*Journal of Applied Statistics* Vol. 00, No. 0, Month 2010, 1–11

1

6

11

16

21

26

Copyedited by: KS



# The difference-sign runs length distribution in testing for serial independence

Camillo Cammarota\*

Department of Mathematics, University of Rome "La Sapienza", Piazzale Aldo Moro 2, 00185, Rome, Italy

(Received 9 July 2009; final version 13 February 2010)

We investigate the sequence of difference-sign runs length of a time series in the context of non-parametric tests for serial independence. This sequence is, under suitable conditioning, a stationary sequence and we prove that the normalized correlation of two consecutive runs length is small ( $\approx 0.0427$ ). We use this result in a test based on the relative entropy of the empirical distribution of the runs length. We investigate the performance of the test in simulated series and test serial independence of cardiac data series in atrial fibrillation.

Keywords: runs test; difference-sign; serial independence; entropy; time series; atrial fibrillation

2000 Mathematics Subject Classification: 62G10; 62M10

#### 1. Introduction

The difference-sign runs test plays a central role in non-parametric tests for serial independence. This test is often used in time series analysis for testing the independence of the residuals in fitted deterministic trend models [4]. The definition of difference-sign runs can be given in terms of occurrence times of extrema (maxima and minima) in the series. Let X<sub>1</sub>, X<sub>2</sub>, ... be a sequence of continuous random variables (rv), whose indexes are referred to as 'times'. Denote A = {x<sub>1</sub> < x<sub>2</sub>, x<sub>2</sub> > x<sub>3</sub>} ⊂ R<sup>3</sup> the event corresponding to a maximum, B = {x<sub>1</sub> > x<sub>2</sub>, x<sub>2</sub> < x<sub>3</sub>} ⊂ R<sup>3</sup> the event corresponding to an extreme. For instance, we say that in *i* a maximum occurs if (X<sub>i-1</sub>, X<sub>i</sub>, X<sub>i+1</sub>) ∈ A.

Let  $T_1, T_2, ...$  denote the occurrence times of the event E, with  $T_1 \ge 2$  and  $T_i < T_{i+1}$  and let  $H_i$  denote the associated recurrence times

$$H_i = T_{i+1} - T_i, \quad i = 1, 2, \dots$$

The intervals defined by  $T_i$  are the difference-sign runs, hereafter called simply 'runs', and the  $H_i$  are their lengths. The classical runs test is based on the statistics defined as the number of runs.

46

\*Email: cammar@mat.uniroma1.it http://www.mat.uniroma1.it/people/cammarota/

ISSN 0266-4763 print/ISSN 1360-0532 online © 2010 Taylor & Francis DOI: 10.1080/02664761003758984 http://www.informaworld.com

Techset Composition Ltd, Salisbury

Page#: 11

#### C. Cammarota

Since this statistic is based on ranking of the values, it gives rise to a distribution-free test [2]. In a sequence of independent and identically distributed (i.i.d.) X<sub>1</sub>,..., X<sub>n</sub> continuous rv of size n, the runs statistic, denoted N, is known to be approximated by a normal of mean (2n - 1)/3 and variance (16n - 29)/90 [11,16]. For practical implementation of this kind of tests, we also refer to Sachs [14]; for different definitions of runs we refer to Balakrishnan and Koutras [1]. The covariance matrix of the vector N<sub>1</sub>,..., N<sub>p</sub>, where N<sub>j</sub> is the number of runs of length j, is also known [11]. These results have been used to test pseudo random numbers generators [10].

Physiologic signals provide a lot of data series in which one has to use robust methods such as non-parametric tests for serial independence. There are at least two reasons: the data distribution is generally non-normal or not known and outliers are often present. For a public database and bibliography, we refer to Goldberger *et al.* [9]. We consider here the time series of RR intervals (see below) extracted from the electrocardiograms (ECG). The amount of randomness in these series has been widely investigated in physical literature related to various normal and pathological conditions (see for instance Urbanowicz *et al.* [15] and references therein). In some pathologies, such as atrial fibrillation, the RR series is characterized by a high level of uncorrelated noise.

However, at our knowledge, is still lacking an analysis based on rigorous testing procedures. A first step in this direction is in Cammarota and Rogora [6] and suggests that this series can be modeled by a smooth deterministic trend plus an autoregressive model of Order 0 or 1.

The use of runs test in these data has, in addition to the motivations above mentioned, a third one: the runs have a direct physiologic interpretation in terms of acceleration and decelerations of heart rate (see below). Hence a runs test based on the distribution of the runs length seemed to be more appropriate than the standard one based on the number of runs. Unfortunately, the sequence of runs length extracted from an i.i.d. sequence is not independent. The joint probability of two consecutive runs length was computed in Levene and Wolfowitz [11]. This lack of independence has been noticed later in Knuth [10] and Chen and Kelton [7], where a modified definition of runs was adopted to assure independence.

One of the results of the present paper concerns the dependence structure of the sequence of runs length  $H_1, H_2, \ldots$  Under suitable conditioning this sequence is stationary [5] and ergodic. In this setting, we compute the lag one normalized autocorrelation of this sequence, and show that it is positive, but very small ( $\approx 0.0427$ ). This implies that a sample  $H_1, \ldots, H_n$  of runs length extracted from an i.i.d. sequence can be considered approximately as a random sample. This leads us to a test for serial independence based on the distribution of the runs length. The statistic is defined as the relative entropy of the empirical runs distribution with respect to the runs distribution of i.i.d. The performance of the test is compared with one of the standard runs test both in simulated processes and in data series of atrial fibrillation. An example is given in which the entropy test outperforms the standard one in detecting dependence.

2. The correlation of two consecutive runs length

91

96

86

81

The main new result in this section contained in Proposition 4 and Equation (11) states that the correlation of two consecutive runs length extracted from an i.i.d. sequence is small ( $\approx 0.0427$ ); the exact value is given by Equation (11). The proof requires some preliminary results (Propositions 2 and 3), which go back to Levene and Wolfowitz [11], whose proofs are in the appendix. Some basic results on the sequence of runs length are in Proposition 1 [5].

The first result concerns the conditions under which the sequence  $H_1, H_2, \ldots$  of runs lengths extracted from an i.i.d. sequence is stationary. For this we need to introduce the sequence

$$X'_i = (X_i, X_{i+1}, X_{i+2}) \in \mathbb{R}^3, \quad i = 1, 2...$$

and consider the probability conditioned to the event  $\{X'_1 \in E\}$ , that is, 'in two there is an extremum'. Following general properties for stationary and ergodic sequences of recurrence times

2

61

101 [3], the sequence  $H_1, H_2, \ldots$  is stationary if the probability is conditioned to start in an extreme. A second basic result is the well-known distribution free equation [13]

$$P(X_1 < \dots < X_s) = \frac{1}{s!},\tag{1}$$

where  $X_i$  are i.i.d. variables with continuous product distribution *P*. We summarize the basic properties of runs length in the following proposition.

PROPOSITION 1 If  $X_i$  are i.i.d. variables with continuous distribution, the sequence of runs length  $H_i$  is stationary and ergodic in the measure conditioned to the event  $X'_1 \in E$ . The conditional mean is given by

111

$$\mathbb{E}(H_1 \mid X_1' \in E) = \frac{3}{2}.$$
(2)

*Proof* As a preliminary step we compute the probability of an extrema. By symmetry,

$$P(X'_1 \in E) = P(X'_1 \in A) + P(X'_1 \in B) = 2P(X'_1 \in A)$$

116 and using Equation (1) one has

$$P(X'_1 \in A) = P(X_1 < X_2, X_2 > X_3)$$
  
=  $P(X_1 < X_2) - P(X_1 < X_2 < X_3) = \frac{1}{2} - \frac{1}{6} = \frac{1}{3}$ 

121 and

$$P(X_1' \in E) = \frac{2}{3}.$$
(3)

The sequence  $X'_i$  is stationary and from Equation (3) we get  $P(X'_i \in E \text{ i.o.}) = 1$ . The times  $H_1, H_2, \ldots$  are finite a.e., they form a stationary sequence under the conditional probability  $P(|X'_1 \in E)$ . The stationary sequence  $X'_i$  is two-dependent, that is,  $X'_i$  and  $X'_j$  are independent if |i - j| > 2 and not independent elsewhere. Hence it is also ergodic and  $H_i$  is an ergodic (not independent) sequence in the probability conditioned to  $X'_1 \in E$ . Equation (2) can be obtained easily from the well-known Kac formula for the expectation of the first recurrence time

$$\mathbb{E}(H_1 \mid X_1' \in E) = \frac{1}{P(X_1' \in E)}.$$
(4)

131

136

146

126

*Remarks* By symmetry, the probability of events generated by  $H_1, H_2, ...$  conditioned to *E* is the same as conditioned to *A* or *B*. For instance,  $P(H_1 = s | X'_1 \in E) = P(H_1 = s | X'_1 \in A)$ . The mean  $\frac{3}{2}$  is to be put into correspondence to the leading term  $\frac{2}{3}$  of the expectation of the number *N* of runs in a series of *n* elements [11].

The univariate distribution and the first two moments are summarized in the following proposition, where we denote the conditional probability shortly as P(|E).

#### 141 PROPOSITION 2 The conditional distribution of the runs length is given by

$$P(H_1 = s \mid E) = 3\left[\frac{1}{s+2}\frac{1}{s!} - \frac{1}{s+3}\frac{1}{(s+1)!}\right], \quad s \ge 1$$
(5)

and

$$\mathbb{E}(H_1 \mid E) = \frac{3}{2},\tag{6}$$

$$\mathbb{E}(H_1^2 \mid E) = 3(2e - \frac{9}{2}),\tag{7}$$

$$\mathbb{V}ar(H_1 \mid E) = 3(2e - \frac{21}{4}) \approx 0.560.$$
 (8)

#### *Proof* See appendix 151

PROPOSITION 3 The joint distribution of two consecutive runs length is given by

156 
$$P(H_1 = s, H_2 = t | E) = 3 \left[ \frac{1}{s+t+1} \frac{1}{s!} \frac{1}{t!} - \frac{1}{s+t+2} \frac{1}{s!} \frac{1}{(t+1)!} - \frac{1}{s+t+2} \frac{1}{(s+1)!} \frac{1}{(t+1)!} \frac{1}{(t+1)!} \right], \quad s, t \ge 1$$
(9)

*Proof* See appendix

PROPOSITION 4 The correlation of two consecutive runs length is given by

166 
$$\mathbb{E}(H_1H_2|E) - \mathbb{E}(H_1|E)\mathbb{E}(H_2|E) = 3(\frac{1}{2}e^2 - 2e + \frac{5}{2}) - (\frac{3}{2})^2 \approx 0.024.$$
(10)

*Proof* In order to compute the expectation  $\mathbb{E}(H_1H_2|E)$ , we use the formula

171 
$$\mathbb{E}(H_1H_2|E) = \sum_{s_0, t_0=1}^{\infty} P(H_1 \ge s_0, H_2 \ge t_0|E).$$

Using the telescopic form of the series, we get

176 
$$\sum_{t=t_0}^{\infty} P(H_1 = s, H_2 = t | E) = 3 \left[ \frac{1}{s+t_0+1} \frac{1}{s!} \frac{1}{t_0!} - \frac{1}{s+t_0+2} \frac{1}{(s+1)!} \frac{1}{t_0!} \right],$$
$$\sum_{t=t_0}^{\infty} P(H_1 = s, H_2 = t | E) = 3 \left[ \frac{1}{s_0+t_0+1} \frac{1}{s_0!} \frac{1}{t_0!} \right].$$

161

To compute the last series we use that

 $t = t_0, s = s_0$ 

$$\frac{1}{s_0 + t_0 + 1} = \int_0^1 z^{s_0 + t_0} \,\mathrm{d}z$$

186

and so

$$\sum_{s_0, t_0=1}^{\infty} \frac{1}{s_0 + t_0 + 1} \frac{1}{s_0!} \frac{1}{t_0!} = \int_0^1 dz \sum_{s_0, t_0=1}^{\infty} \frac{z^{s_0}}{s_0!} \frac{z^{t_0}}{t_0!} = \int_0^1 dz (e^z - 1)^2 = \frac{1}{2}e^2 - 2e + \frac{5}{2}.$$

191

Using the above results, the coefficient of correlation between the two variables is given by

$$\frac{\mathbb{E}(H_1H_2 \mid E) - \mathbb{E}(H_1 \mid E)\mathbb{E}(H_2 \mid E)}{\sqrt{\mathbb{V}ar(H_1 \mid E)\mathbb{V}ar(H_2 \mid E)}} = \frac{2e^2 - 8e + 7}{8e - 21} \approx 0.0427.$$
 (11)

196

#### 3. An entropy-based runs test

Let  $X_1, \ldots, X_n$  be a data series that is supposed to be i.i.d. and let  $H_1, \ldots, H_N$  be the runs length extracted from it, where N denotes the number of runs.

Table 1. Rounded values of the probabilities of runs length *s* from 1 to 5 according to Equation (5).

1	2	3	4	5
0.625	0.275	0.079	0.017	0.003

206

211

216

201

The standard runs test commonly in use is based on a normal approximation of the number of runs N for n large:

$$\frac{N - (2n-1)/3}{\sqrt{(16n-29)/90}} \sim Z,$$
(12)

where Z is the standard normal. Hence, a level 0.05 test is usually performed computing the above Z-score and comparing it with the quantiles  $z_{0.025} = -1.96$  and  $z_{0.975} = 1.96$  [14]. According to the result of the previous section, the length  $H_i$  is with good approximation. A random sample extracted from the stationary distribution is given by Equation (5).

These probabilities for lengths from 1 to 5 are given in Table 1. Let

$$g(s) = \frac{P(H_1 = s|E)}{\sum_{s=1}^{5} P(H_1 = s|E)}, \quad s = 1, \dots, 5$$

221

denote the distribution in Equation (5) truncated up to length five.

Let  $f_n(s)$  denote the empirical frequency of runs length up to length five:

$$f_n(s) = \frac{N_s}{N_1 + \dots + N_5}, \quad s = 1, \dots, 5,$$
 (13)

226

where  $N_s$  is the number of runs of length *s* in the data sequence of *n* elements. The test we consider here is based on the comparison of the empirical and the theoretical distributions  $f_n$  and *g*. The comparison is performed using the relative entropy or Kullback–Leibler divergence between two distributions [8].

In our setting the relative entropy of  $f_n$  with respect to g is given by

$$h_n = \sum_{s=1}^{5} f_n(s) \log\left(\frac{f_n(s)}{g(s)}\right),\tag{14}$$

236

241

246

231

where  $f_n(s) \log(f_n(s)/g(s)) = 0$  if  $f_n(s) = 0$  and the natural logarithm is used. One has  $h_n \ge 0$  and  $h_n = 0$  if and only if  $f_n(s) = g(s), s = 1, ..., 5$ .

Denoting  $q_{0.95}$  the 0.95th quantile of the distribution of  $h_n$ , the test rejects the independence hypothesis if the value of  $h_n$  computed on a data sequence exceeds  $q_{0.95}$ . Tests based on relative entropy with rejection region of type { $h_n > c$ } have bounds of Type I and Type II errors that are exponentially small in the number of observations (Hoeffding's entropy test [8]).

The quantiles of the distribution of  $h_n$  for a sequence of n = 200, 500, 1000 i.i.d. variables are obtained simulating 10,000 replicas using a pseudo random number generator (Table 2). In this and in the following computations, we have used the [12] free statistical software. We shall compare the powers of Z-score and entropy tests in the next section.

An alternative goodness-of-fit test could be the standard chi-square test, where the runs of length *s* observed are  $Nf_n(s)$  and the expected are Ng(s) for s = 1, ..., 5. This approach has two drawbacks: the number of runs *N* itself is random and the usual condition on the number of observations per cell,  $Nf_n(s) > 5$ , requires a large *n*. Actually, the runs of length five are expected

	of $n =$	of $n = 200, 500, 1000$ elements.								
	n	1%	2.5%	5%	50%	95%	97.5%	99%		
256	200 500	0.003355 0.000355	0.003838 0.000721	0.004390 0.001145	0.013067 0.005619	$0.035700 \\ 0.014674$	0.041821 0.017268	0.050466 0.020958		

0.000575

Table 2. Rounded values of the quantiles of the empirical distribution of  $h_n$  from simulated i.i.d. sequences of n = 200, 500, 1000 elements.

to occur only three times in a sequence with N = 1000 runs (Table 1), corresponding to  $n \sim 1500$ , according to Equation (12).

0.002707

0.007470

0.008468

0.009851

Another runs test is based on the asymptotic normal approximation of the vector  $(N_1, \ldots, N_s)$ . This test has been used for pseudo random number generators since it requires long series with  $n \sim 4000$  [10].

## <sup>266</sup> 4. Power study

We investigate the performance of the entropy runs test in detecting dependence using as an alternative hypothesis models based on linear AR(1) processes:

$$X_t = \varphi X_{t-1} + Z_t,$$

0.000390

where  $Z_t$  is an i.i.d. sequence of standard normals. This model has a stationary univariate distribution for  $\varphi \in (-1, 1)$ , which is the normal of mean 0 and variance  $1/(1 - \varphi^2)$ . For the properties of these models, we refer to [4]. In our simulation initial datum is put to zero, and  $Z_t$  is simulated using a pseudo random number generator.

We have computed the power of the entropy runs test of level 0.05 for size n = 500 in function of the parameter  $\varphi$  in the interval (-1, 1). For each value of the parameter the sequence has been replicated 500 times and the rejection rate was computed. Using the same sequences the power of the Z-score test has also been computed. The two powers are compared in Figure 1. Other

281 simulations of AR(1) sequences with non-normal (Cauchy) innovations show similar results.



Figure 1. Powers of the runs test of 0.05 level: Z-score (circles) and entropy (stars) as a function of the parameter  $\varphi$  of the AR(1) process with n = 500 elements.

1000

261

276

0.000204



Figure 2. Power of the runs test of 0.05 level: Z-score (circles) and entropy (stars) as a function of the parameter  $\varphi$  of the non-stationary process with n = 500 elements.

We consider a second process obtained by concatenating four AR(1) processes of size n = 125: the first and the third one with  $\varphi$ , the second and the fourth with  $-\varphi$ . This process is not stationary, but its one-dimensional marginal is stationary with respect to mean and variance.

For each  $\varphi \in (-1, 1)$ , the process has been replicated 500 times and the powers of the two tests are computed. The powers are shown in Figure 2.

For the stationary AR(1) process the power of entropy is slightly smaller that the other, in the non-stationary case the former largely dominates the latter.

### 5. Application to atrial fibrillation

341

346

- 331 In the electrocardiogram the main peak (corresponding to the systole) is labeled as R peak and the time intervals between two adjacent R peaks are called RR intervals. These intervals are inversely related to the instantaneous heart rate. The RR series show a strong variability, which is known as heart rate variability (HRV) [9]. This variability is caused by several factors, the main of which is the neuroautonomic control, which acts accelerating and decelerating the heart rate. Hence the
- analysis of the runs up and down of this series may be a tool for investigating the efficiency of this control.

Atrial fibrillation is a commonly diagnosed arrhythmia which affects up to 1% of the general population. In this pathology the conduction of the electrical stimulation through the atria is irregular leading to a corresponding sequence of irregular RR intervals, which are no longer controlled by the neuroautonomic system.

In subjects with atrial fibrillation, the RR series show very large uncorrelated fluctuations if compared with normals and other pathologies (see, for instance, Urbanowicz *et al.* [15] and references therein).

Although the irregular rhythm during atrial fibrillation is generally accepted to be random, rigorous statistical testing is still lacking.

In Cammarota and Rogora [6], data analysis performed using parametric tests on a small group of subjects showed that the hypothesis of serial independence is not rejected in the large majority of time; in the remaining the series can be modeled as an auto regressive model (AR) of very short memory.

#### C. Cammarota

- 351 This type of data has two features that make useful non-parametric tests: the distribution is not normal, having a longer right tail; there are outliers due to the automated detection of the R peaks. Furthermore, adjacent data values are generally largely different so the frequency of ties is negligible and the runs are well defined. We apply both standard and entropy runs tests in one case of atrial fibrillation.
- 356 This series was exported by the native software of a Rozinn Holter (Glendale, USA) equipment for ambulatory diagnostics in Policlinico of La Sapienza University of Rome.

This case shows an episode of paroxysmal atrial fibrillation, a condition in which the irregular rhythm occurs and terminates in a non-predictable way over time having duration from a few minutes up to days. In the case under analysis, the episode of fibrillation was consist-

- 361 ing of about 58,000 beats; extraction of these beats produces an RR time series of the same length (Figure 3, first panel). We have divided the series into 58 consecutive disjoint windows of size n = 1000. The entropy runs test is applied to each window and the values of the statistic are reported in Figure 3 (third panel) and compared with the Z-score of the standard runs test (second panel).
- The same procedure was repeated for windows of size n = 500 and 200 and the results are reported in Table 3. The number of widows in which the hypothesis is not rejected is almost the same for sizes n = 200 and 500. In case n = 1000, the acceptance rates  $(\frac{38}{58} \text{ and } \frac{46}{58})$  are smaller and their difference is larger. Both these facts can be explained since longer data windows could be non-stationary with respect to the mean. Finally, since the third column is less than the fourth,
- the entropy seems to be a more conservative test, which is in agreement with Figure 1.



390

Figure 3. First panel: The time series of the RR intervals in milliseconds extracted from the 24-h Holter ECG during atrial fibrillation. Second panel: The Z-scores of the standard runs test for windows of size 1000 and the acceptance region of level 0.05. Third panel: The runs entropy for the same windows and acceptance region of level 0.05.

n	Windows	Z-score	Entropy
200	290	258	260
500	116	97	102
1000	58	38	46

Table 3. Acceptance rates of the Z-score test (third column) and of the entropy test (fourth column) for three sizes windows in the time series of atrial fibrillation.

First column, size of the window; second, number of windows.

#### 411 **6.** Conclusions

The first result states that the correlation of two consecutive runs length is small. This allows to use all the runs extracted from a data series as an approximately random sample, avoiding to eliminate runs or data values from the series. The second result concerns an entropy-based runs test that uses as statistic the relative entropy of the empirical distribution of the runs length  $f_n(s) = N_s/N$ with respect to the theoretical one in the i.i.d. hypothesis. This test is compared with the Z-score runs test, based on the asymptotic normal approximation of the total number of runs N.

The powers of the two tests have been compared using as alternative processes based on AR(1) models with parameter  $\varphi \in (-1, 1)$ , which describes the strength of the interaction. The results are different if the process is stationary or not. In the stationary case the power of the entropy is smaller than the other, while in the non-stationary case the opposite happens. Power studies were lacking. This is a very preliminary investigation and extensive studies are needed to get some conclusion. We remark that the Z-score depends only on the number N of runs, while the entropy is less sensitive to N, since the empirical frequencies are computed just normalizing with respect to this number. For this reason a compound test which uses both the information should be of interest.

The entropy runs test has been applied to time series of inter beat duration in atrial fibrillation. These series are conjectured to be independent based on physiologic arguments and from previous investigations mainly without tests of statistical significance. The runs up and down of the RR series can be interpreted as decelerations and accelerations of the heart rate, hence their departure

from the i.i.d. can reflect the control of the neuroautonomic system.

Both the Z test and the entropy do not reject the independence hypothesis for a large majority of the time. The rate of acceptance of entropy seems to be larger; both the rates decrease as the size of the window increases, but the entropy seems more stable. These facts depend on several factors;

436 one of them could be the slowly varying mean typical of physiologic signals. In the windows in which the independence is rejected, an AR model of short memory was conjectured [6], and the problem deserves a detailed analysis. The fraction of the windows in which the independence is not rejected could be used in clinics as a an index of the strength of the pathology.

Some other questions are naturally to be considered. The entropy test is based on the numerical evaluation of the distribution of the statistic and relies upon the capability of pseudo random generators to simulate i.i.d. sequences. Investigations on the asymptotic distribution of the statistic can take advantage of the small correlation between two consecutive runs, a result that has not been fully exploited here. Finally, both tests assume that the variables are continuous, but in data series this is only an approximation mainly for low measurement resolution.

446

#### Acknowledgements

We thank Mario Curione (Clinical Science Department, University of Rome 'La Sapienza') for providing data and for valuable discussions. We thank the referees for stimulating criticism.

401

406

416

#### C. Cammarota

#### 451 References

- [1] N. Balakrishnan and M.V. Koutras, Runs and Scans with Applications, Wiley, New York, 2001.
- [2] J.V. Bradley, Distribution-free Statistical Tests, Prentice-Hall, Englewood Cliffs, NJ, 1968.
- [3] L. Breiman, Probability, SIAM, Philadelphia, PA, 1993.
- [4] P.J. Brockwell and R.A. Davis, Introduction to Time Series and Forecasting, Springer-Verlag, Berlin, 2002.
- [5] C. Cammarota and M. Curione, Analysis of extrema of heartbeat time series in exercise test, Math. Med. Biol. 25 (2008), pp. 87–97. ISSN 1477-8599, DOI:10.1093/imammb/dqn005. Available at http://dx.medra.org/10.1093/imammb/dqn005.
  - [6] C. Cammarota and E. Rogora, Independence and symbolic independence of nonstationary heartbeat series during atrial fibrillation, Phys. A 353 (2005), pp. 323–335. ISSN 0378-4371.
  - [7] E.J. Chen and W.D. Kelton, Determining simulation run length with the run test, Simul. Model. Pract. Theory 11 (2003), pp. 237–250.
  - [8] H.-O. Georgii, Stochastics, de Gruyter, Berlin, 2008.
  - [9] A.L. Goldberger, L.A.N. Amaral, L. Glass, J.M. Hausdorff, P.Ch. Ivanov, R.G. Mark, J.E. Mietus, G.B. Moody, C.-K. Peng, and H.E. Stanley, *Physiobank, physiotoolkit, and physionet: components of a new research resource for complex physiologic signals*, Circulation 101(23) (2000), pp. e215–e220. Available at http://circ.ahajournals.org/cgi/content/full/101/23/e215.
- 466 [10] D.E. Knuth. *The art of computer programming*, Vol. 2, Addison-Wesley, Reading, MA, 1988.
  - [11] H. Levene and J. Wolfowitz, The covariance matrix of runs up and down, Ann. Math. Stat. 15 (1944), pp. 58–69.
    - [12] R Development Core Team, R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria, 2008. Available at http://www.R-project.org. ISBN 3-900051-07-0.
    - [13] V. K. Rohatgi, An introduction to Probability Theory and Mathematical Statistics, Wiley, New York, 1976.
    - [14] L. Sachs, Applied Statistics, Springer, Berlin, 1982.
- 471 [15] K. Urbanowicz, J.J. Zebrowski, R. Baranowski, and J.A. Holyst, *How random is your heart beat*?, Physica A 384 (2007), pp. 439–447.
  - [16] J. Wolfowitz, Asymptotic distribution of runs up and down, Ann. Math. Stat., 15(2) (1944), pp. 163–172.

#### Appendix

476 Proof of Proposition 2 The proof of Equation (5) goes back to Levene and Wolfowitz [11]; a recent exposition is in Cammarota and Curione [5]; a proof obtained from the bivariate distribution is given below. Equation (6), a rewriting of Equation (2), can be obtained from the distribution (5) as follows:

491

$$\mathbb{E}(H_1|E) = 3\sum_{s_0=1}^{\infty} P(H_1 \ge s_0|E)$$

$$P(H_1 \ge s_0 | E) = \sum_{s=s_0}^{\infty} \frac{1}{s+2} \frac{1}{s!} - \frac{1}{s+3} \frac{1}{(s+1)!} = \frac{1}{s_0+2} \frac{1}{s_0!},$$

<sup>486</sup> where the last equality is obtained summing the telescopic series. Using that

$$\frac{1}{s_0+2} = \int_0^1 \,\mathrm{d}z \, z^{s_0+1}$$

one gets Equation (6) since

$$\sum_{r_0=1}^{\infty} \frac{1}{s_0+2} \frac{1}{s_0!} = \int_0^1 dz \, z(e^z - 1) = \frac{1}{2}.$$

Let us now compute the second moment  $\mathbb{E}(H_1^2|E)$ . This is given by

496 
$$3\sum_{s=1}^{\infty} s^2 \left[ \frac{1}{s+2} \frac{1}{s!} - \frac{1}{s+3} \frac{1}{(s+1)!} \right]$$

Using 
$$s^2 = (s+1)^2 - 2s - 1$$
 in the second contribution, we get  

$$\frac{s^2}{(s+2)s!} - \frac{s^2}{(s+3)(s+1)!} = \frac{s^2}{(s+2)s!} - \frac{(s+1)^2}{(s+3)(s+1)!} + \frac{2s+1}{(s+3)(s+1)!}$$

456

The first two terms form a telescopic series whose sum is  $\frac{1}{3}$ . The third one gives 501

$$\frac{2(s+1)}{(s+3)(s+1)!} - \frac{1}{(s+3)(s+1)!} = \frac{2}{(s+3)s!} - \frac{1}{(s+3)(s+1)!}$$

which can be treated as before and gives after summation  $2e - \frac{29}{6}$ .

506 *Proof of Proposition* 3 A complete proof is contained in the paper Levene and Wolfowitz [11]. Here we explain the idea of the proof in the particular case  $H_1 = 3$ ,  $H_2 = 3$  to avoid notational complications. Conditioning to E is the same as to B and this gives Factor 3. Conditioning to Bmeans that two is a minimum, five is a maximum and eight is a minimum. One has, denoting fthe density of the  $X_i$ , **C** 1 1

516

521

526

 $P(H_1 = 3, H_2 = 3|E)$ 

$$= 3P(X_1 > X_2, X_2 < X_3 < X_4 < X_5, X_5 > X_6 > X_7 > X_8, X_8 < X_9)$$
  
$$= 3\int_{-\infty}^{+\infty} dx_5 f(x_5) P(X_1 > X_2, X_2 < X_3 < X_4 < x_5, x_5 > X_6 > X_7 > X_8, X_8 < X_9)$$
  
$$= 3\int_{-\infty}^{+\infty} dx_5 f(x_5) P(X_1 > X_2, X_2 < X_3 < X_4 < x_5) P(x_5 > X_6 > X_7 > X_8, X_8 < X_9),$$

where the last equation follows by independence. One also has

$$P(X_1 > X_2, X_2 < X_3 < X_4 < x_5) = P(X_2 < X_3 < X_4 < x_5) - P(X_1 < X_2 < X_3 < X_4 < x_5),$$
  

$$P(x_5 > X_6 > X_7 > X_8, X_8 < X_9) = P(x_5 > X_6 > X_7 > X_8) - P(x_5 > X_6 > X_7 > X_8 > X_9).$$

Denoting F the distribution function of the  $X_i$ , the first contribution is given by

$$P(X_2 < X_3 < X_4 < x_5) = \int_{-\infty}^{x_5} dx_4 f(x_4) \int_{-\infty}^{x_4} dx_3 f(x_3) \int_{-\infty}^{x_3} dx_2 f(x_2) = \frac{1}{3!} F^3(x_5).$$
  
Using similar expressions for the other contributions, we get

Using similar expressions for the other contributions, we get

$$P(H_1 = 3, H_2 = 3|E) = 3 \int_{-\infty}^{+\infty} dx_5 f(x_5) \left[ \frac{1}{3!} F^3(x_5) \frac{1}{3!} F^3(x_5) - \frac{1}{3!} F^3(x_5) \frac{1}{4} F^4(x_5) \right]_{-\frac{1}{4!}}^{-\frac{1}{4!}} F^4(x_5) \frac{1}{3!} F^3(x_5) + \frac{1}{4!} F^4(x_5) \frac{1}{4!} F^4(x_5) \right]_{-\frac{1}{4!}}^{-\frac{1}{4!}} F^4(x_5) \frac{1}{3!} F^3(x_5) + \frac{1}{4!} F^4(x_5) \frac{1}{4$$

531

541

The integration of the first contribution gives

$$\int_{-\infty}^{+\infty} \mathrm{d}x_5 f(x_5) \frac{1}{3!} F^3(x_5) \frac{1}{3!} F^3(x_5) = \frac{1}{7} \frac{1}{3!} \frac{1}{3!}$$

Since the other contributions are similar, this completes the proof of the particular case. 536

*Proof of Equation* (5) We compute the first marginal of Equation (9). The first two contributions in Equation (9) form a telescopic series with respect to *t*:

$$\sum_{t=1}^{\infty} \frac{1}{s+t+1} \frac{1}{s!} \frac{1}{t!} - \frac{1}{s+t+2} \frac{1}{s!} \frac{1}{(t+1)!} = \frac{1}{s+2} \frac{1}{s!}.$$

The same for the third and fourth:

$$\sum_{t=1}^{\infty} \frac{1}{s+t+2} \frac{1}{(s+1)!} \frac{1}{t!} - \frac{1}{s+t+3} \frac{1}{(s+1)!} \frac{1}{(t+1)!} = \frac{1}{s+3} \frac{1}{(s+1)!}.$$

Hence, 546

$$\sum_{t=1}^{\infty} P(H_1 = s, H_2 = t | E) = 3 \left[ \frac{1}{s+2} \frac{1}{s!} - \frac{1}{s+3} \frac{1}{(s+1)!} \right].$$