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, δH 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 μF/(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 $\mathbf{s}(\mathbf{x}, t)$, see the CellML repository [9] for an overview of different types of models.
Finally, $\mathbf{M}$ is a conductivity tensor (in mm^2/ms), that satisfies

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

with $\mathbf{M}_e = \lambda \mathbf{M}_i$. 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 μF/(mm^2)) and the cell membrane area-to-volume ratio (in 1/mm). By assuming that there exists a λ such that $\mathbf{M}_e = \lambda \mathbf{M}_i$ the monodomain equations can be derived from the more complicated bidomain equations [3].

2 A basic test case

For our test case, we take a square of 5 mm $\times$ 5 mm as our domain H. We will use the Grandi cell model to model the membrane kinetics [1]. We solve our test case with the `splittingsolver` module from the cbcbeat Python package [10][1] with the default parameter values and default initial conditions for v and s. The `splittingsolver` solves the monodomain PDE system and its coupled cell membrame dynamics ODE system separately, using the operator splitting scheme as described in [3]. We take typical values $\sigma_l = 0.15$

[1]This electrophysiology solver package is based on the FEniCS Project software [7] and the dolfin-adjoint software [8]

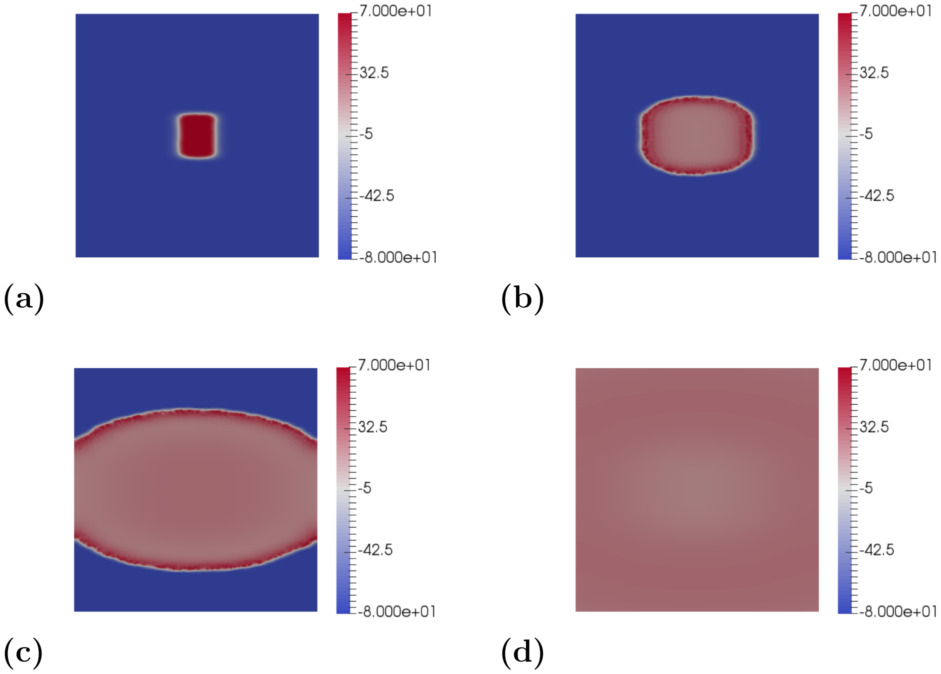

Figure 1: Heat maps of v (in mV) of our basic test case at **(a)** $t = 5$ms, **(b)** $t = 15$ms, **(c)** $t = 40$ms and **(d)** $t = 80$ms.

and $\sigma_t = 0.02$ (in mS/mm) for the longitudinal and tangential conductivity respectively and take $C_m = 0.2$ for the membrane capacitance (in μF/(mm^2)) and $\beta = 200$ for the cell membrane area-to-volume ratio (in 1/mm) [4], data from [5, 6]. We apply a stimulus of 10 mV/ms over 0.25 mm^2 in the centre of the square from $t = 0$ to $t = 3$ ms. In Figure 1, we show a heat map of v at $t = 5, 15, 40$ and 80 ms. In Figure 2, we show a heat map of $[Ca]_i$ at the same times. This variable is one of the 37 state variables $\mathbf{s}$ of the Grandi cell model and measures the cytosolic calcium concentration [1]. In Figures 3 and 4, we plotted v and $[Ca]_i$ (in μM) over time, both at a point at the centre of the domain (in blue) and at a point at the left lower edge (in green).

3 The inverse problem

It is possible to obtain measurements u_{obs} of the transmembrane potential and measurements c_{obs} of the cytosolic calcium concentration $[Ca]_i$ over the whole domain H at discrete points in time. With those measurements, we can estimate the value of the parameters in our model, using an adjoint-based

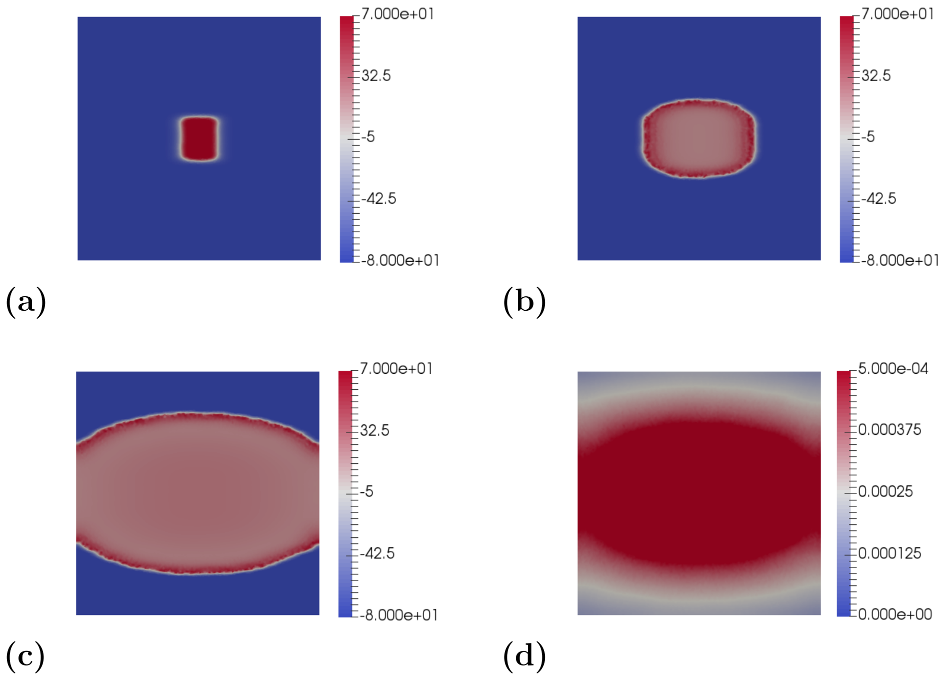

Figure 2: Heat maps of $[Ca]_i$ (in μM) of our basic test case at **(a)** $t = 5$ms, **(b)** $t = 15$ms, **(c)** $t = 40$ms and **(d)** $t = 80$ms.

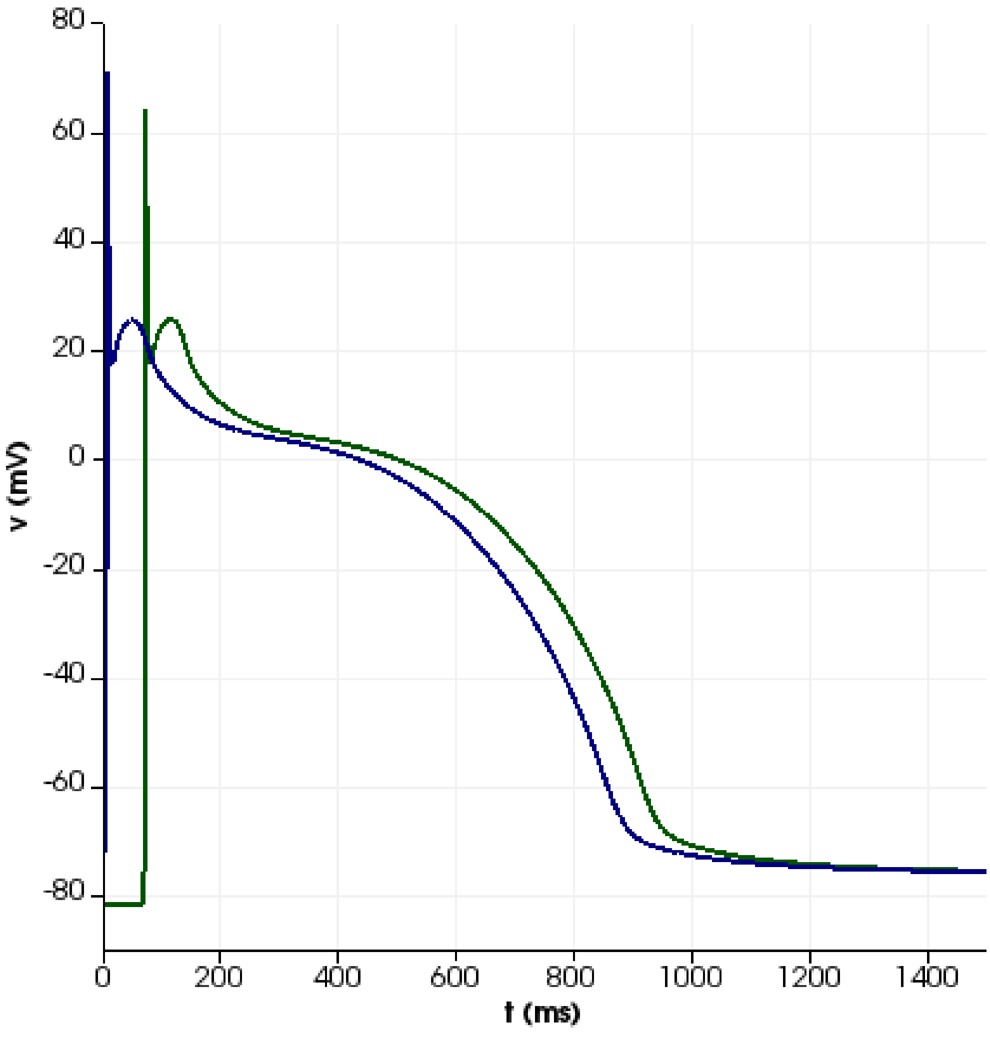

Figure 3: Plot of v against t.

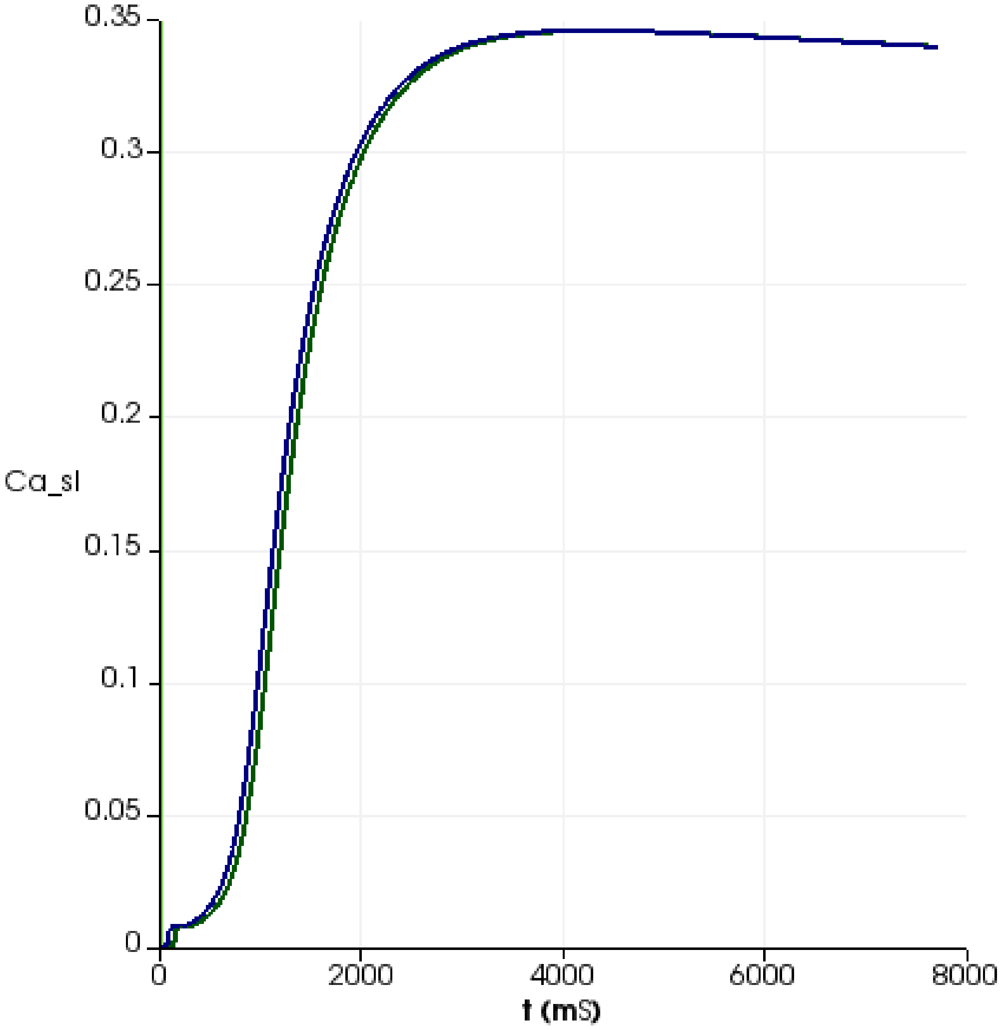

Figure 4: Plot of $[Ca]_i$ against t.

approach.[2] Here, as an example, we will try to estimate the values of the σ_l parameter from the Grandi cell model. We can formulate this problem as an optimisation problem: find σ_l, such that the functional

$$\mathcal{J}(v, [Ca]_i, \sigma_l) = \frac{1}{N} \sum_{i=1}^{N} \frac{||v - v_{\text{obs}}(t_i)||^2_{L^2}}{||v_{\text{obs}}(t_i)||^2_{L^2}} + \frac{||[Ca]_i - [Ca]_{i\text{obs}}(t_i)||^2_{L^2}}{||[Ca]_{i\text{obs}}(t_i)||^2_{L^2}}, \tag{5}$$

is minimized, subject to the requirements that v, c and σ_l satisfy the state system of equations (1)-(3) and initial conditions $v(\mathbf{x}, 0) = v_0(\mathbf{x})$ and $\mathbf{s}(\mathbf{x}, 0) = \mathbf{s}_0(\mathbf{x})$. Here, N are the number of measurements in time and t_i, $i = 1, \ldots N$ the respective moments in time. Using cbcbeat and the dolfin-adjoint software on which it is based, we can automatically compute the total derivative of $\mathcal{J}$ with respect to the optimization parameter σ_l. We can then use the scipy optimisation algorithm `minimize()` -which uses the limited memory BroydenFletcherGoldfarbShanno (BFGS) method with bound support - to find an optimal value for σ_l. We first generated some fake observed data for $\sigma_l = 0.15$, from $t = 0.0$ to $t = 5.0$ ms, with a timestep $dt = 0.05$ ms. With $\sigma_l = 0.10$ as initial guess, the `minimize()` algorithm returned $\sigma_l =?$ after ? iterations. Similarly, we can optimize for other parameters, such as σ_t, or g_Na, g_CaL, g_K1 or g_K2 from the Grandi cell model.

References

[1] Grandi, Pasqualini, Puglisi, & Bers. (2009). A Novel Computational Model of the Human Ventricular Action Potential and Ca transient. *Biophysical Journal, 96*(3), 664a-665a.

[2] Gunzburger, M. (2003). *Perspectives in flow control and optimization* (Advances in design and control). Philadelphia, Pa.: SIAM.

[3] Sundnes, J., Nielsen, B., Mardal, K., Cai, X., Lines, G., & Tveito, A. (2006). On the Computational Complexity of the Bidomain and the Monodomain Models of Electrophysiology. *Annals of Biomedical Engineering, 34*(7), 1088-1097.

[4] Sepulveda, Roth, & Wikswo. (1989). Current injection into a two-dimensional anisotropic bidomain. *Biophysical Journal, 55*(5), 987-999.

[5] Plonsey, R., & Barr, R. (1982). The Four-Electrode Resistivity Technique as Applied to Cardiac Muscle. *Biomedical Engineering, IEEE Transactions on, BME-29*(7), 541-546.

[2]See, for example, [2] for an introductory text in adjoint-based optimization methods.

[6] Barr, & Plonsey. (1984). Propagation of excitation in idealized anisotropic two-dimensional tissue. *Biophysical Journal, 45*(6), 1191-1202.

[7] `fenicsproject.org`

[8] `www.dolfin-adjoint.org`

[9] `models.cellml.org/electrophysiology`

[10] `bitbucket.org/meg/cbcbeat`