# Uncertainty characterization of drug-hERG kinetics

This code performs uncertainty characterization for the pharmacological component of the human Ether-Ã -go-go-Related Gene (hERG) current model using the nonparametric bootstrap method.

## hERG model

The hERG Markov model includes a saturating drug binding component and a drug trapping component:

![hERG model](hERG.png)

The fitted drug parameters are Ku (drug unbinding rate), Kmax (maximum drug effect), n (Hill coefficient of drug binding), halfmax (nth power of the half-maximal drug concentration), and Vhalf (drug trapping potential).

## Running the code

This code uses the following R packages: optparse (version 1.4.4), deSolve (version 1.14), ggplot2 (version 2.2.0), cmaes (version 1.0-11), and FME (version 1.3.5).

Results and figures are automatically saved to [results/](results/) and [figs/](figs/), respectively.

A quick example of the bootstrapping process can be run with [this bash script](run\_example.sh) to ensure the code is working. The full process is explained below.

### Bootstrapping the data

Drug parameters are fit to fractional block time series data obtained using a filtration on the Milnes protocol (Milnes \*et al.\* 2010, Li \*et al.\* 2017).

Filtration process:

compared to the previous/original hERG data in CiPAORdv1.0 (<https://github.com/FDA/CiPA/tree/Model-Validation-2018/hERG_fitting/data>), a new filtering step was applied to select only cells with less than 20% background current. Consequently, 29 cells were rejected compared to previously used in the original development of CiPAORdv1.0. More information is provided in the supplementary materials of the paper “A Lab-specific Calibration and Validation Strategy for Implementing Proarrhythmia Risk Prediction Models: A Case Study of CiPA” (submitted).

The data are located in [data/](data/) in CSV format (see [README.md](data/README.md) for details).

Before fitting the model, bootstrap samples must first be generated from the data using the following command:

```

Rscript generate\_bootstrap\_samples.R

```

The default is to generate 2000 bootstrap samples for each of the 12 CiPA training drugs. Different drugs and/or a different number of samples can be specified:

```

Rscript generate\_bootstrap\_samples.R -d "drug1,drug2" -n 3000

```

The random bootstrap sampling will be reproducible as long as the drugs are specified in the same order. Note that for new drugs, the relevant data files should be located in [data/](data/) (e.g. data/drug1.csv, data/drug2.csv).

The random seed (default 100) can also be changed:

```

Rscript generate\_bootstrap\_samples.R -d "drug1,drug2" -s 200

```

### Fitting the model

The dynamic hERG model C code is provided in [models/](models/) and must be compiled:

```

cd models

R CMD SHLIB hergmod.c

```

Fitting is performed with the Covariance Matrix Adaptation Evolutionary Strategy (CMA-ES) (Hansen \*et al.\* 2006). Non-default hyperparameters for CMA-ES are used (population size of 80, stopping tolerance of 0.001). After compiling the model, the optimal model parameters must be fitted prior to fitting the bootstrap samples:

```

Rscript hERG\_fitting.R -d bepridil -l 80 -t 0.001

```

Once the optimal model fitting is done, bootstrap samples (1-2000) can be fitted based on either single computation run or on HPC.

For a single computation run the following command is used:

```

Rscript hERG\_fitting.R -d bepridil -i "1-2000" -l 80 -t 0.001

```

Note that the bootstrap fitting is computationally intensive, and it is recommended that this be done in parallel on a high-performance computing resource. (See [this script](run\_hERG\_boot\_fit.sh) for an example of how to split up the bootstraps for 28 drugs.)

## References

\* Hansen, N. (2006). "The CMA Evolution Strategy: A Comparing Review," in Towards a New Evolutionary Computation: Advances in the Estimation of Distribution Algorithms, eds. J.A. Lozano, P. LarraÃ±aga, I. Inza & E. Bengoetxea. (Berlin, Heidelberg: Springer Berlin Heidelberg), 75-102.

\* 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.

\* Milnes, J.T., Witchel, H.J., Leaney, J.L., Leishman, D.J., and Hancox, J.C. (2010). Investigating dynamic protocol-dependence of hERG potassium channel inhibition at 37 degrees C: Cisapride versus dofetilide. J Pharmacol Toxicol Methods 61(2), 178-191. doi: 10.1016/j.vascn.2010.02.007.