes can only handle integer data with 12-bit resolution and can be used with batch-files to automate the CD calculation process of huge amounts of data. This option is used to calculate the CD results with the numerous different combinations of the parameters \( p, s \) and \( \tau, m \) (see Table 2.1 and Fig. 2.7). The most computational demanding part of the CD algorithm is divided into two ‘threads’ so that two-processor systems can be optimally utilized (only with windows NT/2000 operating system).

The objective of the studies described in this thesis was to find answers to the following questions: can the correlation dimension algorithm be optimized for improvement of its sensitivity to anesthetic effects and for feasibility of real time estimates? Is CD of the EEG related to DOA? Can CD of the EEG provide relevant information to the anesthesiologist (practical evaluation)? These questions can be adapted to the next four conjectures.

\( H_A \): Appropriate algorithm parameter choices enhance sensitivity of dimensional analysis for the purpose of monitoring DOA.

\( H_B \): The D2 algorithm can be adapted to enable real time estimates.

\( H_C \): CD is related to DOA.

\( H_D \): CD can predict forthcoming changes in DOA.

The results presented in this thesis justify the following answers to these four conjectures. The conjectures \( H_A \) and \( H_B \) are confirmed by the results described in chapter 2. Conjecture \( H_C \) is confirmed by the three rat experiments (chapter 3,4,5) and by the clinical study (chapter 6). Although two examples in chapter 7 reveal probably prewarning of patient movement by CD, it is too preliminary to claim any capability in that direction. Further study is necessary to permit any conclusions regarding conjecture \( H_D \).

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Samenvatting en conclusies

Tijdens een operatieve ingreep wordt de narcosediepte ofwel de diepte van anesthesie (DOA) bewaakt door de anesthesioloog. De bepaling van DOA is echter niet eenvoudig. Traditionele methoden ter bepaling van DOA schieten tekort op onderdelen als: interindividuele variabiliteit, verstorende effecten van spierverslappers, beperkte toepassingstijd en tegenstrijdige resultaten als indicator van DOA. Omdat de traditionele methoden niet in staat zijn gebleken éénduidig over DOA te informeren heeft onderzoek zich verplaatst richting variabelen die worden afgeleid van het EEG. Met daarbij de aannamer dat via het EEG wellicht betere informatie over DOA kan worden verkregen. Resultaten waren soms veelbelovend, maar geen enkele variabele of methode is toepasbaar als een universele maat voor de DOA.

Eerdere studies van onze afdeling op het gebied van de bewaking van anesthesie hielden zich bezig met de meer traditionele methoden en/of met lineaire variabelen afgeleid van het EEG. Resultaten van deze studies waren soms bemoedigend maar niet afdoende genoeg. Het falen van de traditionele methoden en de lineaire EEG-variabelen om een geschikte maat voor DOA te leveren, en de – op dat tijdstip – eerste resultaten van de BIS, versterkten onze opvatting dat niet-lineaire EEG-analyse wellicht informatie oplevert die niet beschikbaar is via lineaire analyse. De beslissing was genomen om het onderzoek op het gebied van de bewaking van anesthesie te verplaatsen in een nieuwe richting met het starten van het onderzoek beschreven in dit proefschrift met de intentie om niet-lineaire EEG-variabelen te onderzoeken.

Literatuuronderzoek op het gebied van toepassing van niet-lineaire analyse voor de bepaling van DOA bracht aan het licht dat mogelijk dimensie-analyse (D₂) en Lyapunov-exponenten toepasbaar zijn voor dit doel. Bij de vergelijking van de te verwachten moeilijkheden bij de implementatie van beide algoritmen bleek dat het algoritme van de Lyapunov-exponenten daarbij als slechtste uit de bus kwam. Daarom besloten we deze in ons achterhoofd te houden en onderzoeksinspanningen eerst te richten op D₂. Uit literatuuronderzoek bleek dat er verschillende moeilijkheden bestonden bij de implementatie van het algoritme ter bepaling van D₂. Één daarvan was de enorme hoeveelheid benodigde rekentijd per bepaling. Andere moeilijkheden waren de invloed van de reconstructieparameters m, τ en de definitie van het schalingsgebied op D₂ (zie paragraaf 1.4.5). We besloten om te onderzoeken in hoeverre het algorithmie kon worden aangepast opdat de negatieve effecten op D₂ door voorgenoemde moeilijkheden zouden worden gereduceerd.

De implementatie van het D₂-algoritme bevestigde de in de literatuur beschreven invloed van m en τ op D₂. Bovendien vonden we een extra bron van variatie op de resultaten van D₂ door
de onduidelijke definitie van het schalingsgebied, die in feite $D_2$ bepaalt. Voor een praktische implementatie – het uiteindelijke doel – zouden deze twee problemen (benodigde computertijd en bronnen van variabiliteit) eerst moeten worden aangepakt. Daarom werd gestart met het optimaliseren van softwareroutines (broncode) om daarmee de benodigde rekentijd per bepaling te verminderen. Door hergebruik van informatie uit eerdere fases van het algoritme kon een substantiële tijdsreductie worden bereikt (hoofdstuk 2). Alhoewel we voor een geschikte bepaling van de parameters benodigd in het $D_2$-algoritme verschillende voorstellen uit de literatuur hebben geprobeerd, bleef de invloed van deze parameters op de resultaten bestaan. Daarom hebben we besloten deze parameters tijdens het doorrekenen van een heel experiment, een vaste waarde te geven. Met als doel daardoor de invloed van zaken, anders dan een veranderende DOA, op $D_2$ zo veel mogelijk te minimaliseren. Hoofdstuk 2 beschrijft het bewandelde pad dat leidt tot het aangepaste Grassberger/Procaccia algoritme. Tevens worden daar de eerste resultaten vermeld van de correlatiedimensie (CD) – een andere afkorting is gebruikt om het verschil met $D_2$ te benadrukken - als een maat voor DOA. Naast de inspanningen die zijn verricht om computer broncode te optimaliseren zodat praktische implementatie binnen handbereik komt, is er aandacht besteed aan de software ($Cordimanes^\circledR$) waarmee CD kan worden berekend. Speciale aandacht ging uit naar de gebruikersvriendelijkheid van de gebruikersinterface zodat het eenvoudig mogelijk was om studenten voor het onderzoek in te zetten.

Om de prestaties van CD als indicato van DOA te testen en de gevoeligheid van CD voor veranderingen in DOA te optimaliseren zijn er drie ratstudies uitgevoerd. EEG-signalen van de rat werden bij verschillende DOA-niveaus gemeten. Twee anesthetica zijn gebruikt: het intraveneus toe te dienen propofol (hoofdstuk 3) en het dampvormige sevofluraan (hoofdstuk 4 en 5). Informatie over DOA werd verkregen door meting van de terugtrekreflex (NIWR) aan de achterpoot van de rat als reactie op een pijnlijk toegediende stimulus. De NIWR fungeert hier in feite als referentiemaat voor DOA. De prestatie van CD als indicato van DOA wordt dan afgemeten aan zijn correlatie met de NIWR. Meting van de NIWR vereist een geavanceerde meetopstelling waarvan de basisversie in het verleden reeds was ontwikkeld. We hebben de meetopstelling verbeterd door het mogelijk maken van geavanceerde bewaking van vitale lichaamsfuncties en het verbeteren van de temperatuurregeling van de rat. Met deze meetopstelling was de rat geplaatst in een meetomgeving die uitstekend was uitgerust om een stabiele conditie van de rat te kunnen garanderen tijdens de uitvoering van het experiment. Bijvoorbeeld, de nieuwe opstelling maakte het mogelijk om de temperatuur van de rat te stabiliseren binnen een bereik van ±0.1 graden Celsius, tegenover temperatuurschommelingen in de oude opstelling van meer dan 1 graad Celsius. Omdat het metabolisme sterk afhankelijk is van de lichaamstemperatuur,
zullen temperatuurschommelingen ook hun effect hebben op het centraal zenuwstelsel en daarmee dus ook op het EEG.

Na aanpassing en optimalisatie van het CD-algoritme en de vaststelling van de relaties tussen CD en DOA in de rat, werd een klinische studie gestart om prestaties van CD gemeten bij de patiënt te kunnen bepalen. Bij deze studie werden bij 20 patiënten het EEG gemeten tijdens 5 tot 7 verschillende ‘steady state’ propofol breinconcentraties (zoals vastgesteld via een computermodel). Tijdens elke fase werd door middel van de observer’s assessment of sedation and anesthesia (OASA) schaal een referentiemaat voor de DOA verkregen. Voor de vaststelling van de prestaties van CD als indicator van DOA werden waarden vergeleken met de OASA-score (hoofdstuk 6). Omdat in deze studie CD alleen tijdens ‘steady state’ condities is berekend, kan het worden beschouwd als een ‘statische’ evaluatie van de prestaties van CD als indicator van DOA. Tenslotte zijn voor een ‘dynamische’ prestatie-evaluatie verschillende patiënten gemeten tijdens de inductie van anesthesie en tijdens de gehele chirurgische ingreep (hoofdstuk 7).

Het CD-algoritme is verwerkt in het programma *Cordimanes*© dat tijdens het onderzoek is geschreven. Om trendanalyses mogelijk te maken is het wenselijk om CD van overlappende EEG intervallen te kunnen berekenen. In *Cordimanes* is deze optie gerealiseerd op een dusdanige wijze dat de informatie uit de overlappende gedeelten hergebruikt kan worden voor de volgende berekening. Daarmee wordt een grote tijdswinst geboekt (zie paragraaf 2.4.4). Alle parameters die van belang zijn voor de berekening van CD kunnen worden aangepast naar eigen inzicht. Bestanden met daarin tot maximaal 16 EEG afleidingen kunnen in één sessie tegelijkertijd worden doorgerekend. *Cordimanes* kan alleen overweg met data met een resolutie van 12-bits. Via een ‘batch’-bestand is het mogelijk een hele serie van bestanden met verschillende parameter-instellingen door te rekenen. Deze optie is gebruikt bij het berekenen van CD voor verschillende combinaties van p, s en τm (zie Table 2.1 en Fig. 2.7). Het onderdeel van het CD-algoritme dat de meeste rekentijd vergt, is verdeeld in twee ‘threads’ zodat een multi-processor systeem optimaal benut kan worden (alleen met Windows NT/2000 besturingssysteem).

Het doel van de studies zoals die zijn beschreven in dit proefschrift was het vinden van antwoorden op de volgende vragen: kan het correlatiedimensie-algoritme worden verbeterd in de zin van praktische toepasbaarheid en gevoeligheid voor veranderingen in de anesthetische toestand van de patiënt? Is er een relatie tussen de CD van het EEG en DOA? Kan de CD van het EEG relevante bruikbare informatie verschaffen aan de anesthesioloog (praktische evaluatie)? Deze vragen kunnen worden vertaald naar de volgende vier stellingen.
\( H_A \): Door een geschikte keuze van parameters van belang bij het CD-algoritme verbetert de gevoeligheid van dimensie-analyse voor de toepassing bewaking van anesthesie.

\( H_B \): Het D2-algoritme kan worden aangepast zodat toepassing voor praktische doeleinden mogelijk wordt.

\( H_C \): CD vertoont een zinnige relatie met DOA.

\( H_D \): CD kan veranderingen in de DOA van de patiënt voorspellen.

De resultaten zoals die in dit proefschrift zijn gepresenteerd onderbouwen de volgende antwoorden op deze vier stellingen. Stelling \( H_A \) en \( H_B \) worden bevestigd door de resultaten beschreven in hoofdstuk 2. Stelling \( H_C \) wordt bevestigd door de drie ratexperimenten (hoofdstuk 3,4,5) en door de klinische studie (hoofdstuk 6). Alhoewel in hoofdstuk 7 twee voorbeelden zijn gegeven van situaties waarin CD mogelijk de beweging van de patiënt voorspelt, is dit nog geen basis om op grond daarvan te mogen concluderen dat in het algemeen CD de beweging van een patiënt kan voorspellen. Stelling \( H_D \) kan dan ook niet met zekerheid worden bevestigd. Uitgebreider onderzoek op dit punt is dan ook wenselijk.
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Curriculum Vitae

Philippus Leonardus Cornelis van den Broek werd geboren op 12 juli 1967 te Almelo. Hij is getrouwd met Marja van den Broek-Duijmelinck. Samen hebben zij drie dochters: Sanne, Floor en Roos.

In 1985 behaalde hij het VWO-diploma aan het PIUS X college te Almelo. In hetzelfde jaar begon hij met de studie elektrotechniek aan de Universiteit Twente. Een jaar later stapte hij over naar de Hogeschool Enschede en rondde deze studie af in 1990. Al tijdens de daarop aansluitende militaire dienst startte hij opnieuw met de studie elektrotechniek, ditmaal aan de Technische Universiteit Eindhoven. Het afstudeerwerk bij de vakgroep Medische Elektrotechniek omvatte de evaluatie van de invloed van de keuze van betrouwbaarheids-intervallen van diverse van het EEG afgeleide signaalparameters voor signaalvalidatie bij de bepaling van ‘auditive evoked potentials’. De daarmee samenhangende werkzaamheden werden deels uitgevoerd op het centraal dierenlaboratorium (CDL) van de afdeling anesthesiologie van het UMC St. Radboud te Nijmegen. Op 17 februari 1994 studeerde hij af en keerde vrijwel direct aansluitend terug als onderzoeker bij de afdeling anesthesiologie. Daar startte hij het onderzoek waarvan de resultaten grotendeels zijn vervat in dit proefschrift. De doelstelling van het onderzoek was het toepasbaar maken van variabelen uit de chaostheorie voor de bepaling van anesthesiediepte tijdens chirurgische ingrepen en de evaluatie van de mate waarin deze variabelen informeren over anesthesiediepte.