

# The Role of Baroreflex Sensitivity in Acute Hypotensive Episodes Prediction in the Intensive Care Unit

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**Abstract**—A life threatening condition in Intensive Care Unit (ICU) is the Acute Hypotensive Episode (AHE). Patients experiencing an AHE may suffer from irreversible organ damage associated with increased mortality. Predicting the onset of AHE could be of pivotal importance to establish appropriate and timely interventions. We propose a method that, using waveforms widely acquired in ICU, like Arterial Blood Pressure (ABP) and Electrocardiogram (ECG), will extract features relative to the cardiac system to predict whether or not a patient will experience a hypotensive episode. Specifically, we want to assess if there are hidden patterns in the dynamics of baroreflex able to improve the prediction of AHEs. We will investigate the predictive power of features related to the baroreflex by performing classifications with and without them. Results are obtained using 17 classifiers belonging to different model families: classification trees, Support Vector Machines (SVMs), K-Nearest Neighbors (KNNs) replicated with different set of hyper-parameters and logistic regression. On average, the use of baroreflex features in the AHE prediction process increases the Area Under the Curve (AUC) by 10%.

## I. INTRODUCTION

Several studies [1][2][3][4] have attempted to predict Acute Hypotensive Episodes (AHE) in the intensive care unit and several valid approaches were shown, often using a great variety of methods. To this extent, international conference challenges were held on the subject [5], thus highlighting the interest from the research community. Heart Rate and Arterial Blood Pressure have already been used to predict hypotension but not beat-to-beat baroreflex. The baroreflex is an important reflex involving the Autonomic Nervous System (ANS), that helps in regulating Arterial Blood Pressure (ABP). The sensors in our body that measure the pressure that permit to create a feedback loop in the cardiac control system are the baroreceptors, mainly present in the aortic arch. From a control system point of view, the baroreflex can be considered as a measure of the interaction between the controlling variable (heart rate, HR) and the controlled variable (Systolic Blood Pressure, SBP). Estimation of measures of baroreflex from waveforms is well documented in literature. In an open loop model, baroreflex gain has been computed with sequential time models as

well as monovariate frequency domain transfer functions [6]. However, these models consider only the influence that SBP has on HR modulation. No feedback is taken in consideration, so that the effect of HR changes on SBP can be taken into account. For these reasons, more accurate closed loop models have been developed [7][8][9]. In any case, none of these measures have been considered within a framework for AHE prediction. In this study, we propose a beat-to-beat analysis from ABP and ECG waveforms using a point process framework to extract coupling features for baroreflex sensitivity assessment, and we investigate the statistical power of these features in predicting AHE in a dataset of 86 subjects from the MIMIC Physionet Database [10][11]. More specifically, we compare the performance of two sets of features, differing in the inclusion or exclusion of baroreflex related features.

## II. METHODS

### A. Modeling

In order to estimate the baroreflex we use a bivariate Point Process model [12] characterizing heart beat dynamics. A point process is a discrete event happening in continuous time, this definition suits perfectly in establishing a probabilistic characterization of the succession of heart beats.

Assuming history dependence, the Point Process model that explains the waiting time until the next heart beat is:

$$p(t) = \left[ \frac{\theta}{2\pi t^3} \right]^{\frac{1}{2}} \exp \left[ -\frac{\theta(t - u_j - u_t)^2}{2\mu_t^2(t - u_j)} \right] \quad (1)$$

Where  $u_j$  denotes the previous heart beat occurred before time  $t$  and  $\mu_t$  the instantaneous heart beat distance value.

Since the effects of the sympatho-vagal influence occur on a millisecond timescale, but its effects last for several seconds, the interval must be modeled as dependent on the recent history of the Sino-Atrial node inputs

$$\mu_t \equiv \mu_{RR}(t) = a_0 + \sum_{i=1}^p a_i RR_{t-i} \quad (2)$$

The time interval between heart beats is defined as the  $RR$  time elapsed between R peaks in the ECG.

The evaluation of the parameters in 1 and 2 is adaptive, since the objective is to track the instantaneous physiological changes along time. The measure of  $\mu_{RR}(t)$  is time varying and is determined by the time varying AR coefficients  $a_i(t)_{i=0}^p$ .

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To account for direct systolic pressure modulation on heart rate variability (baroreflex sensitivity) but also for the mechanical effect that a variation of heart rate has on the hemodynamics, such a model requires to build a bivariate mathematical structure that describes the bidirectional dynamics between the two variables (see Fig. 1).

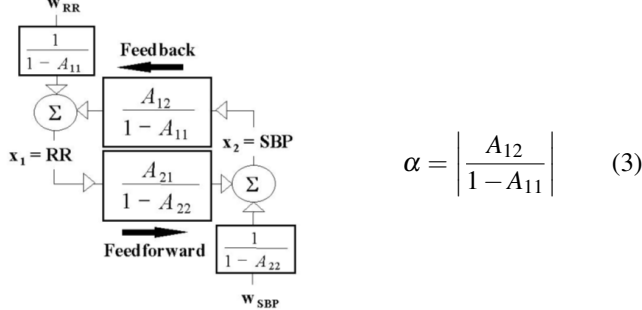


Fig. 1. Bivariate modeling structure

As mentioned before, in order to calculate the baroreflex we need to take into account the action of SBP on HR. For this reason, we will consider SBP as a covariate in the RR interval point process model. The equation 2 becomes

$$\mu_t \equiv \mu_{RR}(t) = a_0 + \sum_{i=1}^p a_i RR_{t-i} + \sum_{j=1}^q b_j S_{t-j} \quad (4)$$

Where  $S_{t-j}$  denote the previous  $j_{th}$  measure of systole before time  $t$ . Now the mean  $RR$  is modeled as a bivariate AR model [9].

It has to be highlighted that this model does not take into account the time lapse between the two inputs: as it is known, the R wave in the ECG precedes the systole in the ABP by the pulse transit time. However this does not affects the transfer amplitude. With a linear system assumption, baroreflex can be estimated as the absolute value of the transfer function of the built bivariate model. Given the parametric model in 4 it is therefore possible to evaluate the baroreflex frequency response as

$$H_{12}(w) = \left. \frac{\sum_{j=1}^q b_j(k)z^{-j}}{1 - \sum_{i=1}^p a_i(k)z^{-i}} \right|_{z=e^{j2\pi f_s}} \quad (5)$$

Where  $f_s$  is the beat rate of the RR.

It is possible also to estimate the power spectrum or the gain in the frequency domain as

$$P_{RR}(\omega, t) = \sigma_{RR}(t) |H_{11}(\omega, t)| \quad (6)$$

$$\text{Baroreflex}_{gain}(\omega, t) = |H_{12}(\omega, t)| \quad (7)$$

### B. Features

Based on other studies [13][9] the information that is more useful in predicting AHE resides mostly in blood pressure, moreover having a confined dataset, we had to limit the number of features. Therefore, we have included only those

predictors that describe SBP and the ANS descriptors on both RR intervals and SBP:

- SBP statistical moments
- LF, HF, VLF spectral powers (for both RR and SBP)
- LF/HF (for both RR and SBP)
- Baroreflex amplitude
- Baroreflex frequency

Regarding the spectral features, using the Point Process model, we were able to extract the spectral power as a function of both time and frequency. The VLF, LF and HF power were calculated as an integral of the time-frequency signal in the following range of frequencies [14]:

- VLF: 0.004 - 0.04 Hz
- LF: 0.04 - 0.15 Hz
- HF: 0.15 - 0.4 Hz

In this way we were able to obtain a time-varying signal tracking the spectral power in these frequency bands.

Using the Point Process method described in Section II-A, and in particular the formulas 5 and 7 we calculated the baroreflex as a function of both time and frequency. The actual signal that we used to compute features took in account only the contribution of the LF range of frequencies, since it is known that in the HF the modulation of the  $RR$  period is due mainly to the influence of the respiration, whereas the VLF are generated by slow mechanisms involving circadian and hormonal influences not necessarily dependent from baroreflex control.

### C. Classification

To estimate the predictive power of the baroreflex, classification was performed with two sets of features: the first set contained information only about  $SBP$  and  $ANS$  descriptors while the second one added to the first the features related to the baroreflex.

We used in total 17 different classifiers that can be grouped by method:

- 4 classification trees
- 6 SVM
- 6 KNN
- Logistic Regression

All these classifiers maintained the same hyper parameters during the two experiments.

## III. EXPERIMENTAL DESIGN

### A. Acute Hypotensive Episodes

There are several definitions of a AHE in literature, of which some relies on absolute assumptions, whereas others use a more relative approach [15]. For the purpose of the following work, we used an absolute definition, using predefined and fixed thresholds, which was proposed by Physionet for the 2009 Computer in Cardiology Challenge [5]: An AHE is any period of 30 minutes in which at least 90% of the Mean Arterial Pressure (MAP) is below 60mmHg.

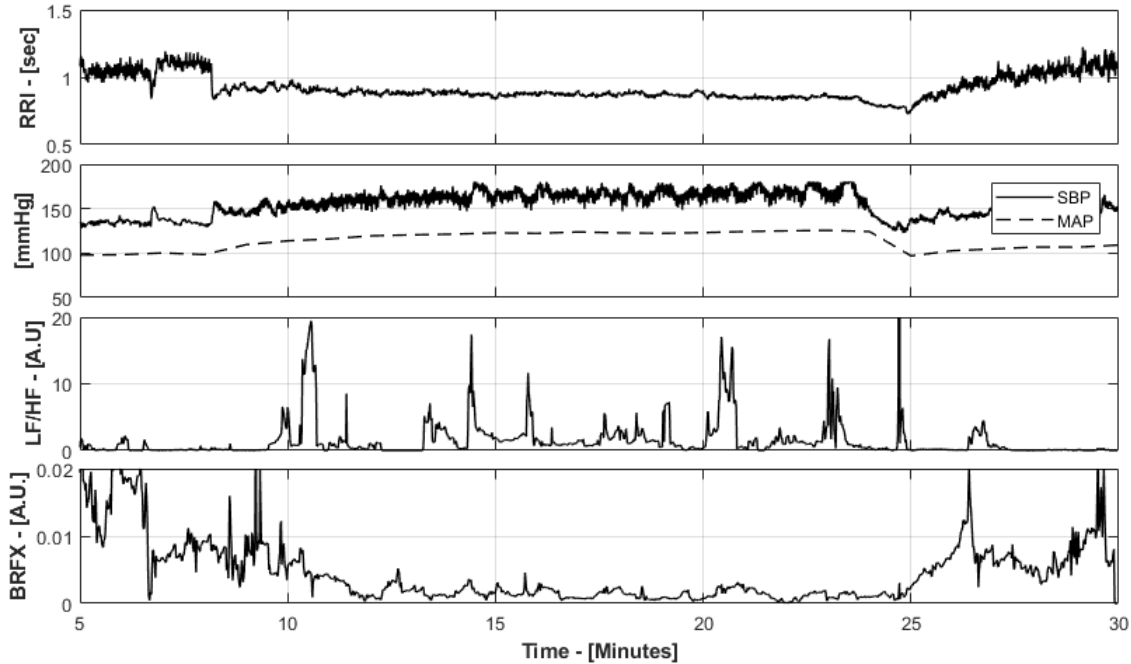


Fig. 2. Baroreflex example from the cohort. The top row are RR intervals, middle top row systolic pressure, middle-bottom row LF/HF power ratio and bottom row baroreflex sensitivity. Note a sympathetic activation due to a critical condition (around minute 7), resulting in a sudden increase of SBP. Afterwards, vagal activation yields to a hypotensive phenomena (circa minute 23).

### B. Data Selection

Records were pulled from the MIMIC-III Waveform Database Matched Subset[11], a large publicly available database containing almost five thousands de-identified ICU entries as recordings from the bedside ICU monitor. Data, before being incorporated into the MIMIC-III database, was first deidentified in accordance with Health Insurance Portability and Accountability Act (HIPAA) standards using structured data cleansing and date shifting.

Each record belongs to a different patient and only those containing at least one ECG lead and the ABP channel were taken into consideration. For the hypotensive population, only the first AHE was considered while control patients were those that never experienced an AHE along the entire MIMIC monitoring. Each selected record is 30 minutes long, if the record belongs to a hypotensive subject, then the waveform represents the 30 minutes right before the first AHE. For control patients it was selected the first available and valid 30 minutes window.

Signal quality was regarded as the highest priority in this study, all signals were treated with different filters, fed to Signal Quality Indexes (SQI), and annotated. To ECGs was applied a Pan-Tompkins like algorithm[16] for R-peak annotations and for blood pressure a pulse waveform delineator[17].

Annotations fusion, the assignment of each R-peak to the relative pulse waveform, was performed using a set of adaptive templates working synchronously with a finite-state machine based on a gaussian model.

In the end each record was visually inspected and ectopic

beats were corrected, when possible, with an adaptive point process filter [18]. In the end, the cohort counted 86 ICU patients of which 41% (35 records) were hypotensive.

### C. Data Window and Lead Time

For the analysis settings we defined two parameters:

- Data Window (DW): the time interval of a given size of the record from which the features for the classification are extracted.
- Lead Time (LT): The time interval between the upper limit of the Data Window and the onset of the hypotension (or end of the record for controls). Data from the LT is withheld and therefore inaccessible

Given these definitions, the main question the study is: is it possible from the information in the DW to tell if an AHE is going to happen in LT minutes?

### D. Quantification of Baroreflex Predictive Power

The predictive power of baroreflex features was assessed through a comparative analysis. From the 86 patients cohort we built two datasets, A and B, differing in the predictors used. Dataset A had features related only to SBP and HRV while dataset B shared with A the same features plus additional regressors computed from the BRFx. If the model trained on B showed equal or worse performance compared to that of A, then it could mean that the extra features in B did not bring additional information. On the other hand, an improved performance would sustain the hypothesis that BRFx features have relevant class separation power.

#### IV. RESULTS

A 30 min segment from the dataset with exemplary RR and SBP time series, together with resulting LF/HF and Baroreflex instantaneous estimates, is shown in Fig.2. Note the sharp dynamic changes around min 7, denoting a shift towards sympathetic driven dynamics possibly due to critical cardiovascular stress. Also note the sharp decrease in Baroreflex up to the hypotensive phenomenon at around min 24, followed by a recovery in stability (and parallel baroreflex increase starting from min 25. Classifiers were trained using values of data window and lead time of respectively 20 and 10 minutes. Using features extracted from these series, as described in Methods, classification performance was assessed through five-fold cross-validation and results were computed in two different datasets: one with (B) and one without (A) baroreflex features. The scope was to understand the real contribution in terms of increased performance of the baroreflex related features. AUCs from different families of classifiers are shown in Table I. The second and third column show respectively the AUC of those models trained on dataset B and A (with or without the features from BRFX). The column labeled variation shows the change in performance for each family. A positive change means that the models using the baroreflex features perform better. Overall, the inclusion of baroreflex sensitivity features increased the classification performance in terms of AUC by 10.7% on average.

TABLE I

Classifier	B - BRFX	A - NO BRFX	Variation (%)
Trees	.67	.63	+7.0
SVMs	.68	.62	+9.7
KNNs	.64	.57	+11.2
Logistic Regression	.62	.54	+14.8

Logistic regression results show baroreflex frequency having an odds ratio of .6 ( $pvalue < .07$ ).

#### V. CONCLUSIONS

We devised an automatic routine able to annotate and extract meaningful time series from the MIMIC Waveform Database, thus extracting information from a non-controlled and unstable environment such as that of the ICU, characterized by artifacts, noise and missing data. We then applied advanced modeling techniques, such as the bivariate point process, to investigate the complex coupling between heart rate and blood pressure. Using this information, it was possible to assess baroreflex sensitivity within a physiological control system critical for hemodynamic stability as driven by the Autonomic Nervous System. In the end, using a two way classification strategy, we have shown how the use of advanced models for quantification of baroreflex improve the prediction of acute hypotensive episodes. Hypotensive episodes are severe conditions and as such require prompt intervention, it is therefore critical to find tools able to alarm clinicians prior to the event. The hidden pattern in baroreflex requires further investigation, but shows promising results,

pointing at how important is the link between ANS dynamics and hypotension.

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