AMPS-QT

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AMPS-QT is a quarterly journal dedicated to all the people and organizations involved in the world of cardiac safety. Published by AMPS LLC, it covers all aspects of methodology and software technology related to clinical trials and Thorough QT studies.

Editorial

This last quarter has seen some relevant changes in the landscape of the industry: from MDS Inc, with the announcement of the MDS Pharma Services late stage operations divesting, and the more recent announcement of the intent to sell MDS Pharma Services altogether, to the acquisition by Medifacts International, Inc. of the Clinical Trials Services division of Spacelabs Healthcare, Inc. We do not consider these events as a sign that the financial crisis is affecting the world of cardiac safety, but rather likely the beginning of a normal consolidation phase: many new core labs entered the market in the last few years, most providing more or less the same cardiac safety services, few others offering very innovative but, logically, not yet proven technologies. It would appear that the industry acknowledges that a change of gear is necessary to successfully survive and grow, but at the same time none of the sponsors really want to take the risk and lean far out on the "new technology" side, to avoid the risk of wasting resources and lose credibility.

In this third issue of AMPS-QT you will find an indication on how AMPS plans to answer the dilemma and help its customers to thrive: for the "ready to use solution" we share some more details on our soon to be released Fully Automatic T-QT study tool, not science-fiction, just proven and faster science, and for the "future solution" we include an AMPS internal article, presenting new ECG biomarkers that we have developed in collaboration with the Electronic Department of the *École Supérieure de Physique et de Chimie Industrielles de la Ville de Paris* (ESPCI, Paris). This new methodology is being published in scientific journals and subject to peers reviews, as any new solid scientific method should be: if it is accepted and approved by the community we will turn it into a tested and proven tool for our customers, otherwise we will keep looking.

AMPS Views on:

ECG Biomarkers

Several drugs were withdrawn from the market during the last twenty-five years due to an increased risk of a potentially lethal ventricular tachycardia called "Torsade de Pointes". The development of this arrhythmia is preceded by the prolongation of the QT interval in the electrocardiogram (ECG).

Congenital Long QT Syndrome (LQTS) has served as a model for drug-induced QT prolongation and TdP. The study of LQTS patients has revealed that the QT interval prolongation is due to genetic ionic channel alterations. Furthermore, there is a statistical correlation between QT interval duration and mortality in several other patient populations.

Drugs that cause QT prolongation and TdP impair ion channel function in a manner similar to abnormal channel function seen in LQTS. Almost all of the QT prolongation and TdP induced by the drugs is caused by the blockade of a specific potassium channel involved with repolarization, the Ikr channel. In general, the more the QT interval is prolonged, the higher the risk of TdP, although, there are notable exceptions such as Amiodarone.

Because of several withdrawals of marketed drugs after extensive patient exposure, a dialogue to develop a prospective approach to detecting QT interval prolongation began in 1997 when the European Committee for Proprietary Medicinal Products issued the first regulatory document that focused on QT risk assessment. This document formed the basis for several later regulatory documents that ultimately evolved into ICH E14, released in 2005.

ICH E14 advocates a "Thorough QT/QTc" study for essentially all new compounds to assess the risk of QT

prolongation. A Thorough QT/QTc is usually performed in a randomized, double-blinded manner in healthy volunteers. In addition to placebo, there is an active control that causes a known amount of QT interval prolongation to serve as a calibration of the study. In addition, the compound is usually given at both a therapeutic and supratherapeutic dose. The supratherapeutic dose is meant to mimic exposures that might be seen in patients with liver disease, with the use of metabolic inhibitors of the compound, or in combination with other compounds that might prolong the QT interval. A drug that does not cause significant QT prolongation at high doses in healthy volunteers would be less likely to cause TdP in patients.

The limitation of the use of prolongation of the QT interval as a marker of risk for TdP is widely recognized. Several other biomarkers examining a variety of aspects of the T wave morphology are currently under active investigation. In the mean time, QT interval prolongation assessment remains the mainstay in assessing risk for drug-induced TdP.

Drug-induced TdP remains a significant drug development problem. The best current assessment of this risk is through the "Thorough QT/QTc" study advocated in ICH E14, but newer biomarkers are being actively investigated. With very few exceptions, all drugs will require a "Thorough QT/QTtc" study.

In the last few years several so called "repolarization biomarkers" have been presented. The majority of these methods are based on simultaneous information from the whole cardiac repolarization, using techniques such as PCA (principal component analysis) and Vector Magnitude.

True comparison between existing and new methods has never been performed and published, and each vendor simply announces the superiority of their method compared to the others.

Here we simply want to introduce the basics theory behind our beyond-QT techniques and no comparison or announcements about our technique being superior to any existing one will be made.

Our technique, originally introduced by Remi Dubois (ESPCI, Paris), combines the use of a new machine learning algorithm that decomposes the ECG into a sum of parameterized functions specifically designed to fit the cardiac characteristic waves. Therefore, it combines the power of a machine-learning algorithm with the insight of the experts through the design of specific modeling functions.

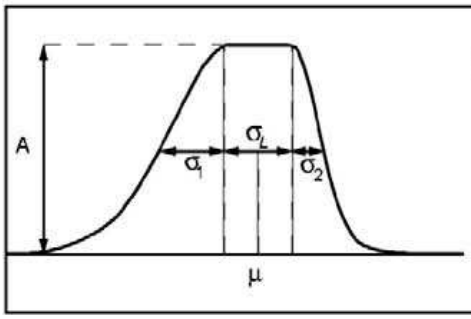
At first, the GOFR (Generalized Orthogonal Forward Regression) learning algorithm is used for fitting parameterized functions to the ECG; subsequently, two types of parameterized function can be use GMF (Gaussian Mesa Function) and BGF (BiGaussian Function).

Brief results will be presented on three applications of the algorithm: (i) wave delineation with GMF, (ii) T wave morphology changes during drug intake, and (iii) T wave morphology characterization of LQTS patients with BGF functions.

GOFR is an extension of the Orthogonal Forward Regression algorithm originally designed for regression and feature selection.

Wave delineation of a given heartbeat consists in (i) locating the characteristic waves (P, QRS, and T) and (ii) positioning markers at the beginning and at the end of these waves. To address the first problem, we designed a family of specific parameterized functions named Gaussian Mesa Functions (GMF); they are able to model the standard shapes of typical ECG waves. Each function is composed of two half-Gaussian functions linked by a horizontal segment (Figure 1) and uniquely characterized by 5 parameters:

- the time localization of the GMF (μ)
- the standard deviation (SD) of the first (ascending) half-Gaussian (σ_1)
- the SD of the second (descending) half-Gaussian



$$B(x,\mu,\sigma_1,\sigma_2,\sigma_L,A) = \begin{cases} A\exp\left(-\frac{1}{2}\left(\frac{x-(\mu-\sigma_L/2)}{\sigma_1}\right)^2\right) & \text{if } x \le \mu-\sigma_L/2 \\ A & \text{if } \mu-\sigma_L/2 \le x \le \mu+\sigma_L/2 \\ A\exp\left(-\frac{1}{2}\left(\frac{x-(\mu+\sigma_L/2)}{\sigma_2}\right)^2\right) & \text{if } x \ge \mu+\sigma_L/2 \end{cases}$$

Figure 1: GMF definition, combination of of two half-Gaussian functions linked by a horizontal segment.

(σ_2)

- the length of the horizontal part (σ_L)
- the amplitude (A)

The variability in shape of such a function is large since it can model either an R wave, a ST abnormal segment, or a T wave.

When applying the GOFR algorithm together with GMF on a heartbeat, the obtained model is a sum of N GMFs, each of which models a specific part of the heartbeat. The purpose of the method is to model each wave of the heartbeat by a single GMF. Thus, for wave delineation, we decided to use N=6 in order to model the 5 characteristic waves and possibly a biphasic wave, or noise (Figure 2).

The N GMFs of the model are subsequently assigned a medical label P, R, T, or possibly X if the GMF does not correspond to any of the ECG waves. This task is performed by three neural network classifiers (NNC).

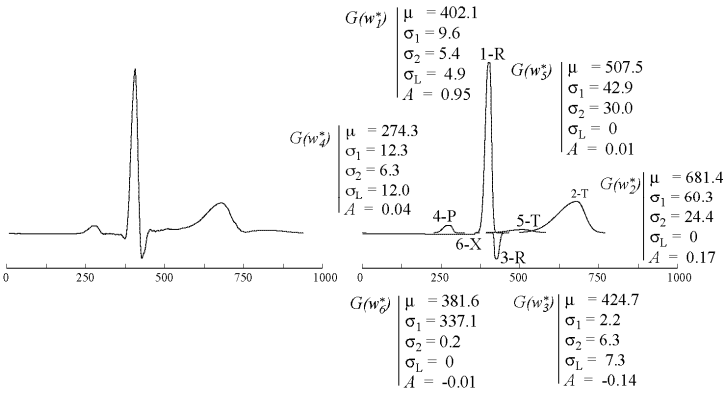


Figure 2: GMF definition, combination of two half-Gaussian functions linked by a horizontal segment.

As initially presented, another application of the algorithm is T-wave modeling.

The T wave does not exhibit the same variability in shape as the whole QRST; in particular, the top of a T wave is never flat, but amplitudes can be different from one side to the other, as is the case for abnormal ST segments for example. Thus, the parameterized function used here consists of two half-gaussian functions with no flat segment and with different amplitudes (Figure 3); in the following, this function is referred to as a Bi-Gaussian function (BGF).

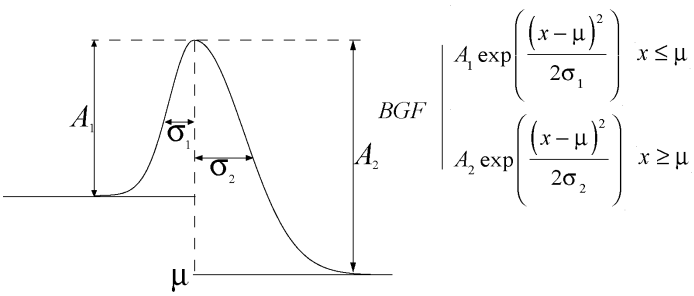


Figure 3: BGF definition, combination of two half-Gaussian functions with different amplitude.

Some Results

Since the representative beats are 12-lead ECG, a preprocessing step was performed to extract a 1-d signal from the 12 channels. It consists in a Principal Component Analysis computed on the 8 independent leads, the resulting 1-d signal being the projection of the original heartbeat onto the principal component.

T-wave analysis - drug effect

The performances for the T wave analysis were estimated on the Sotalol database on the 1-d representation of the T-wave.

Each T-wave was subsequently modeled by a single BGF and its morphology was described by the values of the parameters of the BGF (Figure 4).

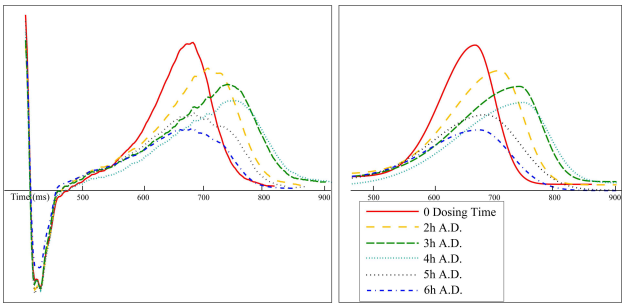


Figure 4: (left) T waves after intake of 320mg of Sotalol. (right) Corresponding BGF models.

Secondly, the performance of the algorithm was validated on the LQTS database. Here again, the 12-lead representation of the T-waves was projected onto a 1-dimensional space by PCA, and the obtained 1-d T-wave was modeled by a single BGF. The parameter vectors of the models were compared to baseline ECGs from the Sotalol database (Table 1).

	Control	LQT_1	LQT_2
Number of ECGs	2351	50	49
$\mu + 2\,\sigma_2$ (ms)	338±24	401±67	410±64
σ_1 (ms)	52±6	61±12‡	69±21‡
σ_2 (ms)	29±3	29±7	35±13‡
σ_1/σ_2	1.8±0.3	2.4±1.7‡	2.1±0.8‡
A_1 (μV)	1073±361	929±431‡	757±502‡
A_2 (μV)	1165±406	974±502‡	761±378‡

Table 1: Result for BGF parametres for LQT database (‡ p<0.05 vs baseline, □ p<0.05 vs Single Dose)

Conclusions

This technique is fully automated and does not require any user input/validation.

Our beyond-QT techniques can be applied to the analysis of 12-lead resting ECGs (within CalECG tool), on Holter extractions as well as on ECG template obtained from holter data with AMPS Holter-bin.

In addition to the presented beyond QT techniques, AMPS offers the tools for traditional analysis such as CalECG and soon the FAT-QT, and for the Holter world the famous AMPS Holter-bin.

The AMPS mission is to keep the focus on current and new methodologies, always in close collaboration with regulatory agencies, and thus continuing to provide state of the art technology to customers.

For more information on this topic, it is possible to refer to the following papers that introduce the concepts here highlighted:

- Dubois R, Quenet B, Faisandier Y, Dreyfus G. Building meaningful representations for nonlinear modeling of 1d- and 2d-signals: applications to biomedical signals. Neurocomputing. 2006;69(16-18):2180-92.
- Dubois R, Maison-Blanche P, Quenet B, Dreyfus G. Automatic ECG wave extraction in long-term recording using Gaussian mesa function models and nonlinear probability estimators. Computer Methods and Programs in Biomedicine. 2007;88:217-33.

Products News

Looking forward

In the next few months AMPS is planning major releases of the following tools:

- FDAEcg Suite v.2: enhanced graphical interface, with advanced scoring display, new scoring metrics and optimized ECG management.
- Holter Suite: redesign of the old WinAtrec tool with enhanced graphical interface, as well as command-line modality for batch analysis, and the Holter analysis, including the famous RR-Bin and Time-Bin methods.
- CalECG v.3: totally redesigned graphical interface, updated with new display on ECG signal in predefined format, such as 3 X 4, 6 X 2 and enhanced automatic algorithm for annotation measurements with abnormal beat classification. This new version will also include a diagnostic algorithm, imbedded thanks to the cooperation with Glasgow University.

FAT-QT

As announced in the last issue a new product will be part of the AMPS portfolio in December: FAT-QT (Fully Automatic Thorough-QT).
FAT-QT is a fully automated tool that combining features of two successful and confirmed AMPS tools, namely CalECG and the FDAEcg Suite, will provide in one single tool the capability to perform a fully automated analysis of 12-lead ECG. ECGs will be automatically annotated with the new and improved algorithm of CalECGv3 and, using different scoring-metrics selected by the user, FAT-QT will classify the measured ECGs in different categories. At the end of the process, minutes later, high quality classified ECGs would not require any further review, thus greatly reducing the need for manual review analysis on a small subset of ECGs.
The development phase of FAT-QT is almost complete and we are now in testing phase with selected partners.

AMPS Notebook

The abstract: *"Efficient Modeling of ECG Waves for Morphology Tracking"* for which both Fabio Badilini and Martino Vaglio are coauthors has been just presented at the Computers in Cardiology 2009 Conference held at Park City, Utah on September 13th – 16th.

AMPS people

Guido Libretti, MS

We continue our round of staff introductions with Guido Libretti.

Guido started his Engineering studies in Italy at the University of Brescia where he obtained his Master Thesis degree in 2006. His graduation thesis was titled: "*The FDA HL7 XML format, for the representation of annotated digital ECG: analysis and validation and comparison with existing public formats*" and was completed with another member of AMPS staff Lamberto Isola, who was presented in the previous issue of AMPS-QT.

He originally joined AMPS back in 2003, as part-time consultant, while he was still a student. He quickly became interested in the graphical design of the interface of the tools and as of today Guido is responsible for the majority of the graphical user interfaces (GUI) of the family of AMPS tools.

Since the beginning he was also the leader of the CalECG product line, including Mizar.

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