# Analysis and Classification of Epilepsy Stages with Genetic Programming

Arturo Sotelo, Enrique Guijarro, Leonardo Trujillo*,
Luis Coria, and Yuliana Martínez

**Abstract.** Epilepsy is a widespread disorder that affects many individuals worldwide. For this reason much work has been done to develop computational systems that can facilitate the analysis and interpretation of the signals generated by a patients brain during the onset of an epileptic seizure. Currently, this is done by human experts since computational methods cannot achieve a similar level of performance. This paper presents a Genetic Programming (GP) based approach to analyze brain activity captured with Electrocorticogram (ECoG). The goal is to evolve classifiers that can detect the three main stages of an epileptic seizure. Experimental results show good performance by the GP-classifiers, evaluated based on sensitivity, specificity, prevalence and likelihood ratio. The results are unique within this domain, and could become a useful tool in the development of future treatment methods.

**Keywords:** Epilepsy Diagnosis, Genetic Programming, Classification.

## 1 Introduction

Epilepsy is a neurological disorder that causes chronic seizures as part of its symptomatology. Some estimates state that the number of people that suffer from

Arturo Sotelo
Departamento de Ingeniería Eléctrica y Electrónica, Instituto Tecnológico de Tijuana, Blvd. Industrial y Av. ITR Tijuana S/N, Mesa Otay C.P. 22500, Tijuana B.C., México
e-mail: soteloo@yahoo.com

Enrique Guijarro
Departamento de Ingeniería Electrónica, Universidad Politécnica de Valencia, Spain
e-mail: eguijarro@eln.upv.es

Leonardo Trujillo · Luis Coria · Yuliana Martínez
Doctorado en Ciencias de la Ingeniería, Departamento de Ingeniería Eléctrica y Electrónica, Instituto Tecnológico de Tijuana, Blvd. Industrial y Av. ITR Tijuana S/N, Mesa Otay C.P. 22500, Tijuana B.C., México
e-mail: {leonardo.trujillo.ttl,luis.coria,ysaraimr}@gmail.com

* Corresponding author.

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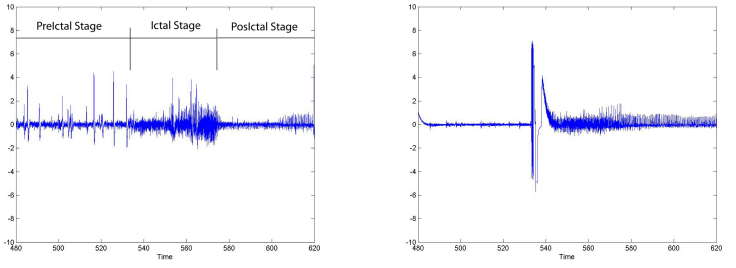
this disorder ranges between 11/100,000 to 134/100,000 [6], or that 1% to 5% of the general population experiments one or more seizures during their life-time [3, 20]. From the group of people with this disorder, two thirds can be treated by anti-epileptic medication and 7 or 8% can be cured by surgery [17]. Unfortunately, however, the symptomatology of the rest cannot be controlled by currently available therapies.

An epilepsy seizure is a sudden episode that disrupts mental functions, motor control, sensorial abilities and autonomic activity. This is caused by a paroxysmal malfunction of brain cells, which is considered an abnormal increase of neural synchrony [15]. Epilepsy can affect a patient's brain partially or completely, respectively inducing partial or generalized seizures [22]. A seizure develops over several basic stages [11], these are: (1) the Basal stage (2) the Pre-Ictal Stage, (3) the Ictal stage; and (4) the Post-Ictal stage. The Basal stage represents normal brain activity, the waveform of brain signals during this stage are characterized by a low amplitude and a relative high frequency. In the Pre-Ictal stage, an Electroencephalography (EEG) or Electrocorticogram (ECoG) can show considerable amplitude increase relative to the Basal stage, with spikes and transitory activity, but no distinguishable symptoms can be seen in a patient during this stage. The Ictal stage is when the seizure occurs, producing jerky movements, olfactory sensations and even the loss of consciousness, depending if it is focal or generalized, brain signals are distinguished by high amplitude discharges, a low frequency and a predominant rhythm. The last stage is called Pos-Ictal, where signal recordings show general amplitude depression and a gradual return towards the Basal stage when symptoms cease.

If an expert neurologist analyzes the EEG or ECoG signal of a patient undergoing an epileptic seizure he can identify the seizure stages as they occur over time. For instance, Figure 1(a) depicts an ECoG signal taken over an entire episode, where the three main stages of the seizure are clearly marked. From this example it is clear that each stage is characterized by a different signal morphology. While a human expert has no problem identifying each stage, to our knowledge an automatic method for stage detection has not been developed. Nonetheless, other works have focused on predicting the onset of a seizure by identifying specific signal features [1, 13, 25]. An important aspect of most works in this area is that they focus on a small number of test subjects. Primarily because different patients tend to exhibit different signal patterns, even if they all share a similar general structure [12]. Therefore, while each stage is identifiable when you analyze the time-series of a seizure as a whole, if only a single two-second segment is considered, for example, then determining the stage to which it belongs is not trivially done.

In this work, we present an approach that can automatically determine the stage to which a signal segment belongs. The problem is posed as a supervised learning task, where the system takes as input a signal sample of a certain duration and from this determines the corresponding epileptic stage. However, deriving automatic processing methods for these signals is definitely not a straightforward endeavor, given the complexities of the brain signals generated during a seizure [4, 12]. In this paper the task is solved using a Genetic Programming (GP) classifier, that analyzes




(a) (b)

**Fig. 1** ECoG signal of a level-5 seizure on Racine scale, showing how signal amplitude varies through time. **(a)** Deep recording through the stimulus electrode. **(b)** Seizure recorded by the cortex electrode.

basic statistical features of each signal and derives a non-linear mapping following a symbolic regression approach. Classifiers, similar to the ones derived here, could be used as computational tools that can assist a human expert during the analysis or diagnosis of epileptic signals. An even more ambitious goal could be to use these classifiers as part of an implanted device, that can monitor and react, in real-time, when a patient is experiencing the onset of specific stages of an epileptic seizure. However, such technological implementations are left as future lines of research.

The remainder of this paper proceeds as follows. Section 2 presents a brief introduction to Electrocorticogram signals from epileptic seizures. Then, Section 3 describes the ECoG dataset used in this study. Afterwards, Section 4 gives a formal description of the learning problem posed in this work and of the GP approach proposed to solve it. Section 3 presents the experimental setup and provides a detailed discussion of the main results. Finally, a summary of the paper and concluding comments are outlined in Section 5.

## 2 Epilepsy Signals

Normally, epileptic seizures occur spontaneously, a significant limitation to properly studying them. Therefore, in research work seizures are induced in a controlled experiment that use rodent test subjects, referred to as models. One of the most common is the amygdale kindling model, a model for temporal lobe epilepsy, the most common in human adults [19]. This model is used in the present work, since it is possible to induce self sustained seizures in rodents when required. This allows for the study of alternative treatments for drug-resistant human partial complex and secondarily generalized seizures [19].

In general, Electroencephalography (EEG) is the main tool for analysis and diagnosis of many neurological disorders. Brain activity produces a highly non-periodical signal with amplitude in the range of $0.5\mu V - 100\mu V$. Such signals can be detected by non-invasive methods when they are recorded at scalp level using EEG. However, EEG signals are normally contaminated by undesirable noise or artifacts produced by unrelated muscle or organ activity, which increases the difficulty of correctly interpreting such signals using automatic computational methods.

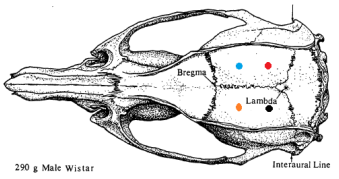
Less distorted signals can be obtained using intracranial recording methods through an Electrocorticogram (ECoG), which are far more amendable to precise analysis and clinical evaluations [8]. Intracranial detection can be accomplished by inserting needles within the brain at the required depths, these are called deep electrodes. Of course, the main drawback of such methods is the fact that they require surgical access to a patients brain, a strong limitation for human test subjects. However, an advantage is that electrodes are bidirectional, and can be used for both detection and direct stimulation of the brain. In the former case, brain activity during a seizure can be intracranially recorded, free of artifacts [28], using metallic electrodes inserted within the cortex (an ECoG signal). In the latter, an electrode can be used to stimulate the brain and, if done correctly, to induce a seizure, as will be described in the following section.

As stated above, an epileptic seizure exhibits various stages as it develops; here we focus on the Pre-Ictal, Ictal and Post-Ictal stages. This paper presents an approach to automatically discriminate between these three stages within an epileptic signal, based on the local dynamics and morphology of a recorded ECoG signal from elicited epileptic episodes.

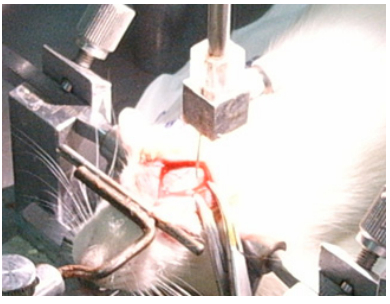
## 3 Experimental Data

It is normally unfeasible to record an epileptic seizure, since it is difficult to predict the onset of a seizure. Therefore, for research purposes artificially induced seizures provide valuable experimental data. Using animal models, it is possible to simulate chronical brain dysfunction that leads to epilepsy, a strategy that has allowed for research regarding the underlying causes and mechanisms behind epilepsy [9]. In particular, animal models are a valuable tool to study temporal lobe epilepsy [7, 19].

The Kindling model is used to study epilepsy that is induced by electrical impulses delivered to a previously healthy (non epileptic) animal. Epileptic conditions are achieved in the animal as the result of applying short duration electrical stimulus in the limbic regions of the brain, such as the amygdale or hippocampus. The amygdale kindling model in rats is considered the most appropriated for the study of alternative epilepsy treatments for partial and generalized seizures [2]. Through the Kindling model, spontaneous seizures are elicited by an electrical stimulus discharged directly to the brain of the rodent. The approach has several advantages, such as: first, precise focal activation; and second, a chronic epileptogenesis is reliably developed [22]. Kindling seizures are rated, depending on their symptoms,




(a)



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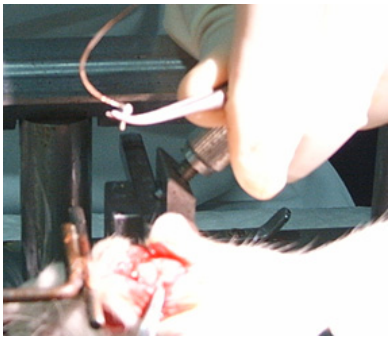

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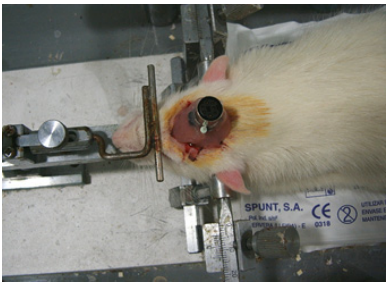



(d)

**Fig. 2** **(a)** Illustration of approximate stereotaxic locations of stimulus, recording, and reference electrodes in a adult male Wistar rat [23]. **(b)** Implantation of the stimulus electrode through the rat's skull using a stereotaxic fixture. **(c)** Implantation the cortical recording electrode. **(d)** Final connector assembled on top of the rat's skull.

into a five level scale, know as the Racine scale [24]. This scale rates seizure intensity, from focal to generalized, depending on the symptomatology exhibited by rats from the Wistar breed, where level-5 is the highest intensity. Symptom for the five levels are: (0) No seizure response; (1) Immobility, eye closure, twitching of vibrissae; (2) Head nodding associated with more severe facial clonus; (3) Clonus of one forelimb; (4) Bilateral forelimb clonus with rearing; and (5) Rearing and falling on the back accompanied by generalize clonic seizures. In the present study, level-5 seizures (generalized motor seizures) are used for the experimental analysis.

## *3.1 Signal Recording*

The electrode implants, the kindling experiments using live rodents (Wistar rats), and signal recording were carried out at the Centro de Investigación, Hospital General Universitario de Valencia, in Valencia, Spain. Stimulation and signal recording were achieved by inserting electrodes within the rodent's skull through symmetric

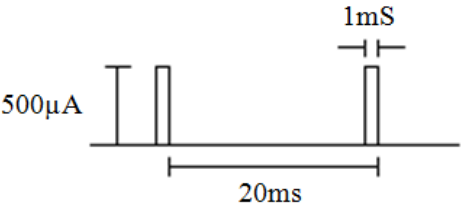



**Fig. 3** The stimulus signal applied to elicit an epileptic seizure on the rodent subject

burr holes at stereotaxic locations in accordance with [2, 14, 18]. Figure 2(a) shows the approximated stereotaxic location of the electrodes, where the black marks represent stimulus electrodes, orange are for reference, and blue and red represent the cortical frontal and occipital recording electrodes.

Stimulation was achieved through an electrode made of twisted pair of Teflon-coated 0.25 mm diameter stainless steel wires separated by 0.5 mm at the tip and 8 mm in length, and implanted through a burr hole, as shows in Figure 2(b). Two stainless steel screws served as cortical recording electrodes, as shown in Figure 2(c), these were attached to a connector assembly, as shown in Figure 2(d). After this process was done, the stimulation of rodent subjects began after 7 days.

The electric stimulation of the subjects brain tissue and deep recording of the epilepsy signal can be done after the electrodes are implanted and the connector is plugged in. Stimulation and recording of brain activity begins as soon as the rodent is connected, so the rodent does not remove the cable. The applied stimulus consist of a $500\mu$A @50Hz rectangular signal with a 5% duty cycle by 1$s$; the signal is depicted in Figure 3.

Electrical manifestations are of variable amplitude, with useful frequency components from 0.5 Hz to 60 Hz [26], and may find useful components up to 100 Hz [21] or 400 Hz [5]. For this work, the signal was bandpass filtered in a 0.5 Hz to 100Hz bandwidth, sampling rate was 256 Hz to avoid aliasing, using 12 bit resolution. The duration of a completely recorded seizure sometimes can be as much as 3 minutes. In some cases, more than a single stimulus needs to be applied to induce a seizure with a level-5 rating, since here we discard any seizure below this rating. Figure 1(a) shows an ECoG for a level-5 seizure.

Figure 1(a) presents the complete time-series record for a seizure, from the Pre-Ictal stage that begins at second 480 and ends at second 535. Then, the Ictal stage continues up to second 575, and finally the Post-Ictal stage represents the final part of the signal. The plot of 1(b) is the signal from the deep recording electrode, that is used as a reference to determine when the seizure is about to start. When the seizure is detected at the cortex level, this means that stimulus has produce an afterdischarge capable of stimulating the nearby neurons up to the cortex, producing a generalize seizure in the rodent. However, in some experiments the deep recording shows epileptic activity, but the cortex does not, which represents a local or focalized seizure.

## 4 Problem Statement

In this paper, the goal is to detect the three main seizure stages described above (Pre-Ictal, Ictal and Post-Ictal) given a short segment of a ECoG signal recorded using a cortex electrode. This problem can be posed as a classification task, where the signal segment represents a pattern $\mathbf{x} \in \mathbb{R}^n$, where $n$ is the total number of sample points given a particular signal duration. For instance, since the sampling rate during recording is 256 Hz, if we take a 2 second signal then $n = 512$. Then, it is possible to construct a supervised learning problem where a training set $\mathscr{X}$ of n-dimensional patterns with a known classification are used to derive a mapping function $g(\mathbf{x}) : \mathbb{R}^n \rightarrow M$, where $M$ are the three distinct classes, in this case the three epilepsy stages.

This work uses a single test subject, a single rodent on which the seizures are induced and the signals recorded. This is partially justified due to the intra-patient variability that is usually observed in epileptic seizures [12]. Nonetheless, future work will focus on deriving classifiers that generalize across multiple patients or possible groups of them.

For this test subject, call him subject $S_A$, a level-5 seizure is induced and recorded on five consecutive days, call them Day-1, Day-2, Day-3, Day-4 and Day-5. Afterwards, the signal is classified manually by a human expert, who specifies where each epilepsy stage begins and ends, this provides the ground-truth for the learning problem. The signal is divided into $N$ number of segments, each constituting a sample from the corresponding stage. All signal segments have the same duration, here we build two different datasets, using segments of 1 second and 2 seconds respectively. When the signal is divided, we allow for a slight overlap between consecutive segments, given by 20% of the total duration. Finally, it is important to state that signal segments that lie on two adjacent stages are removed from the dataset.

Then, the problem we pose can be stated as follows. The goal is to use the signal samples, or segments, from a single day, and use them as the learning data for the classifier. Then, the classifier is tested on the samples from the remaining four days. Therefore, the question is: if the signal from a single seizure is given, can it be used to train a classifier that is able to correctly detect the different signal stages from seizures from the same subject that are recorded on different days?

### *4.1 Proposal*

The above problem is solved using a Genetic Programming (GP) classification system. GP can be used in various ways to solve such supervised classification tasks, see for instance [10, 16]. However, the approach proposed by Zhang and Smart [29] is used here, referred to as the Probabilistic GP Classifier, or PGPC for short [27, 29]. In PGPC, it is assumed that the behavior of $h$ can be modeled using multiple Gaussian distributions, each corresponding to a single class [29]. The distribution of each class $\mathscr{N}(\mu, \sigma)$ is derived from the examples provided for it in set $\mathscr{X}$,

**Table 1** Parameters for the PGPC system used in the experimental tests

| Parameter | Description |
|---|---|
| *Population size* | 200 individuals. |
| *Generations* | 200 generations. |
| *Initialization* | *Ramped Half-and-Half*, with 6 levels of maximum depth. |
| *Operator probabilities* | Crossover $p_c = 0.8$; Mutation $p_\mu = 0.2$. |
| *Function set* | $\left\{+, -, *, /, \sqrt{}, sin, cos, log, x^y, \lvert\cdot\rvert, if\right\}$ |
| *Terminal set* | $\{x_1, ..., x_i, ..., x_P\}$ Where each $x_i$ is a dimension of the data patterns $\mathbf{x} \in \mathbb{R}^P$ |
| *Bloat control* | Dynamic depth control. |
| *Initial dynamic depth* | 6 levels. |
| *Hard maximum depth* | 20 levels. |
| *Selection* | Lexicographic parsimony tournament |
| *Survival* | Keep best elitism |

by computing the mean $\mu$ and standard deviation $\sigma$ of the outputs obtained from $h$ on these patterns. Then, from the distribution $\mathcal{N}$ of each class a fitness measure can be derived using Fisher's linear discriminant; for a two class problem it proceeds as follows. After the Gaussian distribution $\mathcal{N}$ for each class is derived, a distance is required. In [29], Zhang and Smart propose a distance measure between both classes as

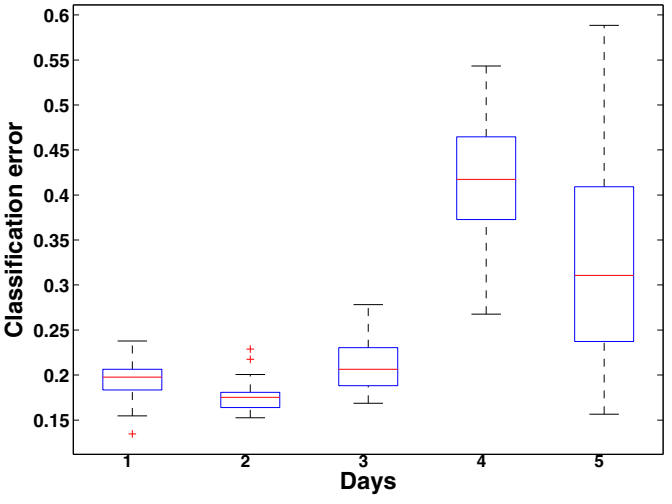
$$d = \frac{|\mu_1 - \mu_2|}{\sigma_1 + \sigma_2} , \tag{1}$$

where $\mu_1$ and $\mu_2$ are the means of the Gaussian distribution of each class, and $\sigma_1$ and $\sigma_2$ are their standard deviations. When this measure tends to 0, it is the worst case scenario because the mapping of both classes overlap completely, and when it tends to $\infty$, it represents the optimal case with maximum separation. To normalize the above measure, the fitness for an individual mapping $h$ is given by

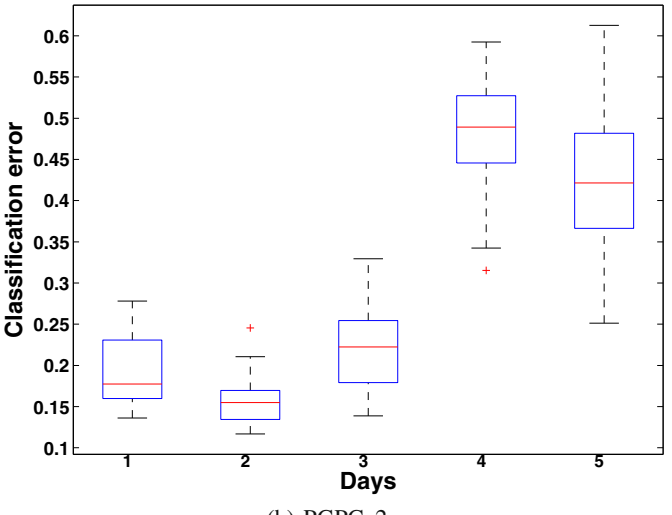
$$f_d = \frac{1}{1+d} . \tag{2}$$

After executing the GP, the best individual found determines the parameters for the Gaussian distribution $\mathcal{N}_i$ associated to each class. Then, a new test pattern $\mathbf{x}$ is assigned to class $i$ when $\mathcal{N}_i$ gives the maximum probability.

In summary, a GP classifier (PGPC) is trained using the epilepsy signal recorded during a single day, from a total of five different days, and then tested on the remaining days. The signal from each day is divided into segments of equal duration; two different partitions are built, the first has 1 second segments and the other uses segments with a duration of 2 seconds. The next section presents the experimental setup and main results.




(a) PGPC, 1s




(b) PGPC, 2s

**Fig. 4** Boxplots of the average classification error (y-axis), computed using different recording sessions for training (x-axis)

## 5 Experiments and Results

The PGPC algorithm uses a standard Koza-style GP, with a tree based representation, subtree-crossover and sub-tree mutation. The basic parameters are presented in Table 1. The terminal elements are basic statistical features computed for each signal segment $x$ that is to be classified. Specifically, the terminal set $T$ contains:

mean value $x_\mu$, median $x_m$, standard deviation $x_\sigma$, maximum $x_{max}$, minimum $x_{min}$ and skewness $x_s$.

The total number of experiments are summed up as follows. Two different segment lengths (1 and 2 seconds) and five different signals used for training (5 different recording days), a total of (2x2x5) 20 different configurations. Moreover, 30 different runs are performed to obtain statistically significant results.

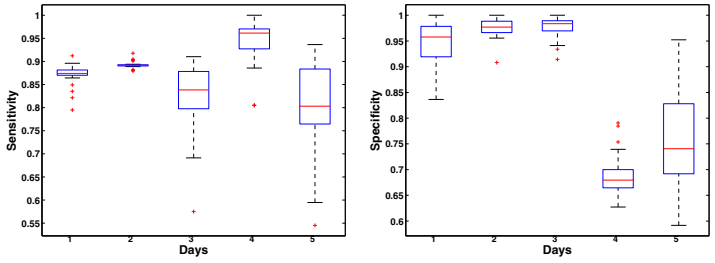
Figure 4 summarizes the results regarding the average test error for each configuration. The figure shows boxplots of the average classification error from each run, relative to the signal used for training (Day). The caption of plot states the GP algorithm used (PGPC) and the segment duration used to build the datasets (1 or 2 seconds). The algorithm is susceptible to the signal used for training, in general the signals from Day-4 and Day-5 produce the worst results. Also, signal length has a slight effect on classification error, with two second segments the classifier achieves better (less error) results. This difference does not seem to be substantial, but to maintain the following discussion compact we focus or analysis on classifier performance with 2 second segments.

To gain a deeper understanding of the performance achieved by the classifier, a detailed analysis of the results is presented using four standard performance indices: sensitivity, specificity, prevalence and likelihood ratio However, given the results shown in Figure 4, only the results for the 2 second segments are analyzed. These measures are derived from the confusion matrix (true positives (TP), true negatives (TN), false positives (FP), false negatives (FN)) generated by the classifier with respect to each class; each index is computed as follows:

- Sensitivity: $S = \dfrac{TP}{TP+FP}$ .
- Specificity: $Sp = \dfrac{TN}{FN+TN}$ .
- Prevalence: $P = \dfrac{TP+FP}{total}$ .
- Likelihood Ratio: $LR_+ = \dfrac{S}{1-Sp}$ .

Figures 5, 6 and 7 presents boxplots that summarize the results regarding the above performance indices computed for the PGPC classifier. Figures 5 corresponds to the values computed relative to the pre-ictal stage. Similarly, Figures 6 presents the values for the ictal stage, and Figures 7 corresponds to the post-ictal stage. Moreover, the following figures correspond to each index, sensitivity (a), specificity (b), prevalence (c) and likelihood ratio (d).

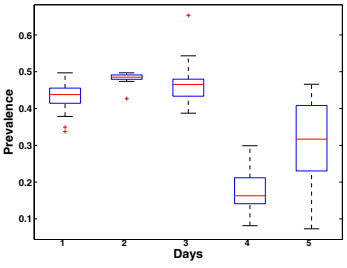
The results suggest that the GP classifier achieves good identification of epilepsy stages. These figures also show how performance depends on the signal used for training, with the best results achieved with the signals from Days 1 - 3, and the worst with Days 4 and 5. This result exhibits how seizures vary for individual subjects; nonetheless, the high performance achieved here is quite promising. This is confirmed by the high sensitivity and specificity achieved, with median values above 85% and 90% respectively for most configurations, a confident classification of



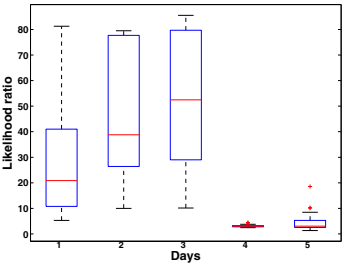

(a) Pre-Ictal




(b) Pre-Ictal

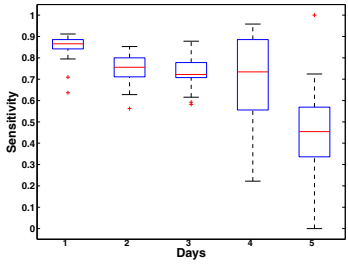



(c) Pre-Ictal

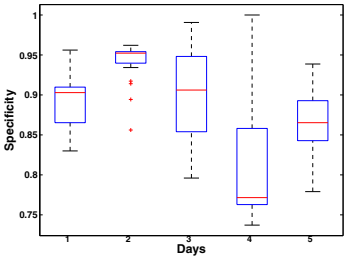



(d) Pre-Ictal

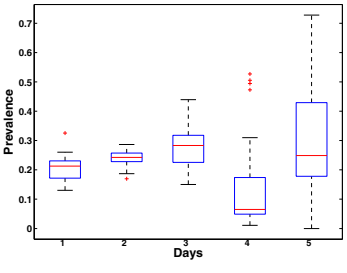
**Fig. 5** Boxplots that summarize the results for the PGPC classifier regarding Sensitivity (a), Specificity (b) , Prevalence (c) and Likelihood Ratio (d); with respect to the Pre-Ictal stage



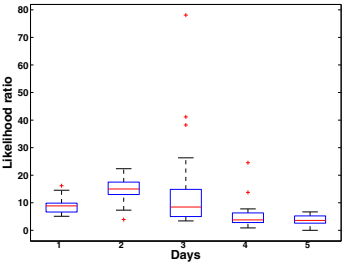

(a) Ictal




(b) Ictal

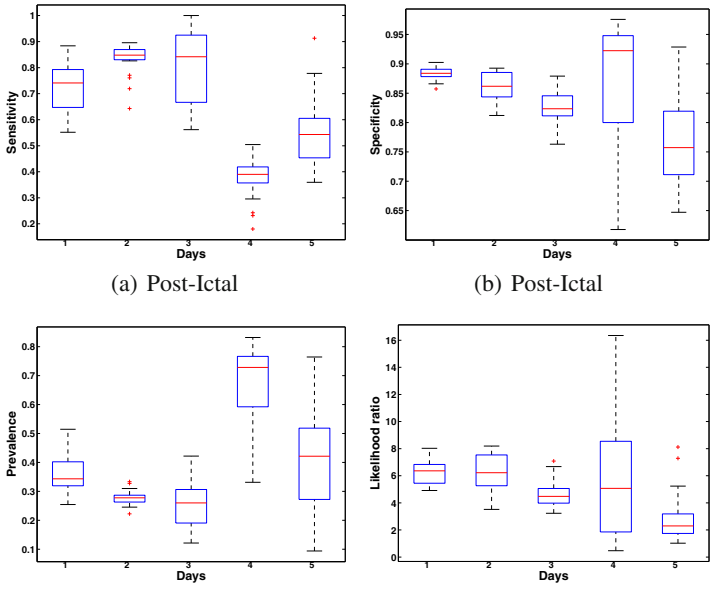



(c) Ictal




(d) Ictal

**Fig. 6** Boxplots that summarize the results for the PGPC classifier regarding Sensitivity 5 (a), Specificity (b) , Prevalence (c) and Likelihood Ratio (d); with respect to the Ictal stage




(a) Post-Ictal (b) Post-Ictal

(c) Post-Ictal (d) Post-Ictal

**Fig. 7** Boxplots that summarize the results for the PGPC classifier regarding Sensitivity (a), Specificity (b) , Prevalence (c) and Likelihood Ratio (d);with respect to the Post-Ictal stage

random signal segments. Meanwhile, the low prevalence values, between 20% and 60%, shows that GP classifier can discard samples with a high confidence. Finally, the likelihood ratio reaches values larger that unity for all stages, the most promising result. The worst results were seen for the Post-Ictal stage, mostly attributable to the similarity it exhibits with the Pre-Ictal stage. If instead of classifying a random segment, the time series was classified progressively, then this shortcoming could be resolved. In general, the results show that the signal features extracted by the GP classifiers are highly discriminative and representative of each epilepsy stage.

## 6 Summary and Conclusions

This paper presents an approach that can automatically detect the corresponding epilepsy stage of random signal segments recorded by means of Electrocorticogram (ECoG). This is done by posing a supervised learning problem, where an epileptic signal captured on a single day is used as training data, and the classifier is then tested on signal segments from five other recordings taken on different Days. The proposed approach is based on a GP-based classifier called the Probabilistic GP Classifier (PGPC) [29]. Experimental results are encouraging, based on the classification error, sensitivity, specificity, prevalence and likelihood ratio of the evolved classifiers. Moreover, since the classifiers are composed of basic mathematical

operations, given the terminal and functional primitives used, it is simple to implement them, in hardware or software, as part of an implanted device for real time monitoring or treatment. In general, these results are unique within the problem domain, and can become a useful tool in the development of future treatment technologies for epilepsy patients.

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