ON INFORMATION-THEORETIC APPROACH TO HRV TIME-SERIES ANALYSIS

Tatjana Lončar-Turukalo, *Dept. of Communications and Signal Processing, Univ. of Novi Sad*, tloncar@eunet.yu
Dragana Bajić, *Department of Communications and Signal Processing, University of Novi Sad*, lmcdra@eunet.yu
Nina Žigon, *Medical Faculty, University of Belgrade*, zigon@eunet.yu

Abstract — *HRV analysis represents one of the most promising and the most commonly used quantitative measures of the cardiovascular autonomic regulatory system. The analysis include traditional statistical analytical tools and a number of new methods based on nonlinear system theory, recently developed to give better insight into complex HR.. This paper deals with approximate entropy (ApEn), its drawbacks and improvements in order to assure statistical consistency of the obtained values.*

1. INTRODUCTION

Heart rate variability (HRV) has become the conventionally accepted term to describe variations of interval between consecutive heartbeats, as well as the oscillations between consecutive instantaneous heart rates. It represents one of the most promising and the most commonly used quantitative measures of the cardiovascular autonomic regulatory system. The analysis include traditional statistical analytical tools both in time and spectral domain and a number of new methods based on nonlinear system theory, recently developed to give better insight into complex HR dynamics, such as fractal correlation properties, the slope of the power law relation and approximate entropy (ApEn). These methods might reveal abnormalities that may not be uncovered by traditional measures. However, the significance and meaning of these different measures of HRV are more complex than generally appreciated, and there is a potential for incorrect conclusions and for excessive or unfounded extrapolations. Besides, in spite of general opinion that HRV time series is easy to obtain, visual inspection and careful manual editing after automatic extraction is absolutely necessary. For 24 hours' holter signal it presents a cumbersome task. [1-4]

This paper is devoted to the improvement of approximate entropy approach to HRV series analysis. The subsequent section gives a brief review of theory of ApEn and methods to reduce its bias (SampEn). The third section outlines further inconsistencies (from the information-theoretic point of view) of both ApEn and SampEn and proposes a method for its overcoming. The method is illustrated using analog ECG holter signal of a clinically healthy child recorded at Children's hospital (Tirsova), digitalized and HRV extracted at FTN. A part of HRV signal (in beats per minute, BPM) is shown in Fig. 1

2. APPROXIMATIVE AND SAMPLE ENTROPY

ApEn can be defined as a "regularity statistic" that quantifies the unpredictability of fluctuations in a time series. Intuitively, one may reason that the presence of repetitive patterns of fluctuation in a time series renders it more predictable than a time series in which such patterns are absent.

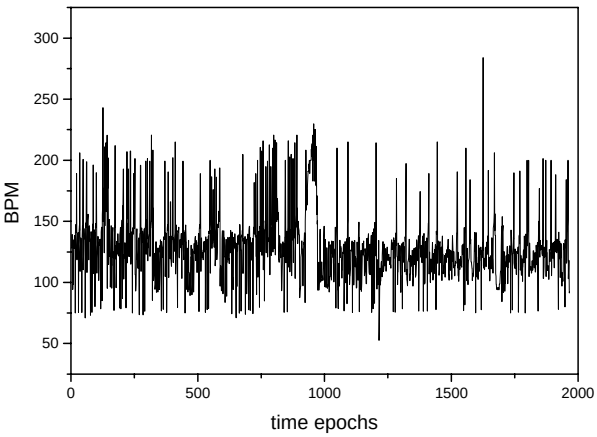

Fig.1. *Sample of HRV time series*

ApEn reflects the likelihood that "similar" patterns of observations will *not* be followed by additional "similar" observations. Therefore, a time series containing many repetitive patterns has a relatively small ApEn; a less predictable (i.e., more complex) process has a higher ApEn. This measure is closely related to Kolmogorov-Sinai (K-S) entropy, a rate of changing the information.

For the evaluation of ApEn the following parameters have to be defined:

- time series (in our case HRV) $[u(j)]$, j=1,…,N;
- "template" $\mathbf{x}_m(i) = [u(i+k-1)]$, $k = 1,\ldots,m$, i=1,…,N-m+1;
- Distance: $d(\mathbf{x}_m(i), \mathbf{x}_m(j)) = \max|u(i+k-1)-u(j+k-1)|$, $k = 1,\ldots,m$
- N – time series length;
- m – template length;

The first m samples of HRV form the first template; the template is then compared to ALL N-m+1 adjacent m-tuples that can be formed of HRV signal. Number of m-tuples for which $d(\mathbf{x}_m(1), \mathbf{x}_m(j))$, j=1,…,N-m+1 is within the specified distance r are counted as a positive outcome "template match", its number noted as B_1. The procedure is repeated for the second template, yielding other numbers of template matches B_i, $i = 2,\ldots,N-m+1$.

The function

$$C_i^m(r) = \frac{B_i}{N-m+1} \tag{1}$$

estimates the probability that any vector $\mathbf{x}_m(j)$ is within the distance r from the template $\mathbf{x}_m(i)$. Another function

$$\Phi^m(r) = \frac{1}{N-m+1} \cdot \sum_{i=1}^{N-m+1} \ln\left[C_i^m(r)\right] \tag{2}$$

is average of the natural logarithms of the previous functions. The process is repeated for a sample longer templates, where A_i presents the number of template matches for the $\mathbf{x}_{m+1}(i)$ template.

$$C_i^{m+1}(r) = \frac{A_i}{N-m} \quad (3)$$

$$\Phi^{m+1}(r) = \frac{1}{N-m} \cdot \sum_{i=1}^{N-m} \ln\left[C_i^{m+1}(r)\right] \quad (4)$$

The entropy of the underlying process can be approximated as:

$$\lim_{r\to 0} \lim_{m\to\infty} \lim_{N\to\infty} \left[\Phi^m(r) - \Phi^{m+1}(r)\right] \quad (5)$$

This definition, known as Eckman-Ruelle (E-R) entropy formula for "direct" evaluation of K-S entropy, is obviously not suited for the finite data sets analysis. Instead of it, its approximate measure is introduced:

$$\mathrm{ApEn}(m,r,N) = \Phi^m(r) - \Phi^{m+1}(r) \quad (6)$$

However, it is soon noticed that counting self-matches introduces a bias in ApEn statistics: if values Eqs. (1) and (3) equal to 0, a logarithm of 0 would appear in (2) and (4). To avoid this, each "self-template" match is included into counts. But, in practice, this bias causes ApEn to lack two important expected properties. First, ApEn is heavily dependent on the record length and is uniformly lower than expected for short records. Second, it lacks relative consistency. That is, if ApEn of one data set is higher than that of another, it should, but does not, remain higher for all conditions tested. This shortcoming is particularly important, because ApEn has been repeatedly recommended as a relative measure for comparing data sets [1,2 and references listed in 3].

To reduce this bias, a new family of statistics, sample entropy (SampEn), that does not count self-matches, is developed [3]. The quantities $B^m(r)$ (the probability* that two sequences will match for m points), and $A^m(r)$ (the probability that two sequences will match for m+1 points are evaluated as:

$$B^m(r) = \frac{1}{N-m} \cdot \sum_{i=1}^{N-m} \frac{B_i - 1}{N-m-1} \quad (7)$$

$$A^m(r) = \frac{1}{N-m} \cdot \sum_{i=1}^{N-m} \frac{A_i - 1}{N-m-1}. \quad (8)$$

The SampEn is then estimated as:

$$\mathrm{SampEn}(m,r,N) = -\ln\left(\frac{A^m(r)}{B^m(r)}\right) \quad (9)$$

Figs. 2, 3 and 4 present an ApEn and SampEn family of curves, using a HRV time series of a clinically healthy child. As ApEn and SampEn might be heuristically defined as measure of the logarithmic likelihood that patterns that are close remain close on next incremental comparison definition of ApEn, it is expected (and mathematically proved [1]) that the measures do not depend on m. Although the differences can be explained by the fact that N should be at least 10^m to obtain significant results, and for small r there are not enough matches to ensure statistical consistency, for differences where r is close to 1 (this is a normalised difference; actually, template match is performed against the factor $r\cdot\sigma$, where σ is the standard deviation of the series).

*Comments would be given within the following section;

3. ESTIMATION IMPROVEMENT

Starting with E-R entropy that was, originally, designed as a average of (log) of conditional probability that $|u((j+m+1)-u(i+m+1)|\le r$, given that $|u((j+k-1)-u(i+k-1)|\le r$, $k = 1,\ldots,m$ a measure of correlation dimension is designed that was, later on, proved to be of no significance. However, ApEn and SampEn estimate likelihood that patterns of certain length that are close one to another would remain close if the pattern length increase. In this case, when the distance of *patterns* is of significance and the distance of samples (important for correlation properties) is not, mean squared difference rather than maximal absolute value might be better choice for pattern distance measure.

$$d(\mathbf{x}_m(i), \mathbf{x}_m(j)) = \sqrt{\frac{1}{m}\sum_{k=1}^{m}\left(u(i+k-1) - u(j+k-1)\right)^2} \quad (10)$$

The same reasoning as for preference of the expected value for best approximation of a random variable vs. its median value applies.

Figures 5, 6 and 7. illustrate the application of this measure. A slight improvement might be noticed indeed. For ApEn, plots for various values of m keep tightly, especially for r>0.3. SampEn seems to be more splashed, until it is noticed that mean sqrt. distance enables existence of more points for lower values of r. But, improvement is not so great to verify increase of CPU time for distance evaluation.

The next notion, however, is of more serious nature. Let us return to estimate of "probability that patterns are within a certain distance of each other", A_i or B_i. These estimates are performed using the sliding window approach that is supposed to average all the events. However, deep mathematical analyses performed and published by various authors including this one [5-9] show that this is a biased approach: test are, obviously, statistically dependent and therefore cannot estimate the probability of an event. Therefore, the proposed estimates of these probabilities should be performed by random testing.

In this investigation, two approaches are tried, one with random testing (with the restriction that no sample would appear within a single test more than once), and "window by window", further illustrated in Fig. 8. The first one , however, needs more CPU time yielding less test samples. Since it is clear that self-matching should be excluded, only SampEn approach is used.

The counting procedure "window-by-window" starts with TEST 1 (Fig. 8) before and after the template. For the second testing position, window slides m+1 samples, for the third further m+2 to avoid eventual ciclostacionarity of a process etc. Then the obtained values are averaged and the second shift is performed, this time starting a sample apart from template position, etc.

From the results plotted in Fig. 9 and 10 it is obvious that SampEn is not dependent upon m when estimated as proposed. Furthermore, estimated values of entropy is higher than the ones obtained by sliding window – quite in accordance with the notion that sliding window tests correspond to Markov sources, while window-by-window tests are memoryless thus yielding higher entropy values.

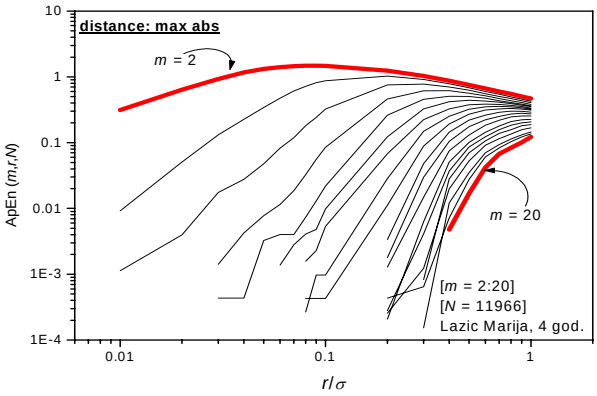

Fig.2. *ApEn(m,r,N) – abs. distance*

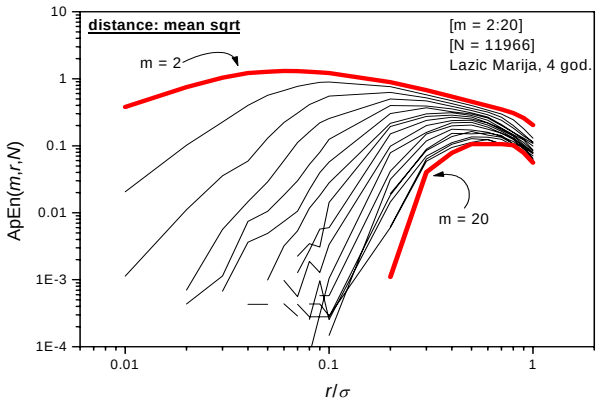

Fig.5. *ApEn(m,r,N) - mean sq. root distance*

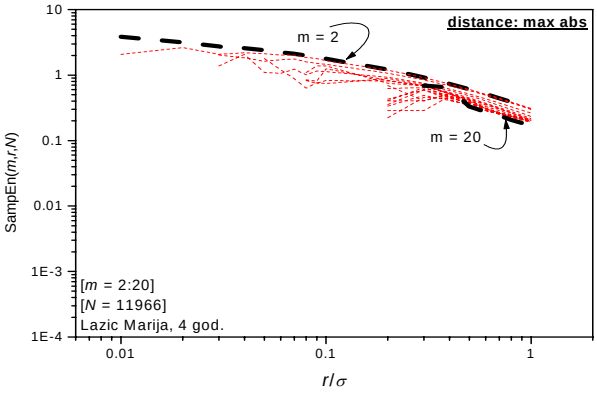

Fig. 3. *SampEn(m,r,N) – abs. distance*

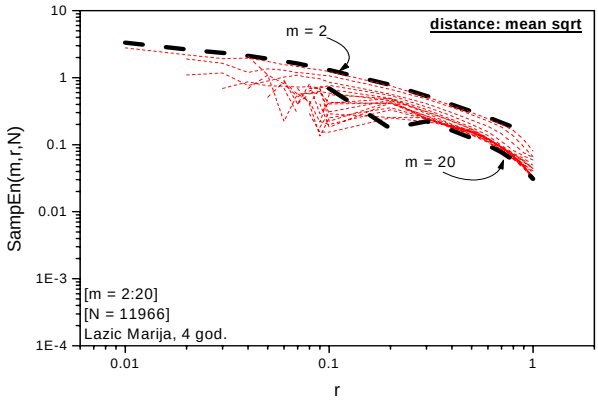

Fig.6. *SampEn(m,r,N) - mean sq. root distance*

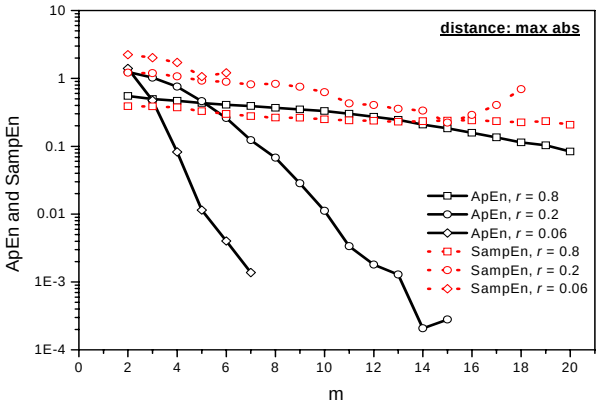

Fig. 4. *ApEn and SampEn – abs. distance*

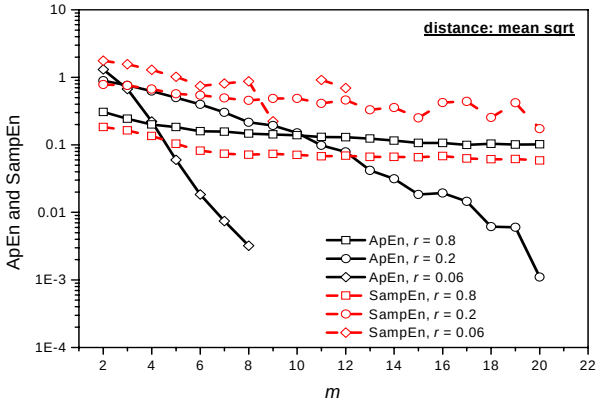

Fig 7. *ApEn and SampEn - mean sq. root distance.*

Other comparative measure is normalized standard deviation, plotted in Fig. 11. The plots are not smooth due to (relatively) small statistical sample, but decrease obtained by the proposed method is obvious.

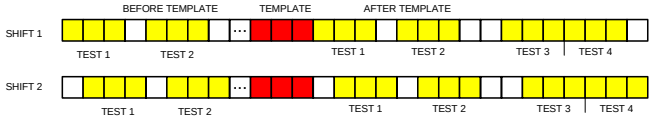

Fig. 8. *"Window by window" sliding procedure*

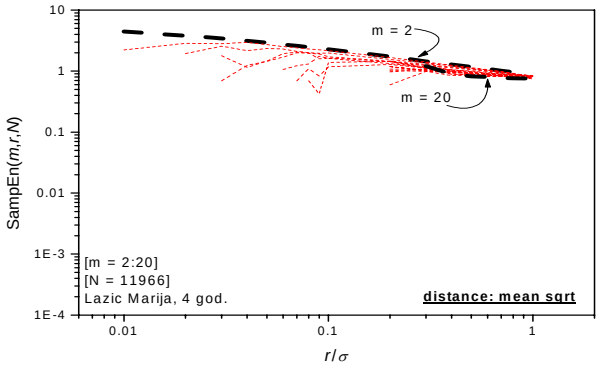

Fig. 9. *SampEn(r) – window-by-window estimates*

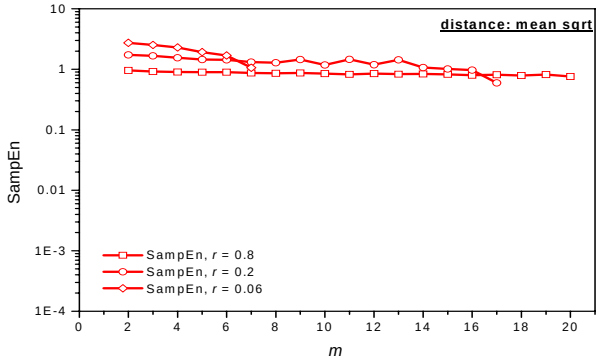

Fig. 10. *SampEn(m) – window-by-window estimates*

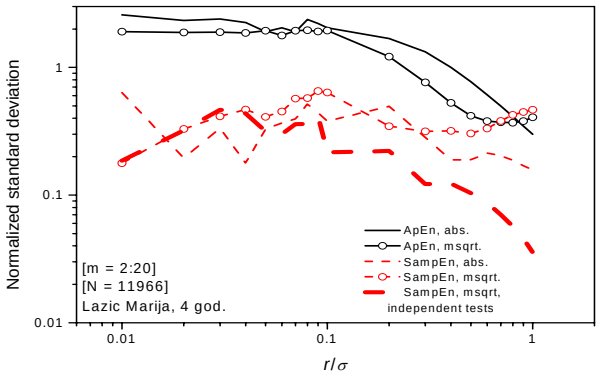

Fig. 11. *Standard deviation of different m values*

4. CONCLUDING REMARKS

There exists a growing interest in the development of new measures to describe the dynamics of psychological systems and use of these measures to distinguish healthy function from disease or to predict the onset of adverse health-related events. While many authors claim spectacular results within the fields of diagnosis and prediction, some do warn about impossibility to use any of the method automatically and straightforwardly.

This paper has not touched the clinical interpenetration yet. It has concentrated upon removing the (more or less) obvious shortcomings in probabilistic averaging. Even the completely statistically coherency has not been established yet: the parameter *r* is scaled with standard deviation in all the papers dealing with the topic; however, the HRV time series is not a stationary process; that is the reason why classical moment statistics can not be applied and various non-linear methods including ApEn and SampEn become so important. And yet, a classical parameter (the one that requires stationarity to be evaluated) is used in a non-linear model introduced because of the non-stationarity of the signal!

Further research would include more multi-disciplinary study of the topic.

REFERENCES

[1] S.M. Pincus: "Approximate entropy as a measure of system complexity", *Proc Natl Acad Sci USA*;Vol. **88**:pp 2297-2301, 1991

[2] A.L. Goldberger, S.M. Pincus: "Physiological time-series analysis: What does regularity quantify?" *Am J Physiol*, Vol. **266**(Heart Circ Physiol), pp H1643-H1656, 1994.

[3] J.S. Richman, J.R. Moorman: "Physiological time-series analysis using approximate entropy and sample entropy" *Am J Physiol Heart Circ Physiol* Vol. **278**(6), ppH2039-H2049, 2000.

[4] L.A. Lipsitz: "Dynamics of Staility", *J. of Gerontology,* Vol. 57A, No3, pp. B115-B125, 2002.

[5] T. McConell: "The Expected Time to Find a String in a Random Binary Sequence" [http://barnyard.syr.edu/cover.pdf], January 2001.

[6] D. Bajić, D. Drajić: "Duration of search for a fixed pattern in random data: Distribution function and variance", *Electronics Letters,* 1995, Vol. 31. No. 8, pp 631-632.

[7] D. Bajić, J. Stojanovic and J. Lindner: "Multiple Window-sliding Search", *Proceedings of 2003 IEEE International Symposium on Information Theory* **ISIT-2003**, Yokohama, Japan, June 2003, pp 249.

[8] D. Bajić, J. Stojanović: "An Analysis of the Search Process for Different Patterns in Random Data", *Proceedings of IEEE Region 8 EUROCON 2003* Ljubljana, Slovenia, September 2003

[9] D. Bajić, J. Stojanovic: "Distributed Sequences and Search Process", IEEE *International Conference on Communications* – **ICC2004**, Paris, France, June 2004.

Sadržaj – U današnje vreme postoji rastući interes za razvoj novih metoda koje bi opisivale dinamiku bioloških sistema i dale mogućnost što jasnijeg razlikovanja zdravog od patološkog funkcionisanja ili mogućnost predviđanja i uočavanja začetaka patoloških procesa u organizmu. Analiza signala promene srčanog ritma (u tekstu HRV – Heart Rate Variability signal) jedna je od najčešće korišćenih kvantitativnih merenja kardiovaskularnog autonomnog regulatornog sistema. Ova analiza uključuje kako metode tradicionalne statističke analize, tako i više novih metoda, baziranih na teoriji nelinearnih sistema, a razvijenih upravo radi boljeg uvida u kompleksni signal koji prikazuje rad srca. U ovom radu predstavlja se jedna od metoda analize HRV signala tzv. metoda aproksimirane entropije (Approximate Entropy), ukazuje se na njene nedostatke i prikazuje mogućnost njenog poboljšanja u cilju postizanja statističke konzistentnosti dobijenih rezultata.

U okviru rada nije se došlo do kliničke interpretacije postignutih rezultata. Rad se prevashodno koncentrše na otklanjanje očiglednih nedostataka na polju probabilističkih usrednjavanja.

ANALIZA SIGNALA PROMENE SRČANOG RITMA SA STANOVIŠTA TEORIJE INFORMACIJA

Tatjana Lončar -Turukalo, Dragana Bajić, Nina Žigon