# The Role of Population Size in Computational Assessment of Pharmacological Cardiotoxicity

Matteo Costi*[1], Jose M. Ferrero[2], Jose F. Rodriguez Matas[1]

1Politecnico di Milano, Milan, Italy
2Universitat Politecnica de Valencia, Valencia, Spain

**Aims**: When conducting computational electrophysiological simulations aimed at assessing pharmacological cardiotoxicity, several parameters play crucial roles. Among theme, the size of the population under scrutiny emerges as potentially critical, negatively impacting on the expected final outcomes. The process of pharmacological pro-arrhythmia classification entails an examination of virtual cardiomyocytes samples, in which at each cell is associated with an action potential. This process involves then the selection of a specific electrophysiological model, followed by the replication of cellular responses subsequent to electrical stimulation. These simulations encompass the assessment of morphological alterations in action potentials as well as intracellular concentration dynamics.

Currently, in literature there's not a standardization concerning parameters and their associated values within pharmacological cardiotoxicity simulations. Particularly noteworthy is the lack of a definitive standards specifying the optimal sample size to be employed. This study attempts to shed light on the influence exerted by population size on the arrhythmic risk classification of drugs.

**Methods**: Initially, a population of 100,000 stable virtual cardiomyocytes was generated. From this initial population, ten different sets of 2989 stable models were extracted, which were subjected to cardiotoxicity analysis. Subsequently, a bootstrapping process was performed, involving the random extraction of 107 cells from a one of the sets of 2989 models. The operation was repeated 200 times for statistical significance.

**Results and Conclusions**: The study reveals a greater variability within the population of 107 cells as opposed to the larger cohort of 2989 cells. This discrepancy is to highlight the potential for considerable errors in pharmacological cardiotoxicity classification deriving from the utilization of inadequate sample sizes.

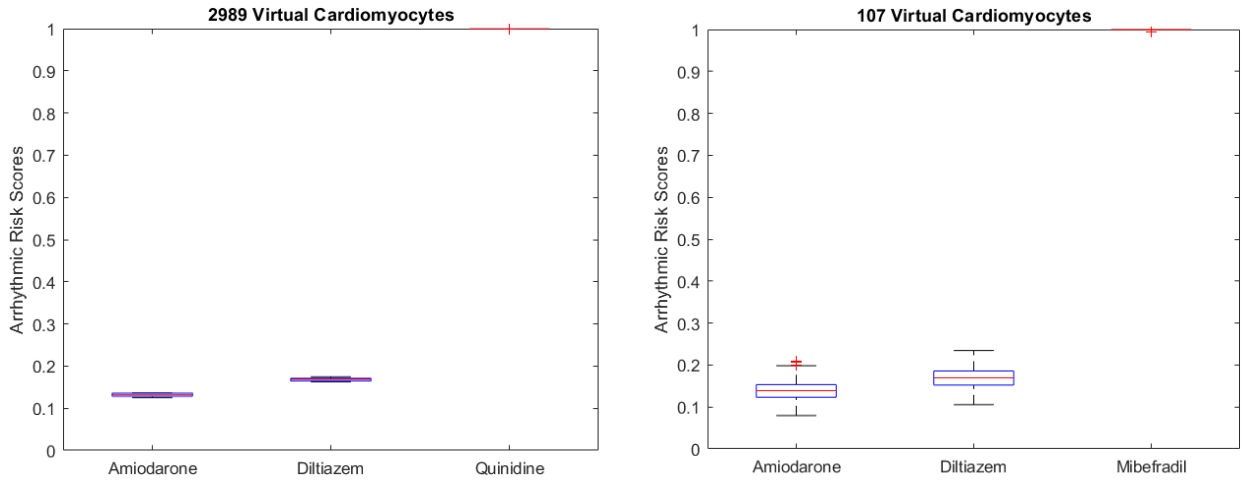


*Figure 1 – The whiskers plot are here depicted describing the Arrhythmic Risk Scores for Amiodarone, Diltiazem and Quinidine respectively for a population size of 2989 cells and 107 cells.*