|  |  |  |
| --- | --- | --- |
| **In-silico study of the effect of a drug on Human Ventricle Cells** | | |
| During drug development, promising compounds are tested to evaluate their potential cardiotoxicity i.e, heart dysfunction as electric or muscle damage. Current safety regulatory guidelines require the measurement of IKr channel block in vitro and QT interval prolongation in vivo to evaluate the arrhythmic risk of a drug. However, it has become apparent that these markers are not sufficient to predict cardiotoxic behavior of a given compound. A recently proposed new paradigm relies on the idea of combining in vitro studies that measure the drug’s effect on each of the different ionic channels and in-silico models of cardiac myocyte electrophysiology. The effect of the drug with a concentration in plasma, [*IC*], on the channel is modeled using a pore block model, that reduces the channel conductance, based on the available half-maximal inhibitor concentration, *IC50*, and Hill coefficient, *n*, through the formula  where *FB* is the fraction of channel block.  Using the MATLAB program provided, the potential cardiotoxicity of a particular drug will be study. The script implements the O’Hara Action Potential model (OHR11). You have been assigned to evaluate **Ritonavir**. The value of *IC50* and *n* for the different channels is given in the following table   |  |  |  | | --- | --- | --- | | Gna | Hill Coeff. | 1 | | IC50 (μM) | 27.96163 | | GNaL | Hill Coeff. | 0.7 | | IC50 (μM) | 7.175 | | Gto | Hill Coeff. | 1 | | IC50 (μM) | ∞ | | GKr | Hill Coeff. | 1 | | IC50 (μM) | 5.157 | | GKs | Hill Coeff. | 1 | | IC50 (μM) | ∞ | | GK1 | Hill Coeff. | 1 | | IC50 (μM) | ∞ | | GNaCX | Hill Coeff. | 1 | | IC50 (μM) | ∞ | | GNaK | Hill Coeff. | 1 | | IC50 (μM) | ∞ | | GCaL | Hill Coeff. | 1.3 | | IC50 (μM) | 8.228 | | EFTPCmax (μM) | | 0.4369 |   \*[EFTPC] states for the Effective Therapeutic Concentration.  To evaluate the cardiotoxic effect more effectively, we are going to consider the electrophysiological variability inherent to the cardiac tissue by means of a population of models approach. The file mask.mat contains channel conductance multiplying factors corresponding to 10 different models of ventricular myocytes. Each column of the file corresponds to an ionic channel in the O’Hara model with the following correspondence.   |  |  |  |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | | Column | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | | Conductance | GCaL | Gto | GNaCa | GK1 | GKr | GKs | GNa | GNaL | GNaK |   For each of these models you will evaluate the effect of the drug for 4 different concentrations: 1x, 2x, 10x, 100x [EFTCP] (A total of 40 simulations). The stimulation protocol consists of stimulating with a current 1.5x the stimulation threshold 500 times with a BCL=800ms, and analyzing the last three beats. A pro-arrhythmic behavior is considered if:   * Alternans in the APD90 are observed. * Abnormal repolarizations appear. * APD prolongation of more than 25% (with respect to control)   Report:   * - Plot the average (and standard deviation) of the APD90 as a function of the drug concentration. * - The arrhythmic risk calculated as the probability of observing arrhythmic behavior over the ten models for each value of the concentration. | | |
| Documentation to be delivered in WeBeeP | Upload a single PDF for group. Identify file as group23.pdf | |
| Deadline | 14/06/2023 (23:59 CET) | |
| Attached Documentation | Articles | O’Hara et al 2011 (model) in WeBeeP  Sager et al 2013 (Cardiac proarrhythmia safety) in WeBeeP |
| Files | Ohara\_main.m [Matlab] Ohara\_model.m [Matlab]  driver.m [Matlab]  mask.mat [Matlab .mat file containing the mask] |