A theoretical model of slow wave regulation using voltage-dependent synthesis of inositol 1, 4, 5-trisphosphate

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ORIGINAL

Abstract

The system of equations and figures presented in Imtiaz et al. (2002) are verified and reproduced in the current curation paper. Here, to demonstrate reproducibility, We describe the model encoded in the CellML and document the differences between our curated model and the one published by Imtiaz et al.. From the primary publication, we extracted data applying the Engauge digitizer software (Mitchell et al., 2020) to compare the current CellML simulation results against those in the primary publication.

Keywords: OpenCOR, Computational model, IP_3 oscillations, Slow wave, CellML, Membrane potential, Feedback

1 Introduction

Slow waves are rhythmic bioelectrical depolarizations that initiate and control the mechanical activity of gastrointestinal (GI) smooth muscles. One of the mechanisms responsible for generating slow waves involves IP_3-induced calcium release and calcium-induced calcium release from IP_3-operated intracellular calcium stores. The resultant calcium increases in the subplasmalemmal space then activate calcium-sensitive inward currents across the plasmalemma that result in slow-wave depolarizations (Dicker et al., 2018; Imtiaz et al., 2002).

According to Imtiaz et al. (2002), IP_3 oscillations are unnecessary for calcium oscillations, as IP_3 oscillations can occur in many different cell types. In the current work Imtiaz et al. (2002), the authors are introducing a new feedback mechanism based on membrane potential, which then modulates IP_3 synthesis. Where the aim is to study the role of membrane potential feedback on IP_3 synthesis and its role in regulating calcium release and slow waves. The system is simplified by considering a single isopotential cell with a single IP_3 receptor-operated intracellular calcium pool. The ryanodine receptor is ignored in the model. It is important to note that the voltage-dependent channels are considered to be blocked.

A persistent workspace for this work is available in the Physiome Model Repository at https://models.physiomeproject.org/workspace/763. The specific version of this implementation used to produce the results presented here is included in the OMEX Archive (Bergmann et al., 2014) for this article.

This implementation includes the Python source code to generate the model simulations in a 'Simulations' directory. The corresponding CellML implementation is available in a 'Experiments' directory containing the encoded mathematical model. This CellML file does not reproduce the figures due to limited solver capabilities at the time of testing. As such, we have elected to describe the required simulation experiments in Python and use the OpenCOR (Garny and Hunter, 2015) Python interpreter to perform the simulations and analyses. In this manuscript, we focus on reproducibility and reusability.

2 Model description

2.1 Primary Publication

The model was formulated using a Hodgkin-Huxley type formulation. The cell membrane lipid bilayer was modelled as a capacitance (C_m), and the ion channels in the membrane were represented as conductance. The change in the transmembrane potential (V_m) over time depended on the sum of the individual ion currents in the cell:

$$\frac{dV_m}{dt} = -\frac{I_{tot}}{C_m}. \tag{1}$$

2.2 Model Implementation

The implementation of the model was performed using CellML (Cuellar et al., 2003). Some simulation values stated in Imtiaz et al. (2002) resulted in different model behaviour, which we adjusted as outlined in Table 1. The simulation experiments presented here were performed using OpenCOR (Snapshot 2021-10-5 (Garny and Hunter, 2015)). Simulation settings and detailed solver information were encoded in SED-ML ducument (Waltemath et al., 2011).

We reproduced the data represented in Imtiaz et al. (2002, Figures 2A, 3A, 4A, 6(A and B) & 8A) by using different settings corresponding to the various model experiments. We implemented the model configuration in Python scrip for each experiment. Then, we perform the Python script to plot the related data.

The name of the simulation and plot scripts indicates the figure number in the primary paper. For example, Fig2_sim.py is used to generate the simulation data, and Plot_Fig2.py reproduces the graph shown in Figure 2A from (Imtiaz et al., 2002).

2.3 Model Modifications

Mathematical Equations were the same as reported in the primary publication of Imtiaz et al. (2002) except for (Imtiaz et al., 2002, Equations 3, 7, and 9). Please see the correction in below:

1. Unit consistency:

    (a) In Eq. 7, the first term, which indicates the lump current (I_i) should carry a negative sign, while in the original work, the lump current is presented with a positive sign.

    (b) In Eq. 7, we correct the consistency in time unit by multiplying the denominator on the right-hand side by the scale factor of 60 s

    $$\frac{dV_m}{dt} = -\left[\frac{I_{Ca} + I_i - I_{inj}}{C_m * 60}\right].$$

    (c) In Eq. 9, the term β indicates the external stimuli has a unit of μM while the term dP/dt which indicates IP$_3$ concentration in the cytosol has a unit of $\mu M/min$. The

Table 1. Correction of primary (Imtiaz et al., 2002, Tables 1,2 & 3)

Table	Parameter	Primary paper	CellML
Table 1	V_1	$3.4 \, \mu M/min$	$3.4 \, 1/min$
Table 3	β	$0.7 \, \mu M$	$0.7 \, \mu M/min$

baseline parameter values are provided in the primary paper Imtiaz et al. (2002).

$$\frac{dP}{dt} = \beta - \epsilon * P - V_{m4}(P) + P(V)$$

2. No initial condition was defined in the primary paper, all initial conditions extracted from the original paper, using Engauge Digitizer software (Mitchell et al., 2020).

$V_{m(init)} \, [mV]$	Z_{init}	Y_{init}	P_{IP_3}	b_{IP_3}
-65.00	4.113	0.478	0.408	0.7533

Table 2. Initial conditions on the current CellML implementations.

3. In the case of model experiments and simulations, there was no clear information about the protocol details they used to inject the current (stimulus) into the cell. The simulation experiments we have inferred from the primary paper in order to reproduce the simulation results are described in subsection 2.4.

2.4 Model Simulations

In the presented figures, the dots denote the simulated data extracted from the primary publication, while the solid lines are the simulation results produced by the current CellML implementation.

Figure 3A was reproduced applying the following protocols Equation 2, while the initial conditions were the same as Table 2.

$$I_{inject} = \begin{cases} 2.25 \, mA & 30 \, min \, < \, time \, <= \, 31.5 \, min \\ 2.25 \, mA & 60 \, min \, < \, time \, <= \, 63 \, min \end{cases} \tag{2}$$

Figure 4A was reproduced using the IP$_3$ model by setting the initial membrane potential (V_m) at a fixed holding potential -65.09 mV and then polarizing the membrane by injecting the current into the cell, for more details information see Equation 3 and Figure 3.

$$I_{inject} = \begin{cases} 0 \, mA & 0 \, min \, < \, time \, <= \, 12 \, min \\ -15 \, mA & 12 \, min \, < \, time \, <= \, 24 \, min \\ +22 \, mA & 24 \, min \, < \, time \, <= \, 36 \, min \end{cases} \tag{3}$$

In Figure 8A, the effect of the interpulse duration on current pulse-induced responses was studied. The aim was to demonstrate the pulse would fail to evoke responses if the interpulse duration was reduced below a critical value. In Fig 8A $t_d = 5.36 \, min$, while in Fig 8B $t_d = 2.36 \, min$.

$$I_{inject} = \begin{cases} 0 \, mA & 5.36 \, min \, < \, time \\ 2 \, mA & 5.36 + n * t_d \, min \, < \, time \, <= \, 5.36 + n * (t_d + 0.64) \, min \end{cases} \tag{4}$$

2.5 Model Results

We employed Engauge Digitizer software (Mitchell et al., 2020) to extract data from all figures from Imtiaz et al. (2002) to present alongside the results of the present work. The reproduction of all figures of Imtiaz et al. (2002) is given in Figures 1-5, which show good agreement with the data of the primary paper. Solid lines show the output from the current curation, and crosses show discrete points found by the Engauge Digitizer of the figures originally published article.

Applying some corrections to the original equations and parameters (see model modifications), the following results were produced:
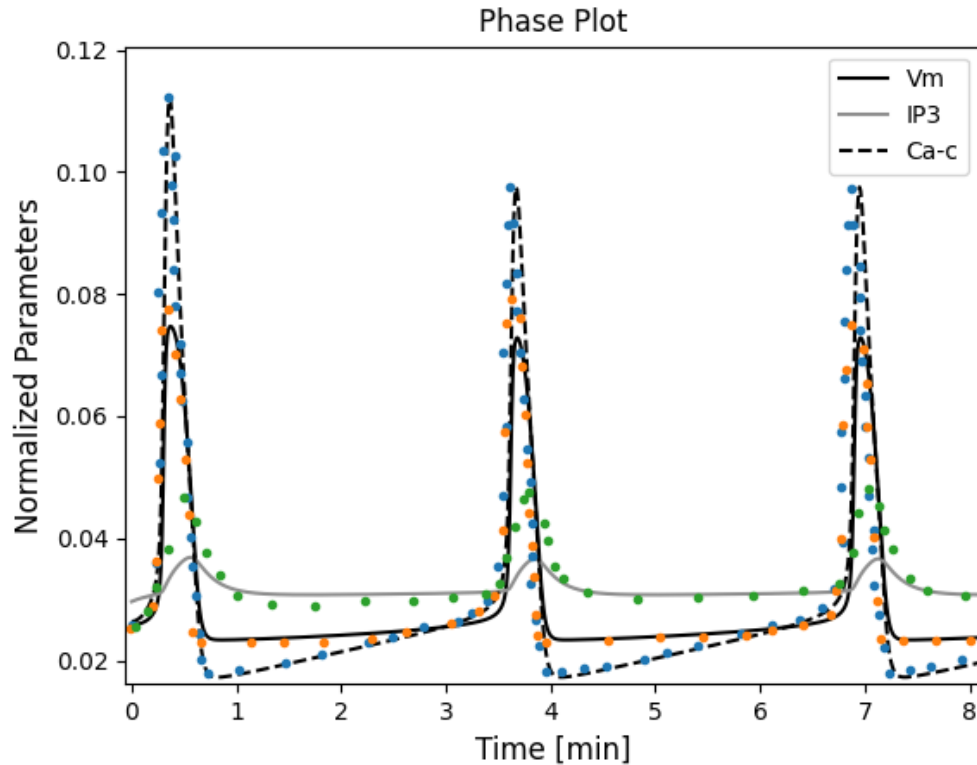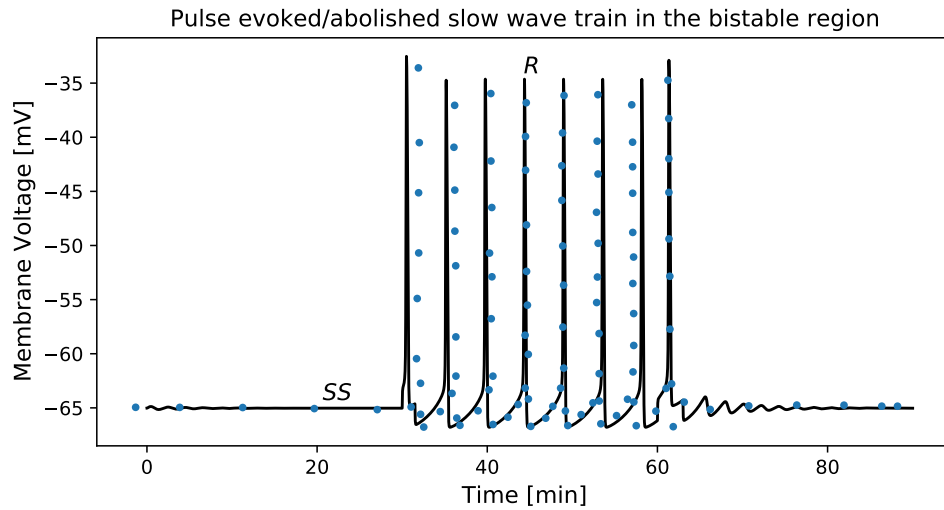

Figure 1. The primary data (*) of (Imtiaz et al., 2002, Figure 2A) with our reproduction of all subfigures. To reproduce (Imtiaz et al., 2002, Figure 2A), use the Python manuscript 'Fig2_sim.py' and to plot it use 'Plot_Fig2.py'.

3 Discussion

We implemented the model of Imtiaz et al. (2002) using CellML which can be reused in future. We successfully replicated simulation results and summarized detailed experiment settings for simulation in subsection 2.4. In doing this, we noticed trivial typographical errors in parameter units and references in (Imtiaz et al., 2002, Table 1, 3). Hence, we highlighted the issues and added correction to remove potential confusion in subsection 2.3.

4 Acknowledgements

Figure 2. The primary data (*) of (Imtiaz et al., 2002, Figure 3A) with our reproduction of all subfigures. To reproduce (Imtiaz et al., 2002, Figure 3A), use the Python script 'Fig3_sim.py' and to plot it use 'Plot_Fig3.py'.
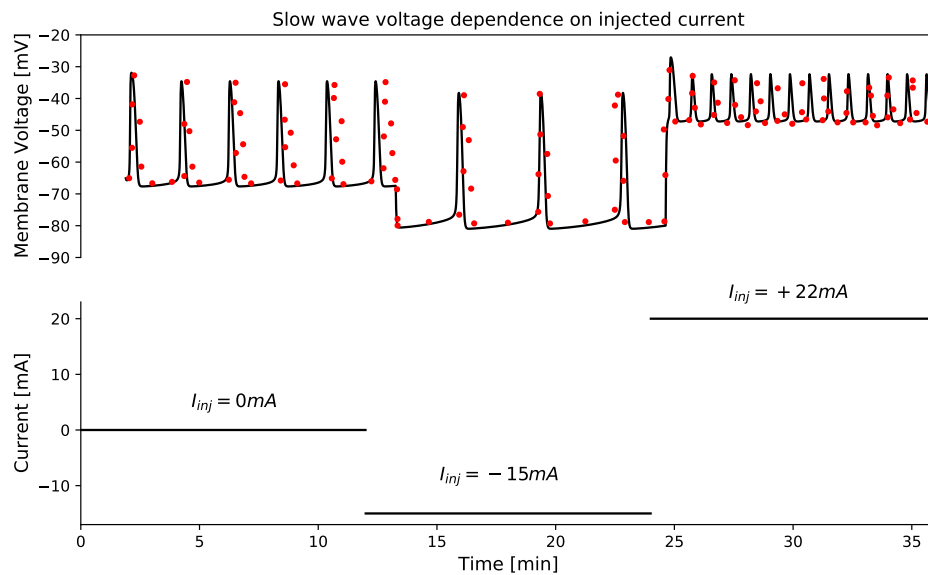
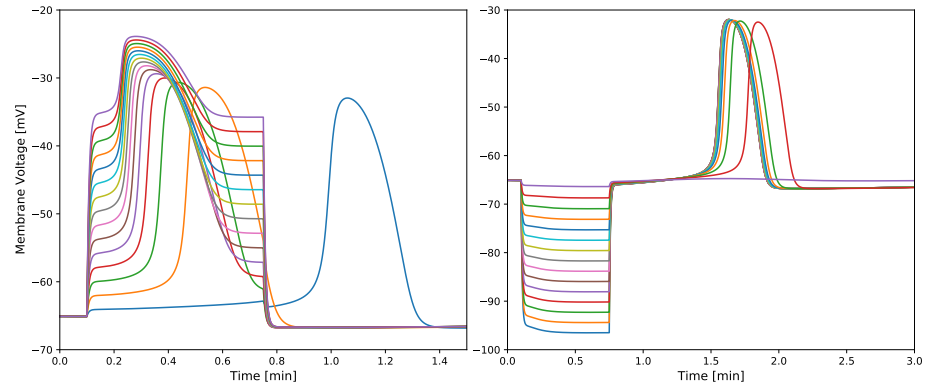

Figure 3. The primary data (*) of (Imtiaz et al., 2002, Figure 4A) with our reproduction of all subfigures. To reproduce (Imtiaz et al., 2002, Figure 4A), use the Python script 'Fig4_sim.py' and to plot it use 'Plot_Fig4.py'.

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Figure 4. The primary data (*) of (Imtiaz et al., 2002, Figure 6(A and B)) with our reproduction of all subfigures. To reproduce (Imtiaz et al., 2002, Figure 6(A and B)), use the Python script 'Fig6_sim.py' and to plot it use 'Plot_Fig6.py'.
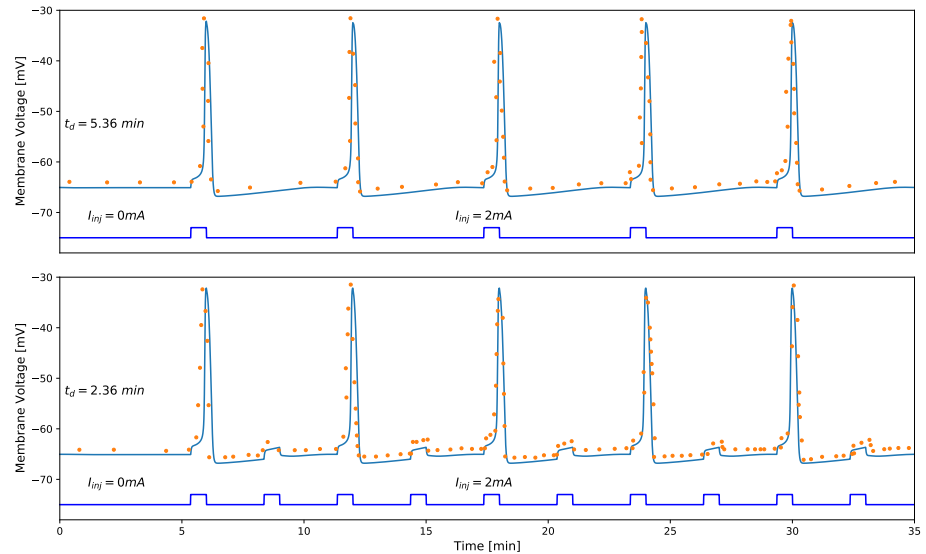

Figure 5. The primary data (*) of (Imtiaz et al., 2002, Figure 8A) with our reproduction of all subfigures. To reproduce (Imtiaz et al., 2002, Figure 8A), use the Python script 'Fig8_sim.py' and to plot it use 'Plot_Fig8.py'.

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Reproducibility report for: A theoretical model of slow wave regulation using voltage-dependent synthesis of inositol 1, 4, 5-trisphosphate
Submitted to: *Physiome*
Manuscript identifier: S000021

Curation outcome summary: Successfully reproduced all the figures presented in this manuscript.

Box 1: Criteria for repeatability and reproducibility

■ **Model source code provided:**

  ■ Source code: a standard procedural language is used (e.g. MATLAB, Python, C)

    ☐ There are details/documentation on how the source code was compiled
    ■ There are details on how to run the code in the provided documentation
    ■ The initial conditions are provided for each of the simulations
    ■ Details for creating reported graphical results from the simulation results

  ■ Source code: a declarative language is used (e.g. SBML, CellML, NeuroML)

    ■ The algorithms used are defined or cited in previous articles
    ■ The algorithm parameters are defined
    ☐ Post-processing of the results are described in sufficient detail

☐ **Executable model provided:**

  ☐ The model is executable without source (e.g. desktop application, compiled code, online service)

    ☐ There are sufficient details to repeat the required simulation experiments

■ **The model is described mathematically in the article(s):**

  ■ Equations representing the biological system

  ■ There are tables or lists of parameter values

  ■ There are tables or lists of initial conditions

  ■ Machine-readable tables of parameter values

  ■ Machine-readable tables of initial conditions

■ **The simulation experiments using the model are described mathematically in the article:**

  ■ Integration algorithms used are defined

  ☐ Stochastic algorithms used are defined

  ☐ Random number generator algorithms used are defined

  ☐ Parameter fitting algorithms are defined

  ■ The paper indicates how the algorithms yield the desired output

Box 2: Criteria for accessibility

■ Model/source code is available at a public repository or researcher's web site

 ☐ Prohibitive license provided

 ☐ Permissive license provided

 ■ Open-source license provided

■ All initial conditions and parameters are provided

■ All simulation experiments are fully defined (events listed, collection times and measurements specified, algorithms provided, simulator specified, etc.)

Box 3: Rules for Credible practice of Modeling and Simulation[a]

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 [a]Model credibility is assessed using the Interagency Modeling and Ananlysis Group conformance rubric:
https://www.imagwiki.nibib.nih.gov/content/10-simple-rules-conformance-rubric

■ Define context clearly: Extensive

■ Use appropriate data: Extensive

■ Evaluate within context: Extensive

☐ List limitations explicitly: Insufficient

■ Use version control: Extensive

■ Document adequately: Extensive

■ Conform to standards: Extensive

Box 4: Evaluation

■ Model and its simulations could be repeated using provided declarative or procedural code

■ Model and its simulations could be reproduced

Summary comments: Model and source code are available in the associated OMEX archive. This was used in our attempt to reproduce the results presented in the paper. We successfully ran the Python, CellML and SED-ML files provided to reproduce Figure 2 - Figure 4 as presented in this manuscript. In order to reproduce Figure 6 and Figure 8, minor changes to the plotting script were made.

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