Maastricht University

Integrative computational modeling of calcium handling and cardiac arrhythmias

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Impact

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Cardiovascular disease is a leading global cause of death, contributing to approximately 17.8 million deaths in 2017. This number is expected to grow to more than 22.2 million by 2030 (638). In accordance, the prevalence of atrial fibrillation (AF) is estimated to be 1-2% of the general population in developed countries (e.g. North America, Europe and Japan) and about 0.5-1% in developing countries, turning AF into the most commonly found arrhythmia in the clinic, affecting more than 33 million people worldwide (639). Despite decades of research, a large number of unmet needs and knowledge gaps remain, preventing more effective management of patients at risk of arrhythmias (540). At the moment, the insights on the pathophysiology of arrhythmias in an individual patient are incomplete, affecting our available approaches to identify the actionable patient-specific molecular arrhythmia mechanisms, to detect and target key dynamic modulators of cardiac arrhythmias, to achieve atrial targeting of specific molecular arrhythmic mechanisms with drugs, and to integrate studies of specific molecular/cellular AF pathophysiology (411, 540).

The chapters in this thesis aimed to address a number of current knowledge gaps by employing the perfect control and observability of computational modeling to better understand the role of cardiomyocyte calcium handling in arrhythmogenesis.

Scientific impact

To recapitulate, **Chapters 1** and **2** of this thesis summarized the roles of cardiomyocyte calcium handling in health and disease. **Chapter 3** discussed our *state-of-the-art* subcellular model of the human atrial cardiomyocyte to investigate the impact of subcellular distributions of calcium-handling proteins on atrial electrophysiology. **Chapter 4** employed this subcellular model to elucidate the cause-effect relationship between calcium-handling abnormalities, acute transient inflammation and POAF. **Chapter 5** evaluated the consequences of calcium-dependent ion-channel regulation on atrial electrophysiology under physiological and pathological conditions. **Chapter 6** presented a multiscale computational framework to investigate ethanol-associated reentrant arrhythmia in both healthy and remodeled hearts. **Chapter 7** presented MANTA, a novel, easy-to-use educational tool to better understand the cellular effects of AADs. Finally, **Chapter 8** highlighted the significance of β-adrenergic receptor stimulation in modulating the cellular proarrhythmic effects of chloroquine and azithromycin.

Of the 8 scientific chapters in this thesis, 7 have been published in international peer-reviewed journals and 1 is still in the process of submission. **Chapter 1** has been published in *Frontiers for Young Minds* in 2019 (640), and due to its unique concept and reasonably high societal impact, this chapter will be discussed separately in the next section. **Chapter 2** has been published in *Progress in Biophysics and Molecular Biology* in 2020 (335). This publication was the first that extensively discussed the potential synergy between *in vitro* and *in silico* studies of cardiomyocyte calcium handling on cardiac cellular electrophysiology. It has been accessed >1500 times in the first 6-months since its publication. **Chapter 3** has been published in *Frontiers in Physiology* in 2018 (4) and the subcellular calcium handling model has been used to address specific molecular/cellular AF pathophysiology as illustrated in **Chapter 4**. **Chapter 4** has been published in *Circulation Research* in 2020 (327) as part of a comprehensive study involving both *in vitro* and *in silico* experiments. **Chapter 6** of this thesis was published in *Journal of Molecular and Cellular Cardiology* in 2020 (346), and during its first month of publication, it has become the journal's most read publication, with a high interest from the general community. This study was the first that employed multiscale computational modeling to study the acute effects of ethanol in cardiac electrophysiology. Moreover, this extensive *in silico* study provides a general framework to computationally investigate other complex arrhythmias. **Chapter 7** was published in *Pharmacological Research* in 2019 (603), and was the first easy-to-use educational tool to better understand the effects of antiarrhythmic drugs (AADs) on cardiac cellular electrophysiology. MANTA has been used in several other unpublished projects to give an overview on how AADs may behave in specific *in silico* models and it is currently used as part of the Master Systems Biology program at Maastricht University. Finally, **Chapter 8** of this thesis was published in *Frontiers in Physiology* in 2020 (617). The study was the first to identify the role of β-adrenergic stimulation in the presence of altered repolarization reserve, for example during the administration of chloroquine and azithromycin. The study was conducted during the COVID-19 pandemic, a disease state in which the sympathetic nervous and β-adrenergic response activation were expected to occur, and thus might interact with such proarrhythmic medications. Of note, all of our (Maastricht-led) publications and models are freely accessible, reflecting our commitment and support to the open science initiative.

One way through which computational models can have scientific impact is the identification of arrhythmia mechanisms based on the perfect control of model parameters. For example, the study in **Chapter 3** was the first to employ computational modeling of subcellular calcium handling to investigate the role of the distributions of calcium-handling proteins in atrial electrophysiology. It is at present not possible to selectively modulate the location of individual proteins experimentally. Using our *state-of-the-art* subcellular model of cardiomyocyte calcium handling, we could show that increased heterogeneity of RyR2 clusters contributed to the propensity for SCaEs and DADs, and future targeting of this arrhythmogenic substrate might be advantageous to treat arrhythmia, for example in heart failure and AF, where increased heterogeneity of RyR2 clusters size has been documented (158, 159). Employing the perfect control of computational modeling, we also unraveled the significance of lateral RyR2 bands and interbands on the atrial wave propagation, something that could also only be addressed by *in silico* modeling. Although there are at present no therapeutic options to target these factors involved in arrhythmogenesis, altering the localization of proteins might be possible in the future, e.g., by modulating targeting of trafficking mechanisms through existing gene-editing technologies, including CRISPR-Cas9.

In addition to its strong educational impact, **Chapter 7** of this thesis also helps the scientific community on highlighting the interspecies diversity of AAD effects and therefore, the importance of selecting the most appropriate animal model for particular arrhythmia research. In the future, MANTA, as well as the other computer models developed in this thesis, can be used as a preliminary screening tool to reduce unnecessary animal experimentations, in line with the spirit of World Medical Association Declaration of Helsinki.

Meanwhile, **Chapter 6** illustrated the future use of multiscale integrative computational modeling to investigate specific risk factors (in this particular case, alcohol consumption) under different conditions (e.g., the absence or presence of heart failure or AF-related remodeling). We could show that the degree, type and pattern of fibrosis had a significant impact on the behavior of reentrant arrhythmias, therefore indicating the need for a more personalized modeling approach. Such personalized modeling is expected to become increasingly used in patient care, as already demonstrated in for computationally guided catheter ablation (636, 637). This, together with the FDA-approved comprehensive *in vitro* proarrhythmia assay (CiPA) initiative (444, 595) to develop safer future pharmacological agents, are steadily bringing computational modeling towards clinically relevant applications. The work presented in this thesis underscores the importance of model personalization (**Chapters 6** and **7**) and provides novel approaches to simulate patient-specific triggers (e.g., post-operative triggers in **Chapter 4**).

Lastly, computational modeling in general and the publications in this thesis in particular have enriched internal and external research collaborations. Computational modeling is inherently collaborative work since the models are built together and improved by computer modelers all over the world and rely on experimental data from many research. For example, the original O'Hara-Rudy dynamic model developed at Washington University in St. Louis, MO (263) has been modified, recalibrated and widely employed by modelers across the globe, highlighting such vast collaborations in the field of computational modeling. As part of this thesis, collaborations were established between the Departments of Cardiology, Physiology, Biomedical Engineering, and Genetics & Cell Biology at Maastricht University. Externally, among others, international partnerships were built with University Duisburg-Essen (DE), Masaryk University (CZ), and University of California Davis (CA).

Societal impact

During the PhD, we also put emphasis on the potential societal impact of our projects and publications. We intentionally designed our projects to not only provide specific scientific insights to the field, but also to improve the basic understanding of calcium handling and the relevance of its dysfunction in the general community. **Chapter 1** of this thesis is one of the examples of these efforts. *Frontiers for Young Minds* is an international journal that aims to disseminate science and new scientific findings to general audiences, especially the future scientists. It is peer-reviewed by children in the range of 8-15 years to stimulate their curiosity and expose them to the world of science, guided by a science mentor. To support this initiative, the author of this thesis has become a science mentor for the journal during his PhD. In the first year after its publication, **Chapter 1** of this thesis has received a huge interest from people around the world, reflected by its high read index (more than 20,000 reads to date; see the map below), turning the paper into one of the top 2% of all Frontiers publications. Moreover, it has received a reasonably good response on social media platforms, such as Twitter, Reddit, Facebook and Mendeley.

In addition to **Chapter 1**, almost all of our publications have received high interests from both scientific and general communities on social media, supporting our aforementioned commitment in disseminating our research. The most interesting example is **Chapter 6** of this thesis that touched on a very sensitive issue: alcohol drinking. Alcohol drinking is a habit in Western and Eastern societies. Therefore, despite the clear clinical-experimental-computational evidence that in high concentrations it can be proarrhythmic, alcohol abuse remains common. Our findings contributed to the ongoing debate on the adverse effects of ethanol. This example shows how our computational study can be as attractive and influential as other forms of research. Of course, lots of work remains to be done to improve the understanding of the general community on the role of calcium in the heart and this, for sure, motivates us to improve our knowledge and perform further research to strengthen our comprehension on the complex connection between calcium-handling abnormalities and cardiac arrhythmias.

Impact figure: The world map per August 2020 showing the demography of reads of **Chapter 1** in this thesis.