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Regularity analysis of nocturnal oximetry recordings to assist in the diagnosis of sleep apnoea syndrome

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Abstract

The relationship between sleep apnoea-hypopnoea syndrome (SAHS) severity and the regularity of nocturnal oxygen saturation (SaO₂) recordings was analysed. Three different methods were proposed to quantify regularity: approximate entropy (AEn), sample entropy (SEn) and kernel entropy (KEn). A total of 240 subjects suspected of suffering from SAHS took part in the study. They were randomly divided into a training set (96 subjects) and a test set (144 subjects) for the adjustment and assessment of the proposed methods, respectively. According to the measurements provided by AEn, SEn and KEn, higher irregularity of oximetry signals is associated with SAHS-positive patients. Receiver operating characteristic (ROC) and Pearson correlation

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analyses showed that KEn was the most reliable predictor of SAHS. It provided an area under the ROC curve of 0.91 in two-class classification of subjects as SAHS-negative or SAHS-positive. Moreover, KEn measurements from oximetry data exhibited a linear dependence on the apnoea-hypopnoea index, as shown by a correlation coefficient of 0.87. Therefore, these measurements could be used for the development of simplified diagnostic techniques in order to reduce the demand for polysomnographies. Furthermore, KEn represents a convincing alternative to AEn and SEn for the diagnostic analysis of noisy biomedical signals.

Keywords: Oxygen saturation, Entropy rate, Approximate entropy, Sample entropy, Kernel entropy, Density estimation

1 Introduction

Regularity is defined as the consistency of subpattern recurrence in a time series [1]. Regularity has shown to be a useful property of biomedical signals to discriminate those either generated by pathological systems or by the same system under different conditions [2]. Regular signals are characterised by a predictable behaviour, with recognizable patterns that repeat. Regularity is associated with the amount of information in a series, which, in a probabilistic sense, is a measure of the unexpectedness in the data [3]. Shannon [4] proposed the concept of entropy to evaluate the information (or uncertainty) in a message, which is modelled as a finite collection of random variables. In the context of infinite sequences or series, the entropy rate has been employed for the quantification of the amount of information [2]. Several metrics have been proposed to estimate the entropy rate of a series, with approximate entropy (AEn) [5] and sample entropy (SEn) [6] being the most common ones. A generalised entropy measure is given by the family of Renyi entropies (R_q), where q denotes the entropy order [7]. Lake [8] analysed the incorporation of the Renyi entropy into the entropy rate framework, showing that AEn and SEn approximate the differential Renyi entropy rate for $q = 1$ and $q = 2$, respectively.

AEn and SEn are based on the computation of probabilities by counting matches between signal subsequences of length m and $m + 1$. A match is found when the distance between two subsequences is lower or equal than a tolerance parameter r [6]. A different procedure to obtain the Renyi entropy rate of a series consists of substituting probability terms in AEn and SEn algorithms by the corresponding probability density functions [8, 3]. Several

26 advantages are found in this approach. It suppresses the need of predefined
27 rules for the choice of the tolerance parameter r , which can be freely varied
28 in order to obtain confident estimates of the density functions. In addition,
29 entropy estimates made with different values of r measure the same inherent
30 quantity and can be compared directly [8, 9].

31 This approach requires the approximation of the (unknown) probability
32 density function of the data, for which a finite set of samples extracted from
33 the underlying series is initially available. Non-parameteric kernel density
34 estimation based on the Parzen window method has been suggested for this
35 purpose [8, 3]. Specifically, Gaussian kernels are of special interest since they
36 result in a smooth and continuous profile of the approximated density [10].
37 Additionally, in the case of the quadratic entropy (R_2), i.e., the Renyi entropy
38 of order $q = 2$, Gaussian kernels lead to the exact evaluation of the integral
39 found in its definition [3]. In a preceding study, a kernel-based estimation
40 of R_2 was adopted to assess the quadratic entropy rate of a time series [11].
41 The resulting measure, termed as kernel entropy (KE_n), was proposed as an
42 indicator of the irregularity of the series [11, 12].

43 Entropy analysis has yield successful results in several applications in-
44 volving time series processing such as earthquake forecasting [13], exchange
45 rating [14] or fault detection [15]. Furthermore, entropy measures of biomed-
46 ical signals have been widely used to assess physiological differences between
47 subjects [16, 17]. The present study focuses on this scenario. We explored
48 the utility of entropy rate measurements of nocturnal oxygen saturation sig-
49 nals (SaO₂) in the context of sleep apnoea-hypopnoea syndrome (SAHS)
50 diagnosis. Nowadays, a definitive diagnosis about SAHS is obtained from

51 in-hospital evaluation of the patient's sleep through nocturnal polysomnog-
52 raphy (PSG). This test enables the assessment of SAHS severity by means of
53 the apnoea-hypopnoea index (AHI), which quantifies the number of apnoea
54 and hypopnoea events per hour of sleep. To obtain the AHI of a patient, the
55 sleep specialist must evaluate a large amount of clinical and physiological
56 data that, in addition to SaO_2 series, include other signals such as the elec-
57 trocardiogram (ECG), the electroencephalogram (EEG) or the respiratory
58 airflow (AF) [18]. Therefore, PSG is a highly complex and time-consuming
59 procedure.

60 Reliable indicators of SAHS severity automatically extracted from these
61 data would enable an objective and simplified interpretation. Nocturnal
62 oximetry recordings are of special interest as they reflect respiratory dy-
63 namics during sleep. Apnoeas and hypopnoeas are usually accompanied by
64 hypoxaemia due to airflow reduction, which is reflected by a marked drop in
65 the saturation value [19]. The diagnostic utility of oximetry signals has been
66 previously evaluated through different methods. A straightforward approach
67 is the use of oximetry parameters based on the computation of desatura-
68 tion events or the time spent below a certain level of saturation [20, 21].
69 In addition, complex signal processing and pattern recognition techniques
70 like neural networks or genetic algorithms have been employed for the ex-
71 traction of useful descriptors from SaO_2 data [22, 23, 24]. According to the
72 reported results, a higher diagnostic accuracy can be obtained through the
73 combination of different features including statistical, spectral and non-linear
74 ones. Correct diagnostic rates close to 90% have been reported for screening
75 algorithms based on this approach [25, 26, 22].

76 Among other features, SaO_2 irregularity measured by the entropy rate
77 has been employed as a descriptor of the influence of SAHS severity on its
78 dynamic behaviour [27, 25]. The non-deterministic occurrence of apnoeic
79 episodes tends to increase the uncertainty in the SaO_2 signal and, equiva-
80 lently, its amount of information. As a result, signals from subjects suffering
81 from SAHS are expected to have a higher entropy rate than those from con-
82 trol subjects. Previously, AEn has been employed to measure SaO_2 irregular-
83 ity [28, 27]. These preceding studies showed the relationship between higher
84 irregularity of oximetry signals and SAHS severity, estimating that a correct
85 diagnosis based on regularity analysis can be obtained for approximately 85%
86 of the patients. However, AEn has proven to be a biased entropy estima-
87 tor [6] and, thus, further analysis is required to extract robust conclusions
88 on the relationship between SAHS severity and SaO_2 irregularity.

89 To this end, the present study proposes a comparative analysis between
90 different entropy metrics. In addition to AEn, we suggest entropy analysis of
91 SaO_2 series based on SEn and KEn, which provide two different approaches
92 to estimate the quadratic entropy rate of a signal. The present study aims to
93 determine to which extent the irregularity of SaO_2 data is related to SAHS
94 severity, as well as the most accurate method to quantify this relationship.

95 We hypothesise that a more confident assessment of the entropy of SaO_2
96 recordings can be obtained by means of kernel-based approximations to prob-
97 ability density functions as implemented by KEn. This method represents
98 a novel approach for entropy estimation with respect to conventional pro-
99 cedures like AEn and SEn. The framework implemented by KEn suitably
100 adapts to oximetry analysis since SaO_2 samples can be interpreted as ob-

101 servations of a continuous variable. Thus, probability density functions may
102 provide a more reliable description of their statistical behaviour. This hy-
103 pothesis is evaluated through an exhaustive regularity analysis of SaO₂ data
104 using AEn, SEn and KEn.

105 **2. Materials and methods**

106 *2.1. Subjects and signals*

107 A total of 240 subjects suspected of suffering from SAHS took part in
108 the study. They underwent PSG in the Sleep Unit of Hospital Universi-
109 tario Pío del Río Hortega, Valladolid, Spain. The Review Board on Human
110 Studies approved the protocol and each subject gave their consent to par-
111 ticipate in the study. To draw useful conclusions on the effect of SAHS on
112 SaO₂ dynamics, subjects affected by any other relevant respiratory disorder
113 were excluded. The selected patients were continuously monitored using a
114 polysomnograph (Alice 5, Respironics, Philips Healthcare, The Netherlands).
115 A medical expert analysed the PSG recordings according to the rules pro-
116 posed by Rechtschaffen and Kales [29]. Once apnoeas and hypopnoeas were
117 identified, the AHI was obtained as the total number of events (i.e., the sum
118 of apnoeas and hypopnoeas) divided by the total sleep time. The resulting
119 value is expressed as the number of events per hour of sleep [30]. A thresh-
120 old given by $AHI = 10 \text{ h}^{-1}$ was used to determine a positive diagnosis of
121 SAHS [31].

122 A Nonin PureSAT pulse oximeter (Nonin Medical Inc., USA) was used
123 to record oximetry signals at a sampling frequency of 1 Hz. These signals
124 were subsequently saved to separate files to be processed offline. A prepro-

125 cessing stage was initially applied to remove artefacts like marked drops or
126 zero samples due to a bad contact of the probe during sleep. The criteria
127 suggested by Magalang et al. [32] were taken into account to perform signal
128 preprocessing. According to these criteria, all changes greater than 4%/s
129 between consecutive sampling intervals and any sample lower than 20% were
130 removed.

131 Figure 1 shows two oximetry recordings from our dataset once artefacts
132 were removed. The signals correspond to a normal subject ($AHI = 0.5 \text{ h}^{-1}$)
133 and a subject with severe SAHS ($AHI = 32.1 \text{ h}^{-1}$), respectively. **In addition,**
134 **a detailed view (12 minutes) of both recordings is provided.** The differences
135 between these signals reflect the influence of repeated apnoeas and hypop-
136 noeas on SaO_2 dynamics. The signal from the normal subject is characterised
137 by a near-constant saturation value along the night, with small fluctuations
138 around the baseline level. **This behaviour is confirmed when observed in de-**
139 **tail, as it exhibits some variability without marked desaturation events.** In
140 contrast, the profile of the signal from the subject with severe SAHS reflects
141 a significant instability as a consequence of repeated desaturations accom-
142 panying apnoeas and hypopnoeas. **As observed in the zoomed segment of**
143 **the signal, these desaturation events are more frequent when compared with**
144 **the oximetry recording from the normal subject. Additionally, they are more**
145 **pronounced and longer. Therefore, a distinct value of the entropy rate can**
146 **be expected for these signals since they reflect different dynamics.**

147 INSERT FIGURE 1 AROUND HERE

148 The hold-out method was used to prevent bias in the estimation of the
149 performance of the three entropy metrics [10]. Therefore, the initial popu-

150 lation was randomly divided into a training set with 96 subjects (40%) and
 151 a test set with 144 subjects (60%). The former was used to adjust user-
 152 dependent parameters in AEn, SEn and KEn algorithms. Signals in the test
 153 set were used to assess the diagnostic capability of these methods. Table 1
 154 summarises the demographic and clinical data for subjects in training and
 155 test sets. Note that a higher proportion of SAHS-positive subjects was ob-
 156 tained due to the initial suspicion of SAHS in the population under study.
 157 In addition, the higher percentage of older males is motivated by the in-
 158 creased prevalence of SAHS in this group, as reported in previous studies. In
 159 the landmark study of the Wisconsin Sleep Cohort, including 602 men and
 160 women, 24% of men and 9% of women had $\text{AHI} \geq 5 \text{ h}^{-1}$, while 9% of men
 161 and 4% of women had $\text{AHI} \geq 15 \text{ h}^{-1}$ [33]. In addition, it has been estimated
 162 that AHI increases with age for both men and women [34].

163 INSERT TABLE 1 AROUND HERE

164 2.2. Methods

165 We compared the utility of three different entropy metrics, namely AEn,
 166 SEn and KEn, to quantify the relationship between SAHS severity and the
 167 irregularity of SaO_2 data. The proposed methods represent distinct imple-
 168 mentations of the Renyi entropy rate of a series. The mathematical definition
 169 of the latter is derived from the expression of the Renyi entropy, which is ob-
 170 tained as follows. Let $\mathbf{x} = [x_1, x_2, \dots, x_N]$ be a continuous stochastic process
 171 composed of a sequence of N random variables x_i . The Renyi entropy of the
 172 process is given by [7]:

$$\begin{aligned}
R_{q,N} &= \frac{1}{1-q} \log \left\{ E \left[f^{q-1} (x_1, \dots, x_N) \right] \right\} \\
&= \frac{1}{1-q} \log \int f^q (x_1, \dots, x_N) dx_1 \dots dx_N
\end{aligned} \tag{1}$$

173 where q determines the entropy order and $f(\mathbf{x}) = f(x_1, \dots, x_N)$ is the joint
174 probability density function of the set of variables x_i that compose the pro-
175 cess. The Renyi entropy evaluates the amount of information (uncertainty)
176 in \mathbf{x} .

177 Adding new variables to the process \mathbf{x} will contribute to increase its
178 information content, showing the dependence of the entropy on the process
179 length specified by N [2]. Thus, a measure of the variation of the entropy due
180 to the inclusion of a new variable x_i , i.e., the entropy rate, can be obtained.
181 The differential Renyi entropy rate is defined by the following asymptotic
182 limit [8]:

$$\begin{aligned}
D_{q,N} &= \lim_{N \rightarrow \infty} (R_{q,N+1} - R_{q,N}) \\
&= \lim_{N \rightarrow \infty} \left\{ -\log \left[\int f^q (\mathbf{x}^{(N+1)}) d\mathbf{x}^{(N+1)} \right] + \log \left[\int f^q (\mathbf{x}^{(N)}) d\mathbf{x}^{(N)} \right] \right\}
\end{aligned} \tag{2}$$

183 where the superscripts (N) and $(N+1)$ denote the length of the process \mathbf{x} .
184 In the following sections, a description of AEn, SEn and KEn is provided,
185 showing the connection between each of these metrics and $D_{q,N}$ as expressed
186 in (2).

187 2.2.1. Approximate entropy (AEn)

188 AEn is a family of metrics developed by Pincus [5] for the analysis of noisy
189 data such as biomedical signals. Briefly, AEn estimates the entropy rate

190 of a series from the computation of the probability of repetition for subse-
 191 quences of length m . To this end, two subsequences are considered similar
 192 if the distance between them is lower than a threshold r . Mathematically,
 193 the algorithm to compute AEn is defined for a finite time series of length
 194 N given by $\mathbf{x} = [x_1, \dots, x_N]$. From this series, extract overlapping m -length
 195 windows, from $\mathbf{x}_i^{(m)}$ to $\mathbf{x}_{N-m+1}^{(m)}$, defined as $\mathbf{x}_i^{(m)} = [x_i, x_{i+1}, \dots, x_{i+m-1}]$.
 196 The distance $d[\mathbf{x}_i^{(m)}, \mathbf{x}_j^{(m)}]$ between two such vectors $\mathbf{x}_i^{(m)}$ and $\mathbf{x}_j^{(m)}$ is cal-
 197 culated as the maximum absolute difference between their respective scalar
 198 components. A tolerance value r is used to obtain the number of vectors
 199 ($j = 1, \dots, N - m + 1$) such that $d[\mathbf{x}_i^{(m)}, \mathbf{x}_j^{(m)}] \leq r$, which is denoted as
 200 $N^m(i)$. Then, the likelihood that a vector is within a distance r from vector
 201 $\mathbf{x}_i^{(m)}$ ($i = 1, \dots, N - m + 1$) is estimated as:

$$C_r^m(i) = \frac{N^m(i)}{N - m + 1} \quad (3)$$

202 The term $C_r^m(i)$ reflects the regularity of patterns of length m similar to
 203 $\mathbf{x}_i^{(m)}$ for a tolerance r . Equivalently, it estimates the probability of observ-
 204 ing the m -length vector $\mathbf{x}_i^{(m)}$, implementing a discrete approximation to the
 205 probability density function $f(\mathbf{x}^{(m)})$.

206 The average of the logarithmic likelihood over the complete set of samples
 207 is computed as:

$$\phi^m(r) = \frac{1}{N - m + 1} \sum_{i=1}^{N-m+1} \log C_r^m(i) \quad (4)$$

208 From the previous analysis, $\phi^m(r)$ represents an estimation of the expected
 209 value of $\log[f(\mathbf{x}^{(m)})]$, which in turn corresponds to the negative value of
 210 the Renyi entropy of order $q = 1$ [8]:

$$\phi^m(r) \approx E \{ \log [f(\mathbf{x}^{(m)})] \} = \int \log [f(\mathbf{x}^{(m)})] f(\mathbf{x}^{(m)}) d\mathbf{x}^{(m)} = -R_{1,N} \quad (5)$$

211 Therefore, AEn approximates $D_{1,N}$, the differential Renyi entropy rate of
 212 order $q = 1$ [8], as expressed by its mathematical definition [5]:

$$AEn(m, r) = \lim_{N \rightarrow \infty} [\phi^m(r) - \phi^{m+1}(r)] \quad (6)$$

213 The following statistic is adopted for the computation of AEn on finite time
 214 series:

$$AEn(m, r, N) = \phi^m(r) - \phi^{m+1}(r) \quad (7)$$

215

216 2.2.2. Sample entropy (SEn)

217 SEn adopts a similar approach to AEn for the estimation of the entropy
 218 rate, which is based on the estimation of the probability of repetition for a
 219 subsequence. As a substantial difference, self-matching is prevented in the
 220 SEn algorithm. It has been shown that self-matching, i.e., the comparison
 221 of a vector $\mathbf{x}_i^{(m)}$ with itself, introduces some bias in the computation of AEn.
 222 Richman and Moorman proposed SEn in order to avoid this problem [6].
 223 For a time series $\mathbf{x} = [x_1, \dots, x_N]$, only the first $N - m$ vectors of length m
 224 are considered for comparison in the SEn algorithm. Let $U_r^m(i)$ denote the
 225 probability that a m -length vector $\mathbf{x}_j^{(m)}$ is within a distance r from vector
 226 $\mathbf{x}_i^{(m)}$:

$$U_r^m(i) = \frac{N^m(i)}{N - m - 1} \quad (8)$$

227 where $N^m(i)$ denotes the number of vectors $\mathbf{x}_j^{(m)}$ ($j \neq i, j = 1, \dots, N - m$)
 228 such that $d[\mathbf{x}_i^{(m)}, \mathbf{x}_j^{(m)}] \leq r$ and r is a tolerance value. Similarly to the term
 229 $C_r^m(i)$ in the AEn algorithm, $U_r^m(i)$ plays the role of the density function
 230 $f(\mathbf{x}^{(m)})$, since it approximates the probability of observing $\mathbf{x}_i^{(m)}$. The average
 231 of the set of $U_r^m(i)$ values is given by the quantity $U^m(r)$:

$$U^m(r) = \frac{1}{N - m} \sum_{i=1}^{N-m} U_r^m(i) \quad (9)$$

232 which provides an estimation of the expected value of the function $f(\mathbf{x}^{(m)})$:

$$U^m(r) \approx E[f(\mathbf{x}^{(m)})] = \int f^2(\mathbf{x}^{(m)}) d\mathbf{x}^{(m)} \quad (10)$$

233 It can be observed that the integral in the previous equation corresponds to
 234 the argument of the logarithm found in the definition of the Renyi entropy
 235 of order $q = 2$ or quadratic entropy. As a result, SEn can be interpreted
 236 as an estimation of the quadratic entropy rate as expressed by the following
 237 equation [6]:

$$SEn(m, r) = \lim_{N \rightarrow \infty} \{ \log[U^m(r)] - \log[U^{m+1}(r)] \} \quad (11)$$

238 SEn is estimated by the statistics:

$$SEn(m, r, N) = \log[U^m(r)] - \log[U^{m+1}(r)] \quad (12)$$

239

240 2.2.3. Kernel entropy (KEen)

241 Unlike AEn and SEn algorithms, which involve the computation of probabil-
242 ities, KEn is based on modelling the statistical properties of the generator of
243 the data. Hence, the algorithm to obtain KEn estimates the density function
244 of the signal subsequences. To this end, KEn approximates the quadratic
245 entropy rate from the use of non-parameteric probability density estima-
246 tion techniques. The KEn assumes that the set of m -length vectors $\mathbf{x}_i^{(m)}$
247 from the original series has been generated according to the density func-
248 tion $f(\mathbf{x}^{(m)})$ [8]. Hence, the Parzen window method with Gaussian kernels
249 is proposed to estimate this function [11, 35, 3], resulting in the following
250 expression:

$$\hat{f}(\mathbf{x}^{(m)}) = \frac{1}{N-1} \sum_{i=1}^{N-m+1} G(\mathbf{x}^{(m)} - \mathbf{x}_i^{(m)}, \Sigma) \quad (13)$$

251 where $G(\mathbf{x}^{(m)}, \Sigma)$ denotes the zero-mean Gaussian kernel with covariance
252 matrix Σ evaluated at point $\mathbf{x}^{(m)}$. In our study, spherical Gaussians with
253 a covariance matrix given by $\Sigma = \sigma \mathbf{I}$ will be considered. The scalar σ is
254 referred to as the kernel bandwidth and \mathbf{I} denotes the identity matrix.

255 Using $\hat{f}(\mathbf{x}^{(m)})$, the expected value of the density function $f(\mathbf{x}^{(m)})$ is
256 estimated by $J^m(\sigma)$, which is given by:

$$J^m(\sigma) = \int \hat{f}^2(\mathbf{x}^{(m)}) d\mathbf{x}^{(m)} \quad (14)$$

257 Note that the use of a Gaussian kernel estimator for $f(\mathbf{x}^{(m)})$ enables the
258 computation of the exact value of the integral:

$$\int \hat{f}^2(\mathbf{x}^{(m)}) d\mathbf{x}^{(m)} = \frac{1}{(N-m+1)^2} \sum_{i=1}^{N-m+1} \sum_{j=1}^{N-m+1} G[\mathbf{x}_j^{(m)} - \mathbf{x}_i^{(m)}, 2\sigma^2\mathbf{I}] \quad (15)$$

259 where $N - m + 1$ is the total number of m -length vectors in the original time
 260 series. The negative logarithm of $J^m(\sigma)$ approximates the quadratic entropy
 261 $R_{2,N}$. Hence, KE_n is an estimation of the quadratic entropy rate, which is
 262 obtained from the incorporation of this expression in the Renyi entropy rate
 263 framework [8]:

$$KE_n(m, \sigma) = \lim_{N \rightarrow \infty} \{\log[J^m(\sigma)] - \log[J^{m+1}(\sigma)]\} \quad (16)$$

264 In practice, the following estimation is used for finite series:

$$KE_n(m, \sigma, N) = \log[J^m(\sigma)] - \log[J^{m+1}(\sigma)] \quad (17)$$

265 It is worth noting that different techniques can be used to select the kernel
 266 bandwidth parameter σ of the Parzen density estimator from the original
 267 data. In this study, the Bayesian approach proposed by Zhang et al. [36]
 268 was applied for this purpose. According to this procedure, the elements of
 269 the covariance matrix $\Sigma = \sigma\mathbf{I}$ are treated as parameters and the aim is to
 270 estimate their posterior distribution $f(\sigma | D)$, where D denotes the training
 271 set.

272 From Bayes theorem [10], the posterior density $f(\sigma | D)$ is proportional
 273 to the product of the prior density $f(\sigma)$ and the likelihood $f(D | \sigma)$:

$$f(\sigma | D) \propto f(D | \sigma) f(\sigma) \quad (18)$$

274 Note that the likelihood of observing the sample set D for a given value of
 275 σ can be approximated from the expression of $\hat{f}(\mathbf{x}^{(m)})$. Therefore, the prior
 276 probability $f(\sigma)$ is the remaining factor to obtain $f(\sigma | D)$. Zhang et al.
 277 suggested the following functional form for the prior in order to make the
 278 sampling algorithm work properly [36]:

$$f(\sigma) \propto \prod_{k=1}^m \frac{\sigma_k}{\lambda + \sigma_k^2} \quad (19)$$

279 where λ controls the shape of the function. This prior density function aims
 280 to avoid large values of σ , for which the associated probability is small.

281 The most probable value of σ given the data in D is selected as the
 282 optimum. This value is obtained by sampling from the posterior probabilit-
 283 ity $f(\sigma | D)$ using Markov Chain Monte Carlo (MCMC) techniques. The
 284 Metropolis-Hastings algorithm was used for this purpose [37, 38].

285 *2.3. Statistical analysis*

286 To assess the performance of the proposed entropy methods in the quan-
 287 tification of SaO₂ irregularity derived from SAHS, two different approaches
 288 were used. First, a two-class classification model was defined by dividing the
 289 initial population into SAHS-negative and SAHS-positive subjects. Receiver
 290 operating characteristic (ROC) analysis was used to assess the capability of
 291 AEn, SEn and KEn measurements for identifying SaO₂ signals from these
 292 two groups [39]. The area under the ROC curve (AUC), which represents
 293 the probability of correct classification for a randomly chosen pair of samples
 294 from the two possible categories [39], was used as a measure of classification
 295 performance.

296 The second model for SAHS diagnosis consists in estimating the AHI from
297 the available oximetry signal. According to the value of this index, subjects
298 are assigned to one of four severity groups [18]: no SAHS ($\text{AHI} < 5\text{h}^{-1}$), mild
299 SAHS ($5\text{ h}^{-1} \leq \text{AHI} < 15\text{ h}^{-1}$), moderate SAHS ($15\text{ h}^{-1} \leq \text{AHI} \leq 30\text{ h}^{-1}$)
300 and severe SAHS ($\text{AHI} > 30\text{ h}^{-1}$). The utility of the three entropy measures
301 to rank SAHS severity was assessed by means of the Pearson's correlation
302 coefficient (ρ). It evaluates the linear relationship between AEn, SEn and
303 KEn and the AHI. The value of ρ can be interpreted as the utility of a given
304 method to predict the AHI.

305 **3. Results**

306 *3.1. Selection of the input parameters*

307 Entropy analysis based on the proposed methods require the prior se-
308 lection of several parameters. These correspond to N , m , and r for AEn
309 and SEn algorithms. In the case of KEn, only N and m are needed since
310 a data-driven technique was used to optimise the value of σ . The parame-
311 ter N denotes the length of the time series to be processed. In our study,
312 the length of oximetry recordings was approximately 7 hours (i.e., more than
313 25000 samples), involving a large amount of data. However, as apnoeic events
314 can take place at different moments during sleep and, in particular, during
315 REM phases [18], the whole recording must be analysed for an objective as-
316 sessment of SaO_2 dynamics. To reduce the computational load, we adopted
317 the strategy suggested in preceding studies [40]. Hence, the original SaO_2
318 signal was divided into epochs of length $N = 512$ samples to estimate AEn,
319 SEn and KEn. As the duration of apnoeas is typically between 10 seconds

320 and 2 minutes, the chosen epoch length (approximately, 8.5 minutes) is large
 321 enough to include one or more complete events. The measurements obtained
 322 from all the epochs were then averaged to determine the final estimation for
 323 each method.

324 On the other hand, parameters m and r involve statistical considerations.
 325 Setting m large and r too small would result in inaccurate estimates of the
 326 probabilities in AEn and SEn algorithms. In contrast, a large value of r
 327 and a small m is generally too coarse to distinguish processes. Thus, m and
 328 r were set to the widely established values suggested by Pincus [5, 41] to
 329 obtain a statistically valid estimate of the proposed entropy measures: $m =$
 330 1 or 2, and $r = 0.1, 0.15, 0.2$ or 0.25 times the standard deviation (SD) of
 331 the original series.

332 It is worth noting that, while KEn enables the automatic selection of
 333 the parameter σ , the applied MCMC-based technique requires several design
 334 parameters to be specified. Figure 2 represents the shape of the prior $f(\sigma)$
 335 for $\lambda = 0.1, 1, 5$ and 10 . This function tends to be more concentrated near
 336 zero as the hyperparameter λ becomes smaller. Zhang et al. [36] did not
 337 find significant differences in the estimated density functions resulting from
 338 λ between 0.1 and 5 . Thus, we set $\lambda = 5$ to avoid an excessive concentration
 339 of the probability density in a small range of σ values, favouring a smooth
 340 profile of $\hat{f}(x^{(m)})$. Furthermore, the variance of the proposal distribution
 341 for the Metropolis-Hastings algorithm must result in an acceptance rate be-
 342 tween 20% and 30% of the total number of samples [36]. In our study, this
 343 requirement was satisfied by setting that variance to 0.015 . Finally, in order
 344 to ensure the convergence of the sampling process, the number of samples to

345 be omitted and the number of samples to be retained were set to 5000 while
346 the starting σ value was set to 1% of the SD of the original series.

347 INSERT FIGURE 2 AROUND HERE

348 3.2. Training set

349 All the experiments in our study were conducted on Matlab 8.2.0. Ini-
350 tially, we evaluated different configurations of AEn, SEn and KEn on SaO₂
351 signals in the training set to find the optimum value of the input parameters
352 m and r . For each method, the configuration with the highest performance
353 was selected. The results achieved on the training set are summarised in
354 Table 2. As can be observed, $m = 1$ and $r = 0.1SD$ resulted in a more ac-
355 curate characterisation of SAHS for AEn and SEn. For the KEn algorithm,
356 the two evaluated configurations provided similar results. An AUC of 0.86
357 and a correlation coefficient of 0.82 were reached when m was set to 1. This
358 configuration was slightly improved by setting $m = 2$ (AUC = 0.86 and $\rho =$
359 0.83). Therefore, $m = 2$ was finally selected as the optimum for KEn.

360 INSERT TABLE 2 AROUND HERE

361 3.3. Test set

362 AEn, SEn and KEn were computed on oximetry signals in the test set us-
363 ing the selected configurations. For each of the three methods, the Lilliefors
364 test [42] was applied to assess the normality of the samples. The results
365 showed a level of significance (p -value) higher than 0.1 for the distribution
366 of AEn, SEn and KEn in both SAHS-negative and SAHS-positive groups,

367 reflecting a valid assumption for normality. Subsequently, ROC and corre-
368 lation analysis were conducted for each method. Table 3 summarises the
369 obtained results. KEn showed to be the most accurate predictor of SAHS
370 from the methods evaluated in our study. It achieved $AUC = 0.91$ and ρ
371 $= 0.87$, which were substantially higher than the results provided by AEn
372 ($AUC = 0.67$ and $\rho = 0.34$) and SEn ($AUC = 0.74$ and $\rho = 0.45$). The
373 experiments reveal that a finer characterisation of SaO₂ irregularity was ob-
374 tained by using a density estimation technique for entropy quantification as
375 implemented by KEn.

376 INSERT TABLE 3 AROUND HERE

377 For each method, Figure 3 depicts the ROC curves and boxplots in
378 SAHS-negative and SAHS-positive groups. The p -value in the figure corre-
379 sponds to the level of significance for the difference between the means of
380 each entropy metric in both groups, as obtained from the one-way ANOVA
381 test [43]. It confirms that SEn and KEn provided statistically significant dif-
382 ferences between both groups of subjects. In particular, a p -value close to 0
383 was obtained for KEn, reflecting notably more significant differences between
384 SAHS-negative and SAHS-positive samples than AEn and SEn. Moreover,
385 the results reflect the utility of the evaluated methods in two-class classifi-
386 cation of patients. As can be observed, the distributions of AEn, SEn and
387 KEn measurements reflect that higher irregularity, i.e., higher entropy rate,
388 is associated with oximetry signals from SAHS-positive subjects.

389 INSERT FIGURE 3 AROUND HERE

390 On the other hand, correlation analysis indicates that SaO_2 regularity is
391 directly related to SAHS severity, with larger entropy values obtained from
392 signals corresponding to subjects with a higher AHI. Figure 4 depicts the
393 AHI versus AEn, SEn and KEn measurements as well as the boxplots of
394 these measurements in each severity group. The highest Pearson's correlation
395 coefficient was obtained for KEn ($\rho = 0.87$), which showed a marked linear
396 trend with respect to AHI. The boxplots obtained for the four severity groups
397 show a higher dispersion of AEn and SEn measurements in each category
398 as well as smaller differences between their median values. As a result, a
399 significant overlap between different groups was observed for them. This
400 overlapping was substantially smaller for KEn measurements, which provided
401 a more accurate assessment of SAHS severity.

402 INSERT FIGURE 4 AROUND HERE

403 For a more rigorous evaluation of the differences achieved by each entropy
404 metric between the four groups, we applied the one-way ANOVA test. The
405 obtained results are summarised in Table 4. As can be observed, KEn pro-
406 vided statistically significant differences for any pair of severity groups under
407 evaluation, but for the comparison between mild and moderate subjects. In
408 the case of SEn, significant differences were found between normal subjects
409 and patients with moderate SAHS, as well as between normal subjects and
410 patients with a severe diagnosis of SAHS. Finally, AEn only achieved signif-
411 icant differences when subjects in normal and severe groups were compared.
412 Thus, the analysis confirms the higher capability of KEn to capture differ-
413 ences in SaO_2 dynamics due to SAHS severity. In addition, the experiment

414 also shows that signals corresponding to subjects with mild and moderate
415 SAHS tend to reflect a similar behaviour, as no significant differences was
416 observed for any of the evaluated entropy metrics.

417 INSERT TABLE 4 AROUND HERE

418 3.4. Comparison with conventional statistical features

419 To complete our study, we assessed the diagnostic utility of regularity
420 analysis of SaO₂ data with respect to other statistical features commonly
421 employed for the evaluation of biomedical signals. Conventionally, these
422 features include the mean (f_{avg}), standard deviation (f_{sd}), coefficient of vari-
423 ation (f_{cv}), interquartile range (f_{iqr}) and dispersion indices (f_{sd1} and f_{sd2})
424 derived from the Poincare plot. The results achieved by these features are
425 summarised in the Table 5.

426 INSERT TABLE 5 AROUND HERE

427 As can be observed, conventional features capture relevant diagnostic in-
428 formation about SAHS from nocturnal oximetry recordings. In particular,
429 they achieved significantly high AUC values, showing a good capability to
430 discriminate between SAHS-negative and SAHS-positive subjects. Our ex-
431 periments reflect that all the evaluated features but f_{avg} achieved AUC higher
432 than 0.95, which improves the AUC results provided by the three entropy
433 metrics assessed in our research. However, correlation analysis reveals a lower
434 ability of the conventional statistical features to detect small variations in the
435 AHI. The obtained ρ values are significantly smaller than that achieved by
436 KEn. The latter reached $\rho = 0.87$, whereas the highest correlation coeffi-
437 cient among the conventional features was $\rho = 0.77$, which was provided by

438 f_{sd1} . Therefore, correlation results show a stronger correspondence between
439 SAHS severity and SaO₂ irregularity when compared to the signal properties
440 evaluated by the proposed conventional methods.

441 **4. Discussion and conclusions**

442 Regularity analysis of SaO₂ recordings was performed using three differ-
443 ent entropy algorithms: AEn, SEn and KEn. The obtained measurements
444 show that more irregular signals are associated with SAHS-positive subjects,
445 reflecting the influence of apnoea events on SaO₂ dynamics. Nevertheless,
446 there were substantial differences between the diagnostic performances of
447 AEn, SEn and KEn. This reveals a distinct reliability of the estimators im-
448 plemented by these algorithms. The latter showed to be the most consistent
449 entropy estimator, outperforming conventional entropy algorithms like AEn
450 and SEn. Specifically, we found that KEn measurements from oximetry data
451 could be used to estimate the AHI of a patient ($\rho = 0.87$).

452 The KEn method represents a novel strategy for entropy estimation. The
453 main difference between KEn and the conventional AEn and SEn algorithms
454 is the use of probability density functions for modelling the statistical distri-
455 bution of the data. According to our results, this approach has shown to be
456 a more suitable procedure when continuous variables like SaO₂ are analysed.
457 In addition, the use of probability density functions involves other advan-
458 tages for entropy estimation. First, a data-driven method as that proposed
459 by Zhang et al. [36] can be applied to determine the value of the kernel band-
460 width. As shown in our experiments, the variance σ of the Gaussian kernels
461 is optimised for the series under evaluation instead of taking an arbitrary

462 value fixed by the user. The automatic optimisation of σ suppresses one
463 of the user parameters in AEn and SEn algorithms, reducing by four the
464 number of KEn configurations to be evaluated. Second, it must be taken
465 into account that kernel density estimation results in the exact computation
466 of the integral in the definition of the Renyi entropy, as expressed in (15).
467 Hence, the KEn algorithm avoids one of the approximations adopted in AEn
468 and SEn, which corresponds to the expectation operator.

469 It is worth noting that the use of density functions overcomes the strong
470 dependency of conventional entropy metrics like AEn or SEn on the tolerance
471 parameter r . Small values of r lead to higher and less confident entropy
472 estimates due to the reduced number of matches of length m and $m + 1$. In
473 the context of density estimation, the value of r is chosen in order to obtain an
474 accurate approximation of the target probability density function [8, 3, 9].
475 As a result, any value of r can be used for any time series, enabling the
476 comparison between entropy results computed for distinct r [9]. As a matter
477 of further study, the influence of the kernel chosen for density approximation
478 (e.g., Gaussian, uniform, triangular or cosine kernels) on the resulting entropy
479 estimates should be assessed.

480 From our experiments, we have found that SaO₂ irregularity is more
481 closely related to SAHS severity than conventional statistical properties in-
482 cluding mean, variance or dispersion indices extracted from Poincar plots. It
483 is reflected by the Pearson's correlation coefficient, which was close to 0.90
484 in the case of KEn. This results shows the utility of the entropy rate of
485 oximetry data to discriminate subjects with subtle differences between their
486 AHI. Nevertheless, conventional statistical features should be taken into ac-

487 count for the implementation of accurate methods based on oximetry data.
488 As reported in preceding studies, multivariate analysis including several un-
489 correlated features can yield higher diagnostic performance than univariate
490 measures of a given signal property [22, 24].

491 Several limitations can be found in our study. We have demonstrated that
492 KEn is a valuable approach to perform regularity analysis of SaO₂ data in the
493 context of SAHS diagnosis. However, the information captured by KEn is not
494 sufficient to provide a definitive diagnosis about SAHS as reflected by AUC
495 < 1 and $\rho < 0.9$. KEn analysis should be then considered as a tool for the
496 interpretation of SaO₂ data. In this vein, the role of nocturnal pulse oximetry
497 in SAHS diagnosis must be analysed. As in our study, the results reported
498 by other researchers reveal suboptimal diagnostic performance of oximetry-
499 based methods, with sensitivity and specificity lower than 100% [26, 22, 24].
500 Hence, the number of false negative and false positive cases would prevent the
501 use of these methods as an alternative for PSG. Instead, home unattended
502 pulse oximetry could be adopted as a screening tool to reduce the number of
503 required PSG tests, contributing to minimise the waiting time for a diagnosis
504 about SAHS. On the other hand, KEn is computationally more expensive
505 than AEn and SEn. We have estimated that the time required to compute
506 KEn is approximately a hundred times that of AEn and SEn. Specifically,
507 we estimated that the time required to compute AEn, SEn and KEn on a
508 signal epoch (512 samples) was 0.72, 0.91 and 96.78 seconds, respectively,
509 using Matlab 8.2.0 on an Intel i7 CPU at 3.4 GHz. Mainly, this difference
510 is due to the MCMC-based procedure for automatic adjustment of σ . This
511 procedure requires thousands of samples to converge, with several operations

512 carried out for each of these samples. In order to reduce the computational
513 load, the value of σ could be previously set by the user for the estimation of
514 KEn. Nevertheless, this does not ensure the choice of the optimum σ for the
515 underlying data.

516 In summary, our study confirms that SaO₂ signals from patients suffering
517 from SAHS tend to be more irregular. This result suggests the unpredictable
518 occurrence of apnoeas and hypopnoeas during sleep. Hence, regularity anal-
519 ysis could be used for the interpretation of nocturnal oximetry dynamics
520 in the context of SAHS diagnosis. In particular, KEn showed to be a re-
521 liable predictor of SAHS. It could be considered to build new methods for
522 automatic assessment of SAHS severity in order to reduce the demand for
523 conventional PSG. Furthermore, it has been proved that KEn is a valuable
524 metric for regularity analysis of biomedical data, representing an alternative
525 to conventional methods such as AEn and SEn.

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664 **Figure captions**

Figure 1: Two examples of the SaO_2 signals analysed in our study. (a) SaO_2 signal from a subject with $\text{AHI} = 0.5 \text{ h}^{-1}$; (b) SaO_2 signal from a subject with $\text{AHI} = 32.1 \text{ h}^{-1}$; (c) detailed view of the signal corresponding to the subject with $\text{AHI} = 0.5 \text{ h}^{-1}$; (d) detailed view of the signal corresponding to the subject with $\text{AHI} = 32.1 \text{ h}^{-1}$.

Figure 2: Prior probability distribution $f(\sigma)$ of the bandwidth parameter σ for $\lambda = 0.1, 1, 5, 10$.

Figure 3: Analysis of the results on two-class classification of subjects. ROC curves computed from the measurements of (a) AEn, (c) SEn and (e) KEn. Boxplots in SAHS-negative and SAHS-positive groups for (b) AEn, (d) SEn and (f) KEn.

Figure 4: Utility of the evaluated entropy metrics to rank SAHS severity. AHI versus SaO₂ regularity quantified by (a) AEn, (c) SEn and (e) KEn. Boxplots in the four SAHS severity groups for (b) AEn, (d) SEn and (f) KEn.

⁶⁶⁵ **Table captions**

Training Set			
	All	SAHS-positive	SAHS-negative
Subjects	96	64	32
Age (years)	52.35 ± 13.76	54.88 ± 14.53	47.31 ± 10.59
Males (%)	77.08	84.38	62.50
BMI (kg/m ²)	29.83 ± 4.17	30.61 ± 3.86	28.27 ± 4.38
Recording Time (h)	7.25 ± 0.33	7.25 ± 0.35	7.25 ± 0.29
AHI (h ⁻¹)	24.75 ± 25.19	35.01 ± 25.16	4.23 ± 2.22
Test Set			
	All	SAHS-positive	SAHS-negative
Subjects	144	96	48
Age (years)	52.19 ± 13.73	54.71 ± 13.35	47.17 ± 13.20
Males (%)	77.78	83.33	66.67
BMI (kg/m ²)	29.83 ± 4.53	30.98 ± 4.65	27.54 ± 3.26
Recording Time (h)	7.24 ± 0.66	7.22 ± 0.78	7.30 ± 0.33
AHI (h ⁻¹)	26.39 ± 26.74	37.71 ± 26.17	3.75 ± 2.51

Table 1: Clinical and demographic features for subjects in training and test sets. Data are presented as mean ± standard deviation. BMI: body mass index; AHI: apnoea-hypopnoea index.

	AUC	ρ
AEn ($m = 1, r = 0.1$ SD)	0.68	0.32
AEn ($m = 1, r = 0.15$ SD)	0.57	0.19
AEn ($m = 1, r = 0.2$ SD)	0.50	0.18
AEn ($m = 1, r = 0.25$ SD)	0.48	0.15
AEn ($m = 2, r = 0.1$ SD)	0.56	0.18
AEn ($m = 2, r = 0.15$ SD)	0.55	0.13
AEn ($m = 2, r = 0.2$ SD)	0.51	0.13
AEn ($m = 2, r = 0.25$ SD)	0.52	0.14
SEn ($m = 1, r = 0.1$ SD)	0.74	0.40
SEn ($m = 1, r = 0.15$ SD)	0.68	0.31
SEn ($m = 1, r = 0.2$ SD)	0.63	0.33
SEn ($m = 1, r = 0.25$ SD)	0.63	0.34
SEn ($m = 2, r = 0.1$ SD)	0.67	0.22
SEn ($m = 2, r = 0.15$ SD)	0.61	0.13
SEn ($m = 2, r = 0.2$ SD)	0.58	0.17
SEn ($m = 2, r = 0.25$ SD)	0.60	0.19
KEEn ($m = 1$)	0.86	0.82
KEEn ($m = 2$)	0.86	0.83

Table 2: Selection of the input parameters using training data. Results achieved on the training set by the evaluated configurations of AEn, SEn and KEEn. AUC: area under the ROC curve; ρ : Pearson’s correlation coefficient; m : vector length parameter; r : tolerance; SD: standard deviation.

	AUC	ρ
AEn ($m = 1, r = 0.1$ SD)	0.67	0.34
SEn ($m = 1, r = 0.1$ SD)	0.74	0.45
KEn ($m = 2$)	0.91	0.87

Table 3: Assessment of the entropy metrics on test samples. Results achieved on the test set by the selected configurations of AEn, SEn and KEn. AUC: area under the ROC curve; ρ : Pearson’s correlation coefficient; m : vector length parameter; r : tolerance; SD: standard deviation.

	Normal vs Mild	Mild vs Mod.	Mod. vs Sev.	Normal vs Mod.	Normal vs Sev.	Mild vs Sev.
AEn	> 0.001	> 0.5	> 0.05	> 0.005	< 0.0001	> 0.05
SEn	> 0.001	> 0.5	> 0.01	< 0.0001	< 0.0001	> 0.001
KEn	< 0.0001	> 0.001	< 0.0001	< 0.0001	< 0.0001	< 0.0001

Table 4: One-way ANOVA test to evaluate the difference between the means of each entropy metric in the four SAHS severity groups: normal, mild, moderate and severe.

	AUC	ρ
f_{avg}	0.85	0.59
f_{sd}	0.96	0.76
f_{cv}	0.96	0.71
f_{iqr}	0.96	0.74
f_{sd1}	0.97	0.77
f_{sd2}	0.96	0.76

Table 5: Diagnostic results obtained for conventional statistical features of oximetry samples on the test set. AUC: area under the ROC curve; ρ : Pearson’s correlation coefficient; f_{avg} : mean; f_{sd} : standard deviation; f_{cv} : coefficient of variation; f_{iqr} : interquartile range; f_{sd1} : first-order dispersion index from Poincare plot; f_{sd2} : second-order dispersion index from Poincare plot.

Figure 1
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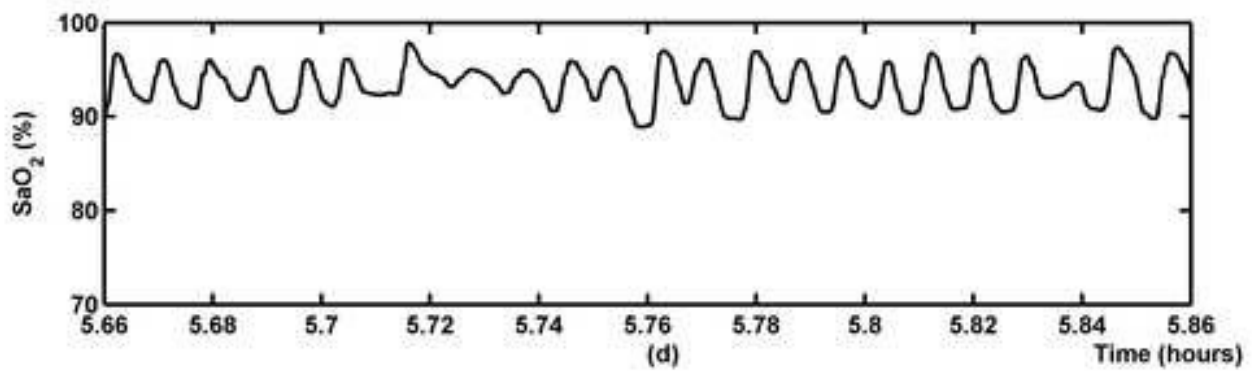
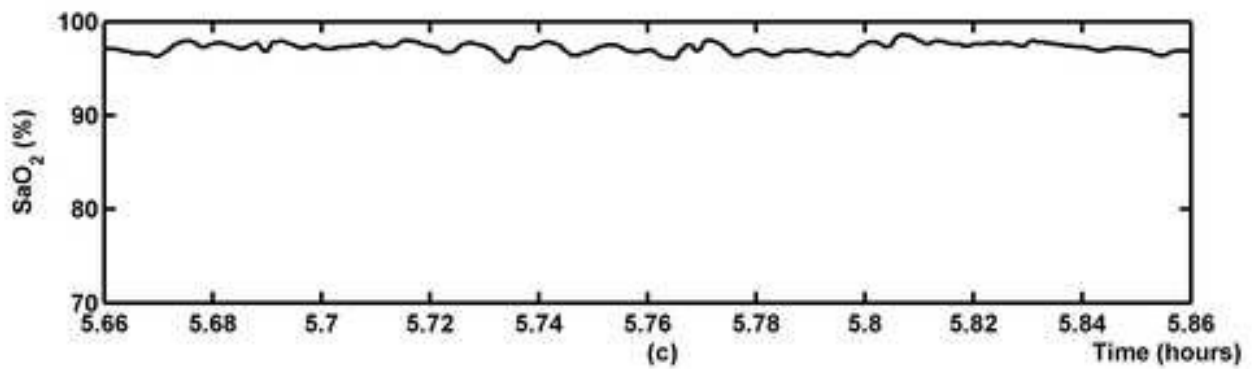
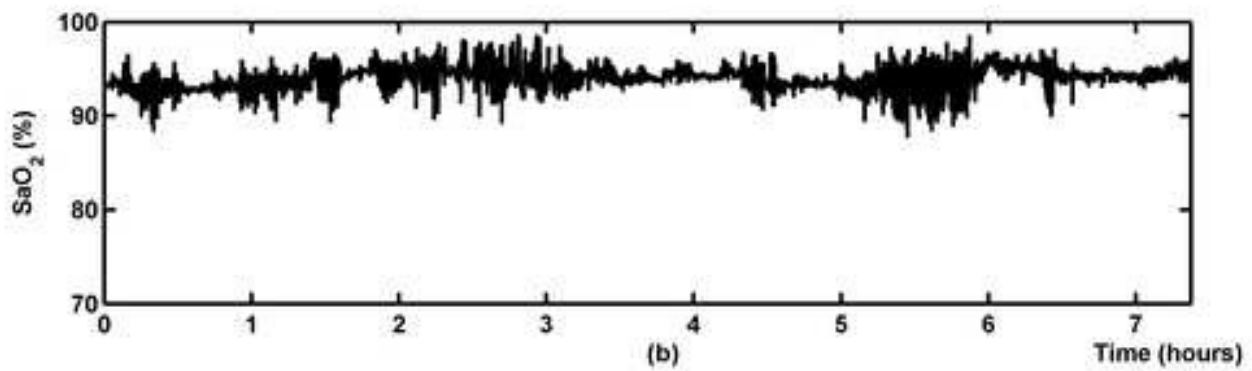
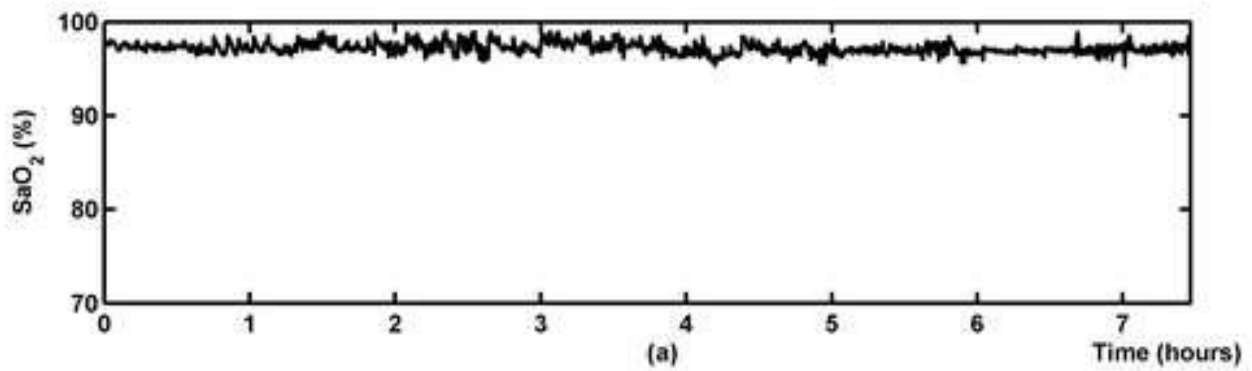


Figure 2

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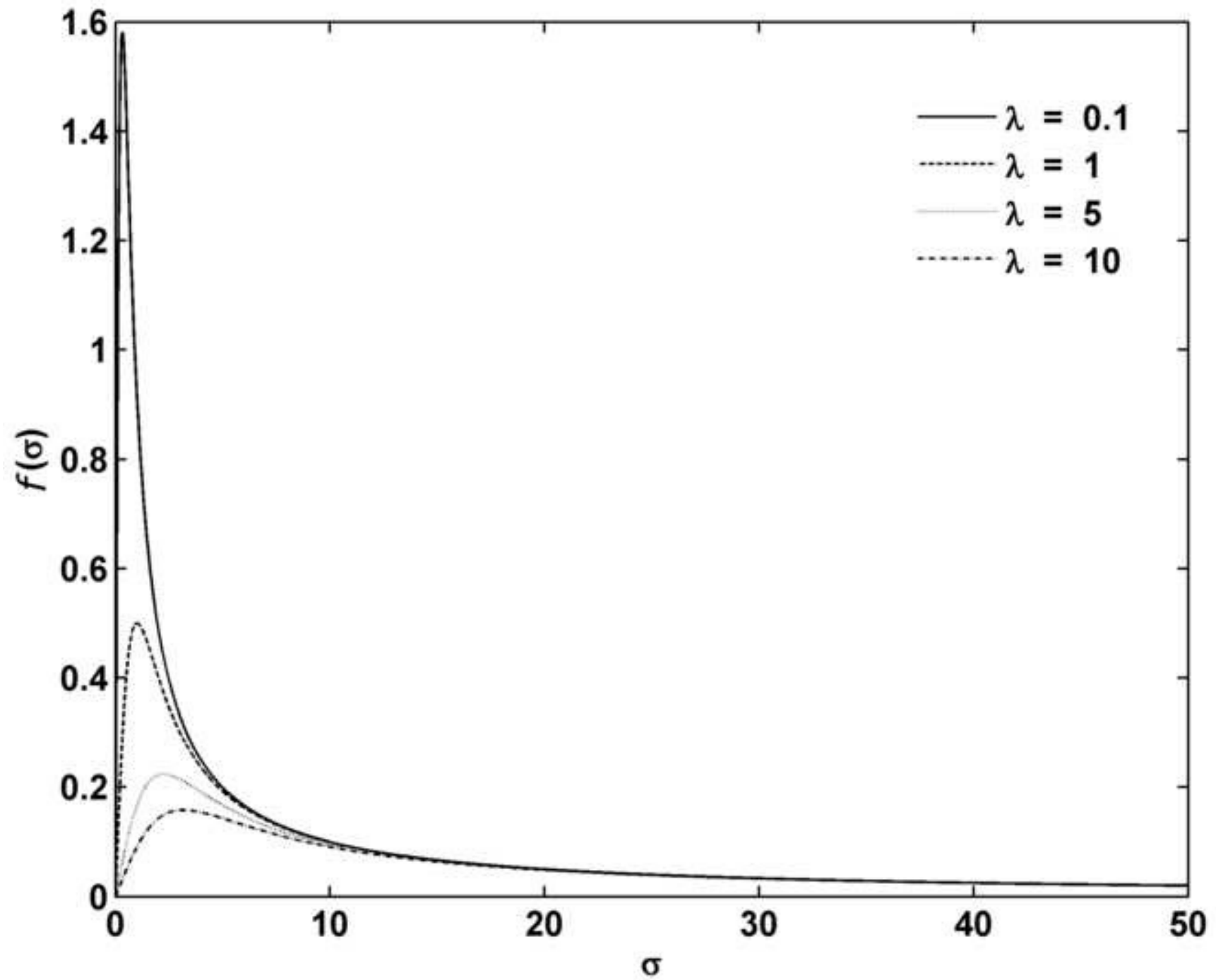


Figure 3

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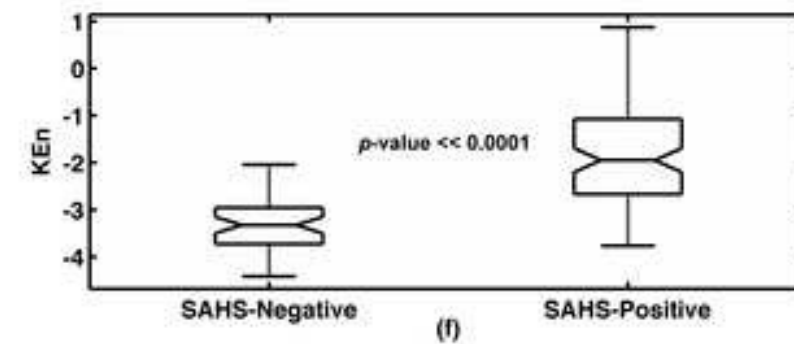
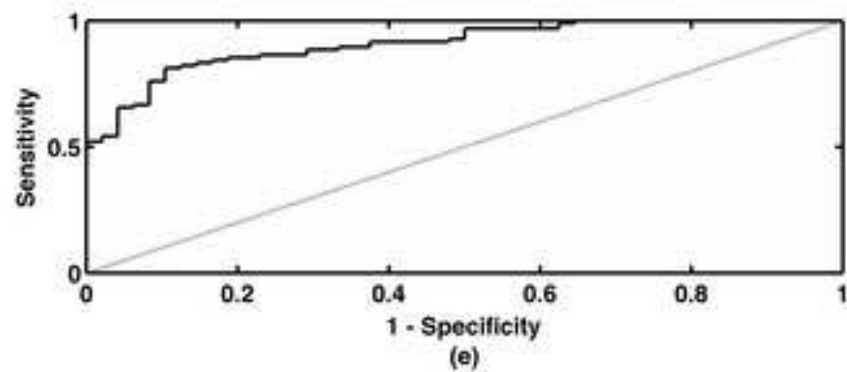
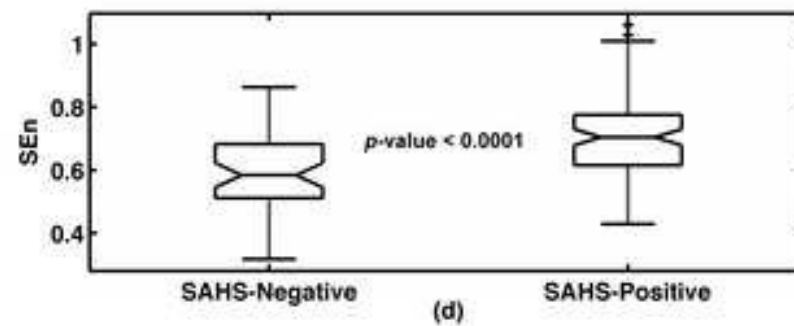
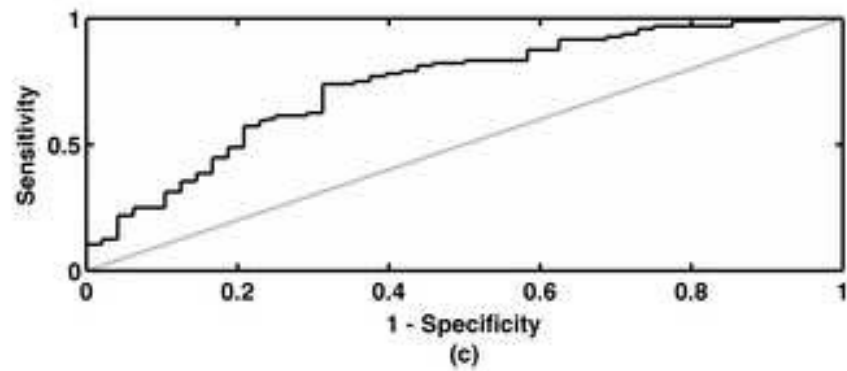
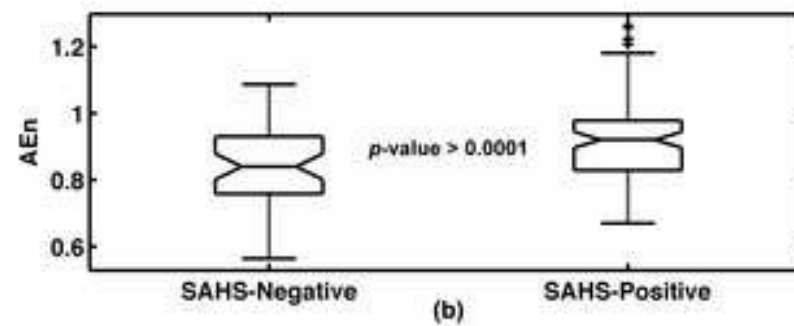
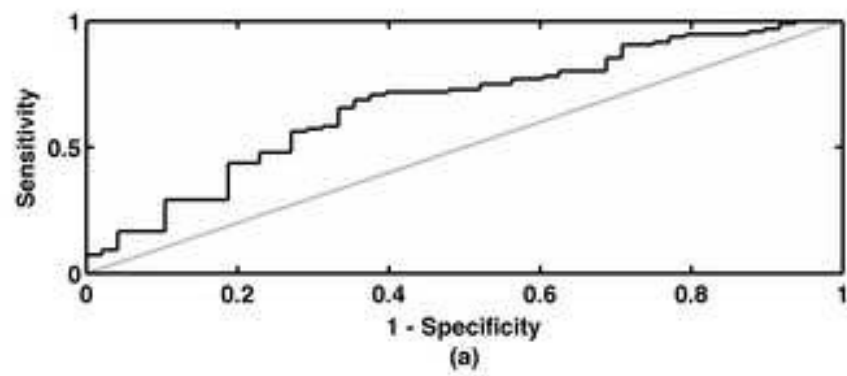


Figure 4

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