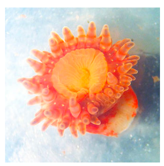
Information Processing in Invertebrates: Jellyfish, Worms, Leeches, and Flies

Even the most basal multicellular nervous systems are capable of producing complex behavioral acts that involve the integration and combination of simple responses, and decision-making when presented with conflicting stimuli. (Saterlie, 2015)

Coping with Competing Stimuli



- To escape or to eat?
  - *Stophia* is a sea anomie that normally is attached to rock but can "swim" when attacked
  - But it doesn't swim if it is enjoying a meal!
- As soon as an organism has a choice of behaviors, it must make choices
  - Choosing differently between competing alternatives on different occasions rules out that these responses are simply reflexes
  - Rather, the organism expresses a preference through a decision process

Division of Labor in Multicellular Organisms

- In a single-cell organism, each cell has to perform all of the activities needed for life
  - Take in nutrients
  - Digest and distribute them
  - Synthesize new tissue out of them
  - Get rid of waste products
  - Coordinate all of these processes
- Multi-cellular organisms allow for different cell types to specialize in doing different tasks
  - Example: contractility in muscle cells
    - take advantage of the more ancient actin-myosin molecular mechanism
  - But this requires a way to coordinate individual muscle cells

Evolving Neurons

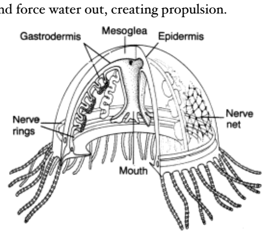
- Electrical transmission along cell bodies and the establishment of modes of transmission between cells is found in both bacteria and plants
- What is special about neurons are the extended processes—axons and dendrites—which allow for long distance transmission of electrical potentials within a single cell
- Among other things, they can distribute signals so as to enable muscle cells to contract in a coordinated fashion (together, in a wave, in sequence, etc.)

General Principles

- Neurons are not just electrical components (e.g., transistors)
  - Electrical components operate the same whenever called upon
  - The electrical behavior of neurons is heavily modulated by chemical processes
- Neuroanatomy provides valuable information for understanding the wiring of the system
  - But it is far from sufficient for determining how the system will behave

The Jellyfish Nerve Network

- The bell of jellyfish is characterized by two layers of myoepithelia cells (epidermis and gastrodermis) that act like muscles
  - By contracting, they squeeze the bell and force water out, creating propulsion.
  - In many species, the myoepithelia cells are connected by gap junctions, which enables direct cell-to-cell communication
    - This is relatively slow
  - An additional form of communication provided by a network of neurons existing between the layers
    - communicate bidirectionally—whenever processes cross, one releases peptides that gate ion channels in the other



Clicker Question

What do Keizer et al. mean by a skin-brain?

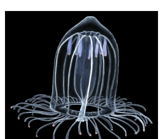
- Skin cells carry out the tasks of processing information
- Neurons probably evolved from skin cells
- Skin cells probably evolved from neurons
- The earliest function of neurons was to coordinate contractions of protomuscle skin cells

The Skin-Brain of Jellyfish

- Within the nerve net, some neurons act as sensors, others as effectors, coordinating behavior
  - In some species (e.g., among cubomedusae or box jellfish), these form two distinguishable nerve nets
    - These neurons are identified by stains that react to different peptide transmitters (RFamide or tubulin)

- Rhopalia (proto-ganglia)—sites where sensory information is integrated to regulate motor nerve network
  - also integrate signals from their own sensory ocelli
  - serve as pacemakers to generate rhythmic contractions of the bell
- Ring neurons—coordinate between rhopalia

Aglantha digitale



- Giant neurons forming two rings around the base of the bell as well as running up the bell
- Inner ring of neurons functions as a pacemaker: generating spikes every 2 seconds, it causes muscular contractions to occur on the same interval
- Outer ring of neurons responds to stimulation of the tentacles, resulting in a much higher frequency activity in the inner nerve ring that leads to fast swimming (an escape response)
- Many other signals (14 conducting systems have been detected) impinge on the ring neurons, resulting in diversity of behaviors
  - Four inhibit swimming, including inhibiting swimming briefly while eating (preventing dislodging of food)

Lessons from the Jellyfish

- A basic function of neurons is to coordinate the activity of muscles
  - By generating rhythms
  - Maintained in central pattern generators in later evolved species
- A variety of other signals, derived from sensors, impinge of the nerve net, halting or altering its operation
  - These various inputs enable regulation appropriate for various conditions
    - without there being a central executive directing overall activity

Clicker Question

How important, according to Bargmann, is knowing how neurons are connected for understanding how a circuit of neurons will behave

- Just as with a wiring diagram, from knowing how neurons are connected one can infer the behavior of the circuit
- It is of almost no use. Connectivity tells us nothing about what will happen in the circuit
- It is useful but far from sufficient since activity in the circuit can be altered by neuromodulators
- Other

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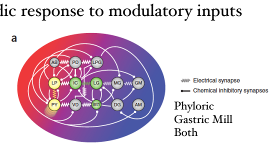
Stomatogastric Ganglion of the Crab

- Eve Marder and colleagues have spent decades analyzing the pattern generating circuit controlling stomach actions in the crab
- Connected networks generates two rhythmic patterns of stomach movements
  - Pyloric rhythm—continuously active triphasic motor patterns
  - Gastric mill rhythm—episodic response to modulatory inputs from sensory neurons
  - Two circuits are highly interactive—several neurons are involved in both

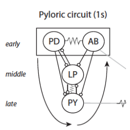


Different Types of Synapses

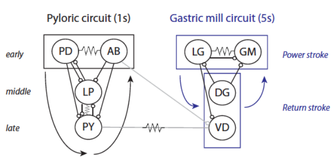
- Gap junctions (electrical synapses): direct cell to cell contact (as Golgi assumed)
- Chemical synapses: neurotransmitters are synthesized in axons and released at the terminals, which they
  - Either bind receptors in postsynaptic cells or being degraded and retaken up
- Neuromodulators: biogenic amines (serotonin, dopamine, etc.) or neuropeptides (>100 in *C. elegans*)
  - diffuse widely, even in the circulatory system
  - released by other cells and not just at synapses
  - alter neuron function
  - modulate the motivational and emotional state, arousal and sleep, pain sensitivity, etc., of the organism

Pyloric Circuit

- Simple pyloric circuit producing three-phases of response:
  - AB is a pacemaker with rhythm of 1 sec
  - Electrical synapse of AB to PD neurons drive one muscle group
  - AB and PD together release inhibitory transmitters onto LP and PY neurons that drive other muscle groups
  - But dopamine switches LP to PY circuit from depolarizing to hyperpolarizing



Interactions of Pyloric and Gastric Mill Circuits



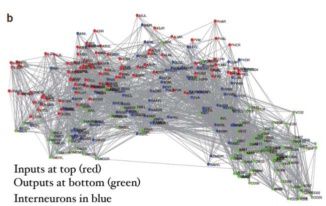
- Neurons can switch circuits depending on circumstances
  - Neuro-modulators can lead VD to join pyloric circuit
  - LG can exhibit pyloric rhythm if gastric mill circuit receives no input
  - VD and LG can reset the phase of both circuits

Lessons from the Crab Stomatogastric Network

- Even relatively simple circuits can generate complex (dynamic) behavior
- But unlike electrical circuits, these circuits function differently under different inputs
  - and can change behavior as a result of neuromodulators

C. elegans Connectome

- Using serial electron microscopy, in the mid 1980s White identified a nearly complete connectome for the worm *C. elegans*
  - 302 neurons
  - standardized wiring plan
  - differentiation of sensory, inter, and motor neurons

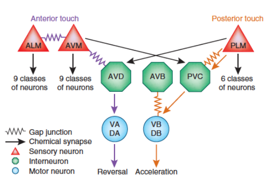


Inputs at top (red)
Outputs at bottom (green)
Interneurons in blue

Bargmann & Marder, 2013

Touch Avoidance Circuit

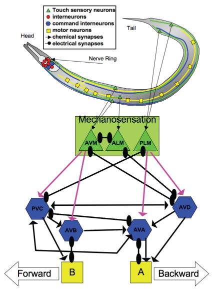
- Subcircuit controlling responses to touch
  - Anterior causes worm to back up
  - Posterior causes worm to move forward



Bargmann & Marder, 2013

Learning and Memory in Nematodes

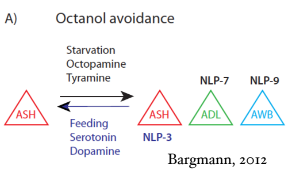
- Wicks and Rankin (1995) identified the circuits worms use in short and long-term habituation to taps to their dish
  - Rankin and her colleagues showed that spaced but not massed training generates long-term habituation
  - Mutations to *glr-1*, a gene expressed in a glutamate receptor in the interneurons of the tap-withdraw circuit, impairs long-term habituation
  - In long-term habituation the amount of GLR-1, but not the number of receptors, is reduced
  - Only spaced training resulted in reduction of GLR-1 expression, suggesting that the source of the spacing effect is in the synthesis of GLR-1



Rankin and Dubnau, 2007

Different Circuits for the Same Behavior

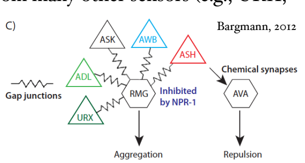
- In different circumstances, either one or three nociceptive sensory neurons elicit octanol avoidance (each producing a different neuropeptide).
  - Switch induced by either feeding/starvation or neural amines



Bargmann, 2012

Different Behaviors from Same Neuromodulator

- Both aggregation and retreat from noxious stimuli regulated by nociceptor ASH, but in different ways
  - Chemical synapse to AVA
  - Gap junction to the hub neuron RMG, which integrates signals from many other sensors (e.g., URX, an oxygen sensor)
    - if RMG is inhibited, aggregation is prevented



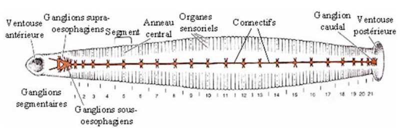
Bargmann, 2012

Lessons from *C. elegans*

- With just 302 neurons, *C. elegans* seemed to provide an easily tractable nervous system
    - Thirty years should have been plenty to figure out how the whole system works
- Part of the problem is that each neuron is connected to many others, creating what is known as a *small world*
- But a bigger problem is posed by the fact that the parts don't always do the same thing

Decision Making in Leeches

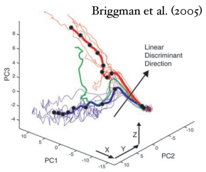
- The medicinal leech provides a useful invertebrate model for decision making
    - Its decisions whether to swim or crawl are made in the 21 segmental ganglia in the nerve cord, which can be exposed so as to record from the approximately 400 neurons in each ganglion
    - Overall behavior results for interactions between these ganglia



Decision Making in Leeches

- Briggman, Abarbanel, and Kristan (2005) used a stimulus equally likely to elicit swimming and crawling
- If there were command neurons engaged in competition, they should be found among the 17 neurons exhibiting activity predictive of a behavior before motor neurons begin to respond
    - But hyperpolarizing these neurons did not affect behavior
- Principal components analysis and linear discriminant analysis revealed a different population of neurons that collectively behaved in a way that corresponded to subsequent behavior
    - Manipulating the activity of these 17 neurons, the researchers found one that, 208, did reliably bias subsequent behavior
    - Briggman et al. interpreted this as reflecting attractor dynamics in a population, not competition between command neurons

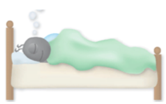
Briggman et al. (2005)



Discussion Question

What is the function of sleep?

- To enable encoding of long term memories
- To let us to avoid working both day and night
- To allow restoration of neurons
- To allow muscles to be repaired



Example: Studying Sleep in Fruit Flies

- Understanding sleep (both why it occurs and the mechanisms that generate it) remains a major challenge
  - Sleep, and deficiency in sleep, has important roles in cognitive performance
- In 2000 two groups of researchers
  - Joan Hendricks and colleagues at the University of Pennsylvania
  - Ralph Greenspan and colleagues at the Neurosciences Institute in La Jolla

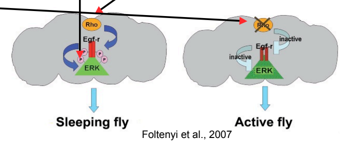
  demonstrated that fruit flies exhibit the behavioral criteria for sleep
  - they are immobile for several hours at night, during which they exhibit heightened thresholds to vibratory, visual, or auditory stimuli
  - prior to these episodes they move to locations away from food sources (sites of social activity)
  - when deprived of sleep, they exhibit rebound effects

Using Flies to Identify Part of the Sleep Mechanism

- Sleep is partly controlled by the circadian clock mechanism
- In mammals, one suspected output of the central circadian clock, transforming growth factor-α (TGF-α), is a known ligand of ErbB-1, a receptor suspected to be involved in sleep regulation
  - But the mammalian mechanism is complicated as there are four members of the ErbB family
  - Such redundancy makes it difficult to determine what operations the individual components perform
- Flies have only one receptor (EGFR)
  - Three of its four ligands are homologs of TGF-α
- Accordingly, flies provide investigators a much simpler version of the mechanism for sleep

Using Flies to Identify Part of the Sleep Mechanism

- Foltenyi et al. (2007) found that over-expression of Rho (a protease that cleaves membrane bound TGF-α ligands) in the pars intercerebralis (homolog of the hypothalamus) activates EGFR
  - Using heat shock to stimulate EGFR, they showed that Rho increased sleep episodes
  - They determined that the likely mechanism involves EGFR phosphorylating extracellular signal-regulated kinase (ERK) in the tritocerebrum
- Blocking Rho blocks generation of pERK and shortens sleep bouts (as in insomnia)
- This model provides a basis for investigating the more elaborated mechanism in us



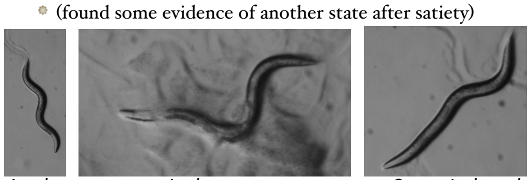
Foltenyi et al., 2007

Sleep: Its Spreading

- Since the research finding sleep in fruit flies in 2000, researchers have found it in a variety of organisms:
  - Octopus
  - *C. elegans*
  - Jellyfish

Sleep in Worms

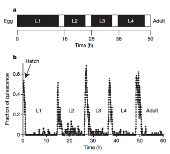
- Starting in 2008 David Raizer at Penn identified two sleep states in round worms (C. elegans):
  - lethargus: 2-3 hour bouts during each larval stage
  - stress-induced sleep in adult worms
  - (found some evidence of another state after satiety)



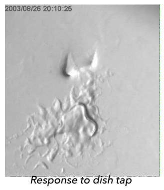
Awake *Lethargus* *Stress-induced*

Establishing that Lethargus is Sleep

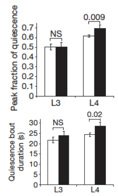
- Lethargus involves:
  - Periodic behavioral quiescence in which a worm
    - assumes stereotypical posture
    - exhibits decreased response to sensory stimuli
  - Homeostatic response to enforced wakefulness in which peak quiescence and mean bout duration both increase
    - but with a fixed termination time



Raizen et al., 2008



Response to dish tap



Could the Mechanism of Lethargus be the same as that of sleep?

- Worms do not exhibit circadian rhythms
  - Yet already in 1999 they were shown to have *lin-2* — a homolog of period (*per*)
    - the first discovered circadian gene (in flies)
    - three homologs of *per* are found in mammals
  - LIN-2 (the protein product of this gene)
    - does not oscillate on a circadian basis but in phase with molting time
    - when mutated, generates aberrant timing of molting and lethargus