ABBIOS (ABbott BIOsignal System): A Workbench System Software for Data Mining in Biosignals, with Applications in Drug Research and Development

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Abstract

ABBIOS software is designed to facilitate extraction of biosignal features for an industrial environment in drug research and development. It is dedicated to handling large amounts of data with a high level of user control. Its purpose is to enable high quality data elaboration for the improvement of drug safety and efficacy, and to ensure improved economic efficacy.

1. Introduction

We developed ABBIOS during the past six years. Early versions only were supported to improve the quality of analysis in holter ECG used for SIM calculations. In the meantime, fourteen clinical and pre-clinical studies with different types of biosignals have been evaluated, primarily for the assessment of drug safety in research and development.

2. Principal features

ABBIOS (and its precursor KLUBIOS [1]) is a modular and flexible software system, built upon a flexible, user-defined workbench architecture. It allows the import of biosignal raw data and annotations of various origins from different data sources (ECG, Holter ECG, animal telemetry, EEG, polysomnography, Physionet data sources). It can process these multi-channel sources with up to 12 channels per source. Processed results and annotations may be delivered to standard database interfaces like ODBC or OLE DB for further statistical processing and reporting purposes.

As an expert tool, ABBIOS evolves its strengths from its object-oriented properties, and user-friendly application.

The ABBIOS software:

- Allows full user control over each feature in the evaluation of data and processing steps, since there are no "black-box" steps;
- organizes the work hierarchically by user-definable workbenches or by invocation of pre-prepared templates;
- accepts input from foreign pre-classification contained in biosignal sources, or provides tools for recognition and reclassification of recurrent events (like ECG). It helps the user to check the type of event classification, to detect misclassifications and to correct them automatically or manually. Graphic tools like 3D plot with marker functions facilitate this task (fig. 1);
- offers an abundance of tools for processing raw data and to keep control over changes in signal properties in order to recognize artifacts, and clear out artifacts from the evaluated data tables (fig. 2);
- includes an automated case-reporting output procedure based on XML/XSLT and thus produces detailed reports about all technical definitions, settings of analysis workbenches and results;
- grants access to major analytical mathematical and statistical tools, like IIR-type filters, Wavelet filters, FFT, PCA, etc.;
- includes advanced methods based upon neural networks (Perceptron-NN, RBF-NN, PNN) and helps to handle combinations of all methods easily;
- grants access to methods from nonlinear dynamics based upon patent-protected Scaled Index Method (SIM; fig. 3; method licensed to Abbott by Garching International GmbH);
- is a versatile tool for the evaluation of pre-clinical in-vitro studies (isolated organs; cell culture) and in-vivo studies (telemetric instrumented animal), as well as for the electrophysiological parts of clinical studies (Phase I to IV);
- supports workflow of evaluation processes and automatization, since it is easily controlled by enveloping processes. Any programming or database language can handle ABBIOS workbenches from outside, pushing the program through study schedules and collecting results in database structures for further processing.

3. Medical requirements

Recent development in powerful PC resources as well as sensor technology have helped to gain acceptance for new methods in the field of biosignal based evaluation with applications in cardiology, pulmology and neurology. Some developments are considered remarkable:

- Continuous multichannel recording has been established, enabling a detailed beat-to-beat analysis of ECG, blood

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pressure data, blood oxygen saturation, as well as time-domain analysis in EEG and respiration sensor data. This step gives access to the regulating mechanisms of many body functions. It reveals short and long term components of regulation, and has its rationale in understanding biorhythms as well as drug induced regulation changes. Drug discovery and development gain insights in drug to biorhythm interactions, a benefit in the optimization of drug efficacy and safety.

- It has been shown that mathematical methods in variability evaluation are an important issue in the assessment of drug safety. Rhythms and rhythm changes are now in the focus of science, and enhance the quality of information on potential drug risks. An abundance of pre-clinical and clinical studies has proven the correlation between variability measures (heart rate variability, QT variability, T-wave alternans) and the risk of sudden cardiac death, cardiac infarction, hypertension and stroke.
- Many drugs which have been considered safe in the past have lately been proven to be dangerous after their market launch, and thus had to be recalled afterwards. Prolongation of repolarization duration (QT) in ECG particularly is a big issue. Early recognition of hazards like drug induced QT prolongation and Torsade de Pointes arrhythmia is essential to avoid risks for patients, and significant financial risks for the phamaceutical industry. Pre-clinical testing can predict some of the risks, but not all. Testing in man will remain an essential step in drug safety assessment. It is a matter of signal quality and cost that QT assessment in clinical studies is still limited to the resting ECG. Improvement in the signal capturing and evaluation of long term (Holter) ECG will enable QT assessment during wakefulness and sleep, thus providing more complete and meaningful repolarization data.

Influence of drug treatment on physiological functions during sleep is one of the upcoming issues which have not been given much attention to in the past. Since it has turned out that many patients suffer from sleep apnoea, it is at least necessary to investigate the impact of drug treatment on respiration during sleep. Evaluation of Holter ECGs may provide an easy and efficient way to achieve sleep apnoea screening, as the results of the Computers in Cardiology challenge 2000 [2] have pinpointed.

4. Implementation

When we began to develop ABBIOS precursor development, it was intended as a pure research instrument dedicated to ECG evaluation and assessment of RR variability. The more we applied the system to research tasks, the more it turned out that we were confronted with a considerable number of vendor specific ECG applications, all equipped with proprietary data formats, secret methods and settings of data processing, and insufficient capabilities to integrate into the workflow of pharmaceutical industry research and development.

The general conceptional idea is to establish a flexible IT solution, which

- serves as a unified platform for all tasks in biosignal processing;
- makes better use of information collected by what we call an E-physiology concept;
- makes data processing and methods completely transparent;
- and seamlessly integrates to any object oriented environment.

For the part of data input, these ideas are implemented by an import module capable of importing the common raw data formats structures and annotations. Internally we maintain a general object oriented structure build upon a level model.

To obtain the event type information (e.g. the beat classification according to a standard classification scheme) from the raw data, we have the choice to either import event type notification from an external source annotation, or to apply internal classification algorithms. Events may be classified semi-automatically by ABBIOS (method needs to be set or trained NN has to be delivered) or imported from a annotation file.

For each event, we can determine event attributes which describe raw data properties, on time or voltage scale (at a given time). Event attributes are determined by event analysers which allow to control algorithms to process the raw signal data, referring to the annotated events. In time domain driven environment, a fixed preset segment length (like 4 second-segments in EEG) may be used.

Event parameters (like RR-interval or QT interval) are derived from event attributes by mathematical manipulations. The calculated parameters can be displayed in various ways to visualize the data and detect abnormalities and artifacts, which may be marked for further examination or exclusion.

For a more global perspective neuronal network approaches are currently implemented to improve attribute assessment, or to classify sequences of events (e.g. multi beat stages like episodes of supraventricular tachycardia or apnoea arousal) into state classes.

In every aspect of the classification, analysis or detection several filters like Wavelet, IIR or FFT can be used to obtain desired results while knowing, which method and parametrization has been used to acquire them. The summary of exploration is to be exported and saved automatically to HTML-formatted report files on basis of XML data structures. Each event (or in case of time domain: time segment summary) may easily be exported to any database for further examinations.

All these methods were implemented in an object

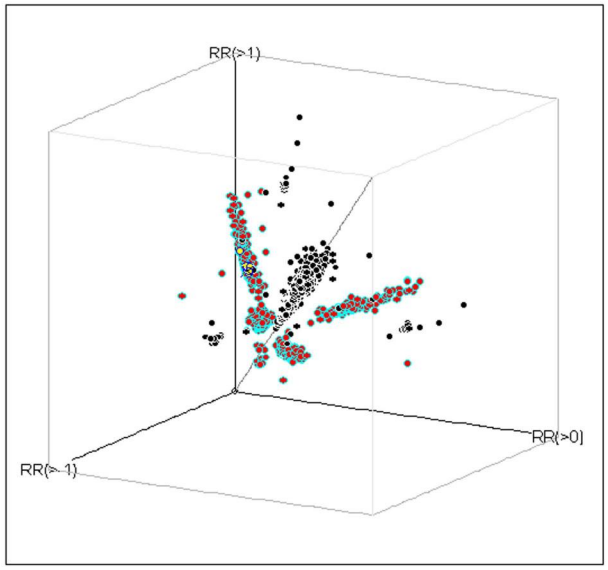

Figure 1. 3-D view (RR phase space), mouse-rotated

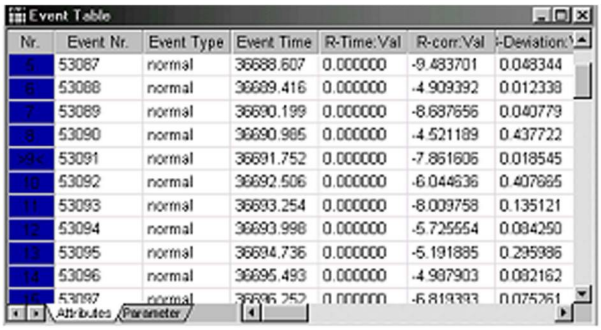

Figure 2. Event table presentation & control

oriented fashion so they can easily be con-trolled by any object oriented environment, to automate studies and ease data mining. This making ABBIOS a flexible, highly transparent and complete tool for biosignal exploration.

The graphical user interface is easily adapted by common Windows users, providing six view types: raw data, time series, scatter (2-D)-plot, phase-space (3-D)-plot, event and state table. Data in time series are divided into active and inactive time window segments, and either unmarked or marked. Marked events are cross-linked over all windows, which allows to wander through events, and observe different data properties same time. Workflow within ABBIOS is organized into collections of views to be observed same time, which is called ”workbench” structure. Workbenches may be ordered and assigned to different groups.

Evaluation methods have been implemented for data summaries by statistical parameters, like variability

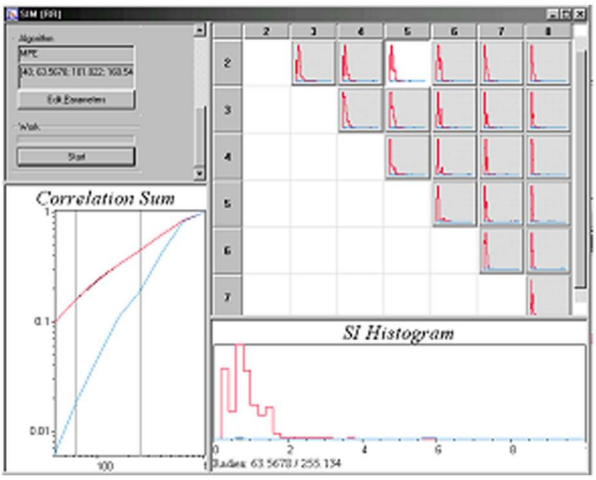

Figure 3. Result window SIM method

measures, time sequence measures, characterization of parameter distributions, parameter spectrum (FFT of parameters), signal distribution and the nonlinear dynamic SIM method.

Automated processing by scripts refers to the groups, workbenches within group and view within workbench.

The current version is capable to control user access (according to 21CFR part 11 requirements), and in near future will be subject to GxP compliance, keeping an audit trail feature.

The software has been developed in a standard Windows environment, using MS Visual Studio C++ Version 6.0. Standard PC configuration needed is Windows 98/NT4/NT2000/XP with at least Pentium or equivalent AMD processor, 128 MB RAM and takes 10 MB space on the computer disk.

ABBIOS supports multiprocessing and multi-threading, and thus takes full advantage of computational power of multiprocessor systems.

5. Discussion

We found it extremely useful that the user experts have complete command over the data and procedures. This affords high quality of data, and the improved reliability of results.

ABBIOS is not yet completely validated according to 21 CFR part 11 rules, but a validation project is in progress. Validation of the methods used for conventional RR, PQ, QT time measurement from 24 hour Holter ECGs proved successful.

Requirements from the regulatory authorities FDA and EMEA to meet GCP/GLP requirements force us to keep all intermediate changes in the data evaluation in an audit

trail file, together with user identification, date/time and reason of change. This puts us into real problems from the speed of processing as well as from amount of overhead data to keep. Furthermore, processing speed is curbed down considerably. Especially with long term data, this will be a growing issue. The more, as it is really questionable, whether each elimination of artifacts among one hundred thousand heartbeats in a 24 hour Holter ECG should be completely documented.

6. Summary

ABBIOS is an efficient, user-friendly workbench for the evaluation of drug safety and efficacy in an industrial environment. It meets the needs of the drug development business as well as those of the expert user. Full validation is required to comply with GLP and GCP legacy requirements.

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References

[1] Safer A, Bystricky W, Schweizer M. Klubios: A flexible and modular software system for cardiovascular research. In Computers in Cardiology. 1999; 559–562.

[2] Moody G. Detecting and quantifying sleep apnea based on the ecg: A challenge from physionet and computers in cardiology 2000. Http://www.physionet.org/challenge/2000/.

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