# Assessing Baroreflex Sensitivity in the Sequences Technique: Local versus Global Approach

S Gouveia[1,2], AP Rocha[1,2], P van de Borne[3], P Lago[1]

[1] Dep de Matemática Aplicada, Faculdade de Ciências, Universidade do Porto, Portugal
[2] Centro de Matemática da Universidade do Porto, Portugal (CMUP)
[3] Dep of Cardiology, Erasme Hospital, Brussels, Belgium

## Abstract

*The sequences technique is the most used time domain technique for the assessment of arterial baroreceptor reflex sensitivity (BRS) and is based in the analysis of the beat-to-beat spontaneous variability of systolic blood pressure and heart period. Although a common used method, the sequences technique imposes the setting of several parameters to determine what is a valid baroreflex event and no consensual opinion about these parameters is found in the literature. The theory is overlooked, and linear regression over three values is the usual procedure. The methodology itself can be questionable and the estimator has not been clearly examined regarding its statistical properties, namely bias and variance. In this work, an alternative estimator that we have been using is evaluated and compared with the traditional approach, considering real and simulated data. The results obtained show that the proposed estimator is less biased and presents lower variance than the traditional approach.*

## 1. Introduction

The sequences technique is a standard method for estimating arterial baroreflex sensitivity (BRS). This method uses time domain analysis of the beat-to-beat spontaneous variability of systolic blood pressure (SBP) and heart period (RR) and is based on the assumption that changes in RR are driven by linear independent changes in SBP, through the baroreflex effect. The sequences technique is based on the identification of valid baroreflex sequences and in a linear regression over the correspondent SBP and RR values, in each sequence. An overall estimate is obtained by averaging the regression slopes calculated during the recording period. This approach will be denoted as *local approach* and its estimate as $BRS_{local}$ (in sec per mmHg).

In this work, an alternative approach, that we have been using for estimating the BRS, is described and compared with the local approach: instead of taking the mean of the slopes obtained for each baroreflex sequence, the BRS is characterized by the slope obtained from all RR and SBP values, in the set of all baroreflex sequences. This approach gives a global measure of the baroreflex sensitivity and will be referred as *global approach* and the correspondent estimator $BRS_{global}$.

## 2. Methods

The *sequences technique* is a method for BRS estimation using time domain analysis of spontaneous SBP and RR variability [1, 2]. For this analysis, as illustrated in Figure 1, it is usual to consider sequences of consecutive beats characterized by a simultaneous ramp in RR and SBP in the same direction, either decreasing (bradycardia, BRAD) or increasing (tachycardia, TAC). These spontaneous *baroreflex sequences* represent physiological rather than chance interactions between SBP and RR [1]. In practice, it is usual to define thresholds in order to identify sequences that correspond to a real baroreflex effect, although no consensual opinion about their values is found in the literature. In this work, a valid baroreflex sequence must satisfy 3 beats minimum length, 5 $ms$ (1 $mmHg$) minimum step-wise changes in RR (SBP) and at least 0.8 of correlation coefficient.

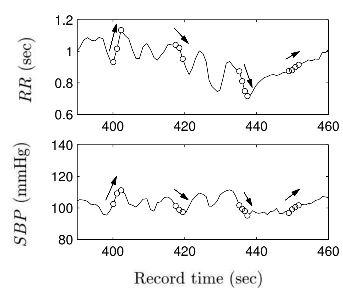



Figure 1. Examples of bradycardia (BRAD) and tachycardia (TAC) baroreflex sequences for BRS estimation using the *sequences technique*.

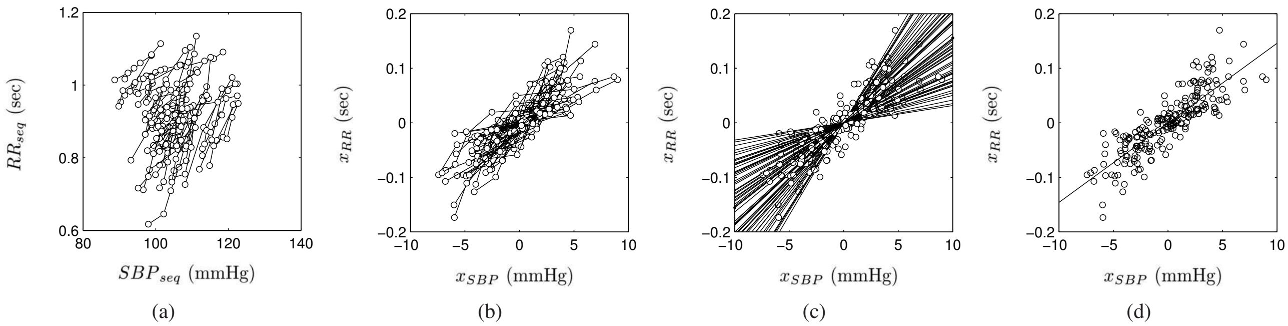



Figure 2. Dispersion diagram of $RR_{seq}$ and $SBP_{seq}$ (a) and after sequences mean detrend (b). The local regression slopes (c) and the global regression slope (d), used in local approach and global approach for BRS estimation, respectively. Real data from [3].

For each data segment and after the identification of all the $n$ baroreflex sequences, the $k^{th}$ sequence is characterized by at least 3 pairs of values ($SBP^k_{seq}$,$RR^k_{seq}$). These pairs can be represented in a dispersion diagram, as in Figure 2(a). In this work, a preprocessing step in the cardiovascular data has been introduced. It consists in local detrending the data ($SBP^k_{seq}$,$RR^k_{seq}$), by subtracting its mean value

$$\begin{aligned} x^k_{SBP} &= SBP^k_{seq} - \overline{SBP^k_{seq}} \\ x^k_{RR} &= RR^k_{seq} - \overline{RR^k_{seq}} \end{aligned} \quad (1)$$

as represented in Figure 2(b). Since the mean value is naturally not the same for each baroreflex sequence, each one is translated to the origin by a different factor. Therefore, regarding a baroreflex sequence, the relative position of its points is not altered, but the relative location of all baroreflex sequences is changed.

The traditional (local) approach provides a local measure of the baroreflex sensitivity $BRS_k$, associated to the $k^{th}$ baroreflex sequence, assuming the linear regression

$$x^k_{RR} = BRS_k \, x^k_{SBP} + c_k + \epsilon_k, \;\; k = 1, 2, ...n \;\; , \quad (2)$$

where $\epsilon_k$ is a random error term and $c_k$ and $BRS_k$ are estimated by ordinary least squares (Figure 2(c)). An overall estimate is obtained from

$$BRS_{local} = \frac{1}{n} \sum_{k=1}^{n} BRS_k. \quad (3)$$

Alternatively, a global measure of the baroreflex sensitivity can be considered as the slope $BRS_{global}$, obtained from all the $x_{RR}$ and $x_{SBP}$ values in the set of all $n$ sequences,

$$x_{RR} = BRS_{global} \, x_{SBP} + c + \epsilon, \quad (4)$$

as is illustrated in Figure 2(d).

Both approaches consist in different ways of quantifying the baroreflex effect. The *local* approach provides localized information and the overall estimator can be seen as the *mean of the local baroreflex behaviours*, whereas the *global* approach can be interpreted as the *global baroreflex behaviour*. Regarding the preprocessing step, mean detrend has no influence on the *local* approach estimator, but it has a relevant effect on the *global* approach. As illustrated in Figures 2(a) and 2(b), the global linear relation between the variables is *hidden* when the sequences mean is present.

## 3. Real data

The experimental data used in this work consists in 68 independent records of simultaneous RR and SBP [3]. The records were acquired from 11 young normal individuals (10 males, 1 female), with mean age 26 years (range 19-37 years) and not taking any medication. For this study, the records were separated into 53 stationary segments with 512 beats of duration, free from ouliers and abnormal rhythms. The real data presents 2222 baroreflex sequences, as summarized in Table 1. The percentage of sequences with 3 beats length was about 85% and the number of sequences with 4 and ≥5 was progressive and drastically lower, in accordance with [1, 2].

Table 1. Number of baroreflex sequences per type and length.

| | Total | 3 beats | 4 beats | ≥ 5 beats |
|---|---|---|---|---|
| BRAD | 999 | 851 | 136 | 12 |
| TAC | 1223 | 1043 | 147 | 33 |
| All | 2222 | 1894 | 283 | 45 |

## 4. Performance evaluation

The lack of BRS reference values for experimental data imposed a simulation study in order to evaluate and compare local and global approaches.

### 4.1. Simulation model

The model was designed to reproduce the linear relations between $x_{RR}$ and $x_{SBP}$ series found in the real data. In this model formulation, only baroreflex sequences with 3 beats of duration were considered.

For each $k = 1, 2, ..., n$ baroreflex sequence, SBP ramps $s^k_{SBP}$ were generated. The first SBP value was generated from the empirical distribution of the equivalent values in the real data. The following SBP values were subsequently generated constrained to the previous ones.

In order to ensure a linear local relation between the cardiovascular variables RR sequences $s^k_{RR}$ were simulated using the model

$$s^k_{RR} = BRS_{ref}\ s^k_{SBP} + \epsilon_k \quad (5)$$

where $\epsilon \sim N(0, \sigma^2)$ with $\sigma^2$ producing a realistic variance in $s_{RR}$, ie

$$\sigma^2 = var(x_{RR}) - BRS^2_{ref} var(x_{SBP}) \quad (6)$$

After this step, the sequences were analyzed in order to reject non baroreflex sequences, that is, SBP ramps that do not originate RR ramps (non-RR ramps). In this work, 5000 realizations of 1000 $s_{SBP}$ ramps and $s_{RR}$ values were generated with $BRS_{ref}$=0.0142 *sec/mmHg* and $n$=200. Figure 3 illustrates the dispersion diagram of two sets of simulated baroreflex sequences. The similarity with the dispersion diagram of the baroreflex sequences in Figure 2(b) (real data) is quite clear.

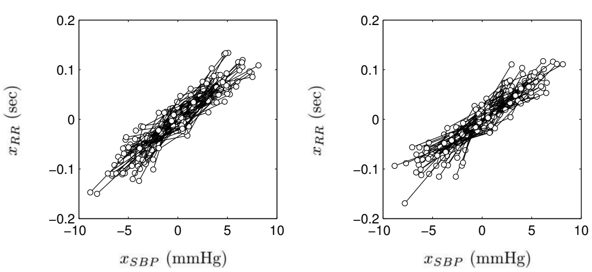



Figure 3. Dispersion diagram of two sets of simulated baroreflex sequences, reproducing the real data in Figure 2(b).

### 4.2. Simulation results

As summarized in table 2, the simulation results indicate that the *global* approach presents lower mean (7% smaller) and lower standard deviation (16% smaller) when compared to the *local* approach. Moreover, both approaches overestimate the reference value $BRS_{ref}$ and the bias in the *global* approach is 43% smaller.

Table 2. Simulation results (5000 realizations, $n$=200 and $BRS_{ref}$=0.0142): mean, variance and bias of the estimates $BRS_{local}$ and $BRS_{global}$.

| | | $BRS_{local}$ | $BRS_{global}$ |
|---|---|---|---|
| Mean | | 0.0171 | 0.0158 |
| Variance | $(\times 10^{-4})$ | 4.5931 | 3.8554 |
| Bias | $(\times 10^{-3})$ | 2.8888 | 1.6539 |

As illustrated in Figure 4(a), it was found that the $BRS_{local}$ estimate is higher than the $BRS_{global}$ estimate.

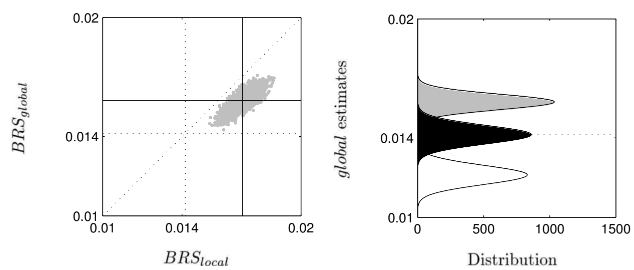
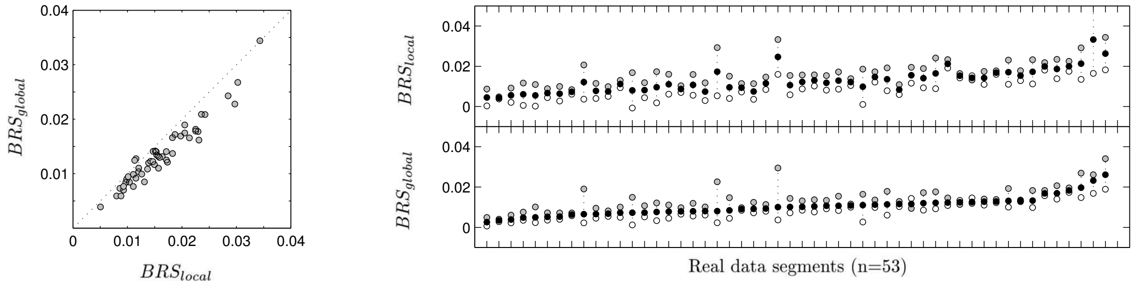



Figure 4. Simulation results (5000 realizations, $n$=200 and $BRS_{ref}$=0.0142): (a) Dispersion diagram of the $BRS_{local}$ versus $BRS_{global}$ estimates. (b) Distribution of the *global* estimates using baroreflex sequences (●), SBP ramps (●) or non-RR ramps (○).

Both approaches overestimate the reference value because:
(i) lower slopes are more likely to be labeled as *invalid* baroreflex sequences and excluded from the analysis, and
(ii) the random error term $\epsilon_k$ in the regression model does introduce itself a tendency towards higher values of BRS.

As is illustrated in Figure 4(b) for the *global* approach, the *invalid* baroreflex sequences (non-RR ramps) tend to underestimate the reference value, and when all SBP ramps are included for the BRS estimation (independently if they are baroreflex sequences or not) is possible to get an unbiased BRS estimate.




(a) (b)

Figure 5. Real data results: (a) Dispersion diagram of the BRS estimates (53 real data segments). (b) Plot of the *local* and *global* estimates using baroreflex sequences (●), SBP ramps (●) or non-RR ramps (○).

## 5. Study in real data

Figure 5 summarizes the results obtained with the real data. The correlation between the estimates was found to be significant and positive (n=53, $p << 0.001$ in a 1-tailed test for the hypothesis of no correlation). Pearson correlation coefficient was $0.91$, revealing a strong linear relation between the two estimates.

There is the confirmation of the relation $BRS_{local} > BRS_{global}$ in the real data, as illustrated in Figure 5(a). Furthermore, Figure 5(b) shows a behaviour entirely concordant with the simulation results: the estimates using baroreflex sequences are higher than the estimates using SBP ramps, which are higher than the estimates using non-RR ramps.

From the 68 independent records, it was possible to extract 10 records of 1024 beats duration and divide each one in 2 segments of 512 beats. A paired comparison on the same segment, between local and global approach, was performed with similar results ($BRS_{local} > BRS_{global}$; n=10, $p < 0.01$), while the paired comparison on different segments of the same record did not reveal statistical differences for the BRS values in either approaches (n=10, $p > 0.4$). Therefore, the characterization of the BRS for one record (or individual) is much more dependent on the choice of the approach than on the choice of the segment.

## 6. Conclusions

The results from the real and the simulated data point out the relation $BRS_{local} > BRS_{global}$. The simulation results also indicate that $BRS_{global}$ presents lower value (7% smaller), lower dispersion (16% smaller) and lower error to the reference value (43% smaller) than $BRS_{local}$. The results indicate that can be advantageous the use of SBP ramps in the estimation of BRS. Besides that, the $BRS_{global}$ estimator is more robust than the $BRS_{local}$ estimator (the mean of the local baroreflex behaviours).

Finally, from the paired comparisons with real data, it was found that the characterization of the BRS for one individual is much more dependent on the choice of the approach than on the choice of the data segment.

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Address for correspondence:

Sónia Gouveia
Departamento de Matemática Aplicada
Faculdade de Ciências da Universidade do Porto
Rua do Campo Alegre, 687; 4169-007, Porto, Portugal.
E-mail address: sagouvei@fc.up.pt.