On Exact Number of Baroreflex Sequences in Surrogate Data Sets

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Abstract

This paper evaluates an exact formula for the number of the systolic blood pressure and pulse interval ramps, as well as spontaneous baroreflex sequences within the surrogate and artificial time series. It discusses the temporal sBR parameters of original and artificially generated data.

1. Introduction

The baroreceptor reflex (BRR) is a major negative feedback regulator of arterial blood pressure (BP). Its role is to keep BP in a homeostatic range by modulating heart rate (HR) and peripheral resistance through efferent vagal and sympathetic activity directed to the heart and the blood vessels. Cardiovascular diseases are associated with alterations in BRR activity, while reduced BRR sensitivity (BRS) has been found to be an indicator of the severity of cardiovascular morbidity. and also an independent marker of the risk of mortality and major adverse cardiovascular events in hypertensive patients [1-3].

Recent development in techniques for the BRR activity analysis allows studying the cardiac BRR without the use of vasoactive drugs - the spontaneous BRR (sBRR) [4-6]. One of the most widely used techniques is sequence method, based on the identification of sequences of consecutive beats in which progressive increases (or decreases) in SBP are followed by progressive increases (or decreases) in pulse interval (PI). Delay of increasing or decreasing PI consecutive beats (PI ramps) in respect to SBP ramps depends on species and for rats it is found to be 3-5 beats [4,7].

Occurrences of ramps and sequences in observed time series might be a mere coincidence. To test the hypothesis that interactions of systolic blood pressure and pulse interval are real sBR events and not the accidental occurrences, a simulated data series should be tested as well. To preserve unique properties of each biological time series, surrogate data approach is usually applied [8,9]. Surrogate time series mimic statistical properties of the data under study, but not the property that is tested for. Spontaneous baroreflex sequences exhibit strong temporal dependence, so scrambled (isodistributional) surrogates - samples of the time series are randomly scrambled to destroy statistical dependence - are applied for testing [10]. However, if the time series are short, the amount of the sBR sequence realizations in scrambled sets is limited and it is often difficult to estimate the reliability of the test results.

This paper deals with statistical properties of time series regarding ramps and sequences, evaluating an exact formula for the number of SBP/PI ramps and sBR sequences within the surrogate sets.

2. Methods

2.1. Experimental protocol

The experimental procedures in this study confirmed to European Communities Council directive of 24 November 1986 (86/609/ECC) and the School of Medicine, University of Belgrade Guidelines on Animal Experimentation. Thirteen outbred male Wistar rats weighing 330 ± 20 g were used. Ten days before the measurements rats were submitted to surgery in which radiotelemetric probes (TA11PA-C40, DSI, Transoma Medical) were implanted in abdominal aorta under combined ketamine and xylazine anesthesia, along with gentamicin and followed by metamizol injections for pain relief. The measurements at baseline conditions lasted 20 minutes. Arterial blood pressure (BP) signal was digitized at 1000Hz and relayed to a PC equipped with Dataquest A.R.T. 4.0. software. PI series were derived from the arterial BP as an inverse of interval between maxima in the pulse wave signal. The original BP waveforms were carefully visually compared to the extracted SBP maxima and artifacts were removed.

2.2. Surrogate data and artificial series

The mean record length was N = 6883 ± 180 beats (SBP/PI pairs). For each one of 13 rats, 15 pairs of artificial streams with the same length, mean and variance as in original record were generated as follows: 1. Isodistributional (scrambled) surrogate data 2. Uniform

distribution 3. Normal ditribuion 4. Binary data with Bernoulli distribution. The last one was introduced for the sake of investigation of a process without memory.

2.3. Estimated parameters

The main goal of the paper was to investigate statistical properties of sBR ramps and sequences within the simulated data sets. Minimal length of sequences M ranged from 2 to 5, expressed in number of inter-beat intervals (the corresponding minimal length in number of beats equals to M+1). The temporal parameters estimated from the recorded and artificial data sets are:

T_R (T_{SEQ}): Mean generated ramp (sequence) length [expressed in inter-beat intervals];

T_{IR} (T_{ISEQ}): Mean inter-ramp (inter-sequence) length;

T_{CR} (T_{CSEQ}): Mean sBR cycle lenth, where cycle is defined as a ramp (sequence) preceded by inter-ramp (inter-sequence) interval;

N_R (N_{SEQ}): Number of ramps (sequences) in record, obtained as an averaged ratio of record length and cycle length; to allow the comparison of unequal record lengths, a normalized mean number (per 100 heartbeats or per 1 minute) is usually employed.

Ramps are identified as streams of successive positive (or negative) differences of adjacent signal samples or recorded and simulated data series, except for Bernoulli process, where they are identified as streams of equal symbols. Sequences are identified if streams of successive positive (negative) signal differences are found both in SBP and in PI series delayed by three beats.

2.4. Model

In both recorded and generated time series both positive and negative signal increments Δ (differences between signal samples, $\Delta_i = x_{i+1} - x_i, i = 1,...,N-1$) occur with the same probability. However, the original signal amplitude is bounded and the probability that increment would remain positive (or negative) depends on number of immediately preceding increments of the same sign. A state transition diagram that corresponds to ramp and sequence generation is presented in Figure 1.

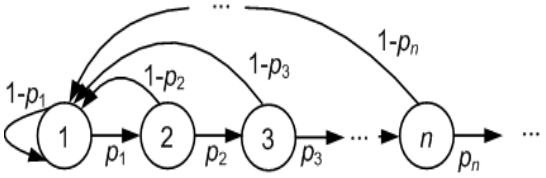

Figure 1. State transition diagram of ramp (sequence) generation

State "*n*" corresponds to the nth increment of the same sign as *n*-1 preceding ones. The dwelling time of each state equals to 1 [interbeat interval]. Although the diagram allows generation of infinite streams of positive (negative) increments, transition probabilities rapidly decrease and the probability that there would be more than M_{max} states approaches to zero.

The model enables evaluation of previously defined parameters T_R, T_{IR}, T_{CR}, N_R. The states are partitioned into two parts: inter-ramp states (states 1, 2, …, *M*-1) and ramp states (*M*, *M*+1, …, M_{max}), given that the minimal ramp length is set to *M*. The ramp and inter-ramp length correspond to mean time the process spends in the corresponding set of states. This problem could be solved using numerous methods (Mason's formula, fundamental matrix of Markov chain, z-transform of Markov chain, etc. [11,12]). This particular chain, however, offers very simple evaluation of state selection probabilities:

$$P(n) = \prod_{i=1}^{n-1} p_i \cdot P(1), \quad n = 2,...,M_{\max}, \tag{1}$$

with an additional constraint:

$$\sum_{n=1}^{M_{\max}} P(n) = 1 \tag{2}$$

This enables much easier evaluation of the stated parameters [13]. After simple manipulations, TR and TIR are evaluated as:

$$T_{IR} = \frac{\sum_{n=1}^{M-1} P(n)}{p_{M-1} \cdot P(M-1)} = \frac{1 + \sum_{n=2}^{M-1} \prod_{i=1}^{n-1} p_i}{\prod_{i=1}^{M-1} p_i} \tag{3}$$

$$T_R = M - 1 + \frac{\sum_{n=M}^{M\max} P(n)}{\sum_{n=M}^{M\max} (1 - p_n) \cdot P(n)} = M - 1 + \frac{\sum_{n=M}^{M\max} \prod_{i=1}^{n-1} p_i}{\prod_{i=1}^{M-1} p_i} \tag{4}$$

A cycle length is then expressed as TC = TR+ TIR.

Transition probabilities p_n, as already stated, are decreasing with each transition. If $f_x(x)$ is probability distribution function of simulated processes, than pdf of its increment is

$$f_\Delta(\Delta) = \int f_x(x) \cdot f_x(x - \Delta) \cdot dx \tag{5}$$

Probability that n^{th} increment in a row is of the same sign as the previous ones is obtained iteratively, averaging the corresponding conditional probability density functions.

3. Results

Figure 2 presents pdf of time series sample increments, for recorded (averaged over the 13 animal records) and simulated data. For the sake of pdf comparison, all the recorded time series were centralized and normalized. The subsequent figures present estimated values for ramp length (Fig. 3), inter-ramp length (Fig. 4) and normalized number of ramps per 100 beats (Fig.5). Maximal ramp (sequence) length estimated for artificial series was found to be M_{max} = 8 and M_{max} = 4, for ramps and sequences respectfully. There was no occurrence of sequence longer than 4 in surrogate and generated data sets, although in original time series longer sequences do exist. For this

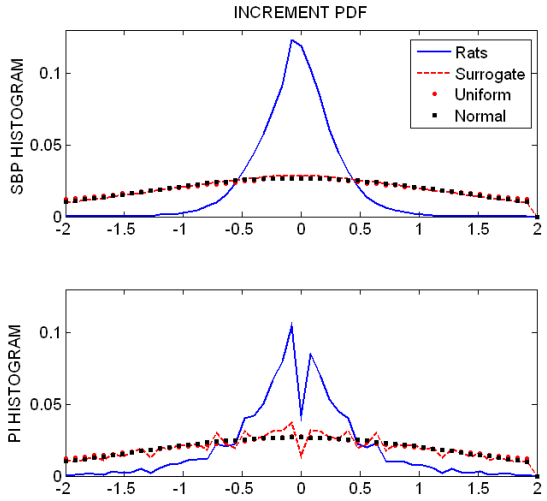

Figure 2: Increment pdf a) SBP; b) PI

reason, Fig. 6 gives number of sequences for M=2 and 3 only.

4. Discussion and conclusions

Increments of samples with uniform distribution follow triangular distribution, while increments of normal samples retain normal distribution with increased variance (Eq. 5), verified in simulated series (Fig. 2). Numerically, both distributions are in perfect accordance with increment distribution of surrogate data series. The time parameters estimated from all these three artificially generated series were exactly the same (middle bars at subsequent figures). Moreover, these values perfectly mach the values derived using formulae (3) and (4), with state transition probabilities evaluated numerically for uniform sample distribution and verified using simulated data.

The generation of increments of the same sign is a process with memory. It is surprising to notice that temporal statistics of SBP recorded time series show no significant difference from parameters estimated from stream of independent memoryless Bernoulli trials (the first and the fifth bar in Figs 3a, 4a and 5a). On the other hand, parameters of PI time series did not differ from the ones estimated from surrogate data and artificially generated sample streams (excluding Bernoulli process).

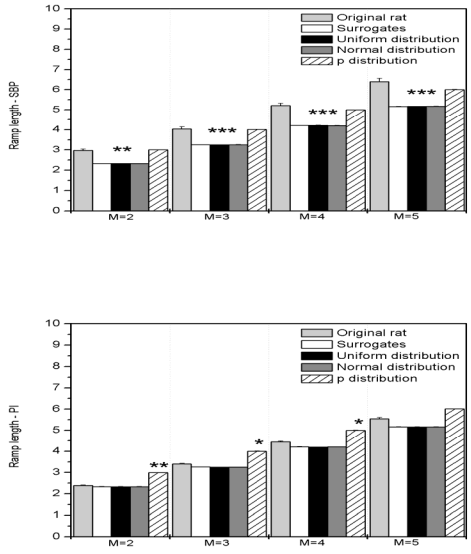

Figure 3: Ramp length a) SBP; b) PI

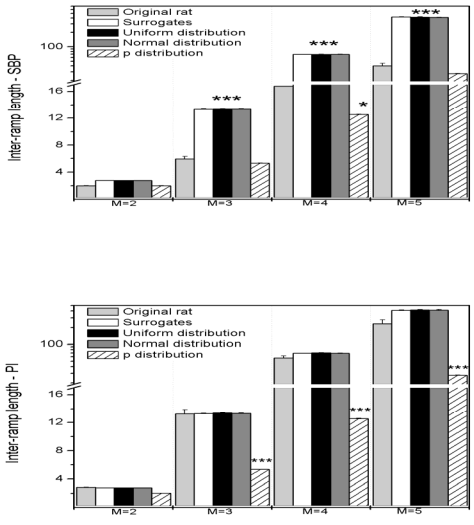

Figure 4: Inter-ramp length a) SBP; b) PI

These results verify different control mechanism that are inherent to SBP and PI time series Number of sequences of length M=2 inter-beat intervals (three successive SBP-

PI pairs!) estimated from SBP-PI series do not change significantly neither in surrogate nor in other artificial data series (Fig. 6). Therefore, it is doubtful whether they are really consequence of sBR, or just a coincidence. Following this result, it might be suggested that the minimal sequence length in sBP studies should be set to three inter-beat intervals (4 SBP-PI pairs).

Sequences longer than 4 inter-beat intervals do not occur in surrogate and artificial data. Therefore, their existence in original SBP-PI series must be a consequence of true sBR. Unfortunately, in records of moderate length their number is too few to allow reliable estimation of sBR parameters and for this reason the minimal sequence length could not be set to such values. Suggestion might be that such long sequences should be observed separately.

Derived expressions (3) and (4) with numerically evaluated (or estimated) transition probabilities might be used instead of counting the number of ramps/sequences in surrogate data, especially when the experiments are of short duration and the counted number of sequences is too small to allow reliable estimation.

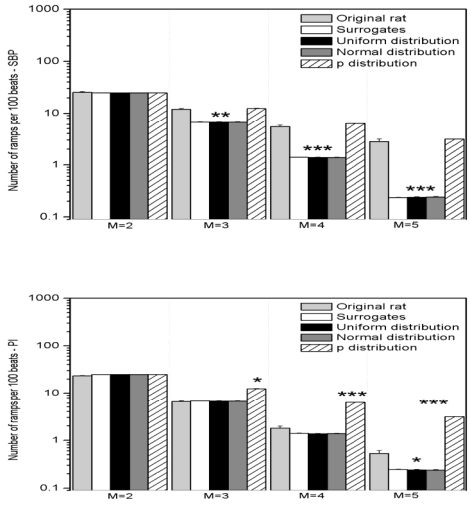

Figure 5: Number of ramps per 100 beats a) SBP; b) PI

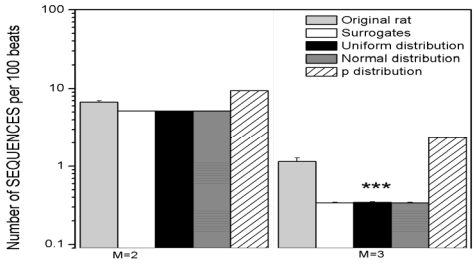

Figure 6: Number of sequences per 100 beats

Acknowledgements

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References

[1] Ormezzano O, Cracowski JL, Quesada JL, Pierre H, Mallion JM, Baguet JP. Evaluation of the prognostic value of Baroreflex sensitivity in hypertensive patients: the EuroBaVar study. J Hypertens 2008; 26:1373-1378.

[2] Narkiewicz K, Grassi G. Impaired baroreflex sensitivity as a potential marker of cardiovascular risk in hypertension. J Hypertens 2008; 26:1303-1304.

[3] Lanfranchi PA, Somers V K. Arterial baroreflex function and cardiovascular variability: interactions and implications. Am J Physiol Regul Integr Comp Physiol 2002; 283: R815–R826.

[4] Oosting J, Struijker-Boudier HAJ, Janssen BJA. Validation of a continuous baroreceptor reflex sensitivity index calculated from spontaneous fluctuations of blood. J Hypertens 1997; 15:391-399.

[5] Laude D, Elghozi JL, Girard A, Bellard E, Bouhaddi M, Castiglioni P et al. Comparison of various techniques used to estimate spontaneous baroreflex sensitivity (the EuroBaVar study). Am J Physiol Regul Inter Comp Physiol 2004; 286:R226-R231.

[6] Di Rienzo M, Parati G, Castiglioni P, Tordi R, Mancia G, Pedotti A. Baroreflex effectiveness index: an additional measure of baroreflex control of heart rate in daily life. Am J Physiol Regulatory Integulatory Comp Physiol 2001; 280:744-751.

[7] Waki H, Katahira K, Polson JW, Kasparov S, Murphy D, Paton JF. Automation of analysis of cardiovascular autonomic function from chronic measurements of arterial pressure in conscious rats. Exp Physiol 2006; 91:201–213.

[8] Blaber AP, Yamamoto Y, Hughson RL. Methodology of spontaneous baroreflex relationship assessed by surrogate data analysis. Am J Physiol 1995; 268:H1682-H1687.

[9] Porta A, Furlan R, Rimoldi O, Pagani M, Malliani A, van de Borne P. Quantifying the strength of the linear causal coupling in closed loop interacting cardiovascular variability signals. Biol Cybern 2002; 86:241-251.

[10] Laude D, Baudrie V, Elghozi JL. Applicability of recent methods used to estimate spontaneous baroreflex sensitivity to resting mice. Am J Physiol Regul Integr Comp Physiol. 2008; 294: R142-150.

[11] Mason S.J. Some properties of Signal Flow Graphs. Proceedings of I.R.E. 1953; 41:1144-1156.

[12] Isaacson DL, Madsen RW. Markov Chains Theory and Applications 1976; New York, Wiley, 1976.

[13] Bajic D. New simple method for solving the first passage time problem. Electronics Letters 1991; 27:1419-1421.

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