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## Highlights

- A new approach for regularity changes detection using ApEn is proposed.
- We propose the use of the maximum ApEn and its r value to discern between dynamics.
- Better discrimination capacity can be accomplished using this method.
- The combined estimators are more robust against noise than using them individually.

# Maximum approximate entropy and r threshold: a new approach for regularity changes detection

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#### 7 Abstract

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Approximate entropy (*ApEn*) has been widely used as an estimator of regularity in many scientific fields. It has proved to be a useful tool because of its ability to distinguish different system's dynamics when there is only available short-length noisy data. Incorrect parameter selection (embedding dimension *m*, threshold *r* and data length *N*) and the presence of noise in the signal can undermine the *ApEn* discrimination capacity. In this work we show that  $r_{max}$  (*ApEn*(*m*,  $r_{max}$ , *N*) = *ApEn*<sub>max</sub>) can also be used as a feature to discern between dynamics. Moreover, the combined use of *ApEn*<sub>max</sub> and  $r_{max}$  allows a better discrimination capacity to be accomplished, even in the presence of noise. We conducted our studies using real physiological time series and simulated signals corresponding to both low- and high-dimensional systems. When *ApEn*<sub>max</sub> is incapable of discerning between different dynamics because of the noise presence, our results suggest that  $r_{max}$  provides additional information that can be useful for classification purposes. Based on cross-validation tests, we conclude that, for short length noisy signals, the joint use of *ApEn*<sub>max</sub> and  $r_{max}$  can significantly decrease the misclassification rate of a linear classifier in comparison with their isolated use.

<sup>8</sup> *Keywords:* Non-linear dynamics, Approximate entropy, Chaotic time-series.

#### 9 **1. Introduction**

The concept of changing complexity has proved to be helpful to characterize and assess different phenomena in areas such as seismology, economy, mechanics, physiology, etc. [1, 2, 3, 4]. In the last 30 years this challenging endeavor has led researchers and practitioners to develop different methods conceived to

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estimate and understand such complexity changes and their relationship with physical and biological system dynamics. In the early nineties, Lipsitz et al. reported that the process of natural aging is attached to a decrease of complexity in the dynamics of physiological functions [5]. This results in a loss in the capacity of the organism to adapt to stress, making it more vulnerable to diseases.

Approximate entropy finds its origins in Kolmogorov-Sinai Entropy (K-S Entropy), defined as the mean 17 rate of information generated by a process [6, 7]. This measure is recognized for being a meaningful 18 parameter to describe the behavior of dynamical systems. In [8] Grassberger and Procaccia provided an 19 algorithm to calculate a lower bound for the K-S Entropy from a finite time series. Takens [9] and Eckmann 20 and Ruelle [7] modified this approach to directly evaluate the K-S Entropy. Motivated by Eckmann-Ruelle 21 Entropy, Pincus introduced the ApEn [10], providing a statistic to assess complexity from noisy short-length 22 data. For an N-dimensional time series, ApEn depends on two parameters: the Embedding Dimension (m) 23 and the *Threshold* (r). ApEn(m, r) and ApEn(m, r, N) can be seen respectively as a family of parametric 24 statistics and estimators, designed to measure the regularity of a system. ApEn has been widely used as a 25 non-linear feature to classify different dynamics, for example epileptic seizures [11, 12, 13] and sleep apnea 26 [14]. 27

Because of the bias introduced by counting self-matches and the finite data length (N), in [15, 16] the 28 authors assert that the estimator ApEn(m, r, N) lacks of consistency. To overcome this limitation, Richman 29 et al. proposed the Sample Entropy (SampEn) as a more consistent regularity measure [16]. However, both 30 ApEn and SampEn are highly dependent on the set of chosen parameters (m, r). Chon et al. [17] assert 31 that neither ApEn nor SampEn are accurate in measuring the signal's complexity when the calculations are 32 made with the values of m and r recommended in the literature [18]. Instead, the use of  $ApEn_{max}$ , i.e. 33 the maximum value of ApEn(m, r, N), with fixed m and N was proposed as a more consistent estimator of 34 system's complexity [17, 19, 20]. 35

The signal's noise level has an important influence on ApEn(m, r, N) estimation and therefore  $ApEn_{max}$ is also affected. Pincus asserts that the reliability in the calculations could be seriously undermined when the Signal to Noise Ratio (SNR) is below 3 dB [18]. To overcome this issue, some authors have proposed a pre-processing step, in which, techniques such as *Empirical Mode Decomposition* (EMD) [21, 22] or *Dyadic Wavelet Transform* (DWT) [23] have been used.

In this paper, we will show that  $r_{max}$  (*r* value at which  $ApEn(m, r, N) = ApEn_{max}$ ) brings useful information and can be also used as a feature for classification purposes. Furthermore, the use of  $ApEn_{max}$  combined with  $r_{max}$  can provide a more consistent method to discern between different dynamics even in presence of noise.

The remainder of this paper is organized as follows. In Section 2 we briefly recall the main approaches used for *ApEn* parameter selection and we present the methodology used in our simulations. In Section 3 the obtained results are summarized and discussed. Finally, in Section 4 the conclusions are presented.

#### 48 **2. Methods**

In order to estimate ApEn(r, m, N) for an *N*-dimensional time series  $\{u_1, u_2, \dots, u_N\}$ , given the parameters  $m, \tau \in \mathbb{N}$ , and  $r \in \mathbb{R}^+$ , the *m*-dimensional embedded vectors  $\mathbf{x}_i^m = [u_i, u_{i+\tau}, u_{i+2\tau}, \dots, u_{i+(m-1)\tau}]$ , with  $1 \le i \le N - (m-1)\tau$ , have to be considered. Then, the *ApEn* is defined as [10]:

$$ApEn(m, r, N) = \phi^{m}(r) - \phi^{m+1}(r),$$

where:

$$\begin{split} \phi^{m}(r) &= \frac{1}{N-(m-1)\tau} \sum_{\substack{i=1\\i=1}}^{N-(m-1)\tau} \ln C_{i}^{m}(r), \\ C_{i}^{m}(r) &= \frac{1}{N-(m-1)\tau} \sum_{\substack{j=1\\j=1}}^{N-(m-1)\tau} \theta\left(d\left(\boldsymbol{x}_{i}^{m}, \boldsymbol{x}_{j}^{m}\right) - r\right), \\ \theta\left(y\right) &= \begin{cases} 0 & \text{if } y > 0, \\ 1 & \text{otherwise,} \end{cases} \end{split}$$

and

$$d\left(\boldsymbol{x}_{i}^{m},\boldsymbol{x}_{j}^{m}\right) = \max\left\{\left|u_{i+k\tau}-u_{j+k\tau}\right|\right\}, \qquad 0 \leq k \leq m-1.$$

The ApEn measures the logarithmic likelihood that two points  $(x_i^m, x_j^m)$  that are close (within a distance 52 r) in a m-dimensional space, remain close in a (m + 1)-dimensional space. Greater (lesser) likelihood of 53 remaining close produces smaller (larger) ApEn values [24]. It is important to recall that ApEn(m, r) was 54 not conceived as an approximate value of E-R Entropy, therefore it can not certify chaos. However, its 55 scope relies on its ability to compare different types of dynamics [10]. Pincus asserts that, for a given 56 system, ApEn values can vary significantly with m and r [18]. For this reason, it can not be seen as an 57 absolute measure. Moreover, this situation emphasizes the importance of the parameters' selection to draw 58 conclusions from ApEn estimations. In order to make this paper self contained, we will review some results 59 for parameter selection. 60

#### 61 2.1. Embedding dimension (m)

The main purpose of embedding a time series is to unfold the projection to a state space that is represen-62 tative of the original system's space, i.e. a reconstructed attractor must preserve the invariant characteristics 63 of the original one [25]. Takens' embedding theorem gives sufficient conditions to accomplish this task 64 using any *m* bigger than twice the *Hausdorff dimension* of the chaotic attractor. The idea is to estimate the 65 minimum embedding dimension since a bigger m will lead to excessive computational efforts. Kennel et al. 66 proposed a parametric algorithm to determine the minimum embedding dimension, named False Nearest 67 Neighbours [26]. Its main disadvantage is that the results highly depend on the choice of the algorithm 68 parameters. A slightly different approach was proposed by Cao [27]. This method does not rely upon 69 subjective parameters other than the embedding lag. 70

Pincus has suggested to set m = 2 or m = 3 [15, 18]. That advice arises from the fact that, once *N* is set, high *m* values conduct to poor ApEn(m, r) estimations. This is due to the bias introduced by self-counting and the decreased number of vectors  $\mathbf{x}_i^m$  available to estimate  $C_i^m(r)$ . The aforementioned approach may be convenient when low-dimensional systems are studied. However, when the dimension is high, this criterion will lead to a poor reconstruction of the process' dynamics [28, 29], causing inconsistencies in presence of noise.

It is worthwhile noting that typical applications with *ApEn* have been conducted using the previously mentioned values of *m*. Aletti et al. set m = 2 to assess congenital heart malformation in children using Heart Rate Variability (HRV) signals [30]. Zarjam et al. use m = 2 and 3 to calculate ApEn(m, r) from electroencephalogram (EEG) signals to investigate changes in working memory load during the performance of a cognitive task with varying difficulty levels [31].

#### 82 2.2. Embedding Lag $(\tau)$

The objective of selecting  $\tau$  is to maximally spread the data in the phase space, removing redundancies and making fine features more easily discernible [29]. In most *ApEn* applications  $\tau$  is set to one. Kaffashi et al. [32] concluded that, for time series generated by nonlinear dynamics and whose *Autocorrelation Function* decays rapidly,  $\tau = 1$  is sufficient to provide a good estimation of signal complexity. However, for signals with long range correlation, a  $\tau$  equal to time occurrence of the first local minimum of the *Mutual Information Function* or to the time occurrence of the first zero crossing of the *Autocorrelation Function* can provide additional information [29, 32].

#### 90 2.3. Threshold (r)

As it was afore mentioned, the statistics ApEn(m, r) can vary significantly with r. Pincus suggests that r should lie between 0.1 – 0.2 times the standard deviation (*SD*) of the raw signal [33, 34]. The r value should be large enough, not only to avoid significant contribution from noise, but also to admit a reasonable number of  $x_i^m$  vectors being within a distance r. This would ensure an acceptable estimation of the  $C_i^m(r)$ probability [18]. However, with too large r values, ApEn(m, r) is unable to perform fine process distinctions and consequently, the r value selection will greatly depend on the application [15].

Although the later approach has been broadly applied [35, 36, 37], some authors assert that sometimes 97 this methodology leads to an incorrect assessment of complexity [17, 19, 20]. They proposed the use of 98  $ApEn_{max}$  as a better complexity estimator. One main issue arises from the fact that the calculation of 99  $ApEn_{max}$  requires high computational efforts. To overcome this limitation, a set of equations was proposed 100 to calculate a parameter  $\hat{r}_{max}$  as an approximation to  $r_{max}$  [17, 20]. Supported on experimental results with 101 HRV signals, Castiglioni et al. concluded that the use of  $ApEn_{max}$  seems to be a reasonable approach, 102 because this choice would allow the time series complexity to be better quantified than any other choice of r 103 [38]. On the other hand, Liu et al. observed that  $ApEn_{max}$  was incapable of distinguishing between groups 104 of healthy and heart failure subjects, in experiments with HRV signals. Further, since they found that  $\hat{r}_{max}$ 105 fails in estimating  $r_{max}$  for the Logistic map, they asserted that care must be taken when using  $\hat{r}_{max}$  [39]. In 106 a recent study, Boskovic et al. [40], present some evidence of  $ApEn_{max}$  instability. They observed that for 107 two time series, the estimated  $ApEn_{max}$  value suggests opposite results when data length decreases. There 108 are other algorithms conceived to reduce the computational effort of calculating the whole profile of ApEn 109 as a function of m and r [41, 42]. 110

#### 111 2.4. Simulations

In the presence of noise, the estimator  $ApEn_{max}$  could be incapable to discern between different dynamics. Here we address the hypothesis that  $r_{max}$  provides additional information valuable for the discrimination process. In other words, the use of both  $ApEn_{max}$  and  $r_{max}$  would increase the ability of discerning between different complexities in the case of noisy time series. To assess this hypothesis four simulations were conducted: three of them with synthetic signals and the last one with an EEG record.

As a first case the Mackey-Glass delay-differential equation was used [27]. Our aim is to assess these estimators on time series from a high-dimensional system [43]. This system have been used not only to study the behavior of complexity estimators on high-dimensions [8] but also to model the dynamics

Model	Equation	Model Parameters	ApEn Parameters
Mackey-Glass	$dx/dt = bx + (a\tilde{x})/(1 + \tilde{x}^{c})$ $\tilde{x} = x(t - \Delta)$	$c = \{4.5, 6\}$ a = 0.9 b = 0.3 $\Delta = 80$ $\Delta t = 1$	$m = \{2, 3, \dots, 20\}$ $r = \{0, 5 \times 10^{-5}, \dots, 0.035\}$ $\tau = 83$ N = 5000
Shilnikov's type	dx/dt = y dy/dt = z $dz/dt = \mu x - y - \varepsilon z - ax^{2} - bx^{3}$	$a = \{0.008, 0.2217\}$ $\varepsilon = 0.55$ $\mu = 0.65$ b = 0.65 $\Delta t = 0.2$	$m = \{2, 3, \dots, 20\}$ $r = \{0, 5 \times 10^{-5}, \dots, 0.035\}$ $\tau = 10$ N = 5000

Table 1. Simulations models and parameters.  $\Delta t$  stands for the time step used to obtain the numerical solutions. The upper bound of the *r* range is equal to the SD of the normalized signal.

of physiological control systems like the neurological system [43], the respiratory system [44] and the hematopoietic system [44].

Two sets of 240 realizations were produced for each value of the c parameter (see Table 1). Each realiza-122 tion with 25000 points has a different initial condition, randomly chosen from a  $\mathcal{U}(0, 0.01)$  distribution. In 123 order to avoid the influence of transients, the first 20000 points of each realization were discarded. The re-124 sulting signals (with length N = 5000) were normalized to have unitary energy. For two randomly selected 125 signals, one from each set, its Mutual Information Function was calculated. Then, the lag correspond-126 ing to each first local minimum was selected, and the  $\tau$  parameter was fixed as the largest between these 127 values. ApEn(m, r, N) was calculated for each signal, with m and r taking the values listed in Table 1 and 128  $ApEn_{max}$  and  $r_{max}$  were found from the ApEn(m, r, N) functions. Additionally an estimator of the minimum 129 embedding dimension was calculated for all signals using Cao's algorithm [27]. 130

With the goal of analyzing synthetic data from a system that resembles a particular physiological dynamics, a Shilnikov's type chaos model was considered as a second case. The same methodology as in the first case was adopted for the Shilnikov's type model using two values of the *a* parameter (see Table 1),



Fig. 1. EEG signal: (a) First pre-ictal and ictal episodes. (b) Second pre-ictal and ictal episodes.

which allow simulating EEG signals recorded during a seizure of petitmal epilepsy [45]. The initial conditions for each realization were selected from a  $\mathcal{U}(0, 0.01)$  distribution and the *x* variable was used for the calculations.

In order to evaluate our method in presence of noise, white Gaussian noise was added to each signal (Mackey-Glass and Shilnikov) with SNR = 5 dB and SNR = 0 dB. Then, all realization were normalized to have unitary energy and both  $ApEn_{max}$  and  $r_{max}$  were calculated as previously described. Table 1 summarizes the models and the parameters values used to obtain the time series as well as the parameter values used to calculate the ApEn.

A real physiological signal recorded using stereo electroencephalography (EEG) with eight multilead 142 electrodes (2 mm long and 1.5 mm apart) was studied. It was filtered and amplified using a 1-40 Hz band-143 pass filter. A four-pole Butterworth filter was used as anti-aliasing low-pass filter. This signal was digitized 144 at 256 Hz through a 10 bits A/D converter. A physician accomplished the analysis of pre-ictal and ictal data 145 by visual inspection of the EEG record. According to the visual assessment of the EEG seizure recording, 146 the patient presented an epileptogenic area in the hippocampus with immediate propagation to the girus 147 cingular and the supplementary motor area, on the left hemisphere. In Fig. 1, the EEG signal of two ictal 148 and two pre-ictal episodes corresponding to a depth electrode in the hippocampus is presented. All these 149 episodes contains 3000 data samples. The first pre-ictal and ictal episodes comprise the signal portions for 150



Fig. 2. Mackey-Glass model: mean and 95% confidence interval. Noiseless: (a)  $ApEn_{max}$ . (b)  $r_{max}$ . With SNR= 5 dB: (c)  $ApEn_{max}$ . (d)  $r_{max}$ .

 $n \in [1500, 4500]$  and  $n \in [5000, 8000]$  data points respectively. The second pre-ictal and ictal portions were selected for  $n \in [18000, 21000]$  and  $n \in [21400, 24400]$  respectively. Each of the data sets were normalized to have unitary energy and the  $\tau$  parameter was selected as described above among the four signals.  $ApEn_{max}$  and  $r_{max}$  were then calculated for  $2 \le m \le 20$ . Additionally, white Gaussian noise was added to the raw EEG signal with SNR = 5 dB (the actual *SNR* of the EEG signal is unknown) and  $ApEn_{max}$ 



Fig. 3. Shilnikov's type chaos model: mean and 95% confidence interval. Noiseless: (a) ApEn<sub>max</sub>. (b) r<sub>max</sub>. With SNR = 5 dB: (c)  $ApEn_{max}$ . (d)  $r_{max}$ . In (b) an enlarged view for m = 2 is presented.

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#### 3. Results and Discussion 157

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Fig. 2 summarizes the results obtained for the Mackey-Glass model simulations. The ApEnmax and  $r_{max}$  mean and 95% confidence interval (CI) are presented as functions of m for two different c parameter



Fig. 4. SNR= 5 dB,  $ApEn_{max}$  vs  $r_{max}$  plot: (a) Mackey-Glass model m = 2. (b) Mackey-Glass model m = 12. (c) Shilnikov's type model m = 2. (d) Shilnikov's type model m = 12.

values. The CIs were empirically obtained by sorting the  $ApEn_{max}$  and  $r_{max}$  values calculated from the 240 realizations and taking the 2.5% and the 97.5% quantiles as the lower and upper bound respectively. In Fig. 2a, it can be noticed that the curves of  $ApEn_{max}$  become closer as *m* increases, achieving the maximum distance at m = 2. On the contrary, in Fig. 2b it can be observed that the distance between the  $r_{max}$  curves becomes larger as *m* increases. Figs. 2c and 2d show the effect of noise over  $ApEn_{max}$  and  $r_{max}$  estimations. First, notice that, compared to noise free figures, the mean values of  $ApE_{max}$  and  $r_{max}$  are increased due to the addition of noise. Additionally, in both cases, the CIs are reduced. Finally, the  $ApEn_{max}$  and  $r_{max}$  curves for different *c* parameter values are closer to each other than in the case without noise. It is important to remark that, in presence of noise, while  $r_{max}$  is still able to discern between dynamics, the discrimination capacity of  $ApEn_{max}$  is highly reduced. In conclusion, these results suggest that  $r_{max}$  can bring useful information even in presence of noise.

Shilnikov's type chaos model results are presented in Fig. 3. In Fig. 3a, it can be noticed that it is 171 impossible to distinguish the two dynamics using  $ApEn_{max}$  calculated with m = 2. Nevertheless, embedding 172 the system in a higher dimension such as m = 3 (minimum embedding dimension), distinctions between 173 dynamics can be made. However, in Fig. 3b, it can be seen that for m = 2,  $r_{max}$  indicates a difference 174 between dynamics. The added noise has the same above mentioned influence over both  $ApEn_{max}$  and  $r_{max}$ 175 (see Figs. 3c and 3d). However, in this case the  $r_{max}$  curves are closer than those corresponding to the 176 Mackey-Glass system. From this simulation we can conclude that using  $ApEn_{max}$  or  $r_{max}$  independently 177 can be inconvenient for classification purposes. Instead, we propose to study the combined use of both 178 estimators for this task. 179

In order to illustrate the advantages of this new approach, Fig. 4 shows scatter plots of ApEnmax vs rmax 180 for both models with noise (SNR= 5 dB), using m = 2 and m = 12. In the presence of noise, it is enough 181 to set m = 2 and to use only  $ApEn_{max}$  to correctly differentiate the two dynamics from the Mackey-Glass 182 model (see Fig. 2c). However, in Fig. 4a it can be noticed that  $r_{max}$  provides additional information that can 183 make easier the classification process. A slightly different situation can be appreciated for the Shilnikov's 184 type dynamics. Fig. 4c shows that it is not possible to discern between classes using  $ApEn_{max}$  calculated 185 with m = 2. Nevertheless, with the information brought by  $r_{max}$ , the two classes can be separated in a more 186 suitable way. As presented before, when there is noise in the signal, the assessment of  $ApEn_{max}$  using an m 187 value equal or larger than the minimum embedding dimension could be more accurate and robust than just 188 setting m = 2. Cao's algorithm suggests that the minimum embedding dimension for both models should 189 be  $m \approx 12$ . Such large m value is the result of noise influence in the estimation of the systems' minimum 190 embedding dimension. The issue is that, for the Mackey-Glass model,  $ApEn_{max}$  losses its discrimination 191 capacity for high m values. Nonetheless, as can be appreciated in Fig. 4b, the two classes can be still 192 successfully separated using only  $r_{max}$ . On the other hand, Fig. 4d shows that for m = 12, the two different 193 dynamics from the Shilnikov's type model can be more conveniently clustered using  $ApEn_{max}$  than using 194

 $r_{max}$ . These results remark the importance of using both estimators together instead of each one individually. In addition to the Mackey-Glass and the Shilnikov's systems we introduce calculations of  $ApEn_{max}$ and  $r_{max}$  using dynamics from the Logistic map,  $x_{n+1} = Rx_n(1 - x_n)$ , in two chaotic regimes (R = 3.75, R = 3.95) with and without white Gaussian noise.  $ApEn_{max}$  and  $r_{max}$  were evaluated using the procedure aforementioned for  $2 \le m \le 20$  with  $\tau = 1$  and N = 5000.

With the goal of quantitatively verify the proficiency of  $ApEn_{max}$  and  $r_{max}$  as classification features, 200 we perform a 10-fold cross-validation using linear support vector machines (SVMs). We choose a linear 201 classifier given that its simplicity will disclose the real quality of the features. The basic idea behind the 202 SVMs is to separate the classes using the optimal hyperplane (the linear decision function that maximizes 203 the distance between the closest points of different classes to the hyperplane) [46]. In Fig. 5 the Misclassi-204 fication Rates (MR) for three classifiers as functions of m and different noise levels (noiseless, SNR= 5 dB 205 and SNR=0 dB) are presented. The first classifier uses only  $ApEn_{max}$  as input feature, the second one uses 206 only  $r_{max}$ , and the third one uses jointly both estimators. 207

For the noiseless Mackey-Glass system, it can be seen in Fig. 5a that the MR of the first classifier 208 increases with m, achieving its maximum (0.065) for m = 19. Further, the second classifier presents a non-209 zero MR only for  $m \ge 15$ . The MR for the third classifier is zero for  $0 \le m \le 14$  with a maximum value 210 of 0.006 at m = 15. A similar behavior can be observed for the Mackey-Glass model immersed in noise 211 (SNR= 5 dB). In contrast with the noiseless case, in Fig. 5b it is shown that the MR of the classifier which 212 uses only  $ApEn_{max}$  has been greatly increased. Additionally, using only  $r_{max}$ , the classifier has non-zero 213 MR for  $2 \le m \le 4$ . Nevertheless, the MR of the classifier that uses both estimators still remains equal to 214 zero for  $2 \le m \le 4$  values. For the case in which the SNR= 0 dB (Fig. 5c), it can be noticed that the MR 215 of the third classifier is always below or equal to the lowest MR between the other two classifiers. The last 216 results attest that, as an ensemble,  $ApEn_{max}$  and  $r_{max}$  provide features that are robust against noise. 217

Regarding the results for the noiseless Shilnikov's model, it is shown in Fig. 5d that, for  $3 \le m \le 11$  the MR of the first classifier is lower than the second classifier's MR. For m = 2 as well as for  $12 \le m \le 20$ , the last statement is reversed. However, the MR for the third classifier remains below the MR of the other two ones, being zero for  $4 \le m \le 11$  and for  $16 \le m \le 20$ . Additionally, from Fig. 5e it can be noticed that for all *m* values the MR of the third classifier is always below or equal to the lowest MR value between the other two classifiers, being zero for  $8 \le m \le 10$  and 0.004 for m = 12. For the *SNR*= 0 dB case, it can be observed in Fig. 5f that for  $m \ge 8$  very low MR values are achieved by the first and third classifiers, being



Fig. 5. 10-fold cross-validation misclassification rate with a linear *SVM* classifier. Mackey-Glass model: (a) noiseless. (b) SNR= 5 dB. (c) SNR= 0 dB. Shilnikov's type model: (d) noiseless. (e) SNR= 5 dB. (f) SNR= 0 dB. Logistic map: (g) noiseless. (h) SNR= 5 dB. (i) SNR= 0 dB.

 $z_{225}$  zero for  $10 \le m \le 15$ .

Very similar results were achieved with the logistic map (Figs. 5g, 5h, 5i). The MR of the classifier that uses in conjunction  $ApEn_{max}$  and  $r_{max}$  is zero for all *m* values in the noiseless case and for  $m \ge 3$  in the *SNR*=5 dB case. From Fig. 5i it can be seen that the MR of the third classifier is below the MR of the other classifiers for all *m* values, being zero for m = 8 and m = 9 and achieves a very low values for  $m \ge 5$ . This results lead us to think about the usefulness of these estimators to discriminate dynamics from discrete-time non-linear systems.

It is important to notice that when these three systems were immersed in high levels of noise (see Figs. 5c, 5f and 5i) the worst results were achieved for low *m* values (specially for m = 2). This suggests that increasing the embedding dimension could be beneficial for the discrimination process. As a conclusion, these results highlight the complementary relationship between both estimators and the benefits of being used together. It is also important to observe that the use of both estimators enlarges the range of *m* values that can be selected to achieve a good classification performance in presence of noise. Nonetheless, using an estimate of the minimum embedding dimension can be a wise choice (see Fig. 5c and 5f for m = 12).

There is an interesting fact in these results concerning the presence of noise in the time series. As it was 239 discussed before, the addition of noise not only decreases the distance of  $ApEn_{max}$  and  $r_{max}$  curves between 240 different dynamics but it also reduces both estimators' CI. The trade-off between these two phenomena is 241 more evident as the SNR is reduced. In Figs. 5b and 5c, it can be seen that for  $m \ge 4$  the MR of the first 242 classifier is larger for SNR = 5 dB than for SNR = 0 dB. As a consequence of this trade-off, the distributions 243 of  $ApEn_{max}$  values for two different dynamics are more overlapped in the case with SNR= 5 dB than when 244 SNR = 0 dB. The last statement can be verified comparing the Battacharyya coefficient ( $B_c$ ) [47] between 245 the  $ApEn_{max}$  distributions of different dynamics for different SNRs. For two density functions p and q over 246 the same domain X, this coefficient is defined as  $B_c(p,q) = \sum_{x \in X} \sqrt{p(x)q(x)}, 0 \le B_c \le 1$ , being zero if 247 p(x) and q(x) do not overlap. The  $B_c$  coefficients between  $ApEn_{max}$  distributions (m = 19) for SNR = 5 dB 248 and SNR=0 dB are 0.91 and 0.53 respectively. This fact explains why the MR of this classifier is lower 249 for SNR = 0 dB than for SNR = 5 dB when high m values are used with systems like Mackey-Glass and 250 Shilnikov's. 251

An important topic that must be considered in the calculation of  $ApEn_{max}$  and  $r_{max}$  is the data length. When the time series is short, the choice of large *m* and  $\tau$  values can be harmful because the estimation of conditional probabilities becomes unreliable [10, 15]. However, there is another issue that can alter their



Fig. 6. Misclassification rate as a function of the data length. Mackey-Glass model: (a) noiseless. (b) SNR= 5 dB. (c) SNR= 0 dB. Logistic map: (d) noiseless. (e) SNR= 5 dB. (f) SNR= 0 dB.

estimation and it is related to the use of small *m* values.

It is known that poor state space reconstructions are obtained when the system is embedded with a m256 value smaller than the system's minimum embedding dimension, and such situation brings to the occurrence 257 of false neighbours [28], i.e. points that are close due to a low embedding dimension rather than because of 258 the system's dynamics. Given that the estimation of conditional probabilities is based on counting neigh-259 bours' occurrences, an appropriate selection of the m value demands to take into account an estimation of 260 the minimum embedding dimension [29]. With the aim of assess the behavior of our method as a function 261 of the data length, the next simulation was conducted over the Logistic map and the Mackey-Glass system. 262 Two sets of 30 realizations were built. Each set was obtained using a different value of the R parameter 263 for the Logistic map and, of the c parameter for the Mackey-Glass system. Each signal of these sets were 264 normalized to have unitary energy. For the Logistic map  $ApEn_{max}$  and  $r_{max}$  were estimated with m =265  $[2, 3, 8, 20], \tau = 1$  and  $N = [0.5, 1, 2, 3, 4, 5, 8, 10] \times 10^3$ . For the Mackey-Glass system these estimators were 266

evaluated with m = [2, 3, 12, 20],  $\tau = 83$  and  $N = [1, 2, 3, 5, 8, 10, 15, 20] \times 10^3$ . Then, the misclassification rate of a linear SVM classifier that uses both estimators as features was computed using *Leave one Out* cross-validation. Additionally, the same procedure was used over the same signals contaminated with white Gaussian additive noise (*SNR*= 5 dB and *SNR*= 0 dB). It is important to mention that the values of m = 8and m = 12 were suggested by the Cao's algorithm [27] as minimum embedding dimensions for the noisy signals (*SNR*= 0 dB) from the Logistic map and, from the Mackey-Glass system respectively. For the Mackey-Glass system the calculations with m = 20 were made for all N values except N = 1000.

In Fig. 6 it is shown the misclassification rate calculated for both systems as a function of N and the noise level. In Fig. 6a are shown the results for the noise free Mackey-Glass system. It can be observed that for small data length values the biggest errors are achieved using m = 20 (N = 2000) and m = 12(N = 1000); this is a consequence of the reduced amount of information available to estimate the conditional probabilities. Nevertheless, as N is increased, the error for all m values goes to zero. It must be noticed that for m = 2 and m = 3 the error is zero for all N values.

On the other hand Fig. 6b shows that, compared with the noiseless case, for m = 2 (at N = 1000) and 280 m = 3 (at N = 2000) the error has increased its value from zero, whereas the error for m = 12 and m = 20281 has decreased its values to zero for N = 2000. Observe that the error is zero from  $N \ge 3000$  regardless the 282 value of m. From Fig. 6c it can be seen that, excluding the error (equal to 0.48) for m = 12 at N = 1000, the 283 biggest error is accomplished using m = 2 followed by the one obtained with m = 3 for  $1000 \le N \le 8000$ . 284 However, the error for m = 12 and m = 20 is always lesser or equal to the error achieved with m = 2 or 285 m = 3, moreover, it is zero starting from N = 3000. Comparing Figs. 6a and 6c for m = 2 and m = 3 it is 286 clear that, for small N values, a poor state space reconstruction added to the presence of noise deteriorates 287 the discrimination capacity of  $ApEn_{max}$  and  $r_{max}$ . 288

For the noiseless Logistic map (Fig. 6d) it can be observed that for N = 500 the biggest error (0.08) 289 belongs to the estimators calculated with m = 20 followed by the error calculated with m = 2 (0.017). 290 However, for m = 3 and m = 8 the error is zero. Moreover, as N is increased, the error remains equal to zero 291 for all m values. It can be seen Fig. 6e that the biggest error is achieved with m = 2 for all N values except 292 N = 10000. Instead, for m = 8 the error is equal to zero for all N values. It is worth to mention that for all 293 N values the error obtained with m = 8 and m = 20 is always below or equal the error attain with m = 2 and 294 m = 3. From Fig. 6f it can be noticed that using m = 2 produces the worst classification error regardless the 295 value of N and the best results are accomplished using m = 8 and m = 20 for almost all N values. 296

Based on these results we can conclude that in the  $ApEn_{max}$  and  $r_{max}$  estimation's process it is highly 297 recommended to keep in mind that there exists a trade-off between m and N, and special attention is needed 298 in the presence of noise. When data length is short and there is not noise in the signal, relative small 299 m values provides the best performance. However, in presence of noise, it would be wise either to use an 300 estimation of the system's minimum embedding dimension whenever it is possible, or to use a value as close 301 as possible to it when the data length is a limitation. It must also be considered that in real applications, 302 such as epileptic seizures' detection, the duration of some events is only of a few samples: for example 303 absence seizures often last less than 5 seconds [48], which corresponds to 1280 samples using a standard 304 sampling frequency of 256 Hz. Although for small N values there is not guarantee of an accurate estimation 305 of  $ApEn_{max}$  nor  $r_{max}$  with relative high m values. The results here presented show that using m values above 306 2 or 3 can increase the discrimination capacity of these estimators, specially in presence of noise. 307

The studies conducted on the EEG recording provided similar results to those obtained with the previous simulations. In Fig. 7 are presented the  $ApEn_{max}$  and  $r_{max}$  curves as functions of *m* for two ictal episodes and their respective pre-ictal segments. The distances (relative to the scale) between the  $ApEn_{max}$  curves of each ictal and its corresponding pre-ictal episodes are small for all the *m* values, as can be observed in Fig. 7a. On the contrary, Fig. 7b suggests that  $r_{max}$  can be used to discriminate between dynamics. Decreasing the *SNR* tends to reduce the distance between  $ApEn_{max}$  and  $r_{max}$  curves (see Figs. 7c and 7d). However, for high *m* values, the information given by  $r_{max}$  can be useful to distinguish between dynamics.

It is worth to mention that, for this signal and with these estimators, it is difficult to separate the ictal and pre-ictal episodes as isolated groups. However, it is possible to state differences between an ictal episode and its corresponding pre-ictal one. This result leads us to think that a suitable approach to detect ictal episodes from EEG signals, using these estimators, should be one in which their temporal evolution could be evaluated.

In order to assess this idea, we corrupted the EEG signal with white Gaussian noise (SNR= 5 dB) and we considered sliding windows of length N = 1000, shifted 128 data points. Each window was normalized to have unitary energy.  $ApEn_{max}$  and  $r_{max}$  were estimated using  $\tau = 10$  for  $2 \le m \le 6$ . With these results we proceed as follows: first, we built the matrices  $C^A$  and  $C^R$ , where the entry  $C^A_{k,i}$  was the value of  $ApEn_{max}$  calculated with the *i*-th value of *m* for the *k*-th window. The matrix  $C^R$  was built alike with the  $r_{max}$  values. Each matrix was statistically normalized (zero mean and unitary SD) by columns. Observe that the temporal evolution of  $ApEn_{max}$  and  $r_{max}$  calculated with the *i*-th *m* value can be evaluated by looking



Fig. 7. EEG signal. Two ictal episodes and their respective pre-ictal segments. Raw signal: (a)  $ApEn_{max}$ . (b)  $r_{max}$ . SNR= 5 dB: (c)  $ApEn_{max}$ . (d)  $r_{max}$ .

the *i*-th column of the  $C^A$  and  $C^R$  matrices respectively. A third matrix named  $C^{AR}$  was conformed by the horizontal concatenation of the above mentioned matrices:  $C^{AR} = (C^A | C^R)$ . Next, we performed a Principal Component Analysis (*PCA*) over each matrix. The first principal component (1<sup>st</sup>PC) can be thought as a summary that best represents the information collected by these estimators through all *m* values. Finally, an algorithm for detection of abrupt mean changes (*CUSUM*) was applied on the 1<sup>st</sup>PC of



Fig. 8. Icatal episodes detection using  $ApEn_{max}$  and  $r_{max}$  from an EEG signal with additive noise (*SNR*= 5 dB): (a) EEG signal. (b) CUSUM over the first PC on the  $C^A$ ,  $C^R$  and  $C^{AR}$  matrices. The ictal episodes can be found between vertical dased lines.

each matrix [49]. The target mean and the reference value were fixed as the average of the first twenty data points and two times their *SD*, respectively.

In Fig. 8 are presented the EEG signal with the four ictal episodes marked between vertical dashed 334 lines (Fig. 8a) and the results of the CUSUM algorithm applied over the 1<sup>st</sup>PC of each matrix (Fig. 8b). It 335 can be observed in Fig. 8b that all ictal episodes can be detected using the information contained in each 336 matrix. Nevertheless, while some ictal episodes are better detected with ApEnmax, others are better detected 337 with  $r_{max}$ . On the other hand, a more consistent identification of ictal episodes can be achieved using in 338 conjunction both estimators. These results suggest that, with the information provided by both  $ApEn_{max}$ 339 and  $r_{max}$  for different m values, the ability to discriminate between different dynamics can be increased (even 340 in presence of noise), since changes that can not be identified in the temporal evolution of one estimator 341 could be identified in the temporal evolution of the other one. It must be remarked that these findings only 342 suggest the suitability of jointly use both estimators to detect ictal episodes from EEG signals. Further 343 experiments with a large data base will be conducted in future works to statistically assess the performance 344 of the proposed method to detect complexity changes in real signals. 345

#### 346 **4. Conclusions**

347

The Approximate entropy has been recognized by its ability to distinguish between different system's

dynamics when short-length data with moderate noise are available. However, it is also known that high 348 noise levels and incorrect parameter selection can undermine its discrimination capacity. In order to over-349 come these difficulties, in this paper we have proposed a method based on the use of  $r_{max}$  along with 350 ApEnmax to discern between different dynamics. Using signals from real physiological and from simulated 351 low- and high-dimensional systems, with and without noise, we have studied the behavior of  $ApEn_{max}$ 352 and  $r_{max}$  as functions of the embedding dimension, the data length and the noise level. The results indi-353 cate that, even in presence of noise,  $r_{max}$  provides valuable information that can be used for classification 354 purposes. Furthermore, as these estimators vary with m, there is a complementary relationship between 355 them, which strengthens the idea of using  $ApEn_{max}$  combined with  $r_{max}$  to distinguish between dynamics. 356 Cross-validation simulations have demonstrated that the jointly use of both estimators as input features, sig-357 nificantly decreases the misclassification rate of a simple linear classifier. Moreover, the conjoint use of both 358 estimators enlarges the range of m values that can be chosen to achieve a good classification performance. 359 Concerning the data length, we have shown that for short-length signals good discriminating features can be 360 achieved using relative small m values if there is no noise. However, in presence of noise the discrimination 361 capacity of  $ApEn_{max}$  and  $r_{max}$  can be increased using m values above 2 or 3. Our results encourage the use 362 of an estimation of the system's minimum embedding dimension when it is possible, or the use of a close 363 enough value when the data length is a limitation. We assert that as well as  $ApEn_{max}$ , the estimator  $r_{max}$  can 364 also be utilized to discern between dynamics even in the presence of noise. Moreover, the use of  $r_{max}$  has 365 shown to be helpful in such cases when  $ApEn_{max}$  is unable to contrast between processes that are immersed 366 in noise. The link between  $r_{max}$  and system complexity will be addressed in future studies, to reveal the 367 nature of this relationship and its physical meaning. 368

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#### 372 References

- S. M. Potirakis, G. Minadakis, K. Eftaxias, Analysis of electromagnetic pre-seismic emissions using Fisher information and
   Tsallis entropy, Physica A: Statistical Mechanics and its Applications 391 (1) (2012) 300–306.
- F. Isik, An entropy-based approach for measuring complexity in supply chains, International Journal of Production Research
   48 (12) (2010) 3681–3696.

377	[3]	Y. He, J. Huang, B. Zhang, Approximate entropy as a nonlinear feature parameter for fault diagnosis in rotating machinery,
378		Measurement Science and Technology 23 (4) (2012) 045603.
379	[4]	D. E. Vaillancourt, K. M. Newell, Changing complexity in human behavior and physiology through aging and disease,
380		Neurobiology of Aging 23 (1) (2002) 1–11.
381	[5]	L. A. Lipsitz, A. L. Goldberger, Loss of complexity and aging, Journal of the American Medical Association 267 (13) (1992)
382		1806–1809.
383	[6]	A. Kolmogorov, New metric invariant of transitive dynamical systems and endomorphisms of Lebesgue spaces, Doklady of
384		Russian Academy of Sciences 119 (N5) (1958) 861–864.
385	[7]	J. P. Eckmann, D. Ruelle, Ergodic theory of chaos and strange attractors, Reviews of Modern Physics 57 (3) (1985) 617–656.
386	[8]	P. Grassberger, I. Procaccia, Estimation of the Kolmogorov entropy from a chaotic signal, Physical review A 28 (4) (1983)
387		2591–2593.
388	[9]	F. Takens, Mechanical and gradient systems: local perturbations and generic properties, Boletim da Sociedade Brasileira de
389		Matemática 14 (2) (1983) 147–162.
390	[10]	S. M. Pincus, Approximate entropy as a measure of system complexity, Proceedings of the National Academy of Sciences
391		88 (6) (1991) 2297–2301.
392	[11]	U. R. Acharya, F. Molinari, S. V. Sree, S. Chattopadhyay, KH. Ng, J. S. Suri, Automated diagnosis of epileptic EEG using
393		entropies, Biomedical Signal Processing and Control 7 (4) (2012) 401-408.
394	[12]	V. Srinivasan, C. Eswaran, N. Sriraam, Approximate entropy-based epileptic EEG detection using artificial neural networks,
395		IEEE Transactions on Information Technology in Biomedicine 11 (3) (2007) 288–295.
396	[13]	C. Shen, C. Chan, F. Lin, M. Chiu, J. Lin, J. Kao, C. Chen, F. Lai, Epileptic seizure detection for multichannel EEG signals
397		with support vector machines, in: IEEE 11th International Conference on Bioinformatics and Bioengineering, 2011, pp.
398		39–43.
399	[14]	U. R. Acharya, E. CP. Chua, O. Faust, TC. Lim, L. F. B. Lim, Automated detection of sleep apnea from electrocardiogram
400		signals using nonlinear parameters, Physiological Measurement 32 (3) (2011) 287.
401	[15]	S. M. Pincus, A. L. Goldberger, Physiological time-series analysis: what does regularity quantify?, American Journal of
402		Physiology-Heart and Circulatory Physiology 266 (4) (1994) H1643-H1656.
403	[16]	J. S. Richman, J. R. Moorman, Physiological time-series analysis using approximate entropy and sample entropy, American
404		Journal of Physiology-Heart and Circulatory Physiology 278 (6) (2000) H2039–H2049.
405	[17]	K. Chon, C. Scully, S. Lu, Approximate entropy for all signals, IEEE Engineering in Medicine and Biology Magazine 28 (6)
406		(2009) 18–23.
407	[18]	S. Pincus, I. Gladstone, R. Ehrenkranz, A regularity statistic for medical data analysis, Journal of Clinical Monitoring 7 (4)
408		(1991) 335–345.
409	[19]	X. Chen, I. Solomon, K. Chon, Comparison of the use of approximate entropy and sample entropy: applications to neural
410		respiratory signal, in: 27th Annual International Conference of the Engineering in Medicine and Biology Society, 2005, pp.
411		4212–4215.
412	[20]	S. Lu, X. Chen, J. K. Kanters, I. C. Solomon, K. H. Chon, Automatic selection of the threshold value r for approximate
413		entropy, IEEE Transactions on Biomedical Engineering 55 (8) (2008) 1966-1972.
414	[21]	S. Alam, M. I. H. Bhuiyan, Detection of epileptic seizures using chaotic and statistical features in the EMD domain, in:

415		Annual IEEE India Conference, 2011, pp. 1–4.
416	[22]	L. Jianxin, W. Husheng, T. Jie, Feature extraction and application of engineering non-stationary signals based on EMD-
417		approximate entropy, in: International Conference on Computer, Mechatronics, Control and Electronic Engineering, Vol. 5,
418		2010, pp. 222–225.
419	[23]	H. Ocak, Automatic detection of epileptic seizures in EEG using discrete wavelet transform and approximate entropy, Expert
420		Systems with Applications 36 (2) (2009) 2027–2036.
421	[24]	S. Pincus, Approximate entropy: a complexity measure for biological time series data, in: Proceedings of the IEEE Seven-
422		teenth Annual Northeast Bioengineering Conference, 1991, pp. 35–36.
423	[25]	O. Faust, M. G. Bairy, Nonlinear analysis of physiological signals: a review, Journal of Mechanics in Medicine and Biology
424		12 (04) (2012) 1240015.
425	[26]	M. B. Kennel, R. Brown, H. D. I. Abarbanel, Determining embedding dimension for phase-space reconstruction using a
426		geometrical construction, Physical Review A 45 (6) (1992) 3403–3411.
427	[27]	L. Cao, Practical method for determining the minimum embedding dimension of a scalar time series, Physica D: Nonlinear
428		Phenomena 110 (1–2) (1997) 43–50.
429	[28]	A. Wolf, J. B. Swift, H. L. Swinney, J. A. Vastano, Determining Lyapunov exponents from a time series, Physica D: Nonlinear
430		Phenomena 16 (3) (1985) 285–317.
431	[29]	M. Small, Applied Nonlinear Time Series Analysis: Applications in Physics, Physiology and Finance, World Scientific, 2005.
432	[30]	F. Aletti, M. Ferrario, T. Almas de Jesus, R. Stirbulov, A. Borghi Silva, S. Cerutti, L. Malosa Sampaio, Heart rate variability
433		in children with cyanotic and acyanotic congenital heart disease: analysis by spectral and non linear indices, in: Annual
434		International Conference of the IEEE Engineering in Medicine and Biology Society, 2012, pp. 4189-4192.
435	[31]	P. Zarjam, J. Epps, N. Lovell, F. Chen, Characterization of memory load in an arithmetic task using non-linear analysis of
436		EEG signals, in: Annual International Conference of the IEEE Engineering in Medicine and Biology Society, 2012, pp.
437		3519–3522.
438	[32]	F. Kaffashi, R. Foglyano, C. G. Wilson, K. A. Loparo, The effect of time delay on approximate and sample entropy calcula-
439		tions, Physica D: Nonlinear Phenomena 237 (23) (2008) 3069–3074.
440	[33]	S. M. Pincus, Assessing serial irregularity and its implications for health, Annals of the New York Academy of Sciences
441		954 (1) (2001) 245–267.
442	[34]	S. M. Pincus, D. L. Keefe, Quantification of hormone pulsatility via an approximate entropy algorithm, American Journal of
443		Physiology - Endocrinology And Metabolism 262 (5) (1992) E741-E754.
444	[35]	D. Sapoznikov, M. H. Luria, M. S. Gotsman, Detection of regularities in heart rate variations by linear and non-linear analysis:
445		power spectrum versus approximate entropy, Computer Methods and Programs in Biomedicine 48 (3) (1995) 201-209.
446	[36]	S. M. Pincus, E. F. Gevers, I. C. Robinson, G. v. d. Berg, F. Roelfsema, M. L. Hartman, J. D. Veldhuis, Females secrete growth
447		hormone with more process irregularity than males in both humans and rats, American Journal of Physiology - Endocrinology
448		And Metabolism 270 (1) (1996) E107–E115.
449	[37]	S. M. Pincus, T. Mulligan, A. Iranmanesh, S. Gheorghiu, M. Godschalk, J. D. Veldhuis, Older males secrete luteinizing
450		hormone and testosterone more irregularly, and jointly more asynchronously, than younger males, Proceedings of the National
451		Academy of Sciences 93 (24) (1996) 14100–14105.
452	[38]	P. Castiglioni, M. Di Rienzo, How the threshold "r" influences approximate entropy analysis of heart-rate variability, in:

- [39] C. Liu, C. Liu, P. Shao, L. Li, X. Sun, X. Wang, F. Liu, Comparison of different threshold values r for approximate en-454 tropy: application to investigate the heart rate variability between heart failure and healthy control groups, Physiological 455 456 Measurement 32 (2) (2011) 167. [40] A. Boskovic, T. Loncar-Turukalo, O. Sarenac, N. Japundzic-Zigon, D. Bajic, Unbiased entropy estimates in stress: a para-457 meter study, Computers in Biology and Medicine 42 (6) (2012) 667-679. 458 [41] S. Zurek, P. Guzik, S. Pawlak, M. Kosmider, J. Piskorski, On the relation between correlation dimension, approximate 459 entropy and sample entropy parameters, and a fast algorithm for their calculation, Physica A: Statistical Mechanics and its 460 Applications 391 (24) (2012) 6601-6610. 461 [42] Y.-H. Pan, Y.-H. Wang, S.-F. Liang, K.-T. Lee, Fast computation of sample entropy and approximate entropy in biomedicine, 462 Computer Methods and Programs in Biomedicine 104 (3) (2011) 382-396. 463 [43] M. R. Guevara, L. Glass, M. C. Mackey, A. Shrier, Chaos in neurobiology, IEEE Transactions on Systems, Man, and Cyber-464 netics 13 (5) (1983) 790-798. 465 [44] M. C. Mackey, L. Glass, Oscillation and chaos in physiological control systems, Science 197 (4300) (1977) 287-289. 466 [45] R. Friedrich, C. Uhl, Evolution of Dynamical Structures in Complex Systems, Springer Berlin-Heidelberg, NY, 1992. 467
- [46] V. Vapnik, The Nature of Statistical Learning Theory, 2nd Edition, Springer, 2000.
- [47] T. Kailath, The divergence and Bhattacharyya distance measures in signal selection, IEEE Transactions on Communication
   Technology 15 (1) (1967) 52–60.
- [48] S. D. Shorvon, D. Fish, W. E. Dodson, The Treatment of Epilepsy, Wiley, 2004.

Computers in Cardiology, 2008, 2008, pp. 561-564.

453

[49] D. C. Montgomery, G. C. Runger, Applied Statistics and Probability for Engineers, John Wiley & Sons, 2010.

23