Systems Biology II 580.422, Homework

In class, the following model for bursting was discussed. This model is taken from the chapter by J. Rinzel and B. Ermentrout "Analysis of neural excitability and oscillations." In: C. Koch and I. Segev Methods in Neuronal Modeling (MIT Press, 1998).

$$C\frac{dV}{dt} = I_{ext} - \bar{G}_{Ca} m_\infty(V)(V - E_{Ca}) - \bar{G}_K w(V - E_K) - \bar{G}_{KCa} z(V - E_K) - \bar{G}_L(V - E_L)$$

$$\frac{dw}{dt} = \phi \frac{w_\infty(V) - w}{\tau_w(V)} \qquad (1)$$

$$\frac{dCa}{dt} = \varepsilon\left(-\mu I_{Ca} - Ca\right) \qquad z = \frac{Ca}{Ca + Z_C}$$

This model is a modification of the *Morris-Lecar* model and consists of a calcium (instead of sodium) channel, two potassium channels, and a leak channel. Compared to the Hodgkin-Huxley model, it has a number of modifications:

1. *m* is assumed to change instantaneously, so $m = m_\infty(V)$ and there is no dm/dt equation.
2. *h* is ignored.
3. Potassium channel gating is proportional to the gating variable *w* instead of n^4.
4. A K(Ca) channel has been added with gating *z* which depends on the accumulated calcium concentration in the cell (*Ca*) and a differential equation for calcium has been added.

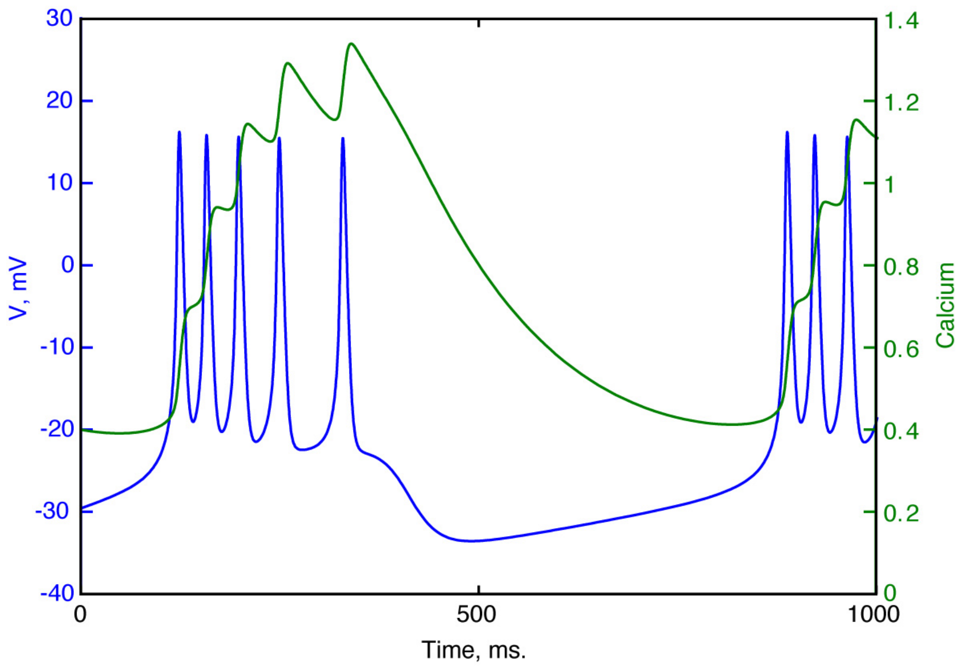
The state variables of this system are membrane potential *V* in mV, *w* which is dimensionless, and calcium concentration *Ca* in μMoles/cm^3. The other units are time in ms, current in μA/cm^2, conductance in mS/cm^2, and capacitance in μFd/cm^2. The parameter ϕ is a dimensionless scale factor for the potassium time constant τ_W which is in ms. The HH gating variables *m*, *w*, and *z* are dimensionless. With these definitions, the parameter value are as follows:

G_{Ca}	4	E_{Ca}	120
G_K	8	E_K	-84
G_{KCa}	0.28	Z_C	1
G_L	2	E_L	-60
ϕ	0.23	C	20

There are a few additional parameters that define the HH functions $m_{\%}(V)$, $w_{\%}(V)$, and $\tau_{\%}(V)$; these are listed in the appendix.

Part a) What are the units of the parameters ε and μ? Assume that the units of dCa/dt are μM/(cm^3 ms).

Part b) Estimate a value of ε from the data at right, which show the membrane potential and calcium concentration as a function of time for the model. Do this by assuming that ε is the time constant of the decay of the green curve (the Ca concentration) for the time when I_{Ca}=0, between bursts of spikes. (It will turn out that this estimate is only roughly accurate, because the assumption is not quite right.) How could μ (actually the product εμ) be estimated by a similar method?



You can get the waveforms in the figure above for this measurement by using the program mleBO, as described below.

The model program: The file mleBOprograms.zip contains a Matlab program that computes bursting from this model, as in the figure above and as shown in class. Unzip this folder and place it in your Matlab path. Run the program as [VV, tv, pml3, iext] = mleBO; with no parameters; it will use the default set of parameters given above, giving the same result. After the simulation, the function returns the state vectors in a matrix *VV* whose columns are the values of *V*, *w*, and *Ca* as functions of time going down the rows. The time values are in the vector *tv*. You should be able to reproduce the plot above with

```
[VV, tv, pml3, iext] = mleBO;
figure(1); clf
plotyy(tv, VV(:, [1,3]))
```

The parameter vector and external current definitions are returned in pml3 and iext. These contain the parameters as follows.

```
pml3 = [Gca, Gk, Gl, Eca, Ek, El, phi, v1, v2, v3, v4, v5, v6, C, vic, wic, …
    eps, mu, Gkca, Caic, Kc];

iext = [Iext, tstart, tstop];
```

vic, wic, and *Caic* are the initial conditions on the state variables at time 0, the start of the simulation. The external current is set to value I_{ext} during time [*tstart*, *tstop*]. For this simulation, this current needs to be on all the time (at 45 μA/cm^2). If you change a parameter in either *pml3* or *iext* and call the program as

```
[VV, tv] = mleBO(1000, pml3, iext);
```

the simulation will run with the modified parameters. The '1000' is the duration of the simulation in ms.

Run the simulation once and look at the value of ε in the parameter vector. How does it compare with your estimate in problem 1?

Part c) Run the simulation with the parameter μ decreased by 10% and increased by 10%. This parameter is 0.0133 by default (i.e. for the plot in the figure above). For example, to make the first change,

```
pml3(18) = pml3(18)*1.1      % To increase the value of mu by 10%
[VV, tv] = mleBO(1000, pml3, iext);      % Do the simulation
```

and so on for the decrease by 10%. Compare the responses you see in these two simulations with the results using the default parameter and explain the changes from the figure above in terms of the behavior of the *Ca* variable.

Part d) In part c), you should have seen that bursting was not present with μ=0.0121 (10% decrease), although spiking continued. Based on your understanding of why bursting stopped, change one additional parameter of the model (i.e. a value in pml3) to restore bursting with μ=0.0121. This can be done in several ways. The purpose of this exercise is to gain an intuitive understanding of this model, so see how many different ways you can find to restart bursting. In doing this, start with small parameter changes (10% or less) and go from there. This model is rather delicate and will stop spiking altogether if you change parameters too much.

Part e) It was claimed in lecture that bursting depends on the K(Ca) channel. To check whether this is so, set G_{KCa} to 0, as pml3(19)=0, and run the simulation. You will be surprised by the results. Look at the values of the state variables at 1000 ms. What has happened to the model?

To get some insight into what is going on, try the simulation with G_{KCa} = 0.14 and 0.21.

Appendix: Gating variables for the mleBO model:

Below are the functions needed in the differential equations:

$$m_\infty(V) = 0.5\left(1 + \tanh\left(\frac{V - v_1}{v_2}\right)\right)$$

$$w_\infty(V) = 0.5\left(1 + \tanh\left(\frac{V - v_3}{v_4}\right)\right)$$

$$\tau_W = \frac{1}{\cosh\left(\frac{V - v_5}{v_6}\right)}$$

where:

v_1	-1.2	v_2	18
v_3	12	v_4	17.4
v_5	12	v_6	17.4