

## Central Pattern Generators. (Based on Book of GENESIS Chapter 8)

**17-1.** What are CPGs? CPGs are neuronal circuits that are able to produce patterned motor output related to natural behaviors (such as locomotion, breathing, chewing, etc) in the absence of patterned sensory inputs.

No external control is necessary to get the sequences of rhythmic activity or oscillations  
The same circuit can produce multiple rhythmic patterns  
Sensory input or feedback or descending control from higher centers can shift or reset the phase of the rhythm and so switch behaviors/

In a very simplistic view, there are two types of oscillators:

- 1) Oscillations that depend on intrinsic pacemaker cells, e.g. the heart Purkinje cell, Aplysia bursters, where the rhythms depend on membrane properties (the ionic channels). The rhythms continue when the cell is isolated.
- 2) Oscillations can be the product of the network. We say there are network oscillators where the rhythm depends on the connectivity of the cells in the network. Examples are the tritonia escape swimming rhythm or the stomatogastric system in the lobster.

The history of our knowledge of CPGs dates back to the early 1900s when Graham Brown found that cats with a spinal cord transection could walk on a treadmill even after dorsal roots were severed. So there was no sensory feedback and no descending input and yet the cats could walk on the treadmill. Brown proposed that movement was not just a set of reflexes adjusted by sensory input, but that there was a central pattern generator. He proposed the simple oscillator illustrated here at the bottom of the overhead.

This simple oscillator was composed of 2 mutually inhibitory half-centers, both receiving tonic excitatory drive, and with reciprocal inhibition. It was this mutual inhibition that causes the activity to oscillate between the half-centers. To get oscillation, the inhibition decays in time and allows the other center to fire.

In the spinal cord there are interneuron networks to coordinate the timing and sequence of activation and inhibition between motoneuron pools innervating different muscles. In particular, if we are to walk, there has to be alternating activation of flexor and extensor muscles and interneurons inhibit the flexors when the extensors are active and vice-versa.

**17-2.** There are some complications to the simplistic dichotomy I proposed earlier between pacemaker and network oscillations.

First, time delays in simple models require non-linear membrane properties. There are particular voltage-gated channels that play prominent roles in oscillations and we will mention them briefly later.

Second, the connectivity tends to be more complex than reciprocal inhibition.

Third, some neurons in “network oscillators” have non-linear properties and may switch between pacemaker mode to inactive mode or bursting mode.

Fourth, synaptic connections may change strength (or sign) depending on time and voltages.

Consequently, knowing the complete connectivity of so called “simple” systems is not sufficient to understand the behavior. Therefore, we need simulations with realistic synaptic interactions and membrane properties. Geometry will also affect timing and location of inputs.

The relationship between emergent collective behavior or a description of the presence of patterns that can be obtained and the circuitry is not easily determined, even for “simple” invertebrate preparations, i.e., the STG system---there is no precise explanation for the mechanisms that control frequency, duration and phase relationships of the motor pattern.

**17-3.** Rather than discuss simulations of CPGs with NEURON, I want to describe how we might gain insight into CPGs from simple mathematical theory.

Clearly, the oscillatory behavior is the result of the interaction of many physical parameters. To gain a theoretical understanding of what is happening, we make some assumptions.

If we model all of the parameters involved, we would have a system of ODEs, but because of the cyclic nature of the behavior, the solution should be a limit cycle of some sort in parameter space that is asymptotically stable. Over time the solution should revisit the same set of points.

So let's assume that the cycle is in some sense equivalent to a circle, with each point on the circle described by a phase angle  $\theta$  (position of the oscillator around its limit cycle). We rescale  $\theta$  so that it flows uniformly around the limit cycle from 0 to  $2\pi$  over one cycle. If we think of the circle as a clock, maybe 3:00 is our starting point and bursting starts at 6:00 and ends at 9:00, for example..

Now assume that in time  $T_0$  you return to the starting point  $0 \leq \theta \leq 2\pi$ . So  $\theta$  is proportional to the fraction of the period that elapses. We also assume that a point on the circle moves with constant angular velocity  $w_0 = 2\pi/T_0$ . (so  $T_0 = 2\pi/w_0$  is the time it takes to go around).

Then we can write  $\theta'(t) = w_0$  or the change in  $\theta$  with a change in time is the velocity.

Then the behavior of the oscillator is represented solely by its phase defined as position along the circle.

**17-4.** So we have reduced the physical variables that define the oscillators to one equation, in terms of phase,  $\theta' = w_0$

This is easily solved, right? Integral of a constant is constant \*t, so

$$\theta(t) = w_0 t + \theta(0) \pmod{2\pi}$$

where  $\theta(0)$  is the initial position and  $\theta$  is defined to always fall in  $[0, 2\pi]$

When 2 oscillators are coupled, then

$$\theta_1'(t) = \omega_1 + h_{12}(\theta_1, \theta_2) \quad \text{and} \quad \theta_2'(t) = \omega_2 + h_{21}(\theta_2, \theta_1)$$

where  $h_{ij}(\theta_i, \theta_j)$  represents the coupling term which depends only on the oscillator phases (effect of  $j^{\text{th}}$  oscillator on the  $i^{\text{th}}$  oscillator).  $H$  must be periodic so the change depends on phase and not on the number of cycles.

Let  $\phi(t) = \theta_1(t) - \theta_2(t)$  or the phase lag or 2 relative to 1

Then, if we take the derivative of both sides and substitute the above expressions for  $\theta_1'$  and  $\theta_2'$  we have

$$\phi'(t) = \theta_1'(t) - \theta_2'(t) = (\omega_1 - \omega_2) + (h_{12}(\theta_1, \theta_2) - h_{21}(\theta_2, \theta_1))$$

which describes the change of phase lag in time.

**17-5.** So with this equation  $\phi'(t) = (\omega_1 - \omega_2) + (h_{12}(\theta_1, \theta_2) - h_{21}(\theta_2, \theta_1))$  the interaction depends on the difference in phases.

Suppose the interactions depend only on the difference between phases, in particular suppose coupling depends only on the phase lag and suppose  $h_{ij}(\theta_i, \theta_j) = 0$  when  $\theta_i = \theta_j$ . (or no coupling when there is no difference in phase lag. This particular case is called diffusive coupling).

What function has these properties? How about  $h_{ij} = a_{ij} \sin(\theta_j - \theta_i)$ ? Here  $a_{ij}$  is the coupling strength and the sin term depends on the difference in phases (the phase lag).  $\sin(0) = 0$  so the additional property is satisfied. Then the above equation becomes

$$\begin{aligned} \phi'(t) &= (\omega_1 - \omega_2) + (a_{12} \sin(-\phi) - a_{21} \sin(\phi)) \quad \text{and using } \sin(-\phi) = -\sin(\phi) \text{ we have} \\ \phi'(t) &= (\omega_1 - \omega_2) - (a_{12} + a_{21}) \sin(\phi) \end{aligned}$$

This latter equation can be solved exactly.

However, let's look at a special case where phase lag is constant (1:1 phase locking) and then solve for the phase lag between the 2 oscillators.

Phase lag constant means that  $\phi(t) = c$  which means that  $\phi'(t) = 0$ . From the previous equation we get  $\phi'(t) = 0 = (\omega_1 - \omega_2) - (a_{12} + a_{21}) \sin(\phi)$

Or  $\sin(\phi) = (\omega_1 - \omega_2)/(a_{12} + a_{21})$  or the phase lag is  $\phi = \arcsin((\omega_1 - \omega_2)/(a_{12} + a_{21}))$ .

**17-6,** This equation has 0, 1, or 2 solutions depending on the value of the argument  $(\omega_1 - \omega_2)/(a_{12} + a_{21})$  which is the frequency difference divided by the net coupling strength.

Suppose the difference in the frequency of the oscillators is fixed,  $\omega_1 - \omega_2$  is fixed.

If  $\left| \frac{w_1 - w_2}{a_{12} + a_{21}} \right| > 1$  then there is no solution.  $-1 \leq \sin(x) \leq 1$  so if the absolute value of the

argument is greater than 1, there is no phase lag that will satisfy the equation.

When can this occur? This can occur if the coupling strength  $a_{12} + a_{21}$  is weak compared to the difference in frequencies. What happens? The oscillators tend to oscillate at their natural frequencies and they drift with respect to each other. Oscillator drift.

If  $\left| \frac{w_1 - w_2}{a_{12} + a_{21}} \right| \leq 1$  then there is one solution. If the coupling is positive or excitatory, the faster

oscillator leads by some phase locked value between 0 and 90 degrees. If the coupling is negative or inhibitory, the slower one leads by 90-180 degrees. If the argument =1 then the faster one leads by 90 degrees and if the argument is -1, the slower one leads by 90 degrees. This is a case of moderate to strong coupling.

It might seem that there should be other solutions and there are.

Solutions are  $\arcsin(\arg)$  and  $\pi - \arcsin(\arg)$  where  $\arg$  is the  $(w_1 - w_2)/(a_{12} + a_{21})$ , but it turns out that one is stable and the other is unstable. (This is problem 19 in Chap. 10 of Izhikevich's book. Chap 10 is on the web site [www.izhikevich.com](http://www.izhikevich.com) because the publisher wouldn't lengthen his book any more).

If  $\left| \frac{w_1 - w_2}{a_{12} + a_{21}} \right| = 0$  then 2 solutions are possible. The oscillators are phase-locked either in phase

or out of phase. (When does  $\sin(x) = 0$ ? When  $x=0$  or 180 degrees). Here either  $w_1 = w_2$  or the coupling is very strong.

**17-7. Example.** The Book of GENESIS mentions the Tritonia escape swimming rhythm and has characteristics of this CPG in the CPG tutorial. In this simulation

The frequency is fixed by current input

Low coupling leads to oscillator drift

Higher coupling leads to phase locked behavior

Excitatory coupling and the faster leads the slower oscillator by 0 to 90 degrees and the

Frequency of the oscillation is faster than the slower cell oscillation

Inhibitory coupling and the slower leads by 90 to 10 degrees and the

Frequency of oscillation is smaller than the faster cell.

If initial conditions were  $w_1 = w_2$  then phase locking occurs ( $\phi=0$  or  $\phi=\pi$ ), either in phase or 180 degrees out of phase.

Notes: Noise in biological systems as well as inherent differences, prevents oscillators from having identical frequencies, so we do not usually see 0 or 180 degree phase locking.

Also diffusive coupling as we have described, may model electrical coupling but isn't really appropriate for synaptic coupling. Synaptic interactions don't depend exclusively on differences in phases (in particular  $\phi=0$  does not mean there is no interaction or influence on each other)

**17-8.** This problem led Ermentrout and Kopell (1990) to develop theory for synaptic coupling.

With synaptic coupling, the coupling does not depend exclusively on the difference in phases, i.e., two neurons with identical behavior CAN influence each other,  $h_{ij}(\theta_i, \theta_j) \neq 0$  for  $\theta_i = \theta_j$  Necessarily.

Suppose we assume identical oscillators

$$\theta_1'(t) = w_1 + p(\theta_2) r(\theta_1) \quad \text{and} \quad \theta_2'(t) = w_2 + p(\theta_1) r(\theta_2)$$

where  $p$  is a periodic smooth pulse function and  $r$  is a phase response function (describes the phase shift that occurs experimentally for a stimulus given at a particular phase—PRC, phase response curve) The stimulus causes a shift in the phase.

Suppose the shift occurs quickly relative to the time between stimuli. If  $\theta^k$  is the phase just before the  $k$ th stimulus, we can say that

$$\theta^{k+1} = w\tau + \theta^k + r(\theta^k)$$

which says that the phase just before stimulus  $k+1$  equals the phase at stimulus  $k$  plus how far along the circle we go in time  $\tau$  between stimuli ( $w\tau$ ) plus the phase shift as a function of the present phase.

**17-9.** We can convert this difference equation into a differential equation by putting the  $\theta$  terms on the left, dividing through by  $\tau$  and letting  $\tau$  go to 0. That is,

$$(\theta^{k+1} - \theta^k)/\tau = w + r(\theta^k)/\tau \quad \text{leading to}$$

$$\theta' = w + \text{pulse function } r(\theta)$$

where the pulse function is the delta function  $\delta(t \pmod{\tau})$  where the pulses are at intervals  $\tau$  apart. Have you heard of the  $\delta$ -function? It is a special function whose value is zero for all  $x$  except  $x=0$ . That is  $\delta(x)=0$  for  $x \neq 0$  and at  $x=0$  it is infinite. However the integral  $\int \delta(r) dr = 1$  and  $\int f(r) \delta(r) dr = f(0)$ .

Since real stimuli are not instantaneous, we can replace this pulse function with a smooth function  $p(\theta)$ , so that

$$\theta' = w_1 + p(\theta_2)r(\theta_1) \quad \text{which is called synaptic coupling}$$

Behavior with this type of coupling is more similar to that in the biological examples, such as the CPG example in the Book of GENESIS.

As coupling increases, the system goes from phase drift (weak coupling) to phase locking (moderate coupling) to oscillator death (very strong coupling). Oscillator death is a stable

critical point where no oscillation occurs and you can't get back to having oscillations. The oscillator remains at a constant state and no perturbation will change this.

While this is more realistic than the previous examples we have been considering, the fact remains that biophysical models can have more complex ranges of behaviors.

**17-10.** Systems generally have more than two oscillators. In the lamprey (an eel) swimming is governed by a chain of oscillators with nearest neighbor coupling. Much work on the lamprey was done by Grillner and colleagues in the early 1990s. In their models they actually have paired chains, one on each side of the animal, but here we will consider just a single chain of oscillators.

The phase lag between segments is proportional to the distance between points and this allows for a constant speed traveling wave of contraction down the spinal cord.

Let's consider a chain of oscillators theoretically, having nearest neighbor coupling (no long range coupling). Suppose we consider:

$$\begin{aligned}\dot{\theta}_1(t) &= w_1 + h_{12}(\theta_1, \theta_2) \\ \dot{\theta}_2(t) &= w_2 + h_{23}(\theta_2, \theta_3) + h_{21}(\theta_2, \theta_1) \\ \dot{\theta}_3(t) &= w_3 + h_{34}(\theta_3, \theta_4) + h_{32}(\theta_3, \theta_2) \\ \dot{\theta}_4(t) &= w_4 + h_{43}(\theta_4, \theta_3)\end{aligned}$$

Now assume diffusive coupling as we did earlier  $h_{ij} = a_{ij} \sin(\theta_j - \theta_i)$

Let the coupling strengths be equal,  $a_{ij} = a$  (for ease of analysis)

Let  $\phi_i(t) = \theta_i(t) - \theta_{i+1}(t)$  be the phase lags.

Take the derivative as before

$\dot{\phi}_i(t) = \dot{\theta}_i(t) - \dot{\theta}_{i+1}(t)$  and substitute in the above expressions for the derivatives.

Then we have a system of 3 equations in  $\phi$  (the phase lag)

Now solve assuming 1:1 phase locked motion, i.e.  $\phi = \text{constant}$ , so  $\dot{\phi} = 0$ , so

$$\dot{\phi}_1 = 0 \quad \dot{\phi}_2 = 0 \quad \dot{\phi}_3 = 0$$

**17-11.** To solve, let's assume that there is a gradient of frequencies along the chain, where  $c = w_1 - w_2 = w_2 - w_3 = w_3 - w_4$  (for example in the CPG simulation  $w_1 = 30$ ,  $w_2 = 25$ , etc.

I won't go through the mathematics here but if you were to do so, you would find that the

equations lead to the condition that  $\left| \frac{c}{a} \right| \leq \frac{1}{2}$  is a necessary and sufficient condition for 1:1 phase

locking. Recall before we had  $|(w_1 - w_2)/(a_{12} + a_{21})| < 1$ . Well here  $c = w_1 - w_2$  and  $a_{12} + a_{21} = 2a$ , so you can see the similarities, but not exactly the same since the factor of 2 doesn't quite go where you might think.

The motion is 1:1 phase-locked at the average frequency of the uncoupled oscillators. If the intrinsic frequencies are identical, then the oscillators behave synchronously with no phase difference, except for the oscillators at the ends of the chain—the ends have only one neighbor.

Note: We could use synaptic coupling and get constant-speed traveling wave of contractions without the presence of a gradient of oscillation frequencies. This was shown by Ermentrout and Kopell

I will remark on the next overhead that these phase models lack some of the variety and complexity seen in nature. In nature the CPG cells have a rich biophysical repertoire that may include :

$I_{\text{Nap}}$  which contributes to slow bursting and plateau potentials

$I_{\text{Ca}}$  which contributes to burst initiation

$I_{\text{A}}$  which slows depolarization and produces delays

$I_{\text{h}}$  which limits the time spent hyperpolarized and may contribute to post inhibitory rebound

$I_{\text{KCa}}$  which terminates bursts through the medium afterpotentials mAHPs

**17-12.** The promised remarks.

The simple phase models are useful in that analytic solutions can be obtained. Relationships can be obtained to express phase locking in terms of frequencies of oscillations ( $\omega$ ) and couplings ( $a$ ).

However these phase models lack the complexity to explain the varieties of behaviors observed.

One example of CPGs is gaits, in this case of horses. Horses can have a walking gait, a trotting gait, as well as pacing and galloping. These different gaits are carried out by the same CPG system, but are very different.

For example for the walking gait, the sequence of foot steps is LH  $\rightarrow$  LF  $\rightarrow$  RH  $\rightarrow$  RF (where H is hind leg, F is front leg and R and L are Right and Left). To get this gait in the CPG simulation requires excitatory coupling between the legs on the same side and inhibitory coupling between legs on opposite sides.

For trotting we have LH and RF  $\rightarrow$  LF and RH. To get this pattern we reverse the couplings in the walking gait. There is inhibitory coupling between the legs on the same side and excitatory coupling for legs on opposite sides.

Pacing is LH and LF  $\rightarrow$  RH and RF. Galloping is LF and RF  $\rightarrow$  LH and RH. These require additional changes to the connectivity.