# Uncertainty characterization of dose-response curves

This code performs uncertainty characterization of dose-response curves (the Hill equation) for ionic current block using a Bayesian inference approach.

## Data format

Patch clamp data should be stored in CSV format with the following headers:

\* \*\*drug\*\*: drug name

\* \*\*conc\*\*: drug concentration in nM

\* \*\*channel\*\*: name of ionic current tested

\* \*\*block\*\*: amount of block (%)

## Data preparation

27 CiPA drugs data provides by Nanion Technologies GmbH.

## Running the code

This code uses the R packages optparse (version 1.4.4) and FME (version 1.3.5).

To fit bepridil:

```

Rscript IC50\_mcmc.R -d bepridil

```

The code attempts to fit an IC50 value and Hill coefficient for each drug-channel pair in the data and then obtains a joint sampling distribution of the parameters using Markov-chain Monte Carlo simulation (MCMC). the Markov Chain Monte Carlo (MCMC) algorithm was updated from the previous version (https://github.com/FDA/CiPA/blob/Model-Validation-2018/Hill\_Fitting/IC50\_mcmc.R). The updated code is under the Hill fitting folder. More information is provided in the supplementary material of the paper “A Lab-specific Calibration and Validation Strategy for Implementing Proarrhythmia Risk Prediction Models: A Case Study of CiPA” (submitted). For data that cannot be fitted, these values are omitted from the output.

New data can be fitted by specifying the data file path and the drug name:

```

Rscript IC50\_mcmc.R -d drug1 -f my\_data\_file.csv

```

By default, 2000 samples are saved from the MCMC run. A different number of samples can be saved:

```

Rscript IC50\_mcmc.R -d drug1 -f my\_data\_file.csv -n 3000

```

For additional help:

```

Rscript IC50\_mcmc.R -h

```

Note that the fitting is computationally intensive, and it is recommended that this be done in parallel on a high-performance computing resource. (See [this script]( IC50\_mcmc\_jobs.sh) for an example of how to split up the fittings for all drugs.)

## References

\* Li, Z., Dutta, S., Sheng, J., Tran, P.N., Wu, W., Chang, K., et al. (2017). Improving the In Silico Assessment of Proarrhythmia Risk by Combining hERG (Human Ether-Ã -go-go-Related Gene) ChannelDrug Binding Kinetics and Multichannel Pharmacology. Circulation: Arrhythmia and Electrophysiology 10(2), e004628. doi: 10.1161/circep.116.004628.

\* Chang, K. C., Dutta, S., Mirams, G. R., Beattie, K. A., Sheng, J., Tran, P. N., Strauss, D. G, et al. (2017). Uncertainty quantification reveals the importance of data variability and experimental design considerations for in silico proarrhythmia risk assessment. Frontiers in physiology, 8, 917. doi: 10.3389/fphys.2017.00917