# Inversion based on simultaneous observations of voltage and calcium concentration

Joanneke E Jansen

May 8, 2017

## 1 Introduction

In this report, we will investigate an inverse problem based on simultaneous observations of voltage and intracellular calcium concentration. Mathematically, inversion means the computation of the most plausible values of not directly observable parameters using a set of measurements. The classic technique to estimate electro-physiological cardiac parameters is patch clamping. With patch clamping, the transmembrane voltage of a single cell can be precisely measured over time. An alternative for the time and labour intensive patch clamping technique could be optical mapping, with which voltage and calcium waves of a cluster of cells can be measured simultaneously [3]. The monodomain model is a commonly used model to simulate cardiac electrophysiology. Here, we will look if we can use this monodomain model to infer parameters based on voltage and intracellular calcium measurements, breaking the single cell tradition. As a motivating example, we will model the behaviour of monolayers of human incuduced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs). In recent years, there has been a large interest in iPSC-CMs as a tool for drug screening and disease modelling and more efficient techniques for doing so are needed.

### 1.1 Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs)

Human induced pluripotent stem cell-derived cardiomyocytes (iPSC-CMs) provide a promising platform for studying cardiac cells in vitro. In 2007, it was first described how iPSCs can be made by reprogramming somatic cells [11]. Since then, there has been a large interest in using those cells

for drug safety screening and disease modelling [10]. Human iPSCs are self-renewing, patient-specific, and can be differentiated to cell types such as cardiomyocytes, hepatocytes and neurons [9]. In recent years, the techniques for efficiently producing homogeneous populations of iPSC-CMs have greatly improved. However, the production process of iPSC-CMs is still very expensive in comparison to most *in vitro* models. The largest limitation of the currently produced iPSC-CMs is their immature, foetal phenotype, although improvements in maturity are still being made [2].

## 1.2 Optical mapping

There are several techniques to study the electrophysiology of iPSC-CMs. The method most commonly used is patch clamping. With this technique the transmembrane potential $v$ of a single cell can be precisely measured, but patch clamping is time and labour intensive and thus precludes efficient large-scale screening. An alternative to patch clamping is optical mapping [2]. With optical mapping, the transmembrane potential $v$ can be measured with a high spatial and temporal resolution. Although optical mapping methods tend to slightly overestimate the duration of action potentials, the shape of the measured action potential is similar for both techniques [4, Figure 2]. Unlike the invasive patch clamping technique, optical mapping allows for action potential measurements of large cell populations and sequential measurements of the same groups of cells. Furthermore, it is possible to not only measure the transmembrane potential, but also the intracellular calcium concentration $[Ca]_i$, at the same time [3].

## 1.3 Overview

The aim of this report is to investigate the possibilities of parameter estimation of iPSC-CMs based on data obtained by optical mapping. In particular, we are interested to see what extra information can be inferred from the high spatial resolution and simultaneous calcium and voltage recordings, in contrast to the single cell voltage recordings obtained by patch clamping. We will model the behaviour of a monolayer of iPSC-CMs with the classic monodomain equations, which we will introduce in Section 2.1. To model the cell membrane dynamics, we will use the Paci2013 cell model. The Paci2013 cell model is specifically developed for the simulation of iPSC-CMs action potentials and is based on data obtained on iPSC-CMs [8, 5]. Due to the already mentioned immature phenotype of currently produced iPSC-CMs, there is a lot of variability in the action potential shape of different cells, even if they are part of the same cell cluster [1, 12]. Therefore, the predictive

value of the Paci2013 and other cell models will be limited and our investigation must be seen as a proof of concept. The development of iPSC-CMs technologies is rapid and produced iPSC-CM clusters are hoped to become more homogeneous and similar to mature cardiomyocytes in the near future [2].

# 2 Mathematical models

## 2.1 The monodomain model

The monodomain equations are given by

$$\frac{\partial \mathbf{s}}{\partial t} = \mathbf{F}(\mathbf{s}, v), \qquad \mathbf{x} \in H, \tag{1}$$

$$\frac{\partial v}{\partial t} + I_{ion}(v, \mathbf{s}) = \nabla \cdot (\mathbf{M}\nabla v) + I_s, \qquad \mathbf{x} \in H, \tag{2}$$

$$\mathbf{n} \cdot (\mathbf{M}\nabla v) = 0, \qquad \mathbf{x} \in \delta H, \tag{3}$$

with $v(\mathbf{x}, t)$ the transmembrane potential (in mV), $H$ the domain, $\delta H$ the boundary of $H$, $\mathbf{n}$ the outward pointing normal of the boundary, and with $I_s$ the prescribed input current (in mV/ms) and $I_{ion}$ the ionic current across the membrane (in mV/ms), both scaled by the cell membrane capacitance (in $\mu$F/(mm$^2$)). Equation (1) is a system of ODE's that models the membrane dynamics. There exist many different cell membrane dynamics models with varying degrees of complexity that can be used to specify $I_{ion}$, $\mathbf{F}(\mathbf{s}, v)$ and the state variables $\mathbf{s}$, see the CellML repository [13] for an overview of different types of models. In this report, we will use the Paci2013 cell model, that is specifically developed to model the electrophysical behaviour of iPSC-CMs [8]. We will introduce the Paci2013 cell model in the next section.
Finally, $\mathbf{M}$ is a conductivity tensor (in mm$^2$/ms), that satisfies

$$\mathbf{M} = \frac{\alpha}{1+\alpha}\mathbf{M}_i, \tag{4}$$

with $\mathbf{M}_e = \alpha\mathbf{M}_i$. Here, $\mathbf{M}_e$ and $\mathbf{M}_i$ are the extracellular and intracellular conductivities (in mm$^2$/ms), divided by the product of the membrane capacitance (in $\mu$F/(mm$^2$)) and the cell membrane area-to-volume ratio (in 1/mm). By assuming that there exists a $\alpha$ such that $\mathbf{M}_e = \alpha\mathbf{M}_i$ the monodomain equations can be derived from the more complicated bidomain equations [7, p. 566-568].

### 2.2 The Paci2013 cell model

The Paci2013 model consists of 18 ODEs and is of Hodgkin-Huxley type (see [6, p. 195-215] for an introduction to the Hodgkin-Huxley equations). The ionic current $I_{ion}$ is a sum of twelve different ion channel type currents:

$$I_{ion} = I_{Na} + I_{CaL} + I_f + I_{K1} + I_{Kr} + I_{Ks} + \tag{5}$$
$$I_{to} + I_{NaCa} + I_{NaK} + I_{pCa} + I_{bNa} + I_{bCa}. \tag{6}$$

An ion channel current $I_k$ is typically of the form

$$I_k = g_k m_k^{p_k} \dots h_k^{q_k} (u_m - u_k), \tag{7}$$

where $g_k$ is the maximum conductance $g_k$ (in $\mu\text{S}/\mu\text{m}^2$), $u_k$ (in mV) the Nernst potential and $m_k$, $h_k \dots$ are a certain number of voltage and time dependent gating variables. Each ion channel type has different types of gating variables. The Paci2013 model contains ODEs for thirteen different ionic gating variables. Apart from the ionic gating variables and an inner calcium dynamics gating variable, the state variables of the Paci2013 model also include the intracellular sodium and calcium, and the sarcoplasmic reticulum calcium concentrations $[Na]_i, [Ca]_i$ and $[Ca]_{SR}$ [8]. The estimation of the model parameters was mainly based on patch clamp iPSC-CM data from [5]. The iPCS-CMs studied by [5] showed atrial-, nodal-, and ventricular-like action potentials. The Paci2013 model contains of two sets of parameters: one to simulate ventricular-like cells and one to simulate atrial-like cells.

# 3 Basic test case

# References


[1] Blazeski, A., Zhu, R., Hunter, D. W., Weinberg, S. H., Boheler, K. R., Zambidis, E. T., & Tung, L. (2012). Electrophysiological and contractile function of cardiomyocytes derived from human embryonic stem cells. *Progress in Biophysics and Molecular Biology, 110*(0), 178195.

[2] Denning, C., Borgdorff, V., Crutchley, J., Firth, K. S., George, V., Kalra, S., ... Prodanov, L. (2016). Cardiomyocytes from human pluripotent stem cells: from laboratory curiosity to industrial biomedical platform. *Biochimica et Biophysica Acta (BBA)-Molecular Cell Research, 1863*(7), 1728-1748.

[3] Lee, P., Klos, M., Bollensdorff, C., Hou, L., Ewart, P., Kamp, T. J., ... Jalife, J. (2012). Simultaneous Voltage and Calcium Mapping of Genetically Purified Human Induced Pluripotent Stem CellDerived Cardiac Myocyte MonolayersNovelty and Significance. *Circulation research, 110*(12), 1556-1563.

[4] Leyton-Mange, J. S., Mills, R. W., Macri, V. S., Jang, M. Y., Butte, F. N., Ellinor, P. T., & Milan, D. J. (2014). Rapid cellular phenotyping of human pluripotent stem cell-derived cardiomyocytes using a genetically encoded fluorescent voltage sensor. *Stem Cell Reports, 2*(2), 163-170.

[5] Ma, J., Guo, L., Fiene, S., Anson, B., Thomson, J., Kamp, T., ... January, C. (2011). High purity human-induced pluripotent stem cell-derived cardiomyocytes: Electrophysiological properties of action potentials and ionic currents. *American Journal of Physiology. Heart and Circulatory Physiology, 301*(5), H2006-17.

[6] Keener, J. P., & Sneyd, J. (2009). *Mathematical physiology (Vol. I)*. New York: Springer.

[7] Keener, J. P., & Sneyd, J. (2009). *Mathematical physiology (Vol. II)*. New York: Springer.

[8] Paci, M., Hyttinen, J., Aalto-Setälä, K., & Severi, S. (2013). Computational models of ventricular-and atrial-like human induced pluripotent stem cell derived cardiomyocytes. *Annals of biomedical engineering, 41*(11), 2334-2348.

[9] Rajamohan, D., Matsa, E., Kalra, S., Crutchley, J., Patel, A., George, V., & Denning, C. (2013). Current status of drug screening and disease modelling in human pluripotent stem cells. *Bioessays, 35*(3), 281-298.

[10] Sala, L., Bellin, M., & Mummery, C. (2016). Integrating cardiomyocytes from human pluripotent stem cells in safety pharmacology: Has the time come?: Implementation of hiPSC-CMs in cardiotoxicity. *British Journal of Pharmacology*.

[11] Takahashi, K., Tanabe, K., Ohnuki, M., Narita, M., Ichisaka, T., Tomoda, K., & Yamanaka, S. (2007). Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *cell, 131*(5), 861-872.

[12] Zhu, R., Millrod, M. A., Zambidis, E. T., & Tung, L. (2016). Variability of action potentials within and among cardiac cell clusters derived from human embryonic stem cells. *Scientific reports, 6*, 18544.

[13] models.cellml.org/electrophysiology