# Fuzzy Logic SBP and RR Modelling Evaluated Under Parasympathetic Blockade

Sónia Gouveia[1,2], Andreia O. Pinheiro[3], Susana Brás[1], Luciana Aparecida Campos[3]

[1] Institute of Electronics and Informatics Engineering of Aveiro (IEETA), Aveiro University, Portugal
[2] Center for R&D in Mathematics and Applications (CIDMA), Aveiro University, Portugal
[3] Center of Innovation, Technology and Education (CITE), Camilo Castelo Branco University and Technology Park, São José dos Campos, Brazil

## Abstract

*Here, fuzzy logic models are used to describe the relation between systolic blood pressure (SBP) and tachogram (RR) values as a function of the SBP level. These methods are now evaluated under parasympathetic autonomic blockade, i.e. a condition which tends to difficult the modelling task once the RR variability is dramatically decreased whereas no SBP changes are observed.*

*As expected, fuzzy logic models obtained under vagal blockade have lower modelling error than those obtained in baseline. The pairwise differences between errors in both conditions are positively correlated with differences in SBP LF power and in RR HF power, markers of sympathetic and vagal activity respectively. The methyl-atropine surfaces are flatter than those in baseline, in agreement with the decrease in frequency domain BRS estimates from baseline to drug condition. Finally, fuzzy models obtained under vagal blockade were found to be statistically significant, which strengths the potential of the fuzzy logic approach to model SBP and RR also during vagal blockade.*

## 1. Introduction

The joint analysis of systolic blood pressure (SBP) and RR variability allows the estimation of the arterial-cardiac baroreflex sensitivity (BRS) and other important biomarkers [1]. Namely, low BRS estimates have been associated with increased cardiovascular disease-related mortality [2]. Traditional BRS estimation is performed in a drug induced setting, which allows to stimulate a large and clear SBP change in order to force a pronounced RR response (i.e., a clear baroreflex activation). Through the consecutive administration of a vasoconstrictor and a vasodilator, it is possible to explore the baroreflex function over a wide SBP range, usually assuming a sigmoidal shaped SBP–RR relationship. In this setting, the BRS is usually estimated as the slope of a tangent line to the sigmoidal curve in a given SBP value. Spontaneous methods, on the other hand, allow BRS assessment near the operating point of the subject, i.e. the SBP and RR values oscillating around the region of the sigmoidal curve representing its baseline. Mimicking drug induced methods, time domain methods for spontaneous BRS estimation assume a linear SBP and RR relation in specific time intervals [3].

All above-mentioned methods provide one slope estimate establishing the SBP and RR proportionality, regardless of the SBP value. We recently explored the use of fuzzy logic models to describe the relation between SBP and RR values [4]. This approach does not assume a shape for SBP and RR relation and opens the possibility to model a non linear SBP and RR relation, which ultimately will make possible to obtain a BRS index as a function of the SBP value. We also demonstrated that fuzzy logic models are statistically significant in lying and standing conditions [4], where lying to standing slightly decreases RR mean and variability, and lowers BRS estimate [3].

The aim is to quantify the ability of fuzzy logic approach to properly model SBP and RR relation under drug-induced vagal blockade (by i.v. methyl-atropine administration - MeA). This experiment dramatically reduces RR mean and variability without relevant SBP changes [5], which difficults the modelling task by the large reduction in the output variability with respect to the input of the system. The resulting vagal blockade changes were compared to baseline and associated with recognized markers of parasympathetic and sympathetic activity (respectively, RR power in HF band and SBP power in LF band) [5, 6].

Finally, the statistical significance of the models was evaluated with surrogate data i.e. an ensemble of random time series that mimic properties of the original data and is consistent with the null hypothesis of no SBP and RR relation. With this approach, we seek to identify statistically significant differences between performances in real and random data and, thus, to demonstrate that fuzzy logic models explain a significant amount of data variance.

## 2. Experimental protocol and data

Beat-to-beat intrafemoral SBP (mmHg) and RR (sec) time series were obtained from 7 conscious freely moving rats. Parasympathetic blockade was achieved by an intravenous administration of peripheral muscarinic methylatropine, MeA (0.5 mg/kg), with full effect around 20 minutes after administration (e.g. [7]). Data collection initiated at least 30 minutes before drug administration. The recording continued 20 minutes after administration (in the process of vagal blockade) and 30 minutes after complete vagal blockade. For each subject, intervals of sufficient duration (512 points) were chosen before (baseline) and after drug blockade (MeA), thus avoiding the transient drug effect and erratic fluctuations in the series. Figure 1 presents the intervals chosen for one experimental subject, representative of baseline and MeA conditions. As expected, MeA introduced tachycardia (i.e., decreased the mean RR value) and diminished RR variability without relevant SBP changes (both in mean and in variability) [5].

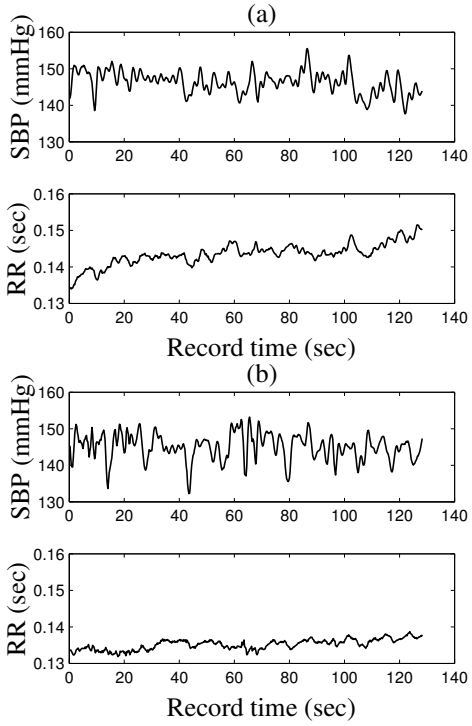


Figure 1. SBP and RR time series for one subject, in baseline (a) and after MeA i.v. infusion (b). Time series have 512 beats length and are resampled at 4 Hz.

For each subject and condition, 100 random replicas of the original RR series were generated while maintaining the original SBP series. The random RR replicas were generated by resampling without replacement the original data, thus preserving the mean and the variability of the original RR time series. This procedure is equivalent to scramble the original RR values to produce a surrogate series with a random order. As a consequence, the temporal structure and the non stationary behavior of the original RR series is not present in the RR surrogates. The shuffling in the RR series additionally destroys the relation between SBP and RR amplitudes. For illustration purposes, Fig. 2 shows one surrogate realization of the data represented in Fig. 1 for the MeA condition.

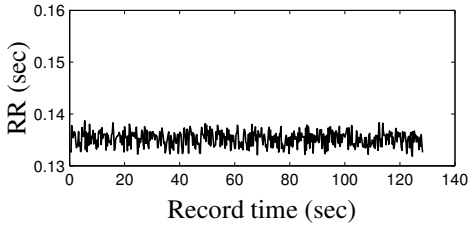


Figure 2. Example of a surrogate RR time series for MeA condition, obtained by resampling the data in Fig. 1(b).

## 3. Methods

### 3.1. Fuzzy Logic model estimation

The methods have been fully described in our previous work [4].The fuzzy logic system was defined as a *Sugeno* model, which considers the system output as a function $z = f(x)$, i.e. RR=$f$(SBP). Given the input $x$, a typical rule $i = 1, 2, ..., N$ with output $z_i$ is defined as

$$\text{If } x \in F_i(x), \text{ then } z_i = a_i x + c_i, \tag{1}$$

where $F_i(x_j)$ are fuzzy sets and $a_i$ and $c_i$ are constants [8]. Each rule output $z_i$ is then weighted by its firing strength $w_i = \Gamma_{F_i(x)}$, where $\Gamma_{F_i}$ is a Gaussian membership function defined by its center $\mu_i$ and standard deviation $\sigma_i$. The final output of the system $\widehat{z}$ is the weighted average of all $z_i$, given by

$$\widehat{z} = \frac{\sum_{i=1}^{N} w_i z_i}{\sum_{i=1}^{N} w_i}. \tag{2}$$

The number of rules $N$ and the parameters $a_i$, $c_i$, $\mu_i$ and $\sigma_i$ for each rule $i = 1, 2, ..., N$ were optimized by ANFIS [9]. The initial $\mu_i$ and $\sigma_i$ values were obtained using subtractive clustering. The first center ($\mu_i$) is identified as the point with maximum likelihood, i.e., the median of $x$. The next center is estimated as the previous, disregarding the data already assigned to the existing clusters. The procedure stops when all data falls within a cluster. This method, iteractively, divides the antecedent domain into clusters, estimating their centers, based on a predefined radius (cluster influence within the data space). Finally, the membership functions appear as the projection of these clusters on the $x$ axis.

### 3.2. Fuzzy Logic model performance

The performace of a fuzzy model was evaluated from

$$\delta = \frac{1}{m}\sum_{i=1}^{m}\frac{|z(i)-\widehat{z}(i)|}{|z(i)|} * 100\,, \qquad (3)$$

where $\widehat{z}(i)$ is the estimate of $z(i)$, $i$ represents the temporal order of the values and $m$ represents the recording length. In this notation, $\widehat{z}$ is the RR estimate of a given SBP value. The lower the $\delta$ the higher the model performance.

### 3.3. Markers of (para)sympathetic activity

Parasympathetic blockade was quantified from frequency domain analysis of SBP and RR variability, under baseline and MeA condition [5, 6]. In particular, literature results suggest that the RR power in high frequency band (HF) may be a marker of parasympathetic tone, whereas the blood pressure power in low frequency band (LF) may be a good marker of sympathetic activity (e.g. [6] and references therein included). Moreover, frequency domain BRS (ms/mmHg) was estimated from the average gain of the SBP and RR transfer function. SBP and RR powers and also BRS gains were evaluated in LF (0.07-0.3 Hz), MF (0.3-0.6 Hz) and HF (0.62.0 Hz) bands [10], from Blackman-Tukey (cross-)spectrum estimates [11].

## 4. Results

Results comparing baseline and MeA conditions are presented in Table 1. As expected, MeA reduced RR mean, RR variability and RR power in HF band, without significant SBP changes. However, RR power in LF band was also markedly decreased after methyl-atropine, which confirms that RR power in LF band is also associated with vagal influence [5]. Decreased RR power and unchanged SBP power after vagal blockade lead to a decreased transfer function gain across all frequency bands and consequently lead to lower BRS estimates.

Table 1. RR (msec) and SBP (mmHg) parameters (mean ± standard error), before and after vagal blockade.

| Parameter | Baseline | MeA |
|---|---|---|
| RR mean | 177.5±11.1 | 138.5±1.4 |
| RR variability | 30.4±10.2 | 2.9±0.7 |
| RR power LF | 27.7±9.5 | 1.4±0.4 |
| RR power MF | 3.1±1.3 | 0.4±0.1 |
| RR power HF | 0.7±0.2 | 0.2±0.0 |
| SBP mean | 148.1±3.7 | 142.4±5.3 |
| SBP variability | 13.8±2.4 | 11.6±1.9 |
| SBP power LF | 23.5±4.0 | 18.1±5.0 |
| SBP power MF | 7.3±1.7 | 9.4±1.4 |
| SBP power HF | 0.4±0.1 | 0.6±0.1 |
| BRS LF band | 0.61±0.08 | 0.15±0.02 |
| BRS MF band | 0.92±0.15 | 0.33±0.04 |
| BRS HF band | 0.47±0.07 | 0.18±0.01 |

The results reported in Table 1 are in accordance with those obtained via atropine bolus in normotensive rats [6], except that no significant mean RR changes were observed from baseline to atropine. This can be explained from the fact that both MeA and atropine block vagal heart rate effects at the periphery while atropine exerts additionally a central stimulating effect on cardiac vagal efferent activity [12]. Thus, our experimental protocol clearly induces solely peripheral vagal blockade on the heart.

For the purpose of illustrating fuzzy logic modelling, Fig. 3 presents the resulting surfaces for the same subject represented in Figs. 1 and 2. It can be observed that the MeA surface is flatter than that obtained for baseline condition and thus surface variation (slopes) are lower in MeA than in baseline for a given SBP value. This result is consistent with the observed reduction in frequency domain BRS estimates. Finally, Fig. 3(b) shows the same representation as in Fig. 3(a) for one random replica in MeA condition. Here, the RR values are randomly distributed over y-axis and the SBP and RR relation is destroyed by RR shuffling. Consequently, the resulting fuzzy surface undulates around the median RR value for all SBP values.

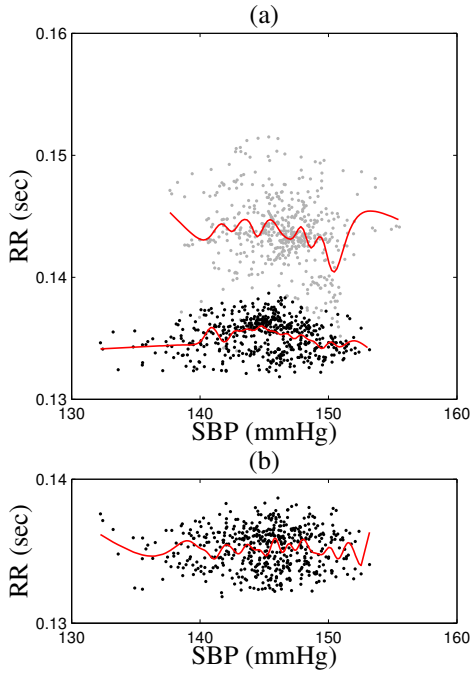


Figure 3. Dispersion diagrams with SBP and RR data in Fig. 1 and 2, distinguishing baseline (grey) and MeA (black) conditions, and highlighting the estimated fuzzy surfaces (red). Fig. (a) and (b) display real and surrogate data for MeA condition.

For each case (subject and condition), the modelling error $\delta$ was quantified for the real data and for the 100 surrogate replicas, following Eq. (3). For the illustrative subject, Figure 4 shows that fuzzy logic modelling in real data has lower error when compared with the random replicas, pointing out that the amount of variability explained by fuzzy models is statistically significant in both conditions.

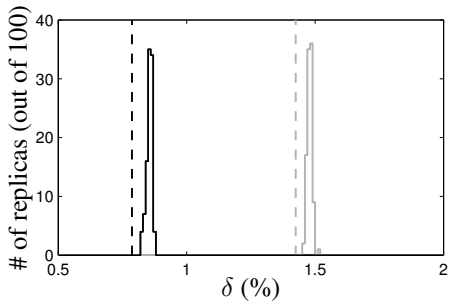


Figure 4. Number of random replicas (out of 100) per $\delta$ value for baseline (grey) and MeA (black). Dashed lines locate $\delta$ for the real data in Fig. 3.

The same conclusions were drawn for the remaining subjects, namely that fuzzy logic modelling achieves higher performance in real than in surrogate data (Fig. 5)). Although there were no significant differences between conditions (Mann-Whitney U test, $p$ = 0.58), differences between real and random $\delta$ tend to be lower in MeA condition. This was expected due to the dramatic effects of MeA in RR mean and variability without SBP changes. However, fuzzy logic modelling under parasympathetic blockade still showed to be statistically significant against the random model for all subjects.

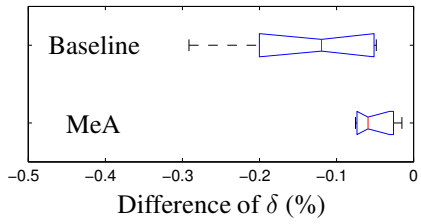


Figure 5. Boxplot of pairwise differences between $\delta$ evaluated for real data and averaged over 100 random replicas.

Finally, the model performance was associated with markers of vagal and sympathetic activity. Namely, $\delta$ was found to be positively correlated with SBP power in LF (baseline, $r = 0.97$, $p < 0.01$; MeA, $r = 0.88$, $p = 0.02$) and not with RR power in HF (baseline, $r = 0.60$, $p = 0.21$; MeA, $r = 0.09$, $p = 0.87$), evidencing that models performance is stable over conditions with different sympathetic and vagal activities. Future work will evaluate fuzzy logic models in conditions activating the sympathetic branch of the autonomic nervous system.

## Acknowledgements

This work was partially supported by the Portuguese Foundation for Science and Technology (FCT), with national (MEC) and European structural funds through the programs FEDER, within UID/CEC/00127/2013 (IEETA), UID/MAT/04106/2013 (CIDMA) and CMUP-ERI/FIA/0031/2013 (VR2Market by CMU-Portugal program). S. Gouveia and S. Brás acknowledge the postdoctoral grants by FCT (refs. SFRH/BPD/87037/2012 and SFRH/BPD/92342/2013).

## References

[1] L. A. Campos, V. L. Pereira Jr., A. Muralikrishna, S. Albarwani, S. Brás, S. Gouveia, Mathematical Biomarkers for the Autonomic Regulation of Cardiovascular System, Front Physiol 2013;4(279).

[2] S. Gouveia, M. G. Scotto, G. D. Pinna, R. Maestri, M. T. La Rovere, P. J. S. G. Ferreira, Spontaneous baroreflex sensitivity for risk stratification of heart failure patients: optimal cutoff and age effects, Clinical Science 2015;129:1163–1172.

[3] S. Gouveia, A. P. Rocha, P. Laguna, P. Lago, Time domain baroreflex sensitivity assessment by joint analysis of spontaneous SBP and RR series, Biomed Signal Process Control 2009;4(3):254–261.

[4] S. Gouveia, S. Brás, Exploring the use of Fuzzy Logic models to describe the relation between SBP and RR values, Proc IEEE Eng Med Biol Soc 2012:2827–2830.

[5] D. Laude, V. Baudrie, J. L. Elghozi, Effects of atropine on the time and frequency domain estimates of blood pressure and heart rate variability in mice, Clin Exp Pharmacol Physiol 2008;35:454-457.

[6] H. Dabié, D. Mestivier, J. Jarnet, M. E. Safar, N. P. Chau, Quantification of sympathetic and parasympathetic tones by non linear indexes in normotensive rats, Am J Physiol Heart Circ Physiol 1998;275:H1290–H1297.

[7] L. Brunton, B. Chabner, B. Knollman, The Pharmacological Basis of Therapeutics, McGraw-Hill, 2006.

[8] P. P. Angelov, Evolving rule-based models: a tool for design of flexible adaptive systems. Physica-Verlag, 2002.

[9] J. R. Jang, ANFIS: Adaptive-Network-Based Fuzzy Inference System, IEEE Trans Syst Man Cybern 1993;23:665–685.

[10] O. Baltatu, B.J. Janssen, G. Bricca, R. Plehm, J. Monti, D. Ganten, M. Bader, Alterations in blood pressure and heart rate variability in transgenic rats with low brain angiotensinogen, Hypertension 2001;37:408–413.

[11] M. Priestley, Spectral Analysis and Time Series, Academic Press, 1981.

[12] P. G. Katona, D. Lipson, P. J. Dauchot, Opposing central and peripheral effects of atropine on parasympathetic cardiac control, Am J Physiol, vol. 232(2), H146-151, 1977.

Address for correspondence:

Sónia Gouveia
IEETA, Universidade de Aveiro, Portugal
E-mail address: sonia.gouveia@ua.pt