Lecture 7: Complex Oscillators & Modulation

I. Endogenous properties of neurons

A. The endogenous properties of individual neurons is often an important determinant of circuit behavior

1. Fig. 1 (Fig. 2 of Nusbaum & Beenhakker) shows the endogenous properties of neurons found in pattern generating neurons

a) Endogenous burster

b) Plateau potentials outlast the initiating stimulus

c) Escape from inhibition

d) Post-inhibitory rebound

e) Delayed post-inhibitory rebound

II. A simple half-center oscillator – the heartbeat control system of the leech

A. Leeches have two laterally positioned hearts (Figs 2 & 3)

B. The heart muscle in innervated by heart excitatory (HE) motor neurons

1. HE cells are found in most segments of the animal

C. The HE cells are driven by heart interneurons (HN) (Fig. 4)

1. HN cells are only found in segments 1 through 7 (leeches have 21 body segments)

2. The HN cells in segments 3 & 4 drive the rhythm

a) The HN cells in segments 3 & 4 have reciprocally inhibitory synapses

b) The HN cells in one segment fire in anti-phase to the other

D. Voltage clamp studies have identified 8 different currents present in the HN cells (each is important for the function of the oscillator)

1. Two sodium, 2 calcium, 3 potassium, hyperpolarization-activated Na^+/K^+ (I_h)

E. By knowing the properties of these current (kinetics, thresholds, etc.), Ron Calabrese's lab was able to construct a mathematical model of the oscillator (Fig. 5)

1. The first iteration of the model didn't behave quite right (the transitions between the off state & on state weren't quite right

2. They then used the model to find out the characteristics that a current would need to make the model behavior more like the real oscillator

a) They found that a slowly activating depolarizing current could do that

b) They hypothesized that this might be a unusual sodium current (quite different than the one that underlies the upswing of the spike)

c) They went back to the real cells & found a sodium current with the predicted properties

III. Half-center oscillators can only produce activity in two phases (on & off)

A. To produce multiphasic activity, a more complex oscillator is needed

IV. The leech swimming oscillator

A. Leeches swim via dorsal-ventral undulations (Fig. 6)

B. The oscillator circuit is more complex that for the leech heart beat

1. There are numerous reciprocally inhibitory connections

a) There are also some inhibitory connections that aren't reciprocal

2. Numerous electrical synapses, including rectifying synapses (pass depolarization in only one direction)

3. One cell has extensive excitatory connections

C. The circuit becomes even more complex when you consider that the individual segmental oscillators have to be coupled to other segmental oscillators to produce coordination among the segments of the animal (Fig. 8)

D. Oscillator neurons fire in one of three distinct phases

1. Exactly how this oscillator functions isn't completely known

2. Otto Friesen & collaborators have produced mathematical models at a systems level that reproduce many of the actions of the system

a) Systems level means that many individual neurons are synapses are grouped together based on similarity

V. Cool way to record neural activity: voltage-sensitive dyes

A. A disadvantage of using microelectrodes to record neural activity is that you have to stick an electrode in each and every cell you're interested in

1. Each additional electrode added to an experiment increases the difficulty of conducting that experiment (it seems to be an exponential increase)

B. Optical recording (by Bill Kristan's lab at UCSD) using voltage-sensitive dyes can allow simultaneous monitoring of many cells (Fig. 9)

1. Up to 100 cells have been monitored simultaneously during swimming

VI. Modulation of the swim network

A. Serotonin acts as a neuromodulator that makes swimming much more likely

1. Hungry leeches have more serotonin in their blood than sated leeches

a) If you're hungry, you gotta swim to where the food is

B. Stimulation of the swim gating neuron cell 204 is ineffective in inducing swimming in the absence of serotonin (Fig. 10)

1. In the presence of serotonin, the same stimulation of cell 204 induces swimming (& even seems to induce a trigger cell ability to cell 204)

C. Serotonin induces changes in synaptic function that should make oscillatory activity easier to achieve (Fig. 11)

1. In presynaptic cell, serotonin induces presynaptic relaxation and postsynaptic fatigue

VII. Changes in oscillator output induced by different neuromodulators: the crustacean stomatogastric system

A. The stomatogastric nervous system in crustacea regulates movements of the stomach

1. The stomatogastric nervous system produces several rhythms that control different parts of the stomach

2. The gastric mill chews the food

B. The stomatogastric system is composed of 11 neurons distributed among 4 ganglia that lie on top of the stomach (Fig. 11)

C. Ten of the 11 neurons are also motor neurons & one is an interneuron (Figs. 11 & 12)

1. There are also descending inputs from the brain onto some of the neurons

a) These descending inputs modify output of the circuit

D. One way to determine which neurons are the important neurons in the oscillator is to perturb their activity

1. Driving cells Int 1 or LG using a sin wave input make the rest of the circuit oscillate relatively normally (Fig. 13)

a) Driving cell DG failed to get the circuit to oscillate

b) Therefore, Cells Int 1 & LG are more central to the oscillatory mechanism

E. A more sophisticated way to drive cells is the "dynamic clamp"

1. Dynamic clamp using voltage clamp technology, but changes the voltage to simulate currents that may be present in the cell

a) In this way you can determine the exact voltage waveform produced by the neuron

b) This allows you to dissect out the important aspects of the voltage waveform in generating the oscillation

VIII. Modeling of the stomatogastric oscillator

A. Selverston et al. constructed a mathematical model of the oscillator (Fig. 14)

B. The model behaves in a similar manner to the biological oscillatory

1. However, modeling of the individual neurons is crude – which probably leads to inaccuracies in how the model behaves

2. Many initial mathematical models are fragile – if you perturb the wrong variable in a minor way the oscillatory may stop functioning

3. **One characteristic of biological oscillators is that they are robust – they tolerate perturbations & still continue oscillating**

IX. Modulation of the stomatogastric system

A. Many of the modulatory influences are mediated by neurons that originate in the brain or subesophageal ganglion

B. Different modulators dramatically alter the behavior of the circuit (which would lead to different movements of the stomach) (Fig. 15)

C. The actions of the modulators is both convergent and divergent

1. **Convergent – several modulators may act upon the same ionic current**

    a) ***This would alter the behavior of affected cells in similar ways***

2. **Divergent – a single modulator will affect different currents in different cells**

    a) ***This allows complex orchestration of diverse types of behavior in different cells***