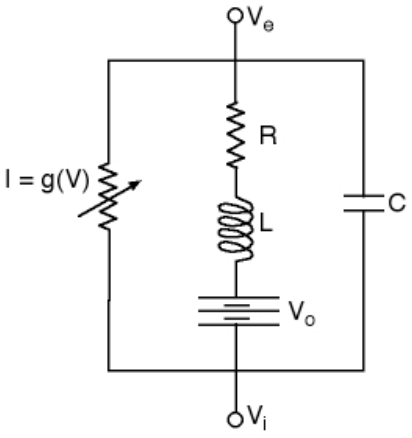
# LIMIT CYCLE OSCILLATORS

## The Fitzhugh-Nagumo Equations

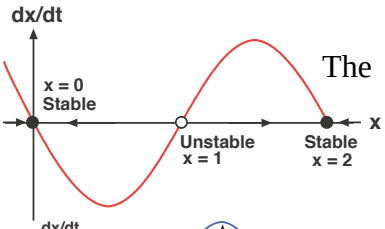



The best example of an excitable phenomenon is the firing of a nerve: according to the Hodgkin and Huxley equations a sub-threshold depolarization dies away monotonically, but a super-threshold depolarization initiates a spike potential. Fitzhugh and Nagumo devised a simplified version of the H-H equations that describes the essential features of the nerve impulse by only two differential equations.

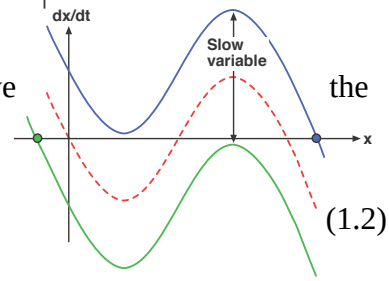
The ionic current that flows through a nerve membrane is controlled by channels whose openings and closings are controlled by the local electrical field (voltage gated ion channels). For such a conductor, Ohms Law has the form I = g(v), where v is the transmembrane voltage and g(v) is the voltage-dependent conductance. Since Q = C·v , applying d/dt to each side the differential equation for the voltage change is:

$$C\frac{\mathrm{dv}}{\mathrm{dt}} = \frac{dQ}{dt} = I = -\mathrm{g(v)} \qquad (1)$$

where C is the membrane capacitance and I = dQ/dt is the current. The voltage gate can be either open or shut; that is the conductance is *bistable*, so it has an S-shape.



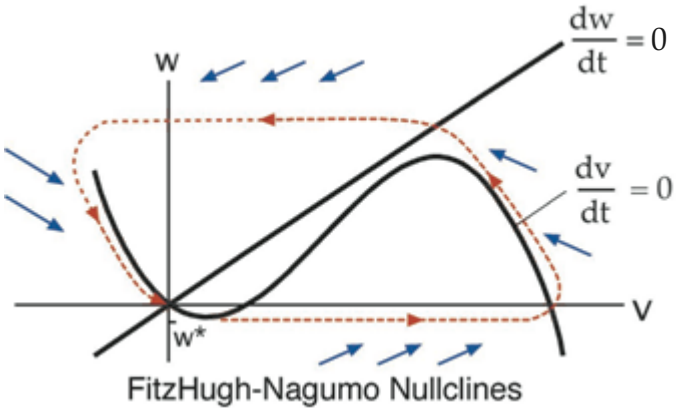

To turn the bistable conductance equation into an excitable system, Fitzhugh defined a *slow depolarization* variable, w(t), that can move the bistable curve up an down. This results in the following system:




$$\frac{dv}{dt} = -g(v) - w + I \qquad (1.2)$$

$$\frac{dw}{dt} = \frac{1}{\tau}\left(v - kw - b\right) \qquad (1.3)$$

where $\tau > 1$, and $k > 0$.

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METHOD RK4

STARTTIME = 0
STOPTIME=2000
DT = 0.2

g = v*(v - v0)*(v -1)
v' = - g - w + I
INIT v = 0.2

w' = (v - k*w - b) / tau
INIT w = -0.1

v0   = 0.15
I    = 0
tau  = 40
k    = 0.5
b    = 0

vnullcline = - v*(v - v0)*(v - 1) + I
wnullcline = (v - b) / k
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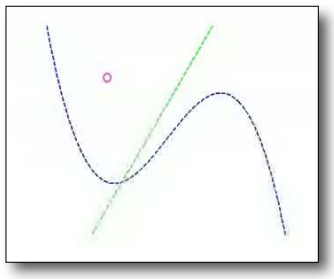
Figure 1. Phase plane for equations (2) and (3) showing the Nullclines that lead to excitable behavior.



The *phase portrait* for this system shows how an excitable system works: the single equilibrium at the origin is *locally* stable, but a small perturbation causes the system to make a large excursion before returning to rest. This sort of phase portrait is typical of excitable systems.

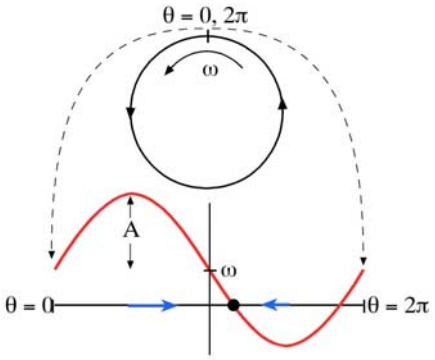
Note that by varying a parameter (e.g. *I*) the excitable system can be transformed into a bistable system in two variables. We will also see that, by adjusting the parameters, the system can oscillate in a *limit cycle*.

Exercise 1. Use the model equations at the right to make *time* and *phase plane* (w vs. v) plots and then

1. Make sliders for the parameters and find a parameter combination that makes the system oscillate.
2. Make a parameter plot of a critical parameter *I* vs. the amplitude of the oscillation to find the '*bifurcation point*' where the oscillations suddenly appear.
3. Use the initial condition button, Ic, on the graph window to explore the pattern of trajectories.
4. Use the *Fourier Transform* button to estimate the period and frequency of the oscillation.
5. Try the RK2 and Stiff solver methods and compare how many iterations Madonna™ had to execute.

# The simplest limit cycles

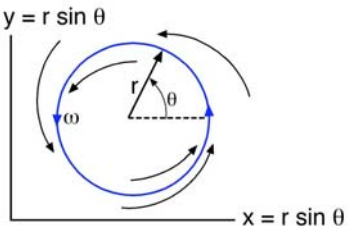
It is sometimes easier to think of periodic phenomena as taking place on a circle: $0 \le \theta \le 2\pi$: $d\theta/dt = \omega(\theta)$. Let $\omega(\theta) = \omega - A\cdot\sin(\theta)$. Sketch the vector field on the circle showing the stability of the equilibrium points and their stability as $\omega$ is varied. To do this, 'snip' the circle at $\theta = 0$ and unwrap it so it looks like this $\longrightarrow$




(Make the length of the vectors proportional to the speed of the 'phase point'.)

A slightly more elaborate version of the circular limit cycle is

$$\frac{dr}{dt} = r(1-r), \quad \frac{d\theta}{dt} = \omega$$




where the radius of the limit cycle, *r*, is governed by the simple logistic equation with amplitude = 1, and the speed around the cycle is $\omega$ = constant.

# Calcium Oscillations and Cellular Signaling

Here we will learn how to model the oscillatory dynamics of the calcium second messenger system. The reference paper for this problem set is [2]. A reprint is on the course web site.

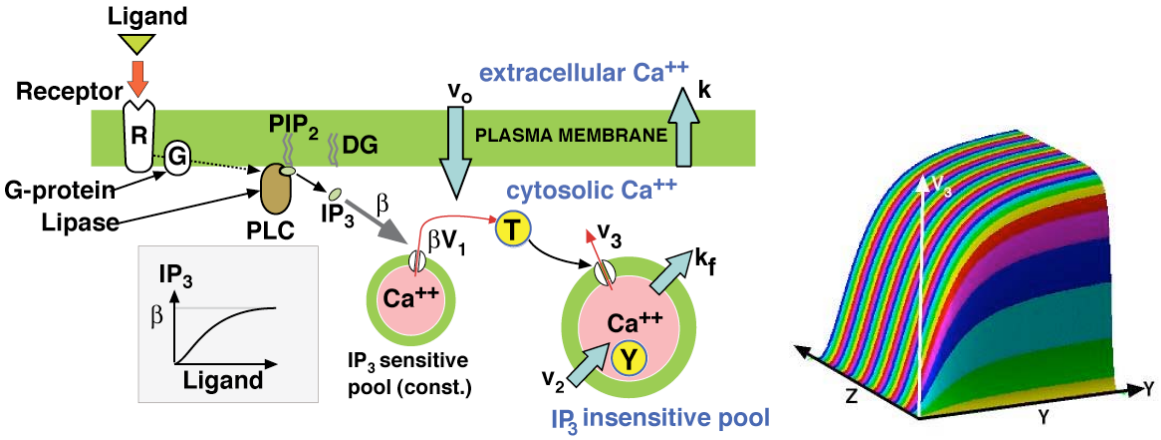



Figure 2. (a) The calcium oscillator. (b) The shape of the reaction velocity functions.

Many types of cells, when stimulated by hormones or neurotransmitters, burst into repetitive spikes of intracellular calcium release. The period of these oscillations ranges from less than 1 second to more than 30 minutes. These oscillations are thought to be an important attribute of

intra and intercellular signaling mechanisms. From our viewpoint they are a good example of "limit cycle" kinetics, and will give us an opportunity to learn how to model periodic chemical dynamics.

Consider the calcium transport system, shown in Figure 2. We write conservation equations for the concentration of intracellular calcium, **Z**, and the concentration in the IP$_3$-insensitive pool (pool 2), **Y**:

$$\underbrace{\frac{dZ}{dt}}_{\substack{\text{rate of change}\\ \text{of cytosolic}\\ \text{calcium}}} = \underbrace{v_0}_{\substack{\text{into}\\ \text{cell}}} + \underbrace{v_1\beta}_{\substack{\text{discharge}\\ \text{from pool 1}}} - \underbrace{v_2}_{\substack{\text{transport}\\ \text{into pool 2}}} + \underbrace{v_3}_{\substack{\text{transport}\\ \text{out of pool 2}}} + \underbrace{k_f Y}_{\substack{\text{leak from}\\ \text{pool 2}}} - \underbrace{kZ}_{\substack{\text{transport}\\ \text{out of cell}}} \qquad (4)$$

$$\underbrace{\frac{dY}{dt}}_{\substack{\text{rate of change}\\ \text{of calcium in}\\ \text{pool 2}}} = \underbrace{v_2}_{\substack{\text{transport}\\ \text{into pool 2}}} - \underbrace{v_3}_{\substack{\text{transport}\\ \text{out of pool 2}}} - \underbrace{k_f Y}_{\substack{\text{leak from}\\ \text{pool 2}}} \qquad (5)$$

The fluxes into and out of the IP3 insensitive pool (2) are the key nonlinearities controlling the behavior of the system. They are Michaelis-Menten type rate laws:

$$v_2 = V_{M2}\frac{Z^n}{K_2^n + Z^n} = 65\frac{Z^2}{1+Z^2} \qquad (6)$$

$$\begin{aligned} v_3 &= V_{M3}\frac{Y^m}{K_R^m + Y^m}\cdot\frac{Z^p}{K_A^p + Z^p} \\ &= 500\frac{Y^2}{2^2 + Y^2}\frac{Z^4}{0.9 + Z^4} \end{aligned} \qquad (7)$$

Table 1 lists the parameters of the model, their units, and the values that produce oscillatory behavior.

Exercise 2. Make a Madonna Flowchart to simulate the system.

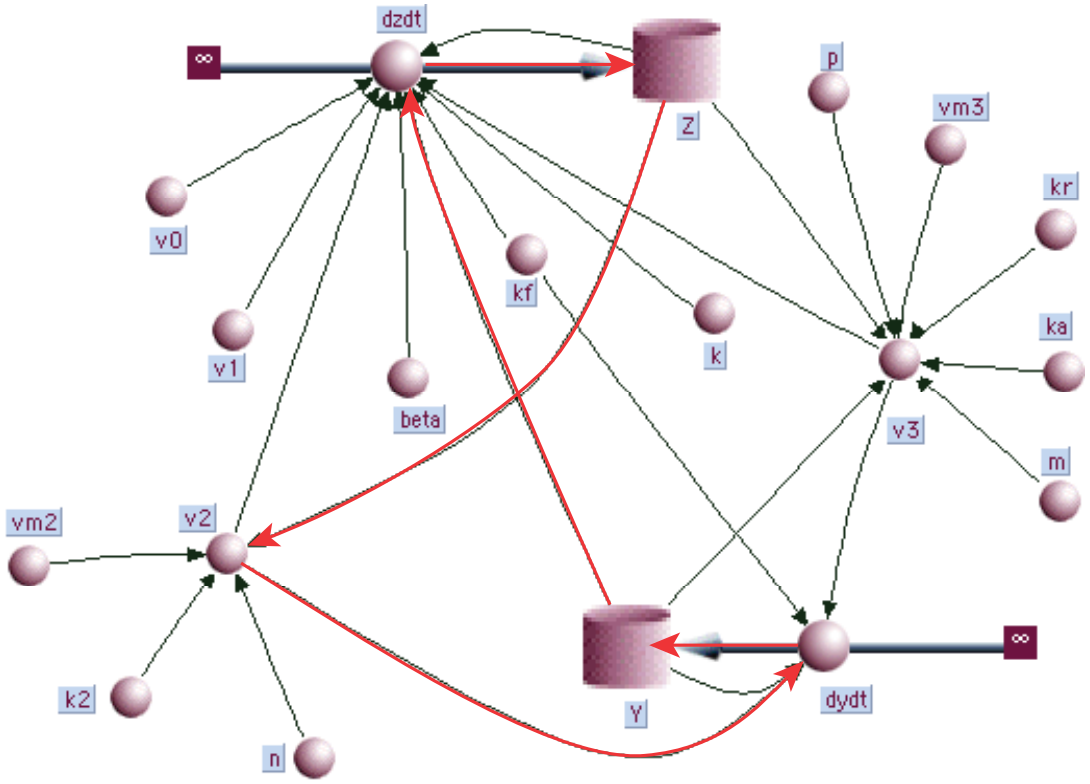
1. Show that the period of the oscillations decreases as β increases.

2. Start with a small value of the composite parameter ($v_o + \beta v_1$) and show that as this quantity increases oscillations begin to appear only after a critical value is reached (this is called a "bifurcation point").

3. Note that the *nullclines* (dZ/dt = 0 = dY/dt) of the calcium regulation system look very such like those of the Fitzhugh-Nagumo equations. Indeed, an examination of the nullclines shows that, with appropriate tuning of parameters, the calcium model can exhibit excitable behavior.

Table 1. **Parameter values**

| PARAMETER | VALUE | UNITS |
|---|---|---|
| $v_o$ | 1 | μM/s |
| k | 10 | 1/s |
| $k_f$ | 1 | 1/s |
| $v_1$ | 7.3 | μM/s |
| V | 65 | μM/s |
| $V_{M3}$ | 500 | μM/s |
| $K_2$ | 1 | μM |
| $K_R$ | 2 | μM |
| $K_A$ | 0.9 | μM |
| m | 2 | 1 |
| n | 2 | 1 |
| p | 4 | 1 |
| $Y_o$ | 0.1 | μM |
| $Z_o$ | 10 | μM |
| β | 0.3 | |



# References

1. Tyson, J., Chen, K., and Novak, B. (2003). Sniffers, buzzers, toggles, and blinkers: dynamics of regulatory and signaling pathways in the cell. Curr Opin Cell Biol. *15*, 221-231.

2. Goldbeter, A., Dupont, G., and Berridge, M.J. (1990). Minimal model for signal-induced $Ca^{++}$ oscillations and for their frequency encoding through protein phosphorylation. Proc Natl Acad Sci U S A *87*, 1461-1465.

A good elementary textbook on modeling of dynamical systems in biology is:

- Edelstein-Keshet, L. (1988). *Mathematical Models in Biology*. Ed.) New York: Random House.

## Nullcline Analysis

http://www.sosmath.com/diffeq/system/qualitative/qualitative.html

http://www.sosmath.com/diffeq/system/nonlinear/linearization/linearization.html