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POPULATION-BASED AND PATIENT-STRATIFICATION APPROACHES APPLIED TO A HUMAN CARDIAC MODEL OF ELECTROPHYSIOLOGY

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Mathematical models of cardiac electrophysiology are usually defined to represent average data from voltage-clamp experiments of ionic membrane current [1]. It is only recently, with the advancement of the computational capabilities, that new modeling techniques have been developed to account for the individual variability that typically affects these biological processes. Among these techniques, the most common is the population-based approach that identifies a set of key model parameters that can be varied to address the scientific question in different phenotypical conditions. In parallel with the development of this population approach, several computational strategies have emerged with the purpose to elucidate the role of each model parameter for specific physiological behaviors. This could be addressed with a parameter sensitivity analysis that, in the context of electrophysiology, is usually performed with multivariate regression methods [2]. The combination of these two approaches with clustering techniques allows an integrative understanding of the individual variability of disease progression, as well as the response to drug actions, thus could play an essential role in the advancement of precision medicine [3].

We used the population-based approach to generate a group of virtual patients, representing the healthy and the heart failure (HF) phenotypes [4, 5], by considering a human cardiac model of electrophysiology [6]. We employed a novel-defined computational pipeline for patient stratification to identify the key mechanisms responsible for the stratification and highlight the importance of including additional phenomenological functions in the mathematical model to better represent the variability of the disease phenotypes. Besides, we compared the results of a global sensitivity analysis (GSA) [7], performed by coupling a sampling algorithm [8] with a logarithmic sensitivity approach [9], with the results of two linear-regression sensitivity algorithms [10, 11]. Both the two regression approaches proved to work well even with a com-

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plex non-linear system, providing similar results to the ones computed with GSA, but with considerable advantages in terms of computational cost.

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