Open Format for Ion Channel Datasets from Cardiac Electrophysiology *In Vitro* Assays under CiPA

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Introduction

To predict the torsade risk of new drugs, the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative proposes to use a mechanistic model of the human ventricular myocyte that integrates multiple cardiac ionic currents.

Drug effects on the ion currents are characterized using standardized *in vitro* assays. Data from these ion channel assays are stored using proprietary formats and exported to formats specified ad-hoc for sharing with others (e.g., spreadsheets with specific layout).

An open data format for results of ion channel experiments under CiPA will foster sharing results in research environments and will facilitate the review of these datasets.

Materials & Methods

Gathering of format requirements included:

- Review and assessment of data formats used by commercially available manual patch clamp and high throughput systems.
- Prototyping of files using actual data from in vitro multi-ion channel patch clamp experiments.
- The annotated ECG HL7 (XML) format was used as reference.

The potential of new drugs to cause abnormal heart rates can be assessed in laboratory experiments quantifying drug effects on multiple ionic currents active during the heart-beat.

We present an open format to facilitate sharing and analyzing ion channel datasets used for proarrhythmic potential assessment of drugs.

Scan the QR code to access additional information online

Results

An open data format specification was developed describing one master XML file with links and metadata to access raw waveform recordings stored in external files.

An R package was also developed with an example dataset and functions to read the format and produce tabulated analysis datasets.

Conclusions

Coordinated by the Health and Environmental Sciences Institute (HESI), a group of researchers from industry, academia, and FDA, developed an open data format for CiPA's ion channel *in vitro* experiments. This format could serve as an interface into CiPA's *in silico* model to predict torsade risk. Next steps include identifying and getting the specification through a data standards body (e.g., HL7). This new format will streamline the submission and review process of nonclinical *in vitro* data as part of the proarrhythmic assessment of new drugs.

Acknowledgments

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Disclaimer

The views presented in this document are the personal opinions of the authors and do not reflect the official views of their respective organizations.

References

[1] Strauss et al., Ther Innov Regul 53(4): 519-525 (2019)
[2] Vicente et al., Clin Pharmacol Ther 103(1): 54-66 (2018)

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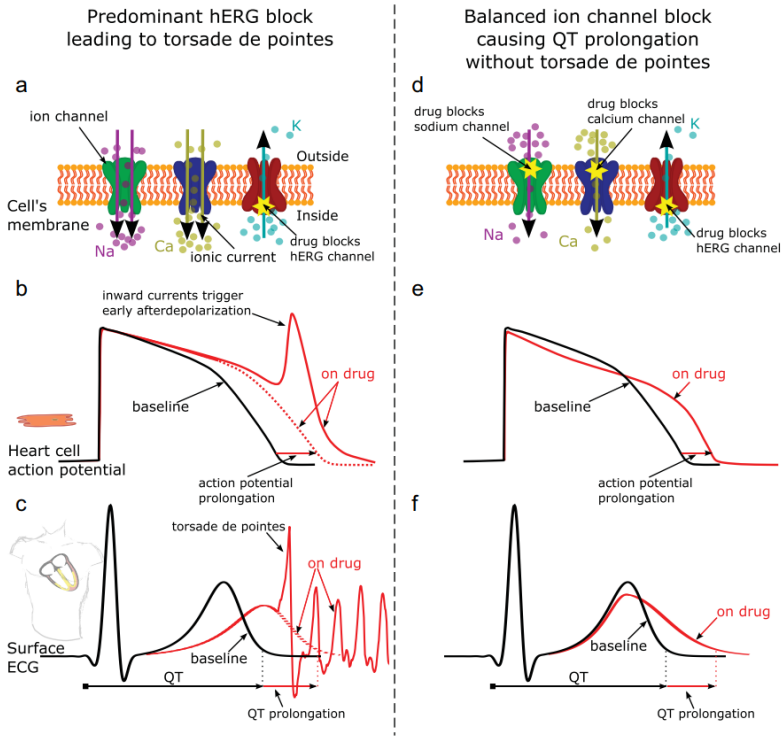
Introduction

- Drugs that block the hERG potassium channel delay cardiac repolarization and prolong the QT interval in the electrocardiogram (ECG). QT prolongation is associated with Torsade de Pointes, a potentially fatal arrhythmia. Current regulatory paradigm focuses on hERG block and QT prolongation (ICH S7B and E14).
- However, there are QT prolonging drugs that have low risk for torsade because they block other inward ion channel currents. Inward current block prevent the occurrence of early afterdepolarizations, the triggers for torsade.
- The paradigm proposed by the Comprehensive in vitro Proarrhythmia Assay (CiPA) initiative will predict the torsade risk of a drug by integrating the drug effects on multiple ion channel currents in an in silico model of the human ventricular myocyte .
- An open data format to facilitate exchange of results of ion channel experiments for CiPA is needed.

Figure 1 – Ion channel currents, ventricular action potential and the ECG



Ventricular repolarization and torsade risk are dependent on a “symphony” or “balance” of multiple inward and outward ion channel currents, not just reduced IKr by hERG block. Reproduced from Vicente et al., Clin Pharmacol Ther 103(1): 54-66 (2018).

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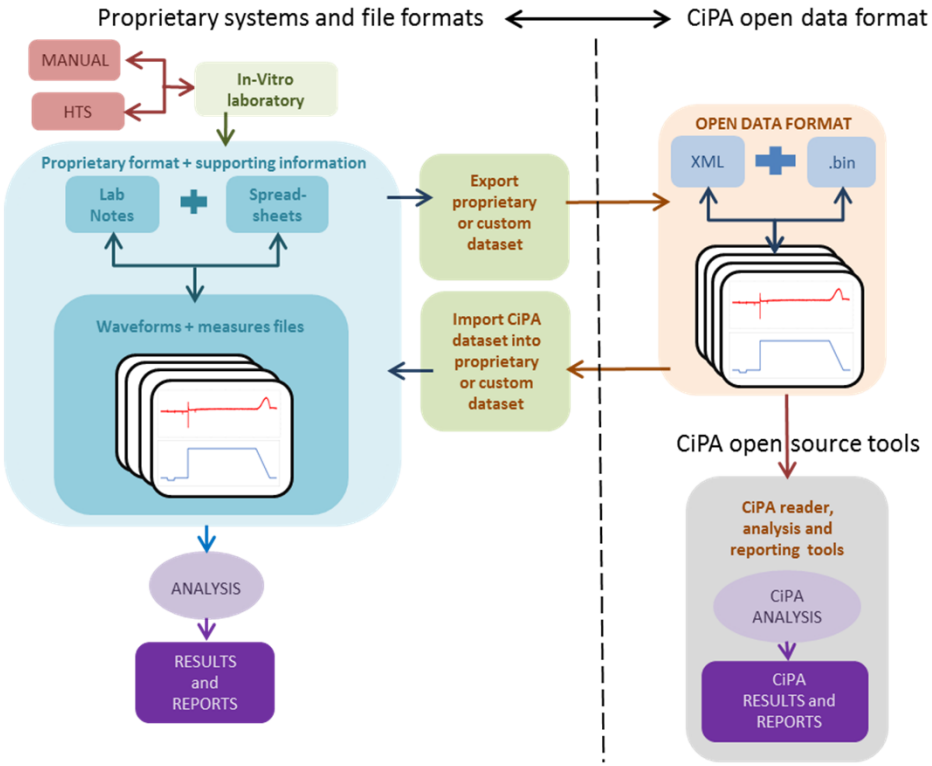
Materials and Methods

- Coordinated by HESI, a CiPA subteam including volunteers from industry, academia and FDA was formed to work on an open data format specification for manual and automated patch clamp data.
- The annotated ECG (aECG) HL7 format was used as reference because there are many similarities that between the data elements captured by the aECG format and the needs for CiPA ion channel datasets.
- The team also considered:
  - Recommendations for minimum information of cardiac electrophysiology experiment (MICEE).[3]
  - File types currently supported by electronic Common Technical Document (eCTD).
- Experimental data from in vitro multi-ion channel patch clamp experiments were recoded into prototype files and tools to guide the development of the format specification.

[3] Quinn, T.A. et al. *Prog Biophys Mol Biol* **107**, 4-10 (2011).

Figure 2 – Potential data formats ecosystem



An open data format for ion channel experiments (top right) will allow sharing results and will facilitate independent analysis of these datasets.

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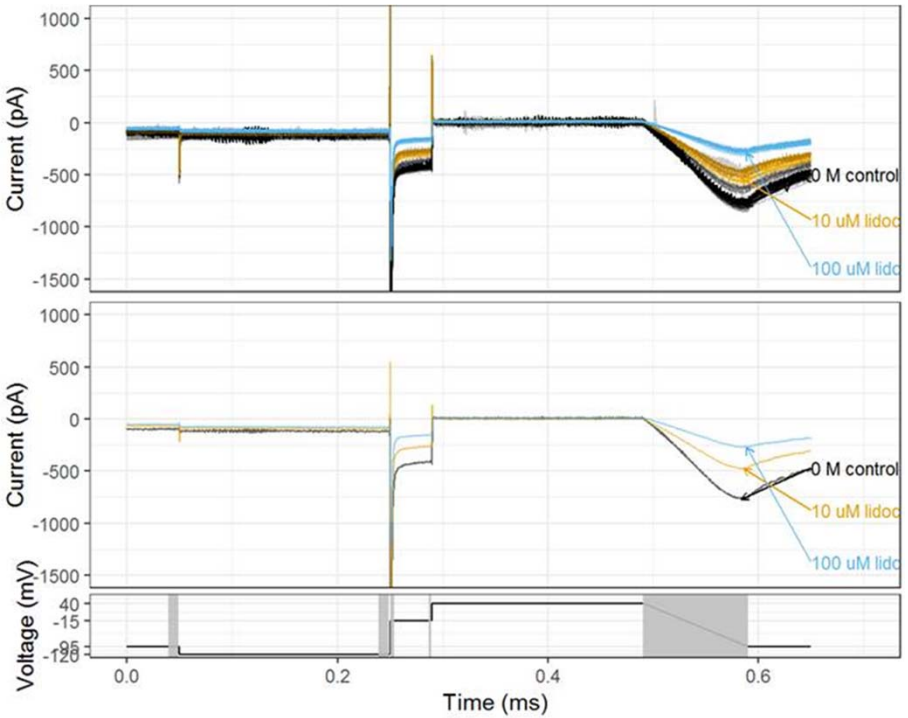
Results

- A format specification was developed describing one master XML file with links and metadata to access raw waveform recordings stored in external files.
- Information stored in the XML file includes
  - Device and software.
  - Plate and well identifiers.
  - Liquids and dosing (i.e., concentration and timing).
  - Protocols used (e.g., voltage, current, temperature).
  - Cells (e.g., single vs. population, ID, batch).
  - Measurements and waveforms information:
    - Voltage, current, temperature.
    - Sampling frequency.
    - Cursors locations and associated measures.
    - Link to external file with time series values.
- An example dataset and an R package* were developed by FDA members:
  - Dataset of late-Na experiments[4] was coded following the draft specification.
  - Reader of XML + waveform files.
  - Basic analysis functionality

Figure 3 – Example of voltage protocol and current traces from one cell



Individual (top) and average (middle) traces of sodium current in control (black), and after addition of lidocaine 10 µM (yellow) and 100 µM (blue). Voltage protocol and cursor locations (bottom, gray).

[4] Wu, M. et al. https://doi.org/10.1016/j.vascn.2019.106605 Original dataset available at: https://osf.io/pkw5f/; * Planned to be released as open source

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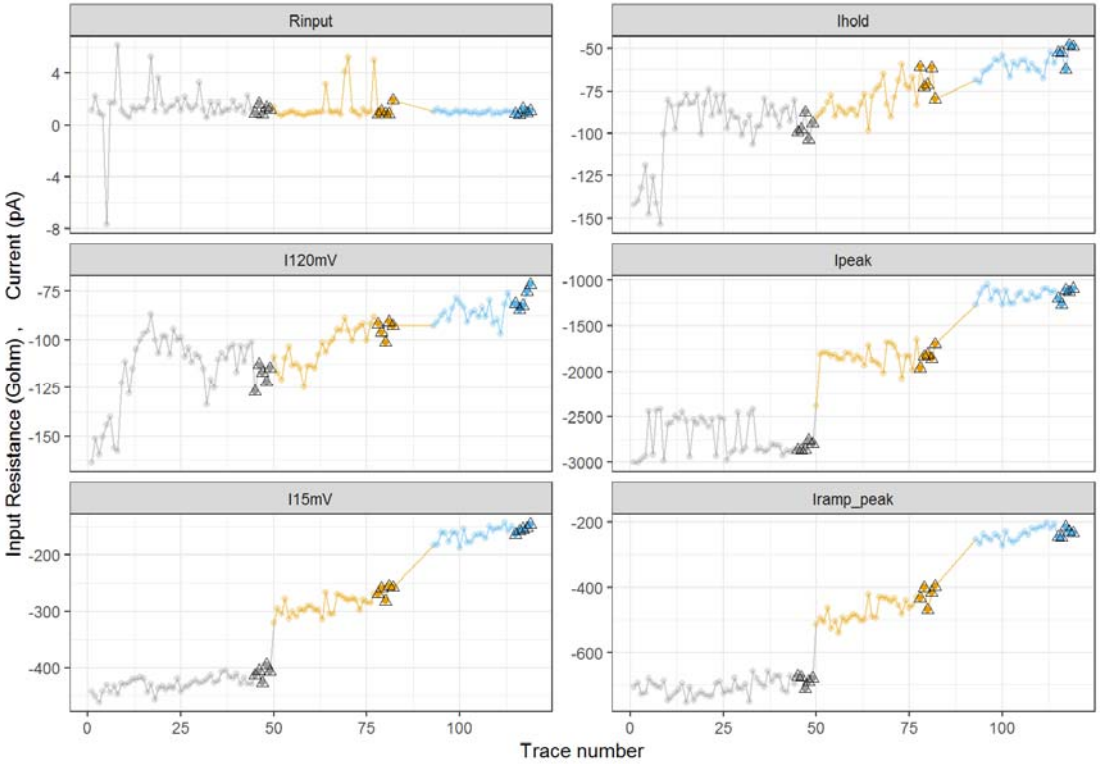
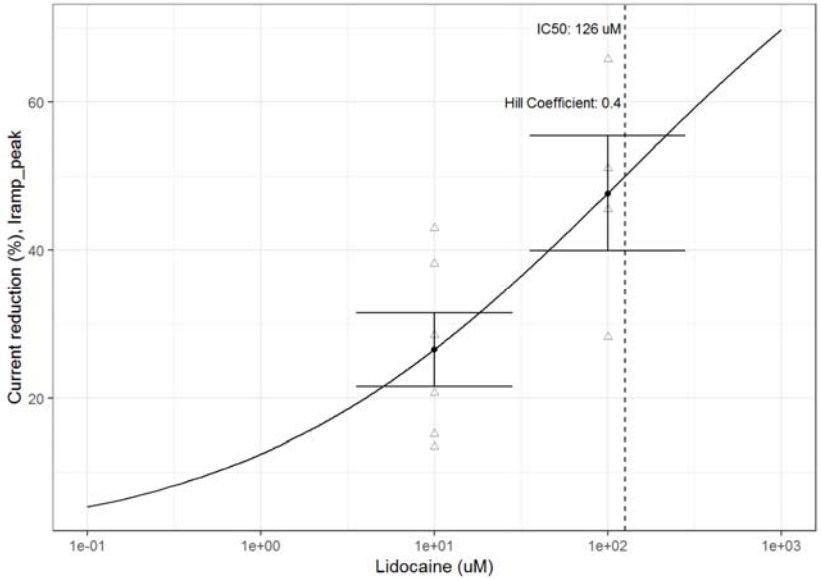
Results

Figure 4 – Example of IT plots from analysis of CiPA file



Current-time (IT) plot for measures from the cursors of the voltage protocol for the cell shown in Figure 3

Figure 5 – Example of concentration-response from analysis of CiPA file



Concentration response curve from all cells and lidocaine doses in the experiment.

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Conclusions

- A group of researchers from industry, academia and FDA developed an open format for CiPA's ion channel in vitro experiments.
- A new open data format together with standardized voltage protocols will streamline the submission and review process of nonclinical in vitro data as part of the proarrhythmic assessment of new drugs under the CiPA paradigm.
- In addition, an example dataset and an R package to read and analyze CiPA open data format files were developed and are planned to be released as open source.

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