**AQuSyNA-matlab application for automatic quantification of sympathetic nerve activity**

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*Abstract:* - The main goal of this paper is to present the way we implement the method for automated quantification of sympathetic nerve activity. The implemented method belongs to the techniques based on the objective detection criteria and has user friendly application interface through which it is possible to eliminate artifacts and preserve a beat-by-beat SNA signal for a variety of subsequent analyses.

*Key-Words:* - sympathetic neural activity, automatic quantification

### 1 Introduction

The accurate assessment of autonomic sympathetic function is important in the diagnosis and study of various autonomic and cardiovascular disorders. Sympathetic function in humans can be assessed by recording the muscle sympathetic nerve activity, which is characterized by synchronous neuronal discharges separated by periods of neural silence dominated by colored Gaussian noise. The raw nerve activity is generally rectified, integrated, and quantified using the integrated burst rate or area. There are several techniques to identify bursts, such as a technique based on the objective decision criteria [1], gamma distribution model [2], or quantification involving spike detection using a two-stage stationary wavelet transform (SWT) de-noising method [3].The main goal of this paper is to present the way we implement the method for automated quantification of sympathetic nerve activity which also belongs to the techniques based on the objective detection criteria together with the user friendly application interface through which it is possible to eliminate artifacts and preserve a beat-by-beat SNA signal for a variety of subsequent analyses.

## 1 Sympathetic Nerve Activity

The Sympathetic Nervous System (SNS) is a branch of the autonomic nervous system along with the enteric nervous system and parasympathetic nervous system. It is always active at a basal level (called sympathetic tone) and becomes more active during times of stress [4]. Its actions during the stress response comprise the fight-or-flight response. The sympathetic nervous system is responsible for up- and down-regulating many homeostatic mechanisms in living organisms. Fibers from the SNS innervate tissues in almost every organ system, providing at least some regulatory function to things as diverse as pupil diameter, gut motility, and urinary output. Science typically looks at the SNS as an automatic regulation system, that is, one that operates without the intervention of conscious thought. Some evolutionary theorists suggest that the sympathetic nervous system operated in early organisms to maintain survival as the sympathetic nervous system is responsible for priming the body for action [4].One example of this priming is in the moments before waking, in which sympathetic outflow spontaneously increases in preparation for action [4].

The general appearance of the human SNA has been described as heartbeat synchronous discharges from a group of sympathetic neurons, separated by periods of neural silence [5] (Fig.1.). These bursts of activity are coupled to changes in the blood pressure and cardiac output through the baroreceptor reflex [6,7,8]. Accurate quantification of sympathetic nerve activity during steady-state conditions or dynamic changes can provide critical information related to numerous physiological systems. Direct recordings of electrical activity emitted by peroneal, tibial, or radial muscle sympathetic nerves and visual identification of sympathetic bursts by a trained microneurographer are the only direct measures available in human research. Bursts have a characteristic shape consisting of a gradual rise and fall that is usually constrained by the cardiac cycle and at least twice the amplitude of random fluctuations.

## 2 SNA identification baclground

Visual identification requires a trained observer to scan the entire raw-voltage neurogram and decide, based on experience, whether the waveform during each heartbeat is the appropriate size and shapes to differentiate it from background noise and be called a sympathetic burst. As one might expect, the inherent subjectivity of this analysis results in significant interobserver variability with variances as high as 9% being reported [10]. This has spurred development of numerous automated

techniques to quantify sympathetic activity [2,9,10,11,12,13].

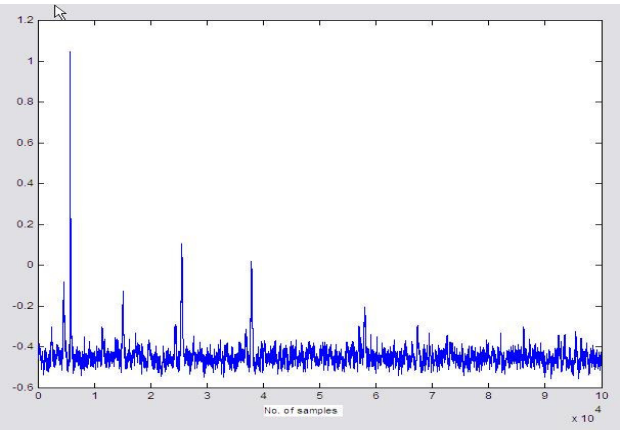


Fig 1. Integrated neurogram

The most widely used SNA processing method involves using an *R–C* circuit to rectifying and integrate the neurogram to achieve its envelope [14, 15], a signal known as the integrated- SNA [16]. At that point, bursts are identified and sympathetic activity can be quantified in terms of burst frequency (bursts/min), burst incidence (bursts/100 heart beats) or burst area rate (arbitrary units$^2$/min) [15].

Quantification of the SNA using bursts in the integrated neurogram has its limitations. For instance, none of the burst parameters are capable of conveying whether a large burst is generated by a few large amplitude sympathetic spikes (or artifacts) or many small amplitude spikes firing in rapid succession. Also, the amount of pass band noise integrated into each burst is dependent on the signal-to-noise ratio (SNR) of each recording, making it difficult to compare the arbitrary unit burst amplitudes and areas across subjects.

An alternative solution to the integrated SNA quantification problem is to implement a spike detection algorithm in the raw neurogram which allows for the possibility of subsequent, automated sorting of spikes into classes derived from individual single unit neurons [16]. Single-unit recordings have identified important differences in diseases such as congestive heart failure and hypertension which were not demonstrated in the multiunit burst rate [17]. Since these single unit recordings are extremely difficult to achieve and sustain manually [18], automated spike detection and classification methods shown to be useful in this area.

It is also possible to identify the SNA using gamma distribution model [2], which effectively deals with the common noise artifacts and transients, but simple burst counting to index sympathetic activity precludes examination of beat-by-beat relations to other variable.

Our goal was to identify SNA in healthy people who were exposed to specific psychophysical stress such as activity during apnea diving. Consequently, our method belongs to the group of objective decision criteria, which is based primarily on the morphology of the measured integrated neurograph and described minutely in the next subsection.

# 3 SNA identification baclground

Apnea is a state of activity during which SNA results with a specific (dynamic) shape bursts which areas under the bursts curve and bursts amplitude become larger along the time line. Consequently, standard identification measures for identifying the bursts activity which are related to the area rate and/or amplitude are not appropriate for this specific physiological state. In other words, it is difficult to compare the arbitrary unit burst amplitudes and areas across the whole time line due the shape and magnitude of bursts differs significantly among themselves. To avoid mentioned particularity, the whole experiments have been divided into several stages: baseline period, apnea period and the period in which the normal arterial pressure has been reached again.

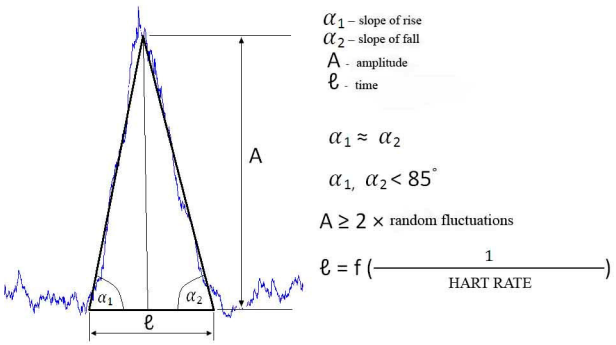


Fig 2. Decision parameters for burst identification

Only in the first period, up to apnea stage, the shapes of bursts could be identified based on the common decision criteria based on the following facts:

- The slopes of the burst's rise and fall are approximately equal and less than 85°, which means relatively gradual rise followed by a similarly sloped fall (Fig.2).
- The bursts are constrained by the cardiac cycle (timing relative to QRS complex, width relative to cardiac cycle and relation to diastolic pressure) (Fig.3.).
- The bursts have at least twice the amplitude of a random fluctuations

Transient noise spikes and muscle twitches are identified as rapid shifts in the neurogram that are unassociated with cardiovascular variables

## 4 The application for automated quantification

The mentioned facts have been implemented in the application for automated identification described in more detail in the next section.

Automated detection of sympathetic activity was written in Matlab software (version 7.1, The Mathworks). The emphasis has been put on the graphical user interface through which it is possible to intuitively collect all the relevant neurogram data. Our intention was to make it as simple as possible for two reasons: it has to be easy for use and it also has to serve as an educational tool for the students or future nurographer. The main window of the user interface is shown in Fig.3. It is divided in several part, each representing appropriate group of activities: the main menu, through which it is possible to reach all possible program abilities, panel part for signal review, and the two group of buttons: the upper one which enables loading of the various signals from previously prepared file, and the group of buttons on the right side which enable appropriate signal analysis, which are, as Fig.3. (the right side) specifies: the filter button and the automatic analysis group of buttons. There are also three different indicators marked with small squares in red, green or grey colors. They clearly indicate when the appropriate options from the user interface are available. For example, it is not possible to analyze anything before the file with signals has been uploading.

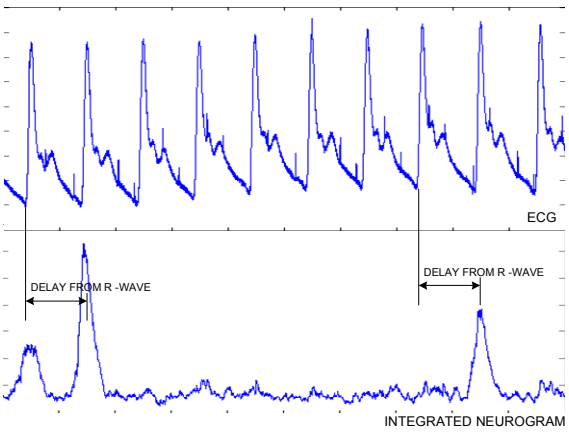


Fig 3. The bursts (above) are constrained by the cardiac cycle

Consequently, the automatic analysis has been disabled (grayed), until the file had been loaded, and also number of detected burst calculation has been disabled, until the automatic analysis had been performed, as well. When appropriate operation has been applied, available options have been automatically set to on (green square indicator), making possible to turn it off, which is then indicated with red box (Fig.5).

Automatic analysis could be performed on the filtered data and on the raw integrated neurogram aswell. For easier decision related to burst identification, the filtering is recommended. We found the most appropriate use of zero-phase filtering in which the signal is averaged and scaled appropriately with the predefined constants depending on the baseline shift and the introduced noise level. To be sure that the automatic identification of bursts is done well, the comparison button is available. Enabling it, the identified bursts are overlapped with the raw integrated neurogram (Fig.6). Consequently, the final decision is always on the side of the experienced neurographer, while others, with less experience, have been suggested with objective decision criteria algorithm. Fig.7. also presents an enlarged detail on which different color circles mark the burst characteristic point: the point of rise start (blue), burst amplitude peak (red), and the point of fall stop (green). These points are responsible for rise and fall slope angles determination as it is described in the Section 4.

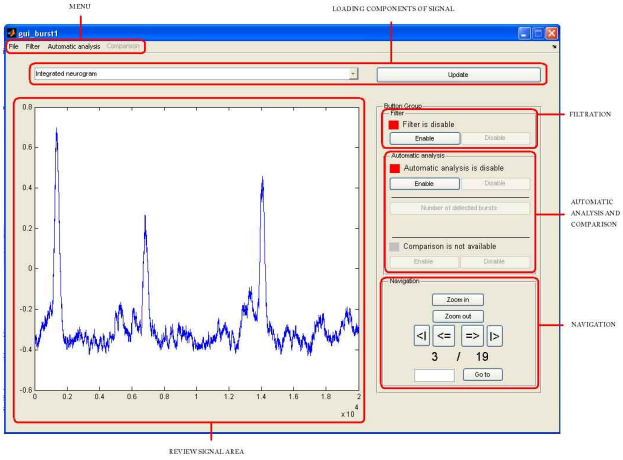


Fig 4. User interface for automated sympathetic neurogram analysis

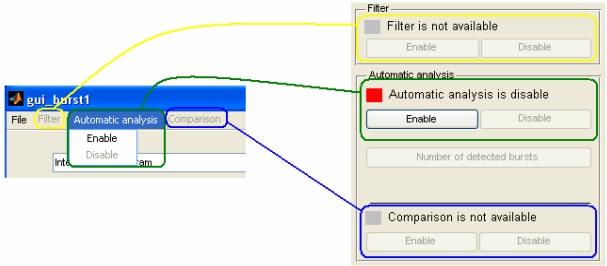


Fig 5. Various options for neurogram analysis have to be performed in the meaningful order. Intuitive sequence of

activities is indicated with square markers in red, gray and green color.

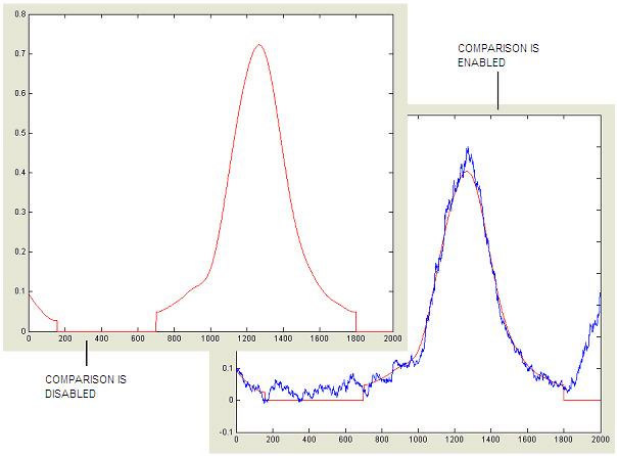


Fig.6. Overlapped signals: identified filtered bursts (red) and raw integrated neurogram (blue), with enlarged detail indicates characteristic point for rise and fall slope angle determination.

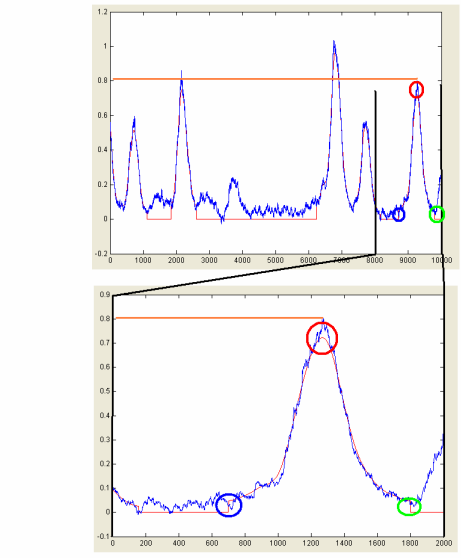

Fig.7. Enlarged detail indicates characteristic point for rise and fall slope angle determination.

Finally, the most useful information is always related to the number of detected bursts which can be obtained by using the appropriate button. In the next version of the program we plan to ensure final decision of detected burst by introducing the possibility of subjective decision correction of the automated objective decision criteria. Therefore, the neurographer will be able to include and/or exclude some of the analyzed bursts by simple mouse click in the surrounding of the signal peak, making the final decision more precise. Similar as in [1], we set out to develop a technique for rapid and objective analysis of sympathetic nerve tracings that was not confounded by transient noise spikes, muscle twitches, and baseline shifts. We wanted to maintain the neurogram's time-domain relationship to other physiological variables and provide maximum flexibility for analysis. To accomplish this, we modeled a burst-detection algorithm on standard methods for visual detection. Using parameters determined from the morphology of visually identified bursts of sympathetic activity, we have successfully developed a flexible, and objective technique for the analysis of sympathetic neurograms.

An objective technique for analysis is clearly an attractive alternative in comparison to issues regarding the inherent subjectivity of visual analysis, and the method, using modern computing techniques, can reduce analysis time on particularly difficult tracings from hours to minutes.

Of course, there is still enough free space for algorithm enhancement, primarily regarding the possibility to maintain the signals which include errors due to baseline shifts and to cope with the sympathetic activity which is not related with cardiac cycle.

## 5 Acknowledgement

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