Multiscale Oscillations

Richard Bertram

Department of Mathematics and
Programs in Neuroscience and Molecular Biophysics
Florida State University
Tallahassee, Florida 32306
Relaxation oscillations are observed in biochemical reactions, in cardiac tissue (very wide action potentials), and models of excitable membranes often produce this type of oscillation. It is characterized by a very slow buildup in the primary variable (like voltage), followed by a sudden discharge, repeated periodically. The name is used because the stress accumulated during the slow buildup is relaxed during the sudden discharge.

A well-analyzed model that can produce relaxation oscillations is the van der Pol equation,

$$\ddot{x} + \mu(x^2 - 1)\dot{x} + x = 0$$  \(\text{(1)}\)

which describes a harmonic oscillator with a nonlinear friction term, \(\mu(x^2 - 1)\dot{x}\), where \(\mu\) is the friction coefficient. We will look at the strongly nonlinear case \(\mu \gg 0\).

We begin the analysis by converting to a system of first-order ODEs. Note that

$$\ddot{x} + \mu \dot{x}(x^2 - 1) = \frac{d}{dt} \left[ \dot{x} + \mu \left( \frac{1}{3}x^3 - x \right) \right].$$  \(\text{(2)}\)

Let \(F(x) = \frac{1}{3}x^3 - x\), and define \(w\) as \(w \equiv \dot{x} + \mu F(x)\). Then from Eq. 1,

$$\dot{w} + x = 0.$$  \(\text{(3)}\)
Altogether, the system becomes

\[ \dot{x} = w - \mu F(x) \] (4)
\[ \dot{w} = -x \] . (5)

Now make the variable change \( y \equiv \frac{w}{\mu} \), obtaining the van der Pol system in Liénard coordinates:

\[ \dot{x} = \mu [y - F(x)] \] (6)
\[ \dot{y} = -\frac{x}{\mu} \] . (7)

The \( x \)-nullcline is \( y = F(x) = \frac{1}{3}x^3 - x \), a cubic curve, and the \( y \)-nullcline is \( x = 0 \) (Fig. 1). The trajectory follows the right and left branches of the cubic \( x \)-nullcline. It moves slowly while on these branches and jumps quickly between branches. The slow movement along the nullcline branches reflects the slow \( y \) time scale (\( \mu \) is large so \( \dot{y} \) is small), while the fast jumps reflect the time scale of the faster \( x \) variable (\( \mu \) is large so \( \dot{x} \) is large).

The \( x \) time course is a square wave, while the \( y \) time course is a saw tooth (Fig. 2).

To be more precise, suppose that the initial condition is not too close to the cubic nullcline or the \( y \)-axis. Then \( y - F(x) = O(1) \) and

\[ |\dot{x}| = O(\mu) \] (8)
\[ |\dot{y}| = O(\mu^{-1}) \] . (9)
Figure 1: The $x$-nullcline (red), $y$-nullcline (green), and limit cycle trajectory (blue) for the van der Pol relaxation oscillation.

Figure 2: Time courses of the fast (top) and slow (bottom) variables.
Hence, the velocity in the horizontal direction is much greater than that in the vertical direction, and the phase point moves almost horizontally toward the \(x\)-nullcline. The time required for this jump is the inverse of the rate, so jump time = \(O(\mu^{-1})\).

Once the trajectory gets close to the nullcline it reaches a point where \(y - F(x) = O(\mu^{-2})\), and then

\[
|\dot{x}| = O(\mu^{-1}) \quad \text{(10)}
\]
\[
|\dot{y}| = O(\mu^{-1}) \quad \text{(11)}
\]

The phase point crosses the nullcline and moves slowly down the back side of the right branch with a velocity of magnitude \(O(\mu^{-1})\), which is slow. This continues until the knee is reached and then a jump occurs to the left branch of the \(x\)-nullcline. The time required for the movement along the right branch is \(O(\mu)\). That is, it takes a long time. The cycle continues in a similar manner, with fast jumps and slow movement along the left and right branches of the \(x\)-nullcline.

Because the trajectory spends most of its time on the \(x\)-nullcline, we can compute the oscillation period, neglecting the time required to jump between branches. Due to symmetry of the \(x\)-nullcline and the location of the \(y\)-nullcline, the time spent on the left branch equals the time spent
on the right branch. Thus, the period $T$ satisfies

$$T \approx 2 \int_{t_A}^{t_B} dt$$

(12)

where $t_A$ and $t_B$ are the times when the phase point is located at $A$ and $B$, respectively.

What is $dt$? On the slow branches, $y \approx F(x)$, so

$$\frac{dy}{dt} = \frac{dF}{dx} \frac{dx}{dt} = (x^2 - 1) \frac{dx}{dt}.$$  

(13)

From Eq. 7, $\frac{dy}{dt} = -\frac{x}{\mu}$, so

$$-\frac{x}{\mu} = (x^2 - 1) \frac{dx}{dt}.$$  

(14)

so that

$$dt = -\frac{\mu(x^2 - 1)}{x} dx.$$  

(15)

Thus,

$$T \approx -2 \int_{x_A}^{x_B} \frac{\mu(x^2 - 1)}{x} dx$$  

(16)

where $x_A$ and $x_B$ are the $x$ coordinates of $A$ and $B$. What are these? At point $A$ the $y$-value is the same as that of the left knee. The knees satisfy

$$\frac{d}{dx} F(x) = 0 \Rightarrow x^2 - 1 = 0 \Rightarrow x = \pm 1.$$  

(17)

Thus, the left knee is at $x = -1$. The $y$ value here is $y = F(-1) = \frac{2}{3}$.

The point on the right branch with this $y$ value satisfies

$$\frac{2}{3} = \frac{1}{3} x^3 - x \Rightarrow x = -1, 2.$$  

(18)
Hence, $x_A = 2$. The point $B$ is on the right knee, so $x_B = 1$.

Doing the integration,

$$T \approx -2\mu \int_2^1 (x - \frac{1}{x}) \, dx$$  \hspace{1cm} (19)

$$= -2\mu \left[ \frac{1}{2}x^2 - \ln |x| \right]_2^1$$  \hspace{1cm} (20)

$$= -2\mu \left[ \frac{1}{2} - 2 + \ln 2 \right]$$  \hspace{1cm} (21)

so

$$T \approx \mu [3 - 2 \ln 2]$$  \hspace{1cm} (22)

We see then that $T = O(\mu)$, so as an approximation the period increases linearly with the damping coefficient $\mu$.

To do this analysis of the motion down the $y$-nullcline we analyzed the slow subsystem (the $y$ ODE) while treating the fast subsystem as if it were at equilibrium ($\dot{x} = 0$ so $y = F(x)$). This is called a quasi-equilibrium approximation. Suppose now that we wish to determine how long it takes for the phase point to move from the top knee to the right branch of the $y$-nullcline. Thus, now we wish to analyze the dynamics of the fast subsystem. What do we do with the slow variable $y$? Treat it as a constant. What is the value of this constant? The value of $y$ at the top knee, i.e., $y = \frac{2}{3}$. The equation for the fast subsystem is then

$$\frac{dx}{dt} = \mu [\frac{2}{3} - F(x)]$$
so that
\[ dt = \frac{1}{\mu\left[\frac{2}{3} - \frac{1}{3}x^3 + x\right]} \, dx \]
and the time required for the jump is then
\[ T_{\text{jump}} = \int_{-1}^{2} \frac{1}{\mu\left[\frac{2}{3} - \frac{1}{3}x^3 + x\right]} \, dx \]
\[ = \frac{1}{\mu} \int_{-1}^{2} \frac{1}{\left[\frac{2}{3} - \frac{1}{3}x^3 + x\right]} \, dx \]
and from this we see that \( T_{\text{jump}} = O(\mu^{-1}) \), which is small when \( \mu \) is large.
**Bursting** consists of periodic clustering of electrical impulses. It occurs in many nerve and endocrine cells. These include:

- thalamic neurons
- hypothalamic neurons
- cortical neurons
- spinal cord
- neurons of the pre-Bötzing complex in brain stem
- pituitary cells
- pancreatic β-cells

The burst period ranges from tens of milliseconds (many neurons), to a few seconds (pituitary cells), to several minutes (β-cells). The example in Fig. 4 shows bursting in a neuron from the hypothalamus, obtained using the whole cell patch technique in a labeled gonadotropin-releasing hormone neuron in a brain slice.
Figure 3: Regions of the human brain.
Why bursting?

There are several possible physiological roles of bursting. These include:

- Bursting avoids desensitization of receptors
- Bursting can amplify neurotransmitter secretion
- Bursting encodes two time scales, while periodic spiking encodes only one
- Bursting is more robust than a single spike; better for use in central pattern generators

Other roles are likely to be revealed over time.
We will look at several mathematical models that produce bursting oscillations, and see how the oscillation can be analyzed using a geometric singular perturbation analysis. We’ll also see that bursting is closely related to a relaxation oscillation.

**Modified Morris-Lecar Model**

We modify the Morris-Lecar model by adding a current that responds to the calcium concentration in the cell. This current is $Ca^{2+}$-activated $K^+$ current, $I_{K(Ca)}$. There are several possible formulations, but we use:

$$I_{K(Ca)} = \bar{g}_{K(Ca)} \left( \frac{Ca_c^3}{Ca_c^3 + K_D^3} \right) (V - V_K)$$  \hspace{1cm} (23)

where a Hill function with exponent 3 is used to describe the $Ca^{2+}$ activation.

With this current, the Morris-Lecar model becomes:

$$\frac{dV}{dt} = -[I_{Ca} + I_K + I_L + I_{K(Ca)}]/C$$  \hspace{1cm} (24)

$$\frac{dw}{dt} = \lambda [w_\infty(V) - w]/\tau(V) .$$  \hspace{1cm} (25)

For now we will treat $Ca_c$ as a constant parameter.

The parameter $\lambda$ is introduced so that we can easily change the speed of the recovery variable $w$. By making $\lambda$ small we make $w$ slow compared to $V$. Set $\lambda = 0.01$, then we get a relaxation oscillation, with the phase point moving along the outer branches of the $V$-nullcline, except for jumps.
If we now increase $\lambda$ 100-fold to $\lambda = 1$, then both variables change at comparable speeds. Phase portraits at five values of calcium concentration $Ca_c$ are shown below. Increasing $Ca_c$ translates the $V$-nullcline leftward.
Figure 6: Oscillation with $\lambda = 1$ and $Ca_c = 0.05 \, \mu M$.

Figure 7: Oscillation with $\lambda = 1$ and $Ca_c = 0.1 \, \mu M$. 
Figure 8: The system is bistable when $Ca_c = 0.15 \, \mu\text{M}$. Basins of attraction are separated by the two branches of the stable manifold.

Figure 9: At about $Ca_c = 0.165 \, \mu\text{M}$ one branch of the stable manifold connects with a branch of the unstable manifold, creating a **homoclinic orbit**.
Figure 10: At about $Ca_c = 0.2 \, \mu M$ there are three steady states, only one of which (the lowest one) is stable.

Figure 11: At about $Ca_c = 0.25 \, \mu M$ there is a single stable steady state, on the lower branch of the $V$-nullcline.
Figure 12: Bifurcation diagram with bifurcation parameter $Ca_c$. SN=saddle-node, HB=Hopf, HM=homoclinic.

This can all be summarized with a bifurcation diagram of the $V$-$w$ (fast) subsystem (Fig. 12).

Thus, we have a type 1 neural oscillator, where the periodic branch ends with an infinite-period homoclinic bifurcation.
Calcium Dynamics

We now bring in the Ca$_2^+$ dynamics. During an impulse, Ca$_2^+$ enters the cells through the Ca$_2^+$ channels. It is also pumped out of the cell by Ca$_2^+$ pumps.

\[ J_{in} = -\alpha I_{Ca} \]  
\[ J_{out} = k_{pmca} Ca_c \]

Then,

\[ \frac{dCa_c}{dt} = f_c(J_{in} - J_{out}) \]
\[ = -f_c(\alpha I_{Ca} + k_{pmca} Ca_c) \]

where $f_c$ is the fraction of Ca$_2^+$ that is free (i.e., not bound by Ca$_2^+$ buffers in the cytosol).

spiking $\Rightarrow |I_{Ca}|$ large $\Rightarrow$ Ca$_c$ increases
The dynamics of the full system can be understood by superimposing the Ca\(^{2+}\)nullcline (called the slow nullcline) onto the bifurcation diagram of the \(V-w\) fast subsystem, which is called the slow manifold or z-curve (Fig. 14). We now think of the bifurcation diagram as a generalized \(V\)-nullcline, so the two nullclines tell us about the flow of the system in the \(Ca_c-V\) plane.

Next we use the fact that \(Ca_c\) changes much more slowly than the other variables. So the phase point will follow the generalized \(V\)-nullcline. During the silent phase the trajectory follows the bottom branch of the z-curve (Fig. 15). When the left knee is reached, the trajectory jumps to the only remaining stable structure, which is the branch of spiking solutions.
(Fig. 16). The full burst trajectory, superimposed on the z-curve, is shown in Fig. 17.
Figure 16: Slow manifold with beginning of active phase trajectory superimposed.

Figure 17: Slow manifold (z-curve) superimposed with the $Ca_c$-nullcline and the bursting trajectory of the full system.
This geometric analysis where we treat one variable as a slowly-changing parameter of the fast subsystem is called fast/slow analysis or geometric singular perturbation analysis. Notice that from this analysis we can make some predictions about the bursting oscillations. What could we predict? (1) Spike frequency should decrease near the end of an active phase, (2) it should be possible to reset from one phase to the next via voltage perturbation, and the immediate following phase should be shorter than normal, and (3) $Ca_c$ should have a saw tooth time course.
Figure 18: Time courses of fast $V$ and slow $Ca_c$ during bursting.
How are bursting oscillations and relaxation oscillations related?

For each value of $Ca_c$ where a periodic (spiking) solution exists calculate the average $V$ over one period of the oscillation. Then

$$V_{avg} = \frac{1}{T_{ap}} \int_{t_{beg}}^{t_{end}} V(t) \, dt$$

where $T_{ap}$ is the period of an action potential, $t_{beg}$ is the time of the beginning of a spike and $t_{end}$ is the time of the end of a spike. This average voltage will be different for different values of $Ca_c$, and the collection of values over the entire periodic branch forms an average voltage curve (Fig. 19). This begins at the Hopf bifurcation and ends at the homoclinic bifurcation.

![Figure 19: Z-curve and Ca_c-nullcline along with the average voltage curve (dark blue).](image-url)
Now superimpose the burst trajectory, but rather than plotting $V$ plot the moving average of $V$, averaged over the duration of a single spike (Fig. 20). That is, plot

$$< V > (t) = \frac{1}{T_{ap}} \int_{t-T_{ap}}^{t} V(\tau) d\tau$$ (31)

Then we have a relaxation oscillation!

Figure 20: Z-curve and $Ca_c$-nullcline along with the average voltage curve (dark blue) and the moving average of the burst trajectory (red).
What happens if the Ca\textsuperscript{2+} nullcline is translated downward so that it intersects the bottom branch of the z-curve?

What happens if it intersects the average V curve?

These are extreme cases that limit the range of bursting. Intermediate cases, where the intersection is on the middle branch between the lower knee and the homoclinic, give variation in the burst period and plateau fraction.

\[
\text{plateau fraction} = \frac{\text{active duration}}{\text{burst period}}
\]

\[
\text{cell silent} \Rightarrow \text{plateau fraction} = 0
\]

\[
\text{cell continuously spiking} \Rightarrow \text{plateau fraction} = 1
\]

How does plateau fraction vary as the intersection on the middle branch is changed from near the knee to near the homoclinic?
Figure 21: Electrical recordings from a β-cell within a pancreatic islet. Different levels of glucose give different values of the plateau fraction. From Drews et al., 2009.
Calcium Handling in the Endoplasmic Reticulum

The **endoplasmic reticulum (ER)** is an organelle that processes proteins that are bound for the plasma membrane. It is also a storehouse for Ca\(^{2+}\). The illustration in Fig. 22 shows some important Ca\(^{2+}\) fluxes between compartments.

![Diagram of Ca\(^{2+}\) fluxes](image)

**Figure 22**: Ca\(^{2+}\) fluxes into and out of cytosol and ER.

With this new ER compartment the cytosolic Ca\(^{2+}\) equations must be modified, and a new ODE introduced.

\[
\frac{dCa_c}{dt} = f_c(J_{in} - J_{PMCA} - J_{SERCA} + J_{leak}) \quad (32)
\]

\[
\frac{dCa_{ER}}{dt} = f_{ER}\mu(J_{SERCA} - J_{leak}) \quad (33)
\]

where \(\mu = V_c/V_{ER}\) is the **volume ratio**.

The Ca\(^{2+}\) **leak** out of the ER is proportional to the concentration
gradient:

\[ J_{\text{leak}} = k_{\text{leak}}(C a_{ER} - C a_c) \]

and a reasonable model for flux through \textbf{SERCA pumps} (SERCA=Sarco-Endoplasmic Reticulum ATPase) is

\[ J_{\text{SERCA}} = k_{\text{SERCA}} C a_c. \]

The ER \( C a^{2+} \) concentration is much larger than that in the cytosol, so that changes in the concentration relative to the mean are much faster for \( C a_c \) than for \( C a_{ER} \). Changes in \( C a_{ER} \) typically have no direct influence on the cell’s membrane potential. However, they do affect the \( C a_c \) nullcline:

\[ C a_c = \frac{-\alpha I_{Ca} + k_{\text{leak}} C a_{ER}}{k_{PMCA} + k_{\text{SERCA}} + k_{\text{leak}}} \]  \hspace{1cm} (34)

The nullcline is now more vertical and it moves when \( C a_{ER} \) changes (Fig. 23).

![Figure 23: The \( C a_c \) nullcline changes with \( C a_{ER} \).](image)
Because the $Ca_c$-nullcline is now more vertical, it intersects the periodic and stable stationary branches of the z-curve, so that bursting does not occur if $Ca_{ER}$ is held constant (Fig. 24).

Suppose that the system starts out spiking (Fig. 25). This brings $Ca^{2+}$ into the cell through $Ca^{2+}$ channels, and some of the $Ca^{2+}$ is pumped from the cytosol to the ER, causing $Ca_{ER}$ to slowly increase. This translates the $Ca_c$ nullcline rightward, eventually moving it past the homoclinic bifurcation, so that spiking is terminated and the silent phase begins (Fig. 26).

The phase point now moves along the bottom branch of the z-curve toward the stable steady state. At the same time, but more slowly, $Ca_{ER}$ declines and shifts the nullcline (and steady state) leftward (Fig. 27).

Eventually the nullcline moves past the lower knee, terminating the
Figure 25: The system is assumed to start out spiking.

silent phase and restarting the active phase (Fig. 28).

The end result is bursting that is driven by both cytosolic Ca$^{2+}$ and the ER Ca$^{2+}$ dynamics. The extent of the contributions of $Ca_c$ and $Ca_{ER}$ dynamics to the burst period depends on how deeply the Ca$^{2+}$ nullcline intersects the periodic branch and the stationary branch. This can be adjusted by stretching or compressing the z-curve. How? One way is to vary the conductance of the K(Ca) current, which is the current acted upon by cytosolic Ca$^{2+}$. When $g_{K(Ca)}$ is increased, a given $Ca_c$ has a bigger hyperpolarizing effect on the cells. Stated another way, when $g_{K(Ca)}$ is larger, it takes less Ca$^{2+}$ to bring the cell to rest, so the stationary branch is longer and the entire z-curve is shifted leftward and compressed. Of course, the opposite is true when $g_{K(Ca)}$ is decreased, the z-curve is stretched (Fig. 29).
Figure 26: As $Ca_{ER}$ increases during the active phase the $Ca_c$ nullcline moves rightward, eventually terminating the active phase.

Figure 27: As $Ca_{ER}$ decreases during the silent phase the $Ca_c$ nullcline moves leftward, dragging the phase point with it.
Figure 28: Eventually the $Ca_c$ nullcline moves past the lower knee, ending the silent phase.

From this, we see that when $g_{K(Ca)}$ is large the nullcline intersects the $z$-curve between the lower SN and the HM, so standard bursting driven by changes in $Ca_c$ will occur (Fig. 30). The ER Ca$^{2+}$ concentration will only exhibit small oscillations about its mean in this case. This is the case of fast bursting, since it is independent of the slower variable $Ca_{ER}$. In fact, one could clamp $Ca_{ER}$ at its mean value and this bursting would continue unaltered.

When $g_{K(Ca)}$ is reduced sufficiently, the nullcline and either/both the periodic branch or stationary branch intersect. The phase point is stuck at this intersection until $Ca_{ER}$ changes enough to release it (Fig. 31). Now both $Ca_c$ and $Ca_{ER}$ contribute to the burst period. This give medium bursting. We see here that the $Ca_c$ time course has the appearance of the fast variable of a relaxation oscillator, while $Ca_{ER}$ has the sawtooth
Figure 29: The $z$-curve is compressed by increasing $g_{K(Ca)}$ (red), stretched by decreasing $g_{K(Ca)}$ (black).

appearance of the slow variable. In this case, if $Ca_{ER}$ is clamped then the bursting will stop, and be replaced by either continuous spiking or rest (the system may be bistable between the two).
Figure 30: During fast bursting ($g_{K(Ca)} = 500$ pS) the oscillation is driven entirely by $Ca_c$.

When the $Ca_c$ nullcline intersects deep in the periodic and stationary branches the ER Ca$^{2+}$ concentration must change a great deal to pull the system from one phase to the other. This is the case when $g_{K(Ca)}$ is small (Fig. 32). Since $Ca_{ER}$ changes slowly, this results in slow bursting. Again, we see that the $Ca_c$ time course has the shape of the fast variable in a relaxation oscillator, while the $Ca_{ER}$ time course has the shape of a slow variable.
Figure 31: When $Ca_c$ and $Ca_{ER}$ dynamics both contribute, medium bursting is produced ($g_{K(Ca)} = 200$ pS).

**Bottom line:** The addition of the ER $Ca^{2+}$ store/sink greatly increases the range of burst periods that can be produced.

This phenomenon, where a wide range of burst periods is produced through the actions of more than one slow variable with disparate time scales, is called **phantom bursting**. This could explain data from pancreatic $\beta$-cells (Fig. 33), showing that bursting can occur with a wide range
Figure 32: When the nullcline intersects deep into the periodic and stationary branches slow bursting results ($g_{K(Ca)} = 50$ pS).

of periods. This range is much greater than could be achieved through the actions of a single slow variable (*why?*).
Figure 33: Experimental recordings of pancreatic \( \beta \)-cell electrical activity. (A) Fast bursting, (B) medium bursting, (C) slow bursting in a cluster of \( \beta \)-cells. The time bar is 20 sec in all traces.

References
