Multi-scale modeling and variability in cardiac cellular electrophysiology

APPENDIX B

Valorization

Since 2013, Maastricht University requires its doctoral theses to come equipped with a "Valorization Addendum", with the intended goal of increasing the "visibility and societal impact" of its research. Among the examples of such "value creation" are open source tools, software and the process of "making models and systems available" (Maastricht University Board of Deans, 2013). This chapter is submitted to comply with this requirement.

Computational models of the cardiac action potential (AP) can form the basis of *multi-scale models* of cardiac physiology and pathophysiology (Southern et al., 2008). In the past decades, several studies have shown how such models can be modified to include the molecular changes caused by genetic defects or drugs, so that their effects on the cell, tissue, and organ levels can be predicted (Chapter 8). The mechanistic insights and predictive power these models provide is badly needed, as the link between such molecular changes and arrhythmias is complex and still incompletely understood (Weiss et al., 2015).

Setting up multi-scale simulations can be a time consuming process and, even for cutting-edge science, often involves reimplementing existing techniques. Having *re-usable*, model-independent software tools can save time and effort, can make numerical methods available to a wide audience, and can help to shift the focus of the experimenter from computational aspects to biology. Chapter 3 of this thesis introduced *Myokit*, a tool for (multi-scale) modeling of the cardiac AP. Myokit contains methods to create models of ionic currents (possibly altered by drugs or mutations), to integrate them into models of the cellular AP, and to use them in simulations of cardiac tissue. In addition, Myokit has support for model import and export, removing the need for manual model (re-)implementation. Chapters 3, 5, and 7 contain examples of Myokit's scientific use.

In this valorization addendum, we highlight examples of non-academic use of AP-model based simulations. We then discuss how we have made Myokit, our tool for such work, available to the community. Finally, we look at the first, promising, signs of early adoption of Myokit outside of Maastricht University.

AP-models have applications beyond academia

Simulations of the cardiac cellular AP have a long history in science, where they have been used to investigate the basic principles of cardiac electrophysiology (see Chapter 2 and Chapter 8). Sharing and promoting Myokit among an academic audience has an impact on society, as it has the potential to accelerate scientific work via the sharing of methods (included in Myokit) and models (using Myokit's support for exchange languages such as CellML, see Hedley et al., 2001). This type of knowledge dissemination is discussed in detail in the introduction to Chapter 3. Outside of science, the predictive power of AP-model based simulation is increasingly being recognized. The examples listed below show how simulations can be used in risk stratification (clinical use), drug development (industrial use), and regulation (governmental use).

Hoefen et al. (2012) showed that simulations of transmural repolarization prolongation can be used to distinguish low-risk and high-risk mutations in *LQT1-syndrome* with increased specificity and sensitivity. This provides a direct use of simulation in the optimization of clinical treatment. Similar transmural simulations were used as the first example in Chapter 3. Risk of inducing *torsades de points* is a common reason to reject drugs during development. Cummins Lancaster and Sobie (2016) simulated the effect of several drugs on the human cellular AP, and found that this provided more reliable predictions of their arrhythmogenicity than existing *in vitro* assays. To increase the reliability of their predictions, they repeated their simulations in multiple models of the AP, much like in the third example shown in Chapter 3. The increasing interest of regulatory bodies to use mechanistic cardiac modeling in drug safety testing is discussed in depth in a review by Davies et al. (2016). While Myokit is aimed primarily at scientific users, it could easily be used outside of academia in pilot projects, exploratory studies, prototyping, or as the inspiration for specialized commercial software.

Myokit is available to the community

Since the start of its development, Myokit has been made available online. This has allowed scientists outside of Maastricht to use it, has generated valuable feedback for its development, and has promoted the visibility of multi-disciplinary biomedical research at Maastricht University.

We have taken care to provide adequate documentation to enable external use. A PDF version of Myokit's documentation currently runs to 277 pages (although the same information is more easily accessed via the Myokit website). In addition, the Myokit website contains several examples of its use and further examples were provided with our recent publication about the tool (Clerx et al., 2016). In 2014, we organized a workshop to introduce Myokit to scientific users, which attracted more than 30 international participants.

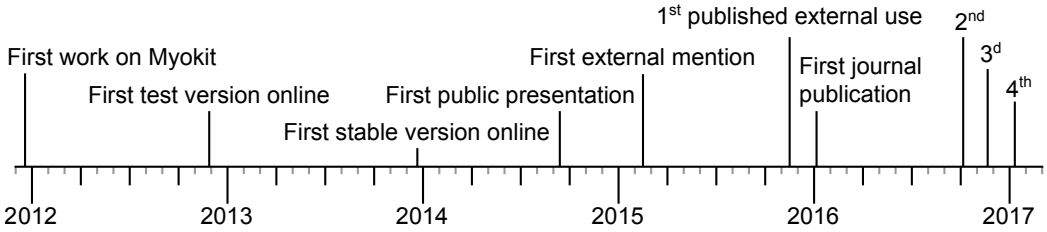

Figure B.1: Myokit development, publications and early adoption. Recent events include its first public presentation (Clerx et al., 2014), the first time Myokit was mentioned in a peer-reviewed article by an external group (Garny and Hunter, 2015), the first time it was *used* in a peer-reviewed article by an external group, (Law and Levin, 2015) and publication of the article that formed the base of Chapter 3 (Clerx et al., 2016).

Myokit is fully open-source and can be downloaded and used free-of-charge under the GNU General Public License (GPL, see also http://myokit.org). In addition, Myokit itself is based entirely on open-source components such as Python, NumPy/SciPy (Jones et al., 2001), Matplotlib (Hunter, 2007) and Sundials (Hindmarsh et al., 2005). Combined with an operating system such as GNU/Linux, this creates an entirely open-source environment, available free of charge. In addition, Myokit can be run on Windows or OS/X (Apple).

Myokit is already being used outside of Maastricht

Myokit development started in December 2011 and it was first presented publicly in September 2014. The first peer-reviewed article discussing it in detail was published in January 2016. A brief timeline of its development and publication is provided in Fig. B.1 and an extended version can be found on the Myokit website (http://myokit.org/changelog). Given the time it takes to adopt a new work flow, perform research, and have it published, it will take some time before Myokit's success in the (scientific) community can be assessed. Some preliminary data is presented below. First, Myokit has been downloaded over 600 times as of July 2016. But while some effort[1] has been made to filter real users from automated downloads, this may not be an accurate statistic. Secondly, a mailing list was started in January 2016 where users can receive updates and ask questions about Myokit, so far this has 15 subscribed users (which is similar to older, more established tools like OpenCOR). Another measure of Myokit's visibility came in 2016, when its principal developer was elected for a three-year term on the CellML editorial board[2]. However, the best feedback has come in the form of personal communication and citations. Based on such feedback, we know of at least three instances where Myokit has been used for teaching outside of Maastricht (at both Bachelor and Master level, see http://myokit.org/publications). The first study (by scientists other than the Myokit developers) using Myokit for simulations came in 2015,

[1] Filtering was applied by excluding any IP address with 20 or more downloads, excluding any downloads with a 'user-agent' indicating an automated search rather than a human user and by requesting that search engines do not download the tracked files.

[2] See https://www.cellml.org/about/news/cellml-editor-election-results-2016

Figure B.2: The blue dots show locations where papers were published using Myokit. Green dots indicate known Myokit users. Red dots indicate mentions of Myokit in papers about related software, while yellow dots indicate universities where Myokit was used for teaching. Finally, the grey dot indicates Maastricht, where Myokit was developed.

just before the first journal article describing Myokit was published (Law and Levin, 2015). Three further publications, including two in high-ranking journals, emerged in 2016 and early 2017 (Park et al., 2016; Boukhabza et al., 2016; Schmidt et al., 2017). Three more publications refer to Myokit when comparing electrophysiology software, which further adds to the visibility of Maastricht University in this field (Garny and Hunter, 2015; Castro et al., 2016; Onal et al., 2016). Fig. B.2 shows the geographic locations of known early Myokit usage and citations.

Conclusion

Multi-scale simulations based on models of the cardiac cellular AP are increasingly being used outside of academia. We have developed Myokit, a tool for such simulations and made it available online with a permissive license and extensive documentation. This has resulted in early adoption and helped (1) to disseminate research done at Maastricht University to a wider community and (2) to increase the world-wide visibility of Maastricht University's computational electrophysiological research.