1 Dynamical System

The following ODEs govern calcium (c) dynamics

$$\frac{dc}{dt} = J_{IP3R} + J_{ERleak} - J_{SERCA} \quad + \delta[J_{ECSadd} - J_{PMCA} + J_{SOC}] \tag{1}$$

$$\frac{dc_{tot}}{dt} = \delta[J_{ECSadd} - J_{PMCA} + J_{SOC}] \tag{2}$$

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \tag{3}$$

where the equations related to h are

$$\tau_h = \frac{1}{a_2(Q_2 + c)} \tag{4}$$

$$h_\infty = \frac{Q_2}{Q_2 + c} \tag{5}$$

$$Q_2 = d_2\left(\frac{p + d_1}{p + d_3}\right) \tag{6}$$

The various fluxes J are given each by

$$J_{IP3R} = v_{IP3R} m_\infty^3 n_\infty^3 h^3 (c_{ER} - c) \tag{7}$$

$$m_\infty = \frac{p}{p + d_1}, \quad n_\infty = \frac{c}{c + d_5} \tag{8}$$

$$J_{SERCA} = v_{SERCA} \frac{c^{1.75}}{c^{1.75} + k_{SERCA}^{1.75}} \tag{9}$$

$$J_{PMCA} = v_{PMCA} \frac{c^2}{c^2 + k_{PMCA}^2} \tag{10}$$

$$J_{SOC} = v_{SOC} \frac{k_{SOC}^2}{k_{SOC}^2 + c_{ER}^2} \tag{11}$$

$$J_{ERleak} = v_{ERleak}(c_{ER} - c) \tag{12}$$

$$J_{ECSadd} = v_{in} - k_{out} c \tag{13}$$

and in equations (1), (2), δ is a scaling size parameter. The other dynamic variable of interest is IP3 (p), which has ODEs

$$IP3_{production} = v_\beta G^* + v_\delta \frac{k_\delta}{1+p} \frac{c^2}{c^2 + k_{PLC\delta}^2} \tag{14}$$

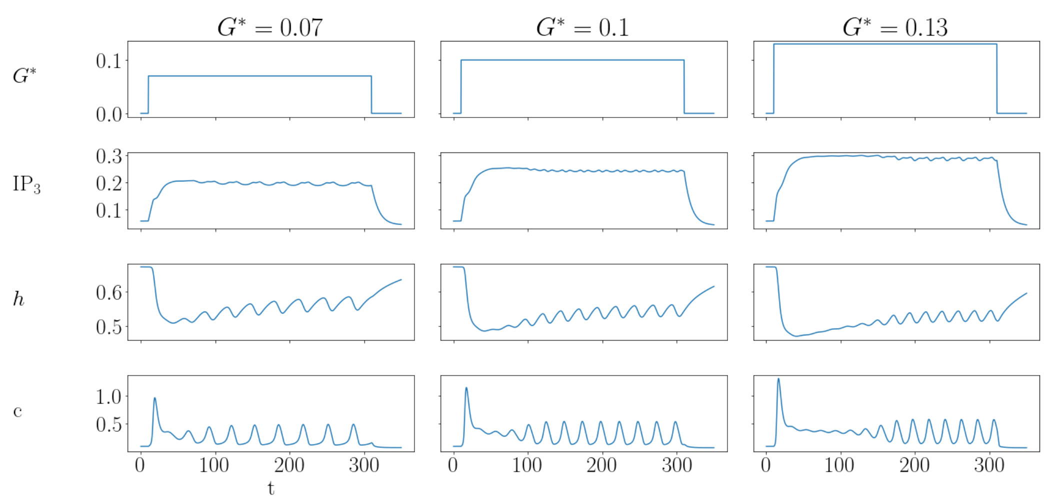
$$IP3_{degradation} = v_{3k} \frac{c^4}{c^4 + k_d^4} \frac{p}{p + k_3} + r_{5p} p \tag{15}$$

$$\frac{dp}{dt} = IP3_{production} - IP3_{degradation} \tag{16}$$

G^* is the strength of external stimulation to the system and our bifurcation parameter. Importantly in equations (14) and (15), v_δ is the strength of positive $c \rightarrow p$ feedback, and v_{3k} is the strength of negative $c \rightarrow p$ feedback. If $v_\delta = 0$ or $v_{3k} = 0$, we say that there is no positive or no negative feedback respectively.

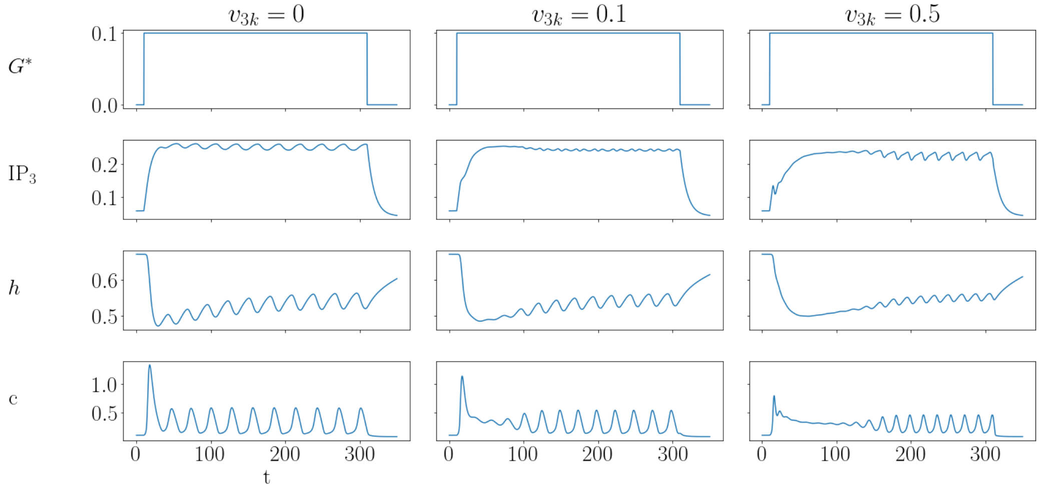
2 Observation of Delay

We apply a long pulse of G^* to the system, and are interested in looking at how long it takes for the system to reach a stable oscillation cycle in the c variable. For smaller stimulation strength $G^* = 0.07$), this is quick to occur after the initial spike in c. For larger stimulation, there is a progressively longer delay when there is negative $c \rightarrow p$ feedback in the system.



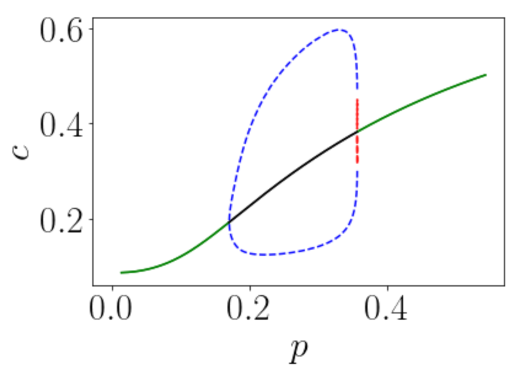
2.1 Variation of Negative Feedback Strength

Note that increases to $c \to p$ negative feedback exacerbate the oscillation delays. Positive feedback appears to have no effect. (For all other figures, $v_{3k} = 0.1$)

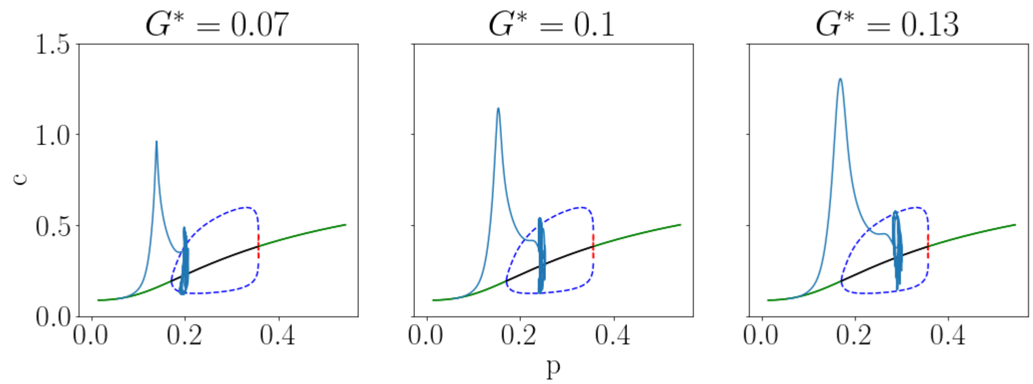


3 Bifurcations

When p is used as a control parameter we can produce the following bifurcation diagram in p, c space:



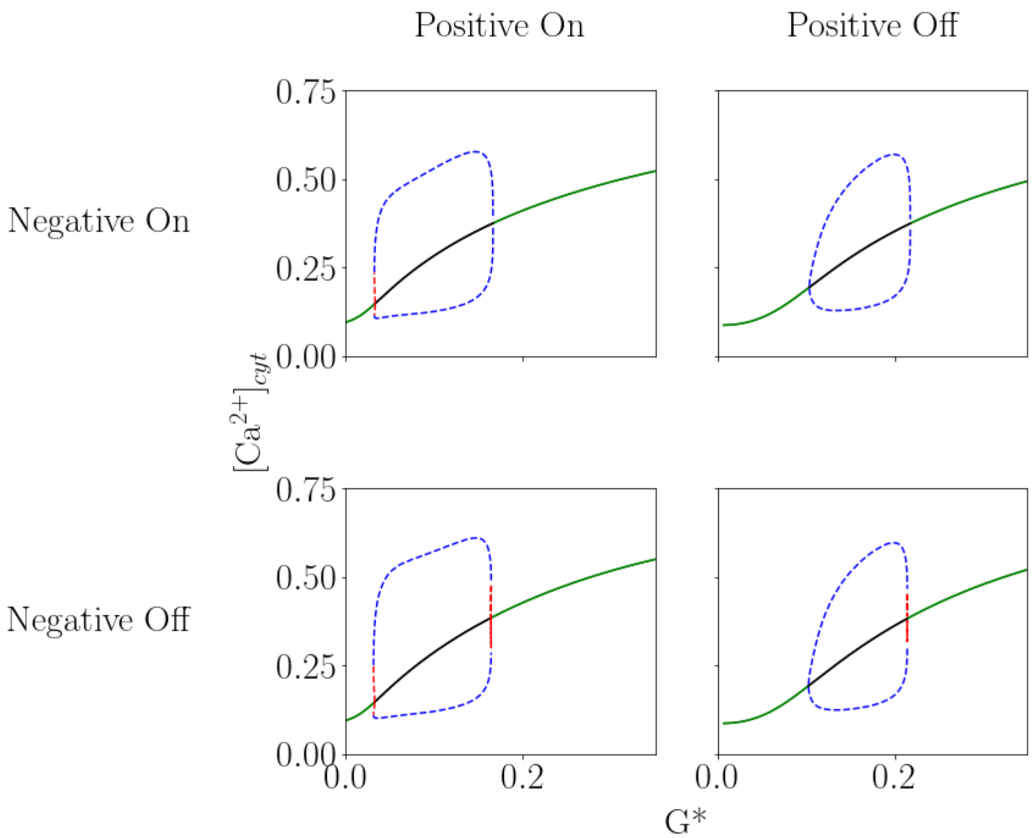
We plot the p-c trajectories from the previous section against this bifurcation diagram (noting that trajectories do not conform exactly to the bifurcation diagram since p is now a variable)



A movie of the above diagram is available with the file name "trajectories_on_bifurcation_p_c.mp4".

3.1 G* Bifurcations

Looking at bifurcations in the full system (including p as a variable) with G^* as the control parameter, we produce the following bifurcation plots, where positive and negative $c \to p$ feedback is either turned on or off.



Positive On
Positive Off
Negative On
Negative Off
0.75
0.50
0.25
0.00
0.0
0.2
$[\mathrm{Ca}^{2+}]_{cyt}$
G*