Thul, Ruediger (2014) Oscillations in a point models of the intracellular Ca2+ concentration. Cold Spring Harbor Protocols . ISSN 1559-6095

Oscillations in a point model of the intracellular Ca^{2+} concentration

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Abstract

Oscillations in the intracellular calcium (Ca^{2+}) concentration form one of the main pathways by which cells translate external stimuli into physiological responses (Thul et al. 2008; Dupont et al. 2011; Parekh 2011). The mechanisms that underlie the generation of Ca^{2+} oscillations are still actively debated in the modeling community, but there is growing evidence that Ca^{2+} oscillations result from the spatio-temporal summation of subcellular Ca^{2+} release events (Thurley et al. 2012). Nevertheless, one prominent modeling approach to intracellular Ca^{2+} oscillations is the use of ordinary differential equations (ODEs), which treat the intracellular Ca^{2+} concentration as spatially homogenous. Although ODEs cannot account for the interaction of Ca^{2+} microdomains to form cell-wide Ca^{2+} patterns, modelers still choose ODEs since (a) the study of ODEs is computationally cheap, and a large body of techniques is available to investigate ODEs in great detail, or (b) there might not be sufficient experimental data to develop a spatially extended model. Irrespective of the reason, analyzing ODEs is a key instrument in the toolbox of modelers. In this protocol, we look at a well-known model for Ca^{2+} oscillations (De Young and Keizer 1992; Li and Rinzel 1994). The main emphasis of this protocol is the use of the open source software package XPPaut to numerically study ODEs (Ermentrout 2002). The knowledge gained here can be directly transferred to other ODE systems and therefore may serve as a template for future studies. For a general background on analyzing ODEs in the context of Mathematical Cell Physiology, I refer the reader to (Keener and Sneyd 2001; Fall et al. 2002; Britton 2002; Murray 2013).

Materials

- The original De Young Keizer model (De Young and Keizer 1992)
- The Li-Rinzel approximation of the De Young Keizer model (Li and Rinzel 1994)
- XPPAUT (http://www.math.pitt.edu/~bard/xpp/xpp.html)

Method

1. Locate the two ODEs – one for the Ca^{2+} concentration c and one for the fraction of non-inhibited IP_3Rs h – in (Li and Rinzel 1994):

$$\frac{dc}{dt} = c_1(v_1 m_\infty^3 h^3 + v_2)(c_{er} - c) - \frac{v_3 c^2}{c^2 + k_3^2}, \quad (1)$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h}, \quad (2)$$

where

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$$m_\infty = \frac{c}{c+d_5}\frac{I}{I+d_1}, c_{er} = \frac{c_0-c}{\alpha}, \quad (3)$$
$$h_\infty = \frac{Q_2}{Q_2+c}, \tau_h = \frac{1}{a_2(c+Q_2)}, Q_2 = d_2\frac{I+d_1}{I+d_3},$$

2. Enter the two ODEs together with the parameter values from (De Young and Keizer 1992) into a text file that is compatible with the XPPAUT format:

```
dc/dt=c1*(v1*minf^3*h^3+v2)*(caer-c)-(v3*c^2)/(c^2+k3^2)
dh/dt=(hinf-h)/tau
minf=c/(c+d5)*I/(I+d1)
caer=(c0-c)/c1
Q2=d2*(I+d1)/(I+d3)
hinf=Q2/(Q2+c)
tau=1/(a2*(Q2+c))
par I=0.2
par c0=2.0,c1=0.185,k3=0.1,v1=6,v2=0.11,v3=0.9
par d1=0.13,d2=1.049,d3=0.9434,d4=0.1445,d5=0.0832
par a1=400,a2=0.2,a3=400,a4=0.2,a5=20
done
```

   The first two lines correspond to the two ODEs, the next five lines show the additional expressions of equation (3), and all lines that start with `par` hold the parameters for the simulation. Save the file, e.g. as `LiRinzel.ode`.
3. Change to the directory where the executable `xppaut` was installed to.
4. Start the program with `xppaut LiRinzel.ode` from the command line, and you will see a screen as in Figure 1.

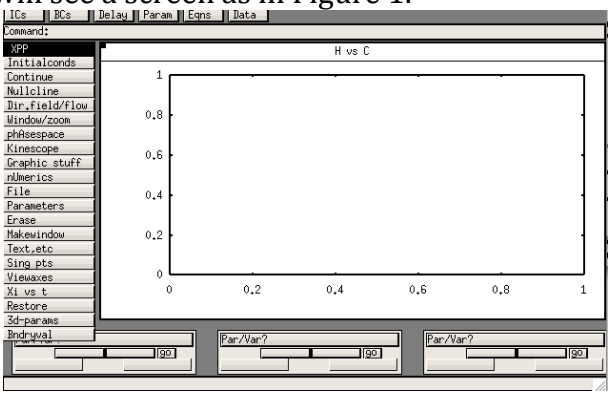

Figure 1: Screenshot of the opening screen of XPPaut under Mac OS.

5. Change the settings so that the Ca^{2+} concentration c is plotted against time by clicking on the button **Xi vs t** in the left column and enter `c` at the input line at the top of the window.
6. Set the total integration time to 200 seconds by clicking on **nUmerics**, **Total**, and then enter 200 at the top of the window. Press **ESC** to return to the main menu.
7. Adjust the plot range of the window by clicking on **Viewaxes** and then on **2D**. In the new window, enter 200 in the box labeled Xmax. Click on **OK**.
8. Set the initial conditions by clicking on **ICs** at the top of the window and enter 0.5 in both boxes. Click on go in the top right of the window, which will show time course of the Ca^{2+} concentration as in Figure 2a

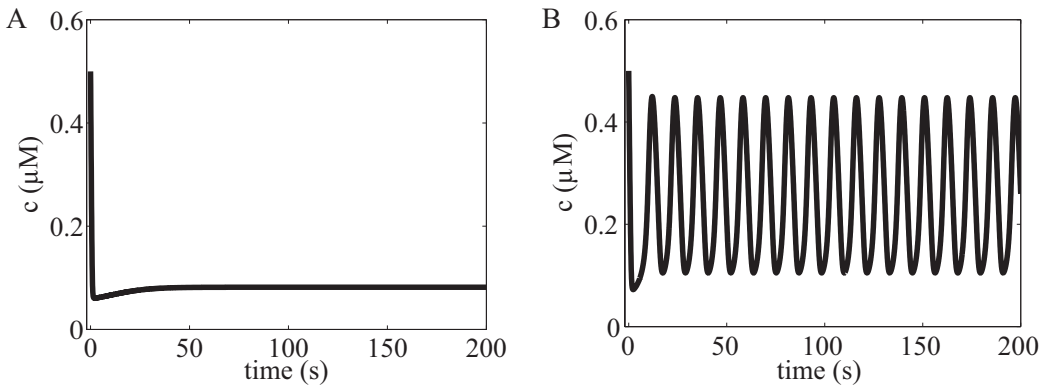

Figure 2: For small IP_3 concentrations (I=0.2), the Ca^{2+} concentration settles at a constant level (A), while for intermediate IP_3 concentrations (I=0.5), the model exhibits regular Ca^{2+} oscillations (B).

9. Clear the window by clicking on **Erase**.
10. Change the IP_3 concentration to 0.5 by clicking on **Param** at the top of the window, enter 0.5 in the first box labeled I and then click on **Go**. The outcome of the simulation is shown in Figure 2b.
11. Change other parameters in the **Param** field to explore the dynamics of the Li-Rinzel model.

Troubleshooting

Problem (Step 4): `XPPaut` does not find the file `LiRinzel.ode`.
Solution: Make sure that `LiRinzel.ode` is in the same directory as the executable `xppaut`. Either copy `LiRinzel.ode` into the same directory as `xppaut`, or use the full path name at the command line, e.g. `xppaut ~/Myxppfiles/LiRinzel.ode`.

Problem (Step 4): `XPPaut` complains when reading in `LiRinzel.ode`.
Solution: Make sure that the last line in the `LiRinzel.ode` file is `done`. Also check that the file suffix is always `.ode`.

Problem (Step 8): The stationary state (straight line) runs at a different value of the Ca^{2+} concentration.
Solution: The release strength of the IP_3R in the Li-Rinzel model is often written as a single constant instead of the product $c_1 v_1$ in Equation (1). Make sure that the factor c_1 is outside the first bracket in Equation (1).

Discussion

The above protocol demonstrates how changes in the IP_3 concentration generate Ca^{2+} oscillations. This is a phenomenon that a large number of ODE models for the IP_3R share, see e.g. (Atri et al. 1993; Sneyd and Falcke 2005; Thul et al. 2008; Swaminathan et al. 2009). This protocol may serve as a blue print for studying Ca^{2+} oscillations in ODE models. For the enthusiastic reader, note that Ca^{2+} oscillations occur in the Li-Rinzel model for the above parameter values for IP_3 concentrations between 0.3552 μM and 0.64728 μM.

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