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ESC First Contact Initiative Grant final report

First of all, I would like to thank the European Society of Cardiology (ESC), and in particular the ESC Council on Basic Cardiovascular Science, for awarding me the ESC First Contact Initiative Grant, that allowed me to visit the Computational Cardiovascular Science (CCS) Group headed by Prof Blanca Rodriguez at the Department of Computer Science of the University of Oxford (UK). The support I received from the European Society of Cardiology was sufficient for a 27-day long stay during February 2016.

The CCS Group (<http://www.cs.ox.ac.uk/ccs/home>) is one of the leading groups for an integrated approach exploiting computational methods to advance cardiovascular research. Of particular interest it is a new *in silico* modeling paradigm to develop populations of models of the cardiac action potential (*Britton et al., PNAS 2013; Passini et al., J Mol Cell Cardiol. 2015*). Such approach allows overcoming the main limitation of the canonical modeling approach for cardiac cells, i.e. not to consider the *in vitro* variability that naturally characterizes such cells. In fact, the canonical approach consists in developing a single *in silico* model of the action potential, representative of a cell population and reproducing the mean experimental data: this approach proved its value during the past decades, but it can be improved with the modern computational resources. In particular, due to the nature of my research, i.e. computational modeling of human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs), variability is a key factor as reported in (*Knollmann, Circ Res. 2013*) and as proven by the amount of different datasets available in literature (*Moretti et al., N Engl J Med. 2010; Ma et al., Am J Physiol Heart Circ Physiol. 2011; Ma et al., Int J Cardiol. 2013; Fatima et al., PLoS One. 2013; etc.*).

The basic methodology for generating a population of models consists in building a wide ensemble of n models (e.g. $n=10000$) by randomly changing specific model parameters within pre-defined ranges. Afterwards, the population is calibrated on specific biomarkers computed on the experimental action potential. Only the $n' < n$ models, fully compliant with the experimental action potential biomarkers, are included in the population (*Britton et al., PNAS 2013*).

The aims of my stay at CCS were:

- to acquire expertise in modeling populations of cardiac *in silico* models under the supervision of Prof. Rodriguez;
- to choose the best procedures and methods for the generations of the populations;
- to start the implementation of the algorithms for the population generation;
- to establish a solid collaboration with CCS.

All the aims were fulfilled.

During my stay in Oxford I learnt:

- how to properly use the Latin Hypercube Sampling and how to decide the ranges of variations of the model parameters. Specific discussions were carried on to provide a better coverage of the experimental space of the morphological biomarkers of the action potentials.
- how to generate in an efficient way populations of models. My own code, drafted before the visit, was terrifically improved.
- how to process and present properly the simulation results and to extract significant statistics. Due to the huge amount of results that can be extracted from 10000 different simulations, it is not easy to present them in a meaningful way. Specific statistics (e.g. the partial correlation coefficients) as well as boxplots, scatter plots, etc. consent a proper presentation of the results.

Moreover, I had chance to improve my hiPSC-CM model (*Paci et al., Ann Biomed Eng. 2013, Paci et al., Br J Pharmacol. 2015*), integrating into it specific currents, which are necessary to simulate specific pathologies.

Mastering the population of models paradigm was functional to two different investigations that are currently in progress:

- assessment of current blockers in hiPSC-CMs, with particular attention to hERG block, aimed to understand potentially cardiotoxic effects of drugs/compounds and the possible changes on the action potential (prolongation, early after depolarizations, fibrillation, etc.) according to the different parametrizations of the models;
- population of mutant hiPSC-CMs, for the assessment of drug effects and comparison to a population of adult mutant cardiac cells. This activity aims to assess how similar is the behavior of hiPSC-CMs to adult cell behavior in pathological conditions. The final aim is supporting hiPSC-CMs as a valid disease model.

Furthermore, a solid collaboration was established with Prof. Rodriguez and Dr. Elisa Passini. In particular, new joint publications (at least one conference paper and one journal paper about the aforementioned activities) were planned and future visits to Oxford will be organized. During my stay I had also the opportunity to present my research during an invited talk to the whole Computational Biology Group, on February 10th, 2016.

In conclusion, I would like to thank Prof. Rodriguez and the whole CCS group for having accepted me there, for the strong research support I had during my stay and the access to the Department of Computer Science facilities. A special acknowledgment goes to the Advanced Research Computing of University of Oxford, which allowed me to use for the population generation its supercomputer Arcus-B: without such support, my stay would not have been so productive.

Yours sincerely

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