Chapter 37
Application of Sample Entropy to Analyze Consciousness in CLIS Patients

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Abstract In this paper, an approach using sample entropy in order to detect the consciousness in two complete locked-in syndrome (CLIS) patients is presented. The typical symptom of CLIS patients is complete paralysis, but internal brain activities are supposed to be still available. On the other hand, there is no certainty about the actual state of consciousness in CLIS patients. For communication reasons and thus the patient's quality of life, it is an important problem to investigate consciousness in CLIS patients. A brain computer interface (BCI) potentially provides the family members a method to communicate with CLIS patients. There are arguments whether the CLIS patients are conscious or not. As consciousness is required to use BCI correctly, this study proposes to use sample entropy to uncover awareness from electroencephalography signals in CLIS patients. In a first proof of concept, data from two patients have been analyzed. The results for these two patients indicate that the use of sample entropy might be helpful to uncover awareness and thus to detect consciousness in CLIS patients.

37.1 Introduction

Locked-in syndrome (LIS) is a state perhaps caused by a stroke, car accident, or motor neuron diseases, such as amyotrophic lateral sclerosis (ALS) and unresponsive wakefulness syndrome (UWS). LIS patients with this medical condition have no movements of limbs and most of facial muscles, but consciousness is supposed to remain. Those patients are frequently misdiagnosed as having no consciousness. Nevertheless, there is one UWS case proofing that the patient is awake after 20 years [1]. LIS patients often communicate only by eye or eyebrow movements before slipping into completely locked-in state. Patients enter the complete locked-in syndrome (CLIS) status while the last remaining eye movements and anal sphincter control

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S.-L. Peng et al. (eds.), *Sensor Networks and Signal Processing*, Smart Innovation, Systems and Technologies 176, https://doi.org/10.1007/978-981-15-4917-5_37

disappear [2, 3]. Chaudhary et al. [4] attempted electroencephalography (EEG) and near-infrared spectroscopy (NIRS) to interact with CLIS patients, but there are still many controversies [5]. The biggest challenge regarding the proof of consciousness in CLIS patients is that the CLIS patients cannot express themselves explicitly anymore; thus, it is difficult to prove the results with last evidence.

In order to detect the state of consciousness, this study proposes to analyze the continuously recorded electroencephalography (EEG) signals using sample entropy. The main objective of this research is to provide a possible method to confirm that consciousness which is present in these patients during a defined time period. The final goal of this investigation is to restore the communication channel between CLIS patients and the outside world via BCI.

The sections of this paper are organized as follows: First, information about the modus operandi, the used analysis software, and the dataset is presented. Then, the method of sample entropy is described. Third, the preliminary results are presented, and the possible influencing factors are discussed. Finally, future developments are considered.

37.2 Method

The flowchart of the proposed data processing approach is shown in Fig. 37.1. First, in order to reduce the computation time, the original EEG signals are down-sampled to 100 Hz. Second, the down-sampled signals were band pass filtered by a sixth-order 1–45 Hz Butterworth filter since thoughtfulness and awareness, which is closely related with consciousness, are considered to be in the beta band (13–30 Hz) [6] and interference of the 50 Hz power-line frequency is avoided. Finally, the sample entropy algorithm was applied to obtain a level of consciousness. All the data were analyzed using MATLAB R2018b.

37.2.1 Dataset

The dataset in question comprises the signals of electroencephalography (EEG) and electrooculography (EOG). The dataset provider published the analysis results from four patients [4]. The same codename is used to facilitate comparison for readers. Two of these patients completed more than 130 sessions over several weeks: patient B completed 56 sessions, patient F completed 80 sessions (we kept the denomination

Fig. 37.1 Data processing flowchart

as in [4]). Because of the high number of completed sessions from two patients, we decided to use the data from these two patients. The EEG data was recorded with an EEG amplifier (Brain Amp DC, Brain Products, Germany) using a sampling rate of 200 Hz.

Figure 37.2 shows the channel positions which were used to acquire EEG signals and four electrodes which were used to acquire the vertical and horizontal EOGs. Table 37.1 shows the electrodes used to record the EEG signals for different patients on different days.

Beside the effect that in LIS the EOG signals that are measured to reject its influence in the recorded EEG data, during the course of disease in ALS toward CLIS, the patients gradually lose the ability to control muscles and even eye movements, and thus, the EOG disappears. Therefore, in this paper, we focus only on the analysis of the source of brain waves, EEG signals.

Patient B is a 61 year old CLIS patient. He was diagnosed with ALS in May 2011. From April 2012 to December 2013, he was able to communicate with the MyTobii eye-tracking device. His family members attempted to train him to move his eyes to different sides to express "yes" and "no," but the response was unstable.

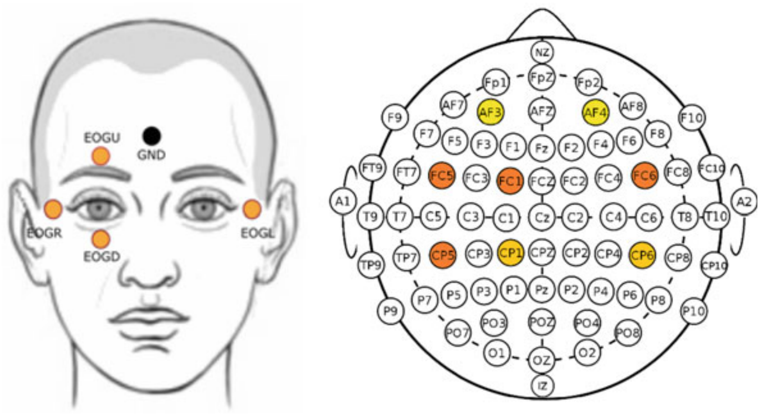

Fig. 37.2 Channels' positions. Left: the channels positions of electrooculographic (EOG). Right: the channels positions of electroencephalography (EEG)

Table 37.1 Electrodes recording the EEG signals of the two patients on different days

Codename	Day	EEG channels
Patient B	Day1	FC5, FC1, FC6, CP5, CP1, CP6, AF3, AF4
	Day2	FC5, FC1, FC6, CP5, CP1, CP6, AF3, AF4
Patient F	Day1	FC5, FC1, FC6, CP5, CP1, CP6
	Day2	FC5, FC1, FC6, CP5

Since August 2014, a communication was no longer possible. Patient F is a 68-year-old completely locked-in state patient. She was diagnosed with ALS in May 2007, locked-in syndrome (LIS) in 2009, and CLIS in May 2010. No communication channel was realized since 2010. Gallegos-Ayala et al. [7] described the details of this patient.

In total, over 22 h (130 sessions) of auditory experiments like [2] were recorded including trigger marks, the states of baseline, presentation, last word, and response. Beforehand of the study, the investigators discussed with family members in order to compile 200 personal questions known by the patients for sure and 40 open questions.

First, the investigators trained the patients ahead the experiments by asking the known questions, for example: “Berlin is the capital of Germany?”/“Berlin is the capital of France?,” in which the patient was expected to answer these paired “yes” or “no” questions.

During the experiments, the investigators asked the patients personal questions as well, such as “Is your husband’s name Joachim?” and also open questions the like “You feel good today?”/“You feel bad today?” related to the topic around the quality of life and compare the answers with the actual physiological status reported by the caretakers.

37.2.2 Sample Entropy

The entropy family is used frequently in nonlinear dynamic analysis to estimate the variability in time and frequency domain [8, 9]. This investigation utilizes sample entropy to analyze noninvasive electroencephalography (EEG) physiological signals as proposed in [10–12].

Richman and Moorman [13] improved the approximate entropy algorithm by developing sample entropy in order to apply it in short-term time series and to be more sensitive. The parameters of sample entropy are the same as approximate entropy, but sample entropy reduced the effect of self-matching. The entropy family is widely used in neuroscience, including evaluating consciousness approaches when patients are in anesthesia during surgery [14–16].

SampEn (m, r, N) indicates the sample entropy where m is the dimension selected in advance, r is the range of the tolerance coefficient selected in advance, and N is the number of data points respective to the data length. Pincus [17, 18] suggested that the appropriate number N of the corresponding data length should be in-between the number 10^{m} and 30^{m}. Thus, for 1000 data points in our case, we set the dimension m to 3 (and therefore, the length of the observed pattern). The range of the tolerance coefficient r is 0.2, which means 20% of the standard deviation of time series. Figure 37.3 shows a time series $X = x[1], \ldots, x[i], \ldots, x[N]$. The color band around the data point $x[1]$, $x[2]$, and $x[3]$ represents point $x[1] \pm r$, $x[2] \pm r$, and $x[3] \pm r$, respectively. All data points in the red band match the data point $x[1]$, and similarly, all the data points in the orange and yellow bands match the data points $x[2]$ and $x[3]$.

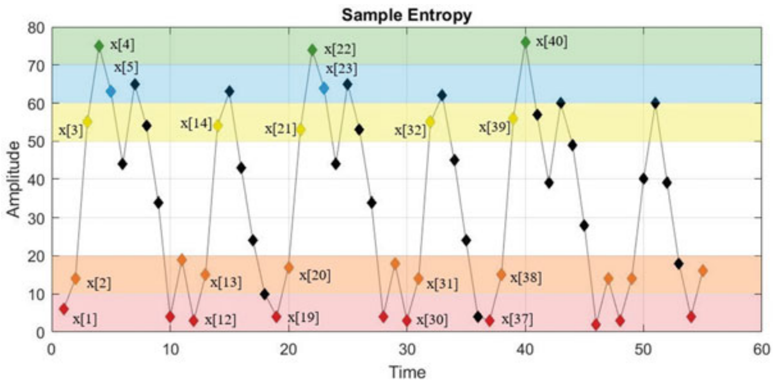

Fig. 37.3 A diagram where each point represents one data point in time domain to explain the operation of sample entropy depending on the row of occurrence over time

Consider the three components red-orange-yellow as consecutive sequence pattern ($x[1]$, $x[2]$, $x[3]$) and the four components red-orange-yellow-green as consecutive sequence pattern ($x[1]$, $x[2]$, $x[3]$, $x[4]$). In this example, there are four red-orange-yellow sequences, ($x[12]$, $x[13]$, $x[14]$), ($x[19]$, $x[20]$, $x[21]$), ($x[30]$, $x[31]$, $x[32]$), and ($x[37], x[38], x[39]$), they match $x[1], x[2], x[3]$ on the same color bands, but only two red-orange-yellow-green sequences that match $x[1]$, $x[2]$, $x[3]$, $x[4]$. Continuing that way with the next three-component sequence (orange-yellow-green) and the four-component sequence pattern (orange-yellow-green-blue), in this case, the number of matches of three-component pattern matches is two, and only one match for a four-component pattern. These numbers of matches are added to the previous numbers, the total number of three-component matches is six, and the total number of four-component matches is three. Now, repeat all possible sequence patterns, $(x[3], x[4], x[5], x[6]), \ldots, (x[N-3], x[N-2], x[N-1], x[N])$ to determine the ratio of all three-component pattern matches and four-component pattern matches. Then, the sample entropy is computing as follows:

$$\mathrm{SampEn}(N, m, r) = -\log \frac{A^m(r)}{B^m(r)} \tag{37.1}$$

$$B^m(r) = (N-m)^{-1} \sum_{i=1}^{N-m} B_i^m(r) \tag{37.2}$$

$$A^m(r) = (N-m-1)^{-1} \sum_{i=1}^{N-m} A_i^m(r) \tag{37.3}$$

where $B_i^m(r)$ is the match number of $x(j)$ with $x(i)$ according to the following conditions, $A_i^m(r)$ is for the situation of $m+1$:

$$d[u_m(i), u_m(j)] = \max\{|x(i+k) - x(j+k)|\} < r \times \mathrm{SD} \quad (37.4)$$

which must be less than a threshold, $R = r * \mathrm{SD}$, where SD is the standard deviation of the time series $X = [x(1), x(2), \ldots, x(N)]$ and r is the tolerance. X is divided into several selected sequences $u_m(i) = [x(i), x(i+1), \ldots, x(i+m-1)]$ $(i = 1 \ldots N - m + 1, k \in [0, m-1], i \neq j)$. Thus, the higher the value of sample entropy, the lower the self-similarity of the series, the higher the probability of producing a new signal, and finally, the more complicated is the data series. Otherwise, the smaller the value of sample entropy, the higher the self-similarity of the series, and thus, the lower the probability of producing a new signal, and consequently, the simpler is the data series.

37.3 Results

As proposed in Sect. 37.2.2, we have applied sample entropy to the dataset as shown in Fig. 37.3. We interpret therefore a higher value of sample entropy as higher brain activity and thus hypothetically more consciousness. This interpretation is based on the results shown in [4] where during the corresponding time slots (see Figs. 37.4, 37.5, 37.6, and 37.7 trigger marks), the experimenter received a good number of correct answers, thus indicating the consciousness of the patient. Figures 37.4, 37.5, 37.6, and 37.7 are showing the results for two patients over two days for each patient.

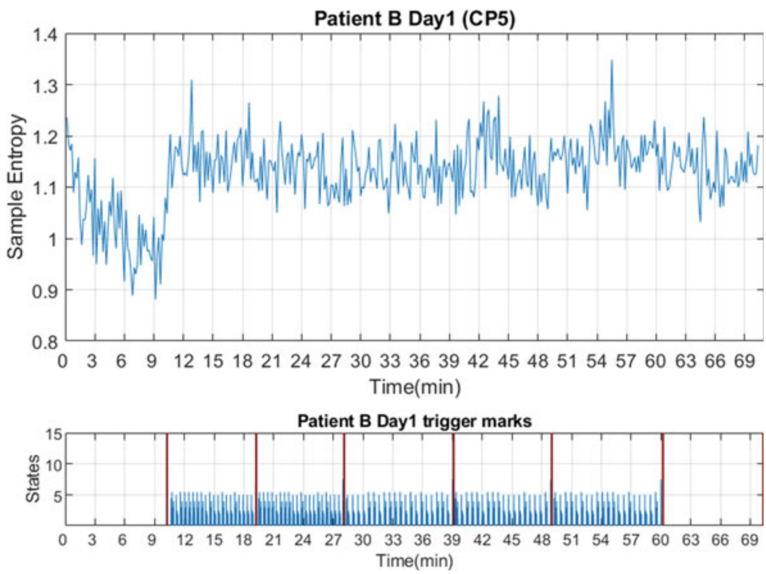

Fig. 37.4 Result of sample entropy (Patient B/Day 1)

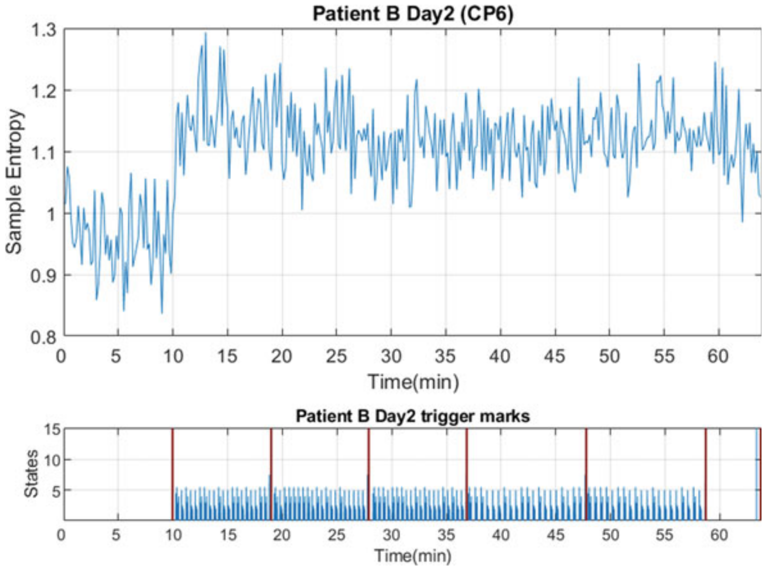

Fig. 37.5 Result of sample entropy (Patient B/Day 2)

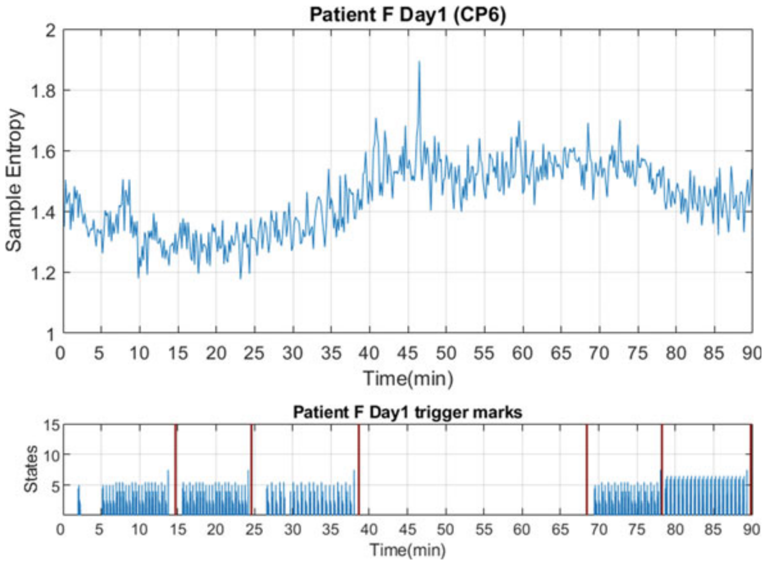

Fig. 37.6 Result of sample entropy (Patient F/Day 1)

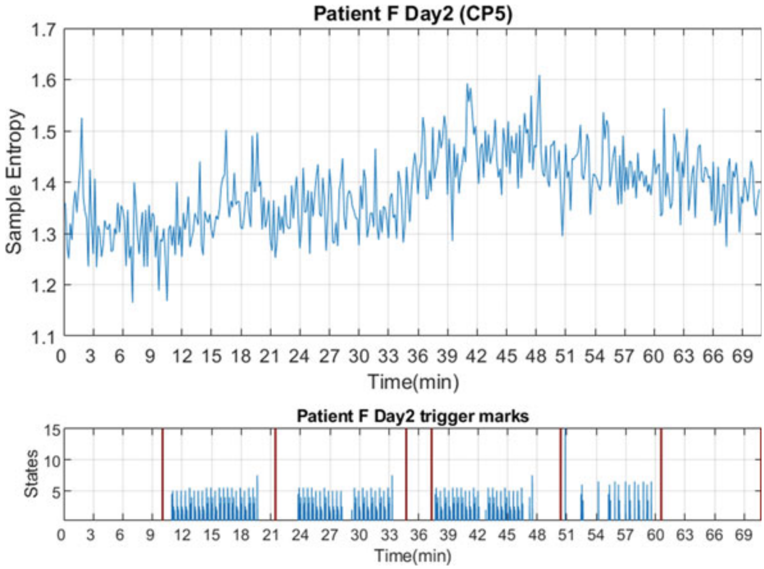

Fig. 37.7 Result of sample entropy (Patient F/Day 2)

These data were selected, since during the two days results to the questions, and therefore, consciousness was reported as being better than during the other days of experiments. In order to obtain relatively clear results in term of consciousness detection, the treated data should potentially contain corresponding information. For this reason, we preselected the two days as argued above.

In Fig. 37.4, we combined seven consecutive sessions over 69 min during day one. The figure below shows the time window between 10 and 60 min in which the investigators asked the questions. The time windows from 0 to 10 min and 60–69 min are the rest states. The top diagram shows the result of the sample entropy: We assume that the higher the value, the higher the relative consciousness of the patient. After 9 min, the value rises obviously, clearly showing the difference between rest and experience state as at that point the questions were started.

In Fig. 37.5, we combined seven consecutive sessions during day 2 all in all over 64 min. The figure below shows the time window between 10 and 59 min in which the investigator asked the questions. The periods from 0 to 10 min and 59–64 min are the rest states. After 10th min, the value of sample entropy rises obviously as well, what we would interpret again as a higher level of consciousness. There is a slow decline after 59 min. The results of patient B in these two days are consistent with the time window of trigger marks. The results for patient B in all other channels (FC5, FC1, FC6, CP5, CP1, CP6, AF3, AF4) have a similar trend.

In Fig. 37.6, a combination of six consecutive sessions during one day with over 90 min is shown for patient F, who performed less good as patient B in general. The figure below shows the time windows between 0 and 39 min and 68–90 min in which the investigator asked the questions. The period of 39–68 min is a rest state.

After the 38 min, the value of sample entropy rises slowly. After the 74 min, the value declines slowly. But the result is the opposite of the result of patient F. The trend of symmetrically positioned electrodes (CP5 vs. CP6, FC5 vs. FC6) is similar, whereas not symmetrical positioned electrodes differ. So, depending on the area over which the electrode is placed (e.g., over the Broca area or the Wernicke area), the task-related signal must be different and thus will indicate different corresponding aspects and show different trends on the related electrodes. We speculate that the level of consciousness depends on how difficult the questions were. Perhaps the questions asked by the investigators can promote the patients' thinking?

In Fig. 37.7, we show the consecutive combination of seven sessions during another day over all in all 70 min during day 2. The figure below shows the time windows between 10 and 35 min and 37–60 min in which the investigator asked the questions. The time windows of 0–10 min and 60–70 min are the rest states. After the 36 min, the value of sample entropy rises slowly. The value declines slowly after the 48th minute. The correct response rate is around 70% by functional near-infrared spectroscopy (fNIRS) and support vector machine (SVM) to ensure that patients are awake [2]. There is a similar result between channel CP5 and the other channels (FC5, FC1, FC6) for patient F on day 2. In the future, we will correlate the different types of questions and related feedback in order to refer to the value of sample entropy and to obtain further results.

37.4 Discussion

The results of patient B shows a relatively higher value of sample entropy while the time window is consistent with the communication period. But not all the results of patient F are in line with this trend. Perhaps, there is an effect related to the difficulty of the questions as well. Therefore, we need to classify with the correct response rate and compare with the type of questions for further analysis. Nevertheless, globally, the obtained results are correlating with the observations in [4]. Even though this does not prove the correctness of the approach in terms of detecting correctly the consciousness, it indicates that the approach might be correct. Remember that in CLIS patients, the final proof of consciousness cannot yet determined without any doubts since the patient cannot tell any more by any means, if she/he was conscious at the moment anymore.

37.5 Conclusion

In this study, sample entropy was proposed to demonstrate consciousness in two complete locked-in state patients. Preliminary results show that it can be hypothetically possible to use sample entropy in the time domain to detect the awareness respective to consciousness in the case of CLIS patients; still, it has to be mentioned that the response rate and the type of questions can be important factors to explain the result presented here. At least these results provide an approach for the detection of the level of consciousness and give the possibility to interpret some meanings from EEG signals instead of supposing unconsciously suspecting them and may finally prove that CLIS patients can recognize the external stimulus and answer questions through a brain computer interface.

Remark that the presented results still state an indication toward consciousness detection in CLIS patients since yet no one other than the patient himself can state about his consciousness and thus proof the correctness of the obtained results at 100%—but cannot communicate it in a manner we understand due to his/her complete inability to communicate by any means we are used to. Nevertheless, we presented an approach that provides a good option to obtain a marker indicating the consciousness of a CLIS patient with a good probability. If this method is combined with competing methods as proposed in [19], it may significantly advance the solution of the consciousness detection problem in CLIS patients.

Acknowledgements Data was kindly provided by Prof. Dr. hc. mult. Niels Birbaumer and Dr. Ujwal Chaudhary from the Institute for Medical Psychology and Behavioral Neurobiology, University of Tübingen. We are grateful for providing the data to us.

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