

# 1 The monodomain model

The monodomain equations are given by

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

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

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

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  $\mu\text{F}/(\text{mm}^2)$ ). 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<sup>1</sup> for an overview of different types of models.

Finally,  $\mathbf{M}$  is a conductivity tensor (in  $\text{mm}^2/\text{ms}$ ), that satisfies

$$\mathbf{M} = \frac{\lambda}{1 + \lambda} \mathbf{M}_i, \quad (4)$$

with  $\mathbf{M}_e = \lambda \mathbf{M}_i$ . Here,  $\mathbf{M}_e$  and  $\mathbf{M}_i$  are the extracellular and intracellular conductivities (in  $\text{mm}^2/\text{ms}$ ), divided by the product of the membrane capacitance (in  $\mu\text{F}/(\text{mm}^2)$ ) and the cell membrane area-to-volume ratio (in  $1/\text{mm}$ ). By assuming that there exists a  $\lambda$  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  $10 \text{ mm} \times 10 \text{ mm}$  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<sup>2</sup> with the default parameter values and default initial conditions for  $v$  and  $s$ . The `splittingsolver` solves the monodomain PDE system and its coupled cell membrane dynamics ODE system separately, using the operator splitting scheme as described in [3]. We take  $\sigma_l = 0.255$  and  $\sigma_t =$

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<sup>1</sup>[models.cellml.org/electrophysiology](https://models.cellml.org/electrophysiology)

<sup>2</sup>[bitbucket.org/meg/cbcbeat](https://bitbucket.org/meg/cbcbeat)

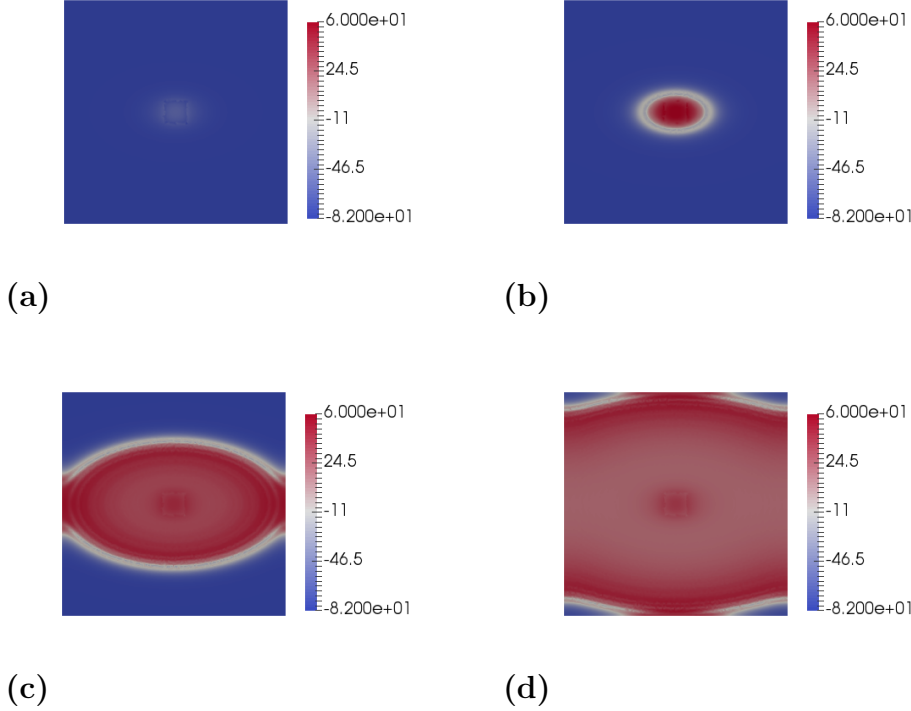


Figure 1: Heat maps of  $u$  of our basic test case at (a)  $t = 5\text{ms}$ , (b)  $t = 15\text{ms}$ , (c)  $t = 25\text{ms}$  and (d)  $t = 35\text{ms}$ .

0.0775, where  $\sigma_l$  and  $\sigma_t$  are the longitudinal and tangential conductivity values respectively. We apply a stimulus of 25 mV/ms over 1 mm<sup>2</sup> in the centre of the square. In Figure 1, we show a heat map of  $u$  at  $t = 15, 20$  and 30 ms.

### 3 The inverse problem

It is possible to obtain measurements  $u_{\text{obs}}$  of the transmembrane potential and measurements  $c_{\text{obs}}$  of the intracellular calcium concentration  $c$  over the whole domain  $H$  at discrete points in time, where the calcium concentration  $c$  is one of the 38 state variables  $\mathbf{s}$  of the Grandi cell model. With those measurements, we can estimate the value of the parameters in our model, using an adjoint-based approach.<sup>3</sup> Here, as an example, we will try to estimate the values of the  $GNa$  parameter from the Grandi cell model. We can formulate

<sup>3</sup>See, for example, [2] for an introductory text in adjoint-based optimization methods.

this problem as an optimisation problem: find  $GNa$ , such that the functional

$$\mathcal{J}(v, c, GNa) = \frac{1}{N} \sum_{i=1}^N \|v - v_{\text{obs}}(t_i)\|_{L^2(H)}^2 + \|c - c_{\text{obs}}(t_i)\|_{L^2(H)}^2, \quad (5)$$

is minimized, subject to the requirements that  $v, c$  and  $GNa$  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  $t_i$ ,  $i = 1, \dots, N$  the respective moments in time. To find a minimum for our functional  $\mathcal{J}$ , we will need to determine its total derivative with respect to the optimization parameter  $Gna$ . We use the

## 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.