Analysis and Reporting Pipeline for Cardiac Ion Channel Pharmacology Data

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Abstract

New draft ICH E14/S7B Q&As describe how nonclinical cardiac repolarization data, including cardiac ion channel pharmacology, derived under “best practices” can be used to support clinical interpretation of QT studies as a part of an integrated proarrhythmic risk assessment. It is anticipated that FDA will receive the raw data of these ion channel experiments as supporting information when implementing the new Q&As. However, there is currently no open data format to facilitate sharing these data. To address this issue and under the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative, a group of researchers from industry, academia, and FDA coordinated by Health and Environmental Sciences Institute (HESI) developed a draft CiPA Open Data (COD) format. To enable exporting existing data to COD format, the FDA sub-team also developed the Tabulated Experimental Data (TED) format, a spreadsheet-based format mapping a subset of COD elements. This research investigated analysis methods and reports frequently used to summarize results from ion channel pharmacology experiments and implemented an automatic analysis and reporting pipeline for COD or TED datasets.
The main steps found in frequent analyses include, linking waveforms with test articles and concentrations, flagging waveforms used for primary analysis, calculating average waveform for residual current subtraction, defining and evaluating measurement points (cursors), calculating changes from control, and modeling dose-inhibition relationship to estimate drug potency. The steps were mapped to COD data elements and implemented in an automated analysis pipeline in a python package that reads from and writes to TED or COD files raw data and results (e.g., annotated waveforms). The reporting component of the pipeline generates a report (R markdown) that includes raw waveforms, current-time (IT) plots by cell and cursor, current inhibition tables by cell and by concentration, and dose-inhibition model results. The results in the report can be used to verify “best practice” elements (e.g., recording quality) or to assess reproducibility of results from other analyses or summaries included in nonclinical reports of the same data.

Introduction

International guidelines recommend “best practices” for nonclinical experiments evaluating the potential of drugs to affect electrical currents of the heart and cause abnormal heart rhythms.

Currently, there are no data standards or open data formats to facilitate sharing raw data from these experiments.

However, the CiPA Open Data (COD) draft specification and the Tabulated Experimental Data (TED) data format, which is a simplified version of COD, are emerging open data formats developed to facilitate data sharing under CiPA.

A computational pipeline that automatically analyzes COD datasets and generates an analysis report could facilitate the evaluation of the presence and adequacy of “best practices” elements and streamline the review process of these data.

Materials and Methods

- Investigate analysis methods and reports frequently used to summarize results from ion channel pharmacology experiments
- Map identified data elements used by analysis methods to data elements in the CiPA Open Data Format
- Map assay report elements and analysis outcomes to analysis processes
- Define an analysis pipeline that takes COD files as input, performs the signal processing and statistical analyses, and generates a report that allows to assess whether “best practices” recommendations are present
- Simulated datasets, real data acquired in manual and automated patch clamp experiments and their corresponding assay reports as reference
- Data processing ,analysis, and graphical user interface were written in python 3.6.10.
- Reporting components were written in R 4.0.3 and R Markdown

Results

The main analysis steps identified included:

- linking waveforms (also referred to as traces) with test articles and concentrations;
- flagging waveforms used for primary analysis;
- calculating average waveform for residual current subtraction;
- defining and evaluating measurement points (cursors);
- calculating changes from control; and
- modeling of dose-inhibition relationship to estimate drug potency.

COD data elements were mapped to the steps enumerated above.

An automated analysis tool (Figure 1) implements the following functionality of the processing pipeline:

- reads from and writes raw data and results to TED or COD files (e.g., annotated waveforms);
- optionally performs residual (background) current subtraction;
- evaluates predefined or custom cursors in each waveform; and
- performs dose-inhibition calculation and modeling.

Additional components of the pipeline include additional analyses scripts and a reporting tool (R) that generates a report that includes (Figure 1):

- intended voltage command and cursors definitions;
- raw waveforms;
- IT plots by cell and cursor;
- current inhibition tables by cell and by concentration; and
- dose-inhibition model results.

The results in the report can be used to verify “best practice” elements (e.g., recording quality) or to assess reproducibility of results from other analyses or summaries included in nonclinical reports of the same data. In addition, a graphical user interface allows for visual inspection of COD files in an interactive fashion.

Figures 2-4 show example plots and tables from the automatic assay report and graphical user interface.

Acknowledgments

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Results (continued)

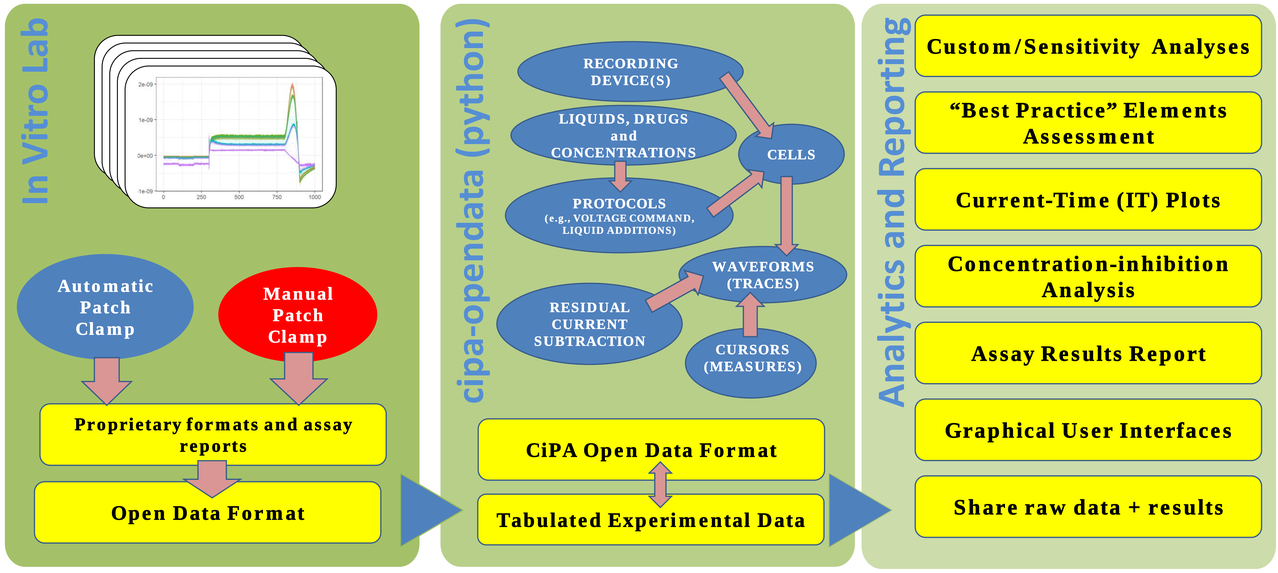

Figure 1. In vitro lab data pipeline and manipulation workflow.

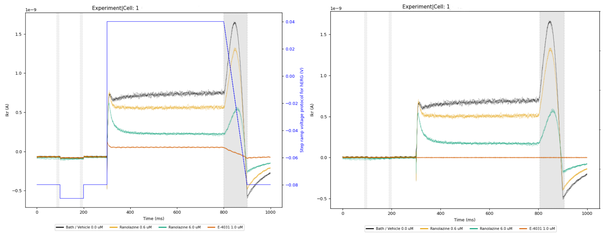

Figure 2. Voltage command (blue), raw waveforms without (left) and with residual current subtraction (right) in bath/vehicle (black) and after drug and E-4031 additions (orange, green, dark orange), and cursor locations (gray).

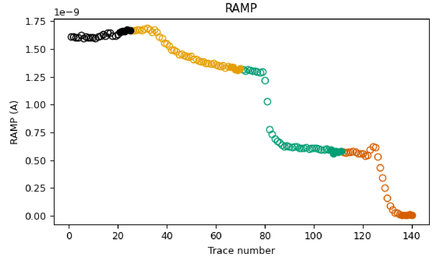

Figure 3. IT plot for the ramp cursor values for traces in Fig 2

Dose	N	Average (%)	SD	SEM
drug 0.3 uM	3	4.9	11.6	6.7
drug 3 uM	6	-13.8	11.9	4.8
drug 30 uM	6	-73.4	6.5	2.6
drug 300 uM	3	-91.6	6.2	3.6

Table 1. Average concentration-inhibition values

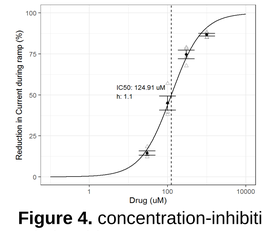

Figure 4. concentration-inhibition relationship

Discussion and Conclusion

New draft ICH S7B Q&As include “best practice” considerations for cardiac ion channel pharmacology experiments that have the potential to support clinical interpretation of QT studies.

However, lack of data standards for sharing cardiac ion channel pharmacology data makes independent analysis and review of these data challenging, time consuming, and error-prone because it frequently requires manual transformation of proprietary data into different files for subsequent analysis.

The presented automatic analysis and reporting pipeline leverages emergent open data formats like CiPA Open Data (COD) and Tabulated Experimental Data (TED) and has the potential to reduce the time needed to independently analyze and review data from cardiac ion channel pharmacology experiments following “best practices” recommendations under the new draft ICH S7B Q&A.