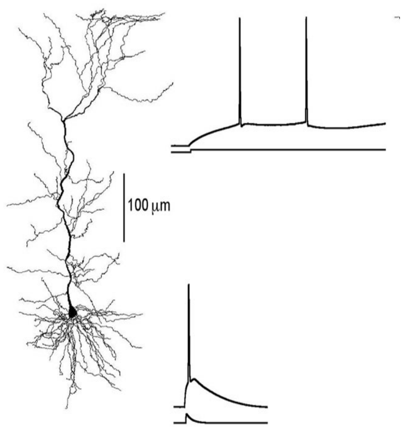
Neuroscience: Exploring the Brain, 3e

Chapter 4: The action potential

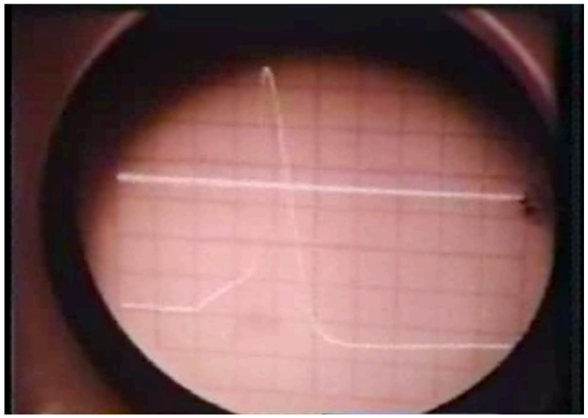
Introduction

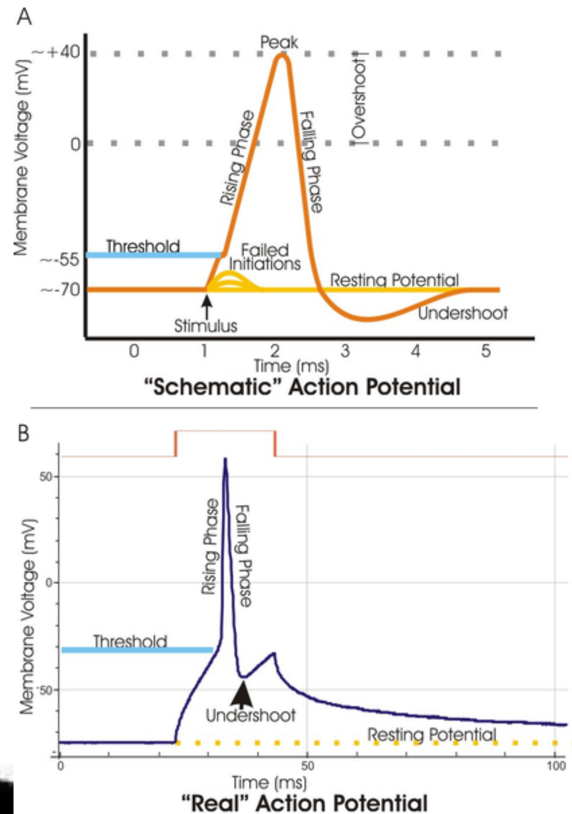
- Action Potential in the Nervous System
  - Conveys information over long distances
  - Action potential
    - Initiated in the axon and travels down the axon but also backpropagates into the dendrite
    - All or none not continuous
    - Threshold
    - Neural code - frequency and pattern

Alan Lloyd Hodgkin and Andrew Huxley described the model in 1952 to explain the ionic mechanisms underlying the initiation and propagation of action potentials in the squid giant axon.[1] They received the 1963 Nobel Prize in Physiology or Medicine for this work.



Hodgkin and Huxley axon





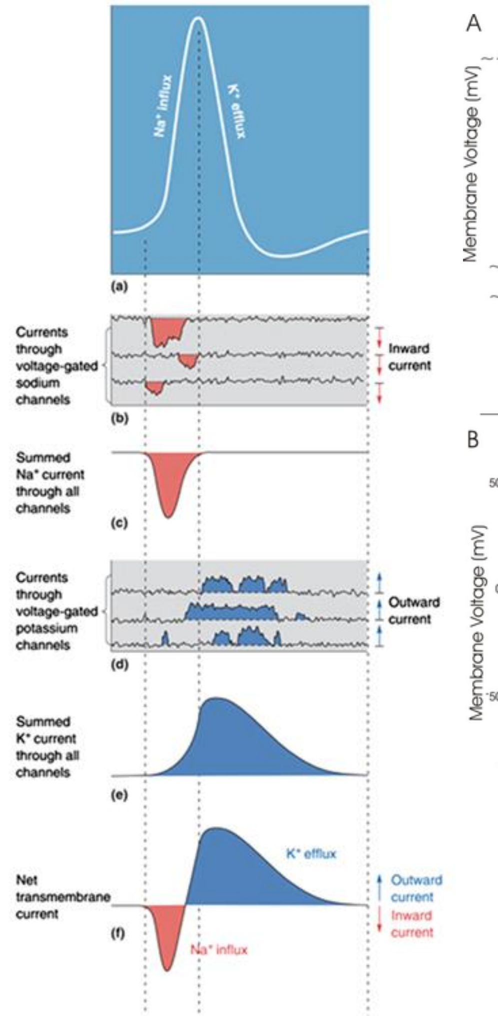
Dissecting the components
of the action potential:

Rising phase-Na+ channels open

Peak- Na+ channels inactivate and
K+ channels open

Falling phase- K+ channels open

Undershoot/Afterhyperpolarization
Na+ channels recover from
inactivation



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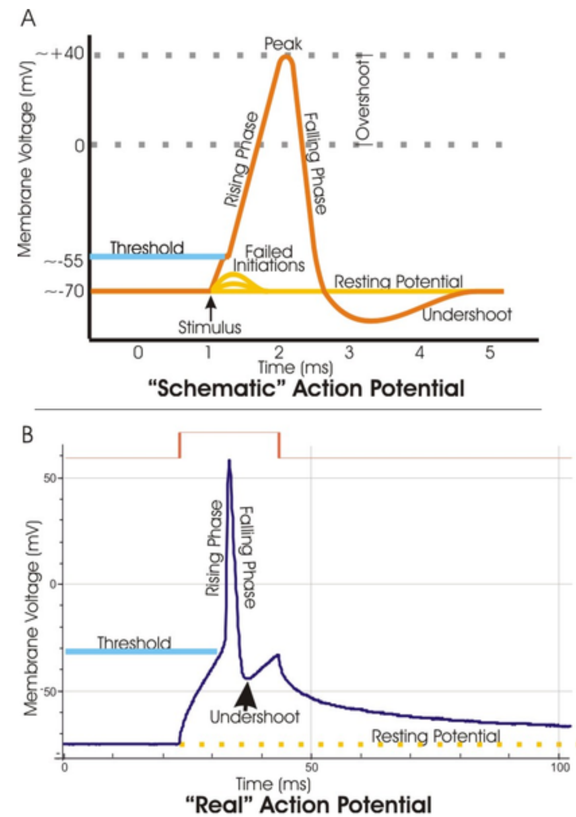

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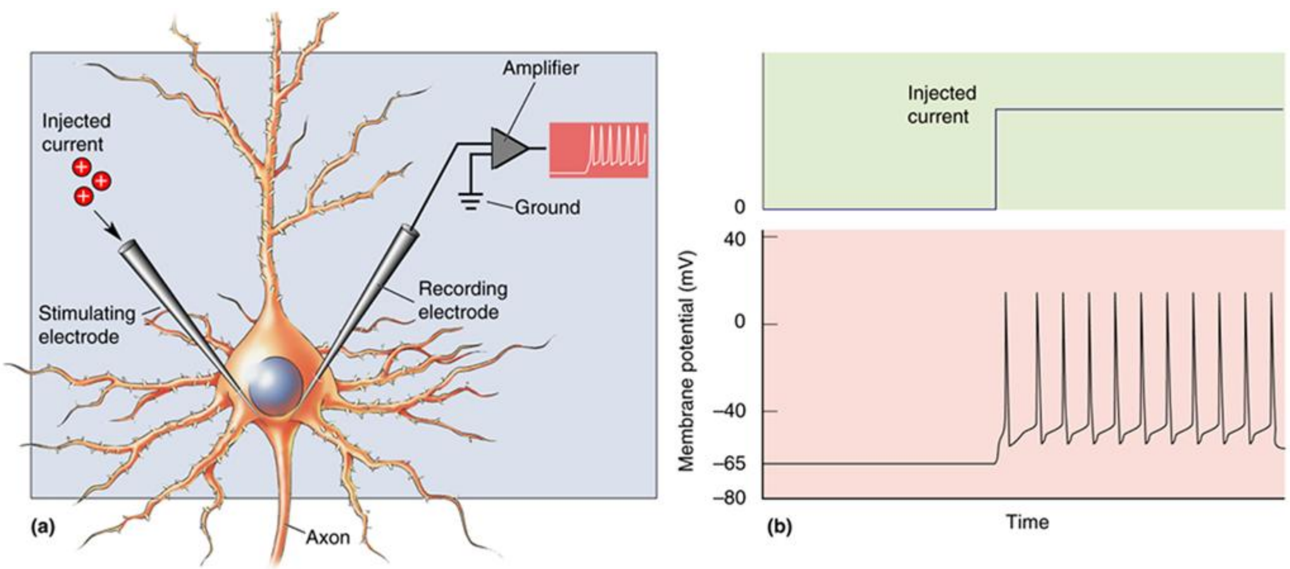
- The Generation of Multiple Action Potentials
  - Artificially inject current into a neuron using a microelectrode



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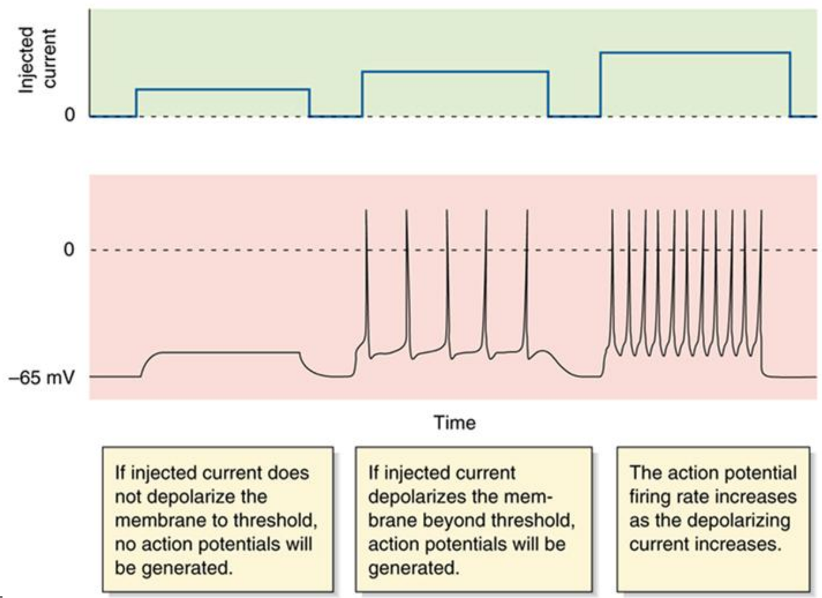
- The Generation of Multiple Action Potentials
  - Firing frequency reflects the magnitude of the depolarizing current
  - AP size does not change with depolarizing current injection



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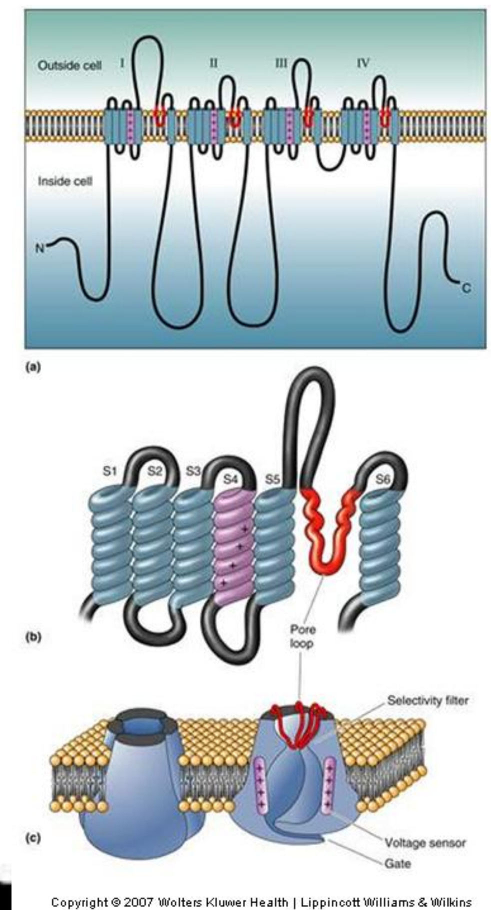
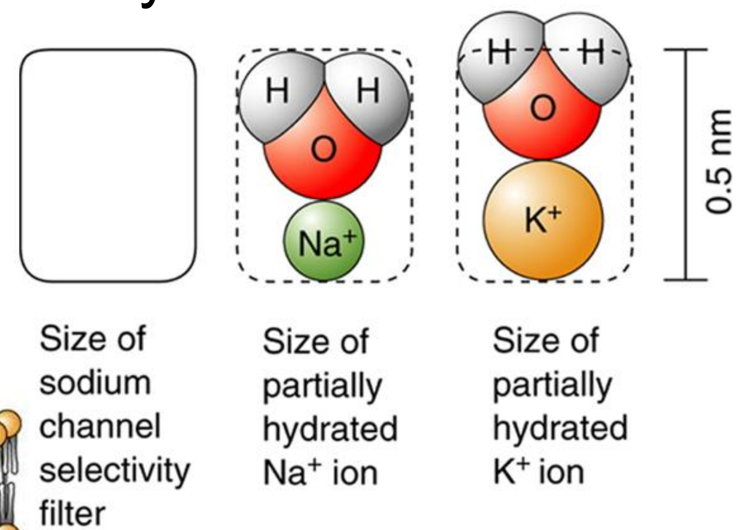
- The Voltage-Gated Sodium Channel
  - Structure –transmembrane domains and ion-selective pore

  - Guide to Sodium Channels
  - http://onlinelibrary.wiley.com/doi/10.1038/sj.bjp.0707755/full



- The Voltage-Gated Sodium Channel
  - Structure – gating and pore selectivity



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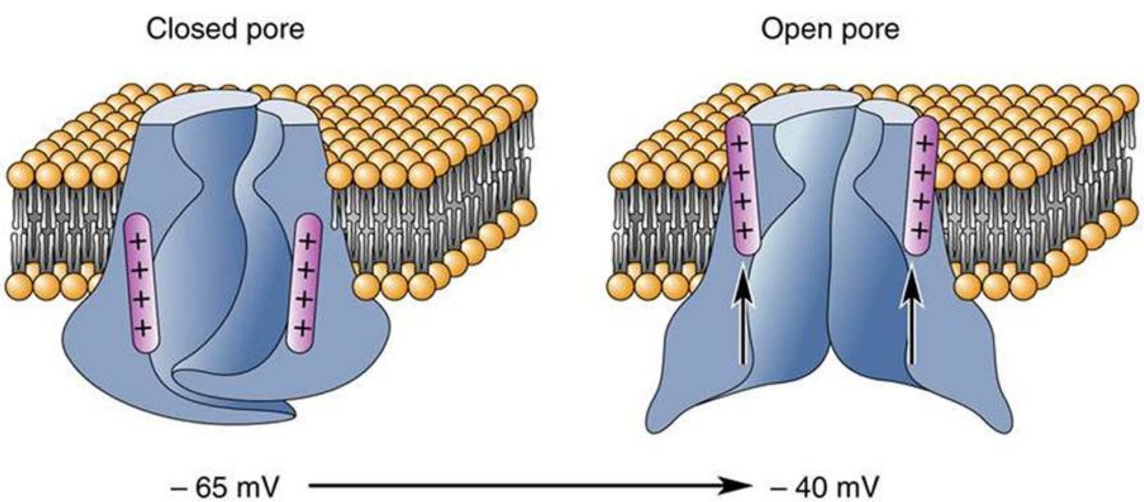

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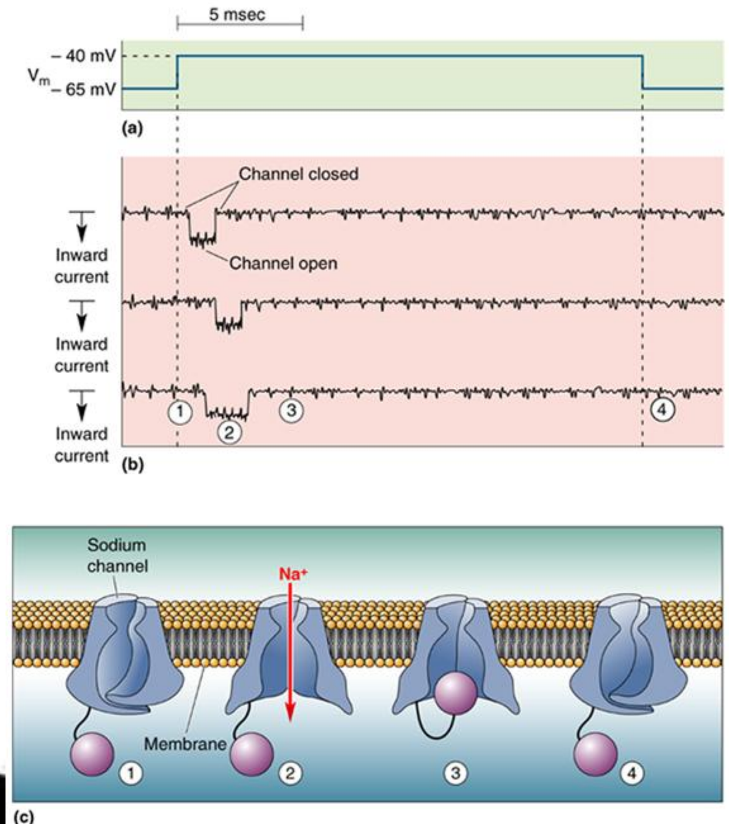
- The Voltage-Gated Sodium Channel
  - Patch-clamp method (Erwin Neher)
  - Closed-Open-Inactivated-Closed

FIGURE 4.9

The opening and closing of sodium channels upon membrane depolarization. **(a)** This trace shows the electrical potential across a patch of membrane. When the membrane potential is changed from −65 to −40 mV, the sodium channels pop open. **(b)** These traces show how three different channels respond to the voltage step. Each line is a record of the electrical current that flows through a single channel. ① At −65 mV, the channels are closed, so there is no current. ② When the membrane is depolarized to −40 mV, the channels briefly open and current flows inward, represented by the downward deflection in the current traces. Although there is some variability from channel to channel, all of them open with little delay and stay open for less than 1 msec. Notice that after they have opened once, they close and stay closed as long as the membrane is maintained at a depolarized V_m. ③ The closure of the sodium channel by steady depolarization is called inactivation. ④ To deinactivate the channels, the membrane must be returned to −65 mV again. **(c)** A model for how changes in the conformation of the sodium channel protein might yield its functional properties. ① The closed channel ② opens upon membrane depolarization. ③ Inactivation occurs when a globular portion of the protein swings up and occludes the pore. ④ Deinactivation occurs when the globular portion swings away and the pore closes by movement of the transmembrane domains.



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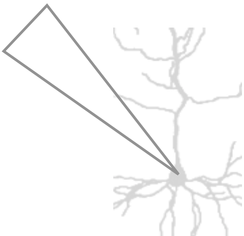
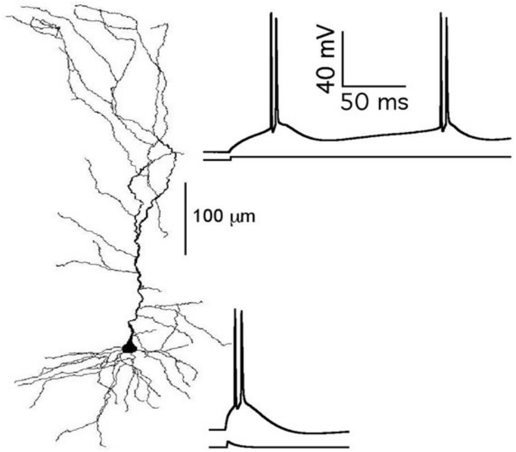


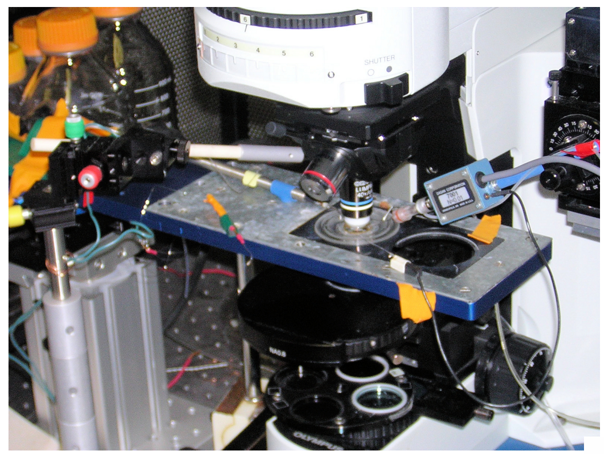
What types of neurons are present in the subiculum?

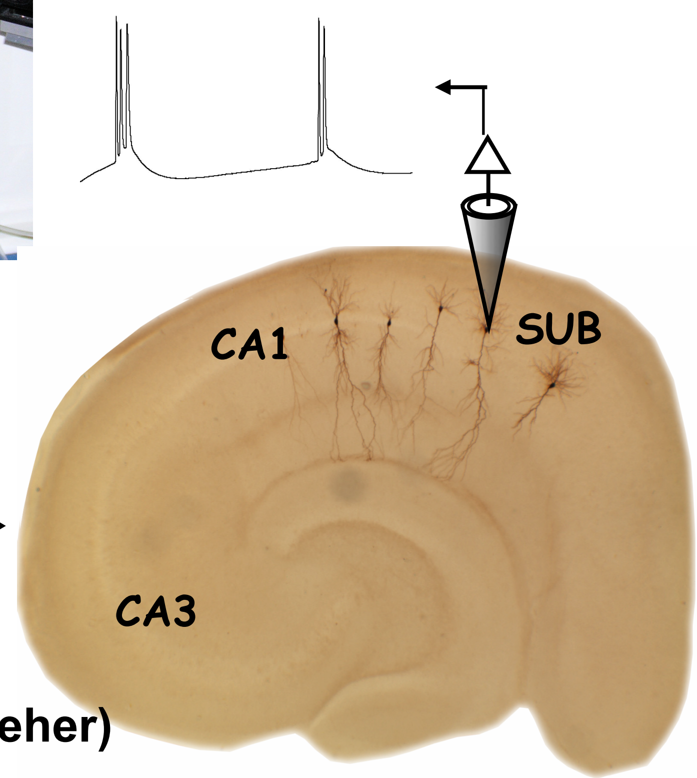
Intrinsic Bursting



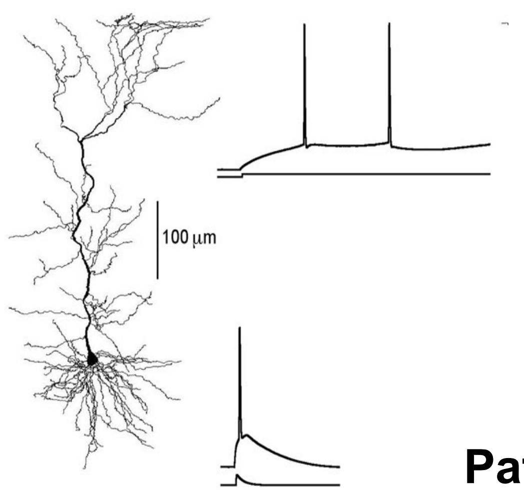
No differences in morphology of the two types of neurons

Whole-Cell Patch-Clamp recording





Single spiking



Patch-clamp method (Erwin Neher)

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Different action potential output modes
A) Tonic firing-Linear input/output relationship
B) Phasic firing-Non linear input/output relationship
(Bursting-high frequency cluster of spikes followed by a pause)

Box 4.6 OF SPECIAL INTEREST

The Eclectic Electric Behavior of Neurons

Neurons are not all alike; they vary in shape, size, and connections. Neurons also differ from one another in their electrical properties. A few examples of the diverse behavior of neurons are shown in Figure A.

The cerebral cortex has two major types of neurons, as defined by morphology: aspinous stellate cells and spiny pyramidal cells. A stellate cell typically responds to a steady depolarizing current injected into its soma by firing action potentials at a relatively steady frequency throughout the stimulus (part a). However, most pyramidal cells cannot sustain a steady firing rate. Instead, they fire rapidly at the beginning of the stimulus and then slow down, even if the stimulus remains strong (part b). This slowing over time is called *adaptation*, and it is a very common property among excitable cells. Another firing pattern is the burst, a rapid cluster of action potentials followed by a brief pause. Some cells, including a particular subtype of large pyramidal neuron in the cortex, can even respond to a steady input with rhythmic, repetitive bursts (part c). Variability of firing patterns is not confined to the cerebral cortex. Surveys of many areas of the brain imply that neurons have just as large an assortment of electrical behaviors as morphologies.

What accounts for the diverse behavior of different types of neurons? Ultimately, each neuron's physiology is determined by the properties and numbers of the ion channels in its membrane. There are many more types of ion channels than the few described in this chapter, and each has distinctive properties. For example, some potassium channels activate only very slowly. A neuron with a high density of these will show adaptation because during a prolonged stimulus, more and more of the slow potassium channels will open, and the outward currents they progressively generate will tend to hyperpolarize the membrane. When you realize that a single neuron may express more than a dozen types of ion channels, the source of diverse firing behavior becomes clear. It is the complex interactions of multiple ion channels that create the eclectic electric signature of each class of neuron.

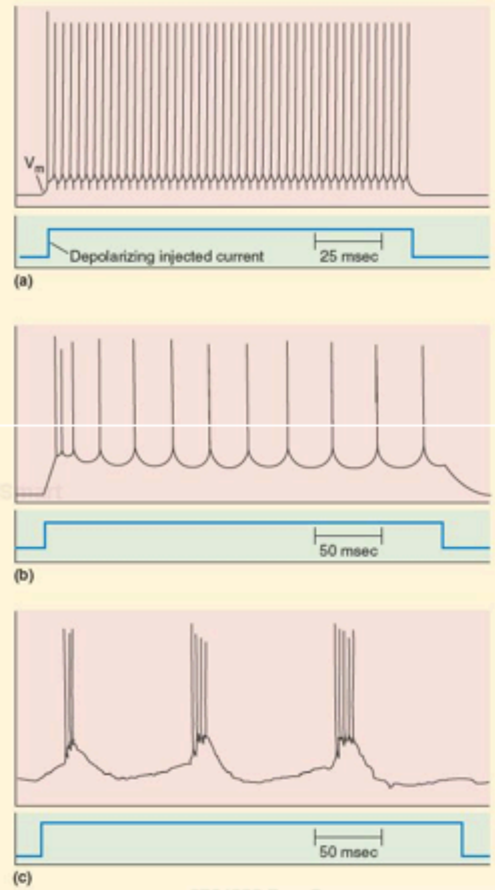
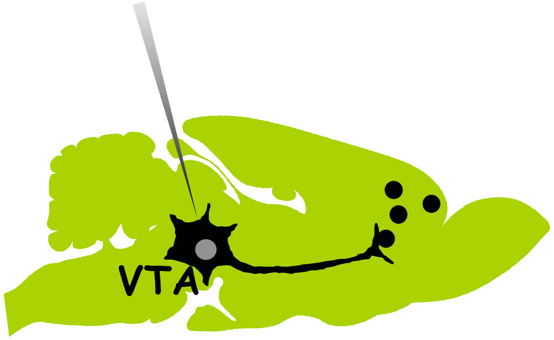
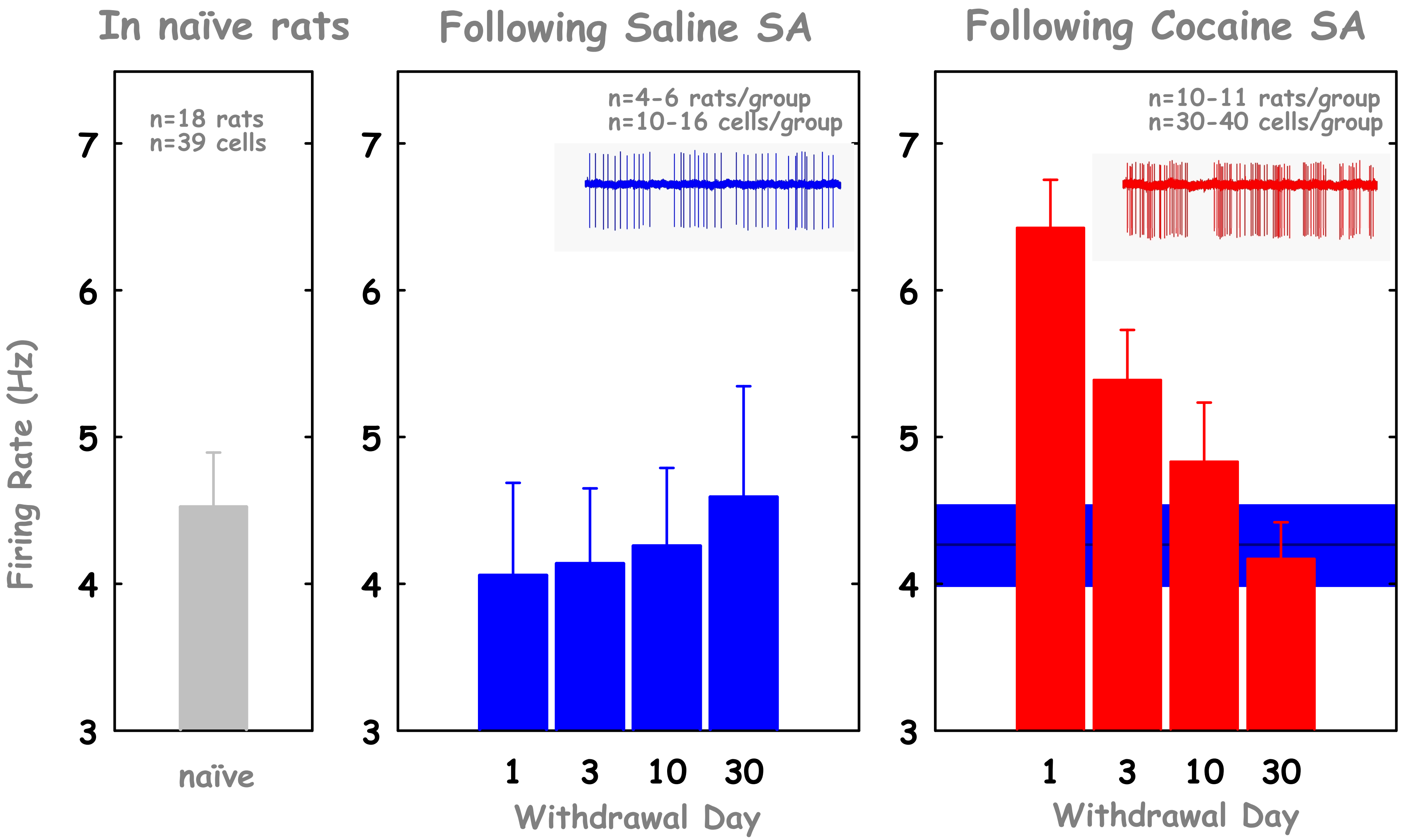


FIGURE A
The diverse behavior of neurons (Source: Adapted from Agmon and Connors, 1992.)

Can neurons switch between output modes and what kind of information is transmitted?



Plasticity of VTA DA firing rate during withdrawal from cocaine SA



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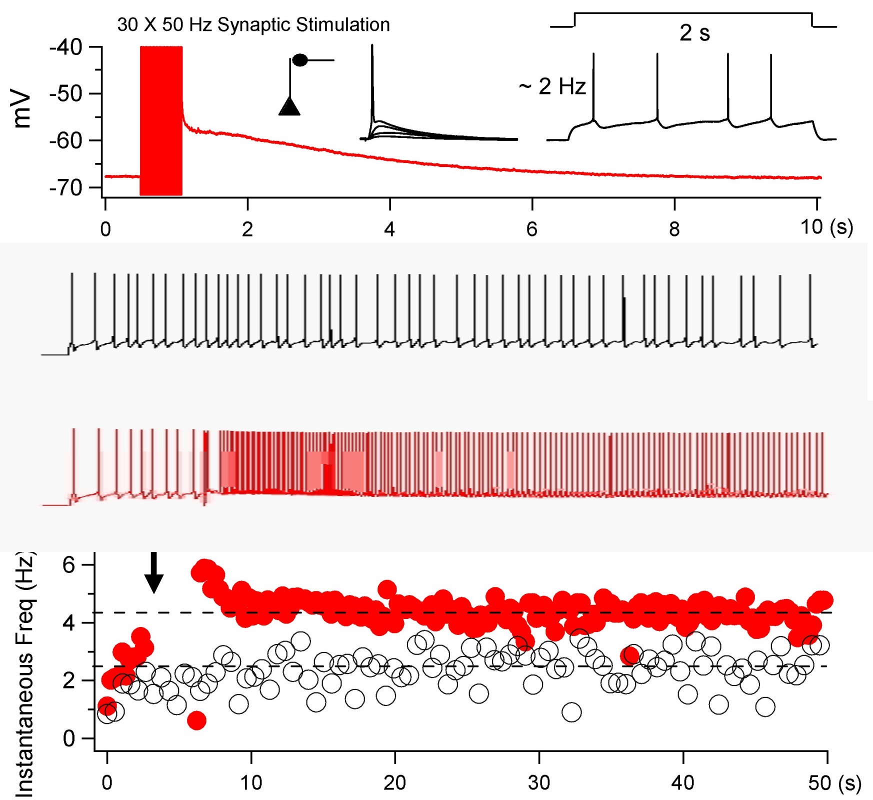
nature neuroscience

Dopamine modulates an mGluR5-mediated depolarization underlying prefrontal persistent activity

Kyriaki Sidiropoulou[1,6], Fang-Min Lu[2], Melissa A Fowler[2], Rui Xiao[3], Christopher Phillips[2], Emin D Ozkan[2], Michael X Zhu[3], Francis J White[4,5] & Donald C Cooper[2]



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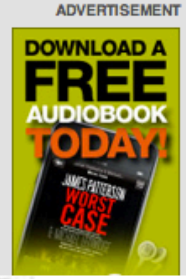

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Single cell 'can store memories'

Just one brain cell is capable of holding fleeting memories vital for our everyday life, according to US scientists.

Dr Cooper has examined individual nerve cells in the brain

A study of mouse brain cells revealed how they could keep information stored for as long as a minute.

A UK specialist said that understanding these short-term memories might help unlock the secrets of Alzheimer's Disease.

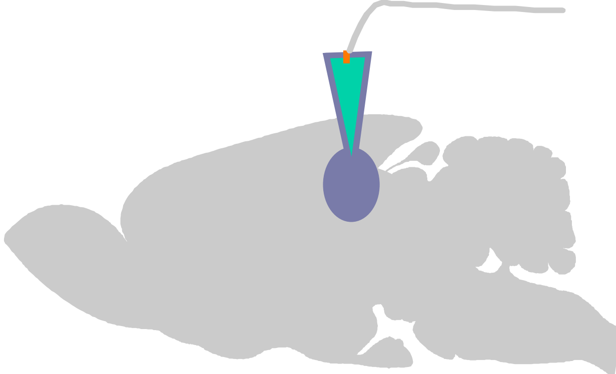
The finding was reported in the journal Nature Neuroscience.

The difference between the brain's long-term and short-term memory has been likened to the RAM of a computer and the hard-drive.

> **"If we can identify and manipulate the molecular components of memory, we can develop drugs... to hopefully allow a person to complete tasks without being distracted"**
>
> Dr Don Cooper
> UT Southwestern

To perform normal functions, we need the ability to store, quickly and reliably, large amounts of data, but only a small amount of this needs to be retained in the longer term.

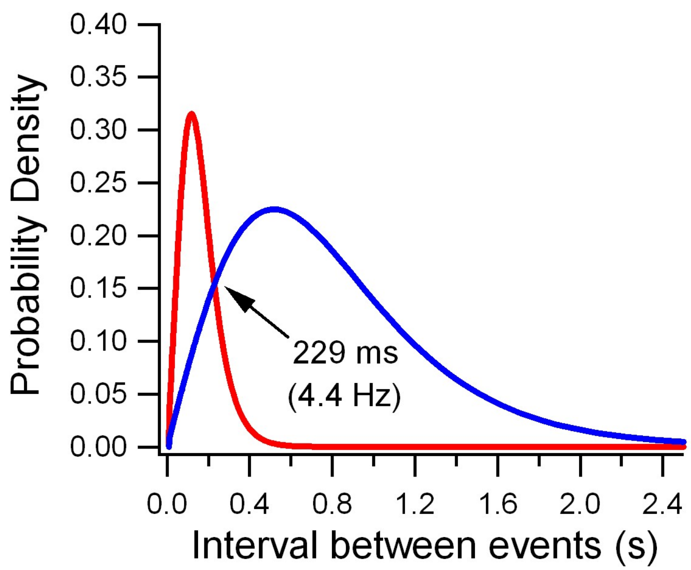
In vivo electrophysiological signature of the subiculum: Bursting to single spiking output mode transitions

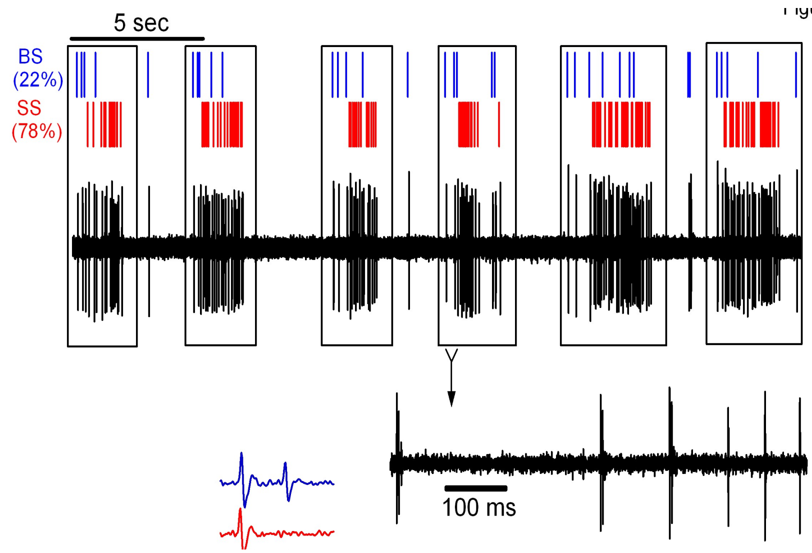


Possible causes for BS-SS transition

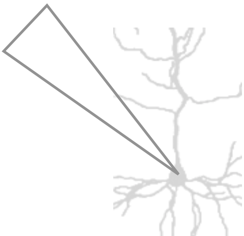
<u>Synaptic/Network</u>
Reduced glutamatergic excitation
Increased GABAergic inhibition

<u>Intrinsic</u>
Increased afterhyperpolarization
Inactivation of Na^+ or Ca^{++} channels
Enhanced K^+ channel



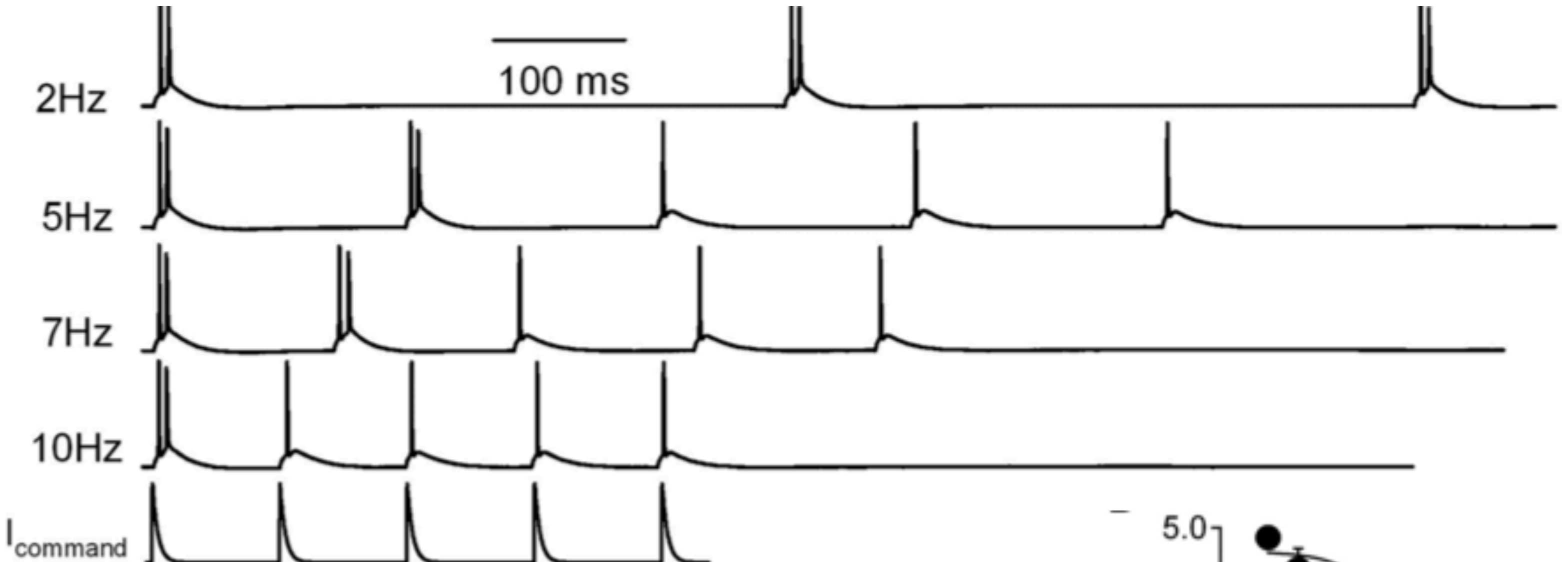


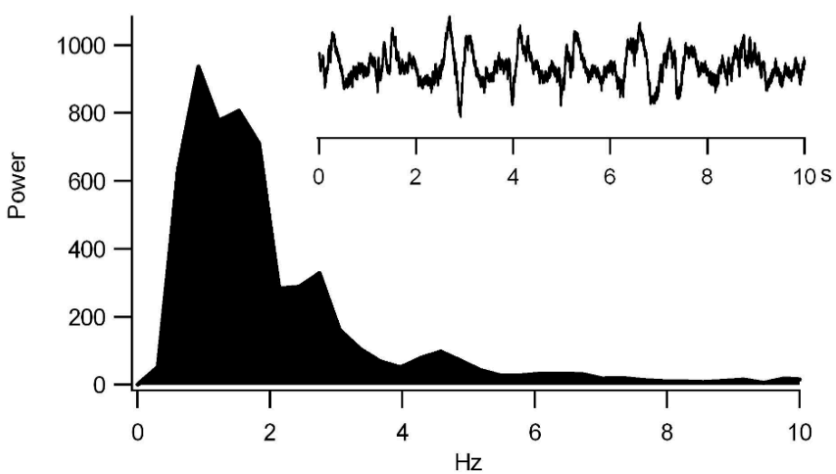
Subicular neurons transition from bursting to single spiking in the delta to theta range in the absence of synaptic input

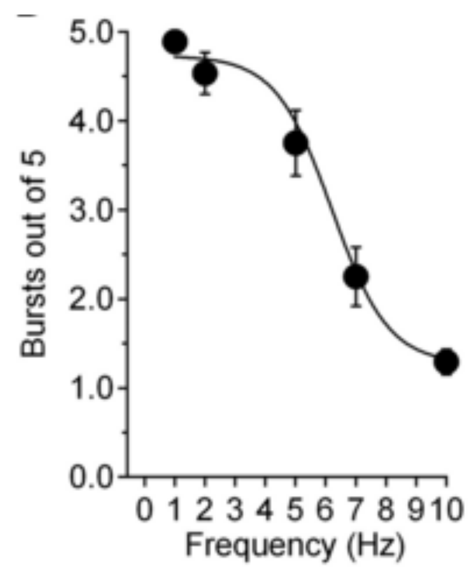


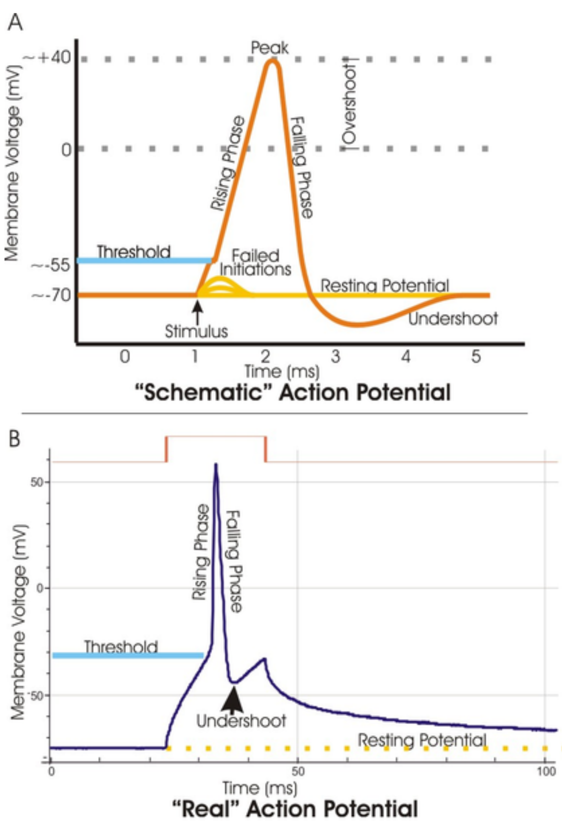
Near threshold oscillations ~ 1-2Hz in the absence of any synaptic input

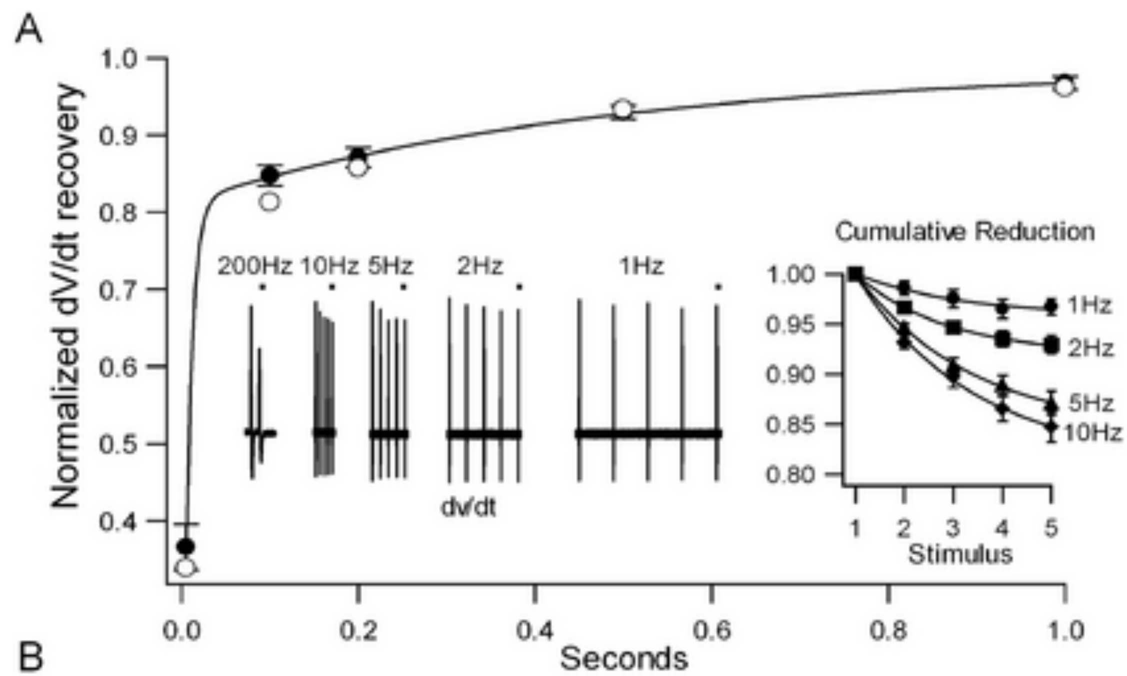
Conclusion: Subicular neurons are tuned to low frequencies








A
Peak
~+40
0
~-55
~-70
Membrane Voltage (mV)
Rising Phase
Falling Phase
Overshoot
Threshold
Failed Initiations
Resting Potential
Undershoot
Stimulus
0
1
2
3
4
5
Time (ms)
"Schematic" Action Potential
B
50
0
-50
Membrane Voltage (mV)
Rising Phase
Falling Phase
Threshold
Undershoot
Resting Potential
0
50
100
Time (ms)
"Real" Action Potential


A
Normalized dV/dt recovery
1.0
0.9
0.8
0.7
0.6
0.5
0.4
200Hz 10Hz 5Hz
2Hz
1Hz
dv/dt
Cumulative Reduction
1.00
0.95
0.90
0.85
0.80
1Hz
2Hz
5Hz
10Hz
1
2
3
4
5
Stimulus
0.0
0.2
0.4
0.6
0.8
1.0
Seconds
B

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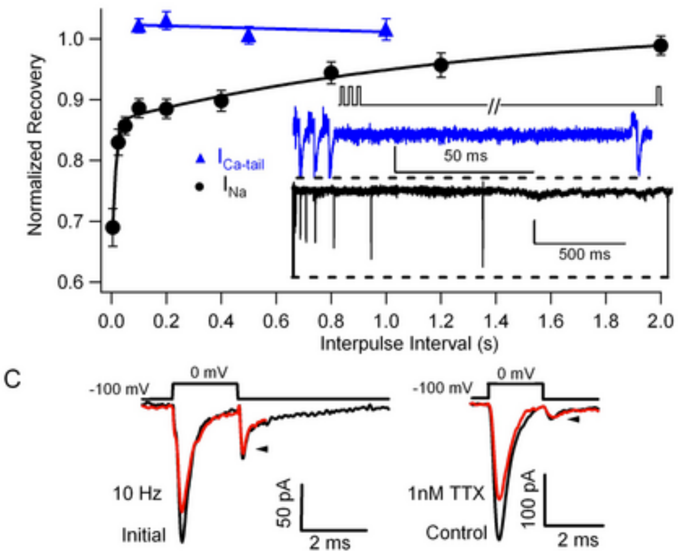
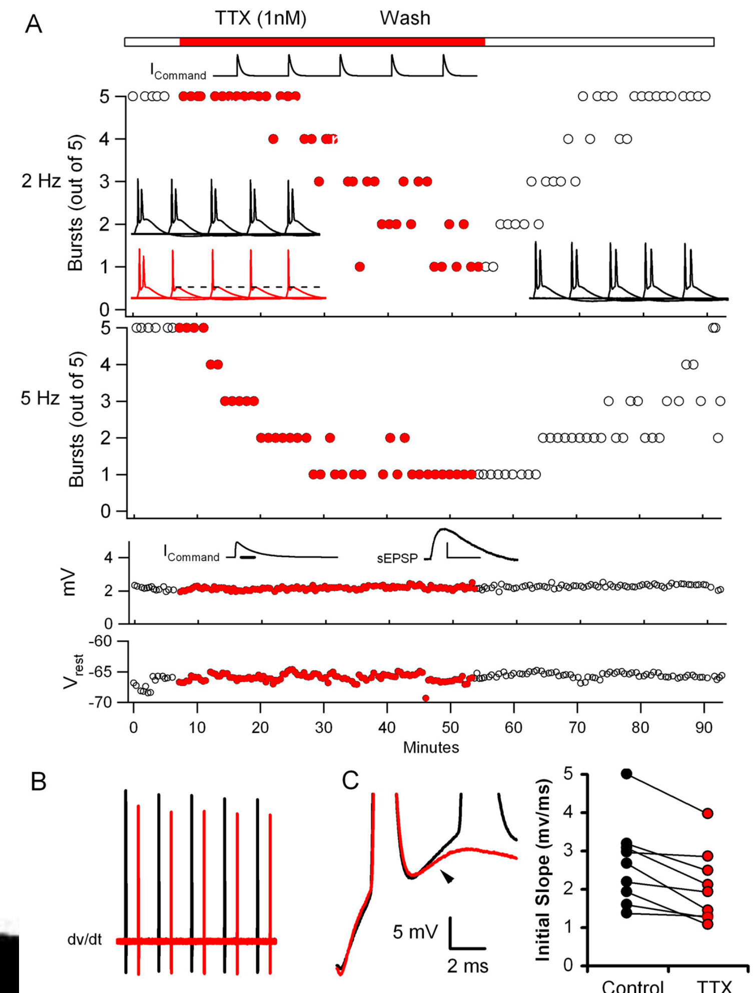
Small changes in Na+ channel availability Can lead to all or nothing failures of AP





Cooper et al., 2005

Functional classification: Direction

Afferent neurons convey information from tissues and organs into the central nervous system and are sometimes also called sensory neurons.

Efferent neurons transmit signals from the central nervous system to the effector cells and are sometimes called motor neurons.

Interneurons connect neurons within specific regions of the central nervous system. Afferent and efferent can also refer generally to neurons which, respectively, bring information to or send information from the brain region.

Discharge patterns

Neurons can be classified according to their electrophysiological characteristics: Tonic or regular spiking. Some neurons are typically constantly (or tonically) active. Example: interneurons in neostriatum.

Phasic or bursting. Neurons that fire in bursts are called phasic.

Fast spiking. Some neurons are notable for their fast firing rates, for example some types of cortical inhibitory interneurons, cells in globus pallidus, retinal ganglion cells.

Classification by neurotransmitter production

Neurons differ in the type of neurotransmitter they manufacture. Some examples are:

Cholinergic neurons – acetylcholine.

1. Metabotropic (GPCRs) muscarinic receptors.

2. Nicotinic receptors

Pentameric ligand-gated ion channels composed of alpha and beta subunits that bind nicotine. Ligand binding opens the channel causing influx of Na+ depolarization and increases the probability of presynaptic neurotransmitter release.

GABAergic neurons – GABA is one of two neuroinhibitors in the CNS, the other being Glycine. GABA has a homologous function to ACh, gating anion channels that allow Cl- ions to enter the post synaptic neuron. Cl- causes hyperpolarization within the neuron, decreasing the probability of an action potential firing as the voltage becomes more negative.

Glutamatergic neurons - Glutamate is one of two primary excitatory amino acids. (Pyramidal Neurons)

1 - AMPA and Kainate receptors both function as cation channels permeable to Na+ cation channels mediating fast excitatory synaptic transmission

2 - NMDA receptors are another cation channel that is more permeable to Ca2+. The function of NMDA receptors is dependant on Glycine receptor binding as a co-agonist within the channel pore. NMDA receptors will not function without both ligands present.

3 – Metabotropic receptors, GPCRs modulate synaptic transmission and postsynaptic excitability.

Dopaminergic neurons - Dopamine is a neurotransmitter that acts on D1 type (D1 and D5) Gs coupled receptors which increase cAMP and PKA or D2 type (D2, D3 and D4) receptors which activate Gi-coupled receptors that decrease cAMP and PKA. Dopamine is connected to mood and behavior, and modulates both pre and post synaptic neurotransmission

Serotonergic neurons – Serotonin (5-Hydroxytryptamine, 5-HT) Of the four 5-HT receptor classes, 3 are GPCR and 1 is ligand-gated cation channel.

The Action Potential

- The Generation of an Action Potential
  - Hodgkin and Huxley
    - Voltage Clamp: “Clamp” membrane potential at any chosen value
    - Rising phase → transient increase in g_{Na}, influx of Na^+ ions
    - Falling phase → increase in g_K, efflux of K^+ ions
    - Existence of sodium “gates” in the axonal membrane

The Action Potential, In Reality

- The Voltage-Gated Sodium Channel (Cont'd)
  - Functional Properties of the Sodium Channel
    - Open with little delay
    - Stay open for about 1 msec
    - Cannot be open again by depolarization
- Absolute refractory period: Channels are inactivated

The Action Potential, In Reality

- The Voltage-Gated Sodium Channel (Cont'd)
  - In genetic disease – channelopathies
    - e.g., Generalized epilepsy with febrile seizures
  - Toxins as experimental tools
    - Toshio Narahashi – ion channel pharmacology
    - Puffer fish: Tetrodotoxin (TTX)- Clogs Na^+ permeable pore
    - Red Tide: Saxitoxin- Na^+ Channel-blocking toxin

The Action Potential, In Reality

- The Voltage-Gated Sodium Channel (Cont'd)
  - Varieties of toxins
    - Batrachotoxin (frog): Blocks inactivation so channels remain open
    - Veratridine (lilies): Inactivates channels
    - Aconitine (buttercups): Inactivates channels
  - Differential toxin binding sites: Clues about 3D structure of channels

The Action Potential, In Reality

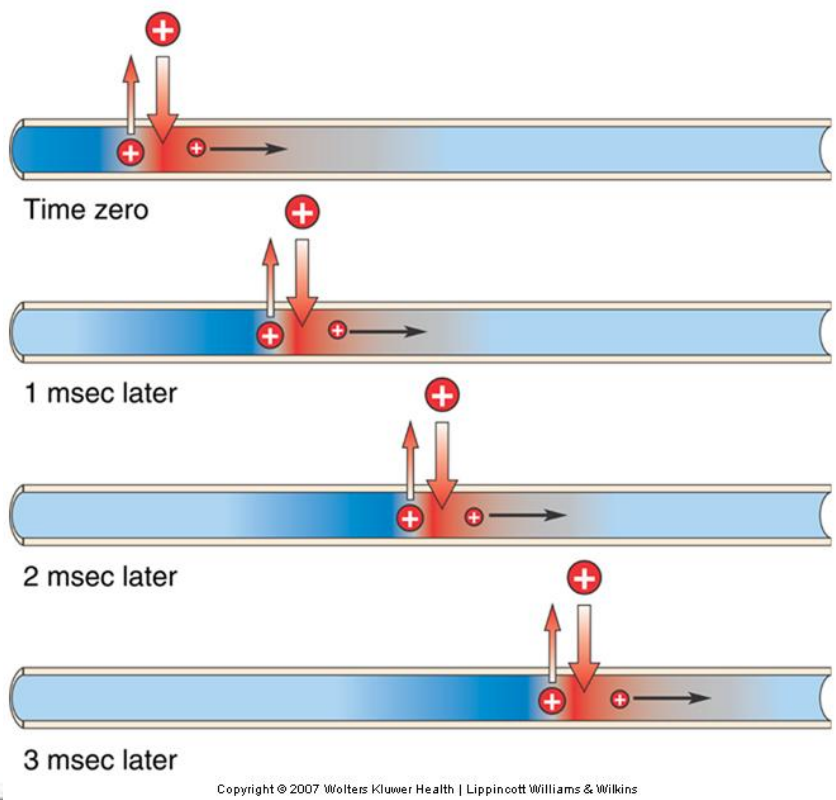
- Voltage-Gated Potassium Channels
  - Potassium vs. sodium gates
    - Both open in response to depolarization
    - Potassium gates open later than sodium gates
  - Delayed rectifier
    - Potassium conductance serves to rectify or reset membrane potential
  - Structure: Four separate polypeptide subunits join to form a pore

The Action Potential

- Key Properties of the Action Potential (to know!)
  - Threshold
  - Rising phase
  - Overshoot
  - Falling phase
  - Undershoot
  - Absolute refractory period
  - Relative refractory period

Action Potential Conduction

- Propagation



Action Potential Conduction

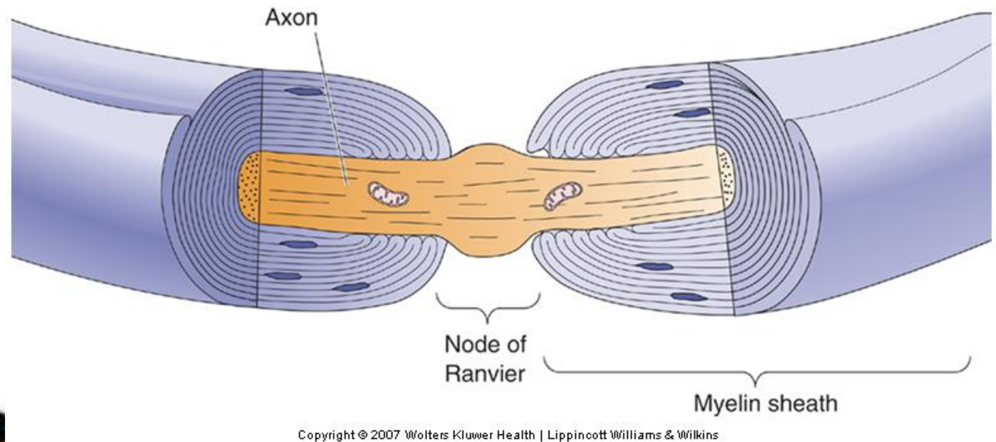
- Propagation of the action potential
  - Orthodromic: Action potential travels in one direction - down axon to the axon terminal
  - Antidromic (experimental): Backward propagation
  - Typical conduction velocity: 10 m/sec
  - Length of action potential: 2 msec

Action Potential Conduction

- Factors Influencing Conduction Velocity
  - Spread of action potential along membrane
    - Dependent upon axon structure
  - Path of the positive charge
    - Inside of the axon (faster)
    - Across the axonal membrane (slower)
  - Axonal excitability
    - Axonal diameter (bigger = faster)
    - Number of voltage-gated channels

Action Potential Conduction

- Factors Influencing Conduction Velocity
  - Myelin: Layers of myelin sheath facilitate current flow
    - Myelinating cells
      - Schwann cells in the PNS
      - Oligodendroglia in CNS



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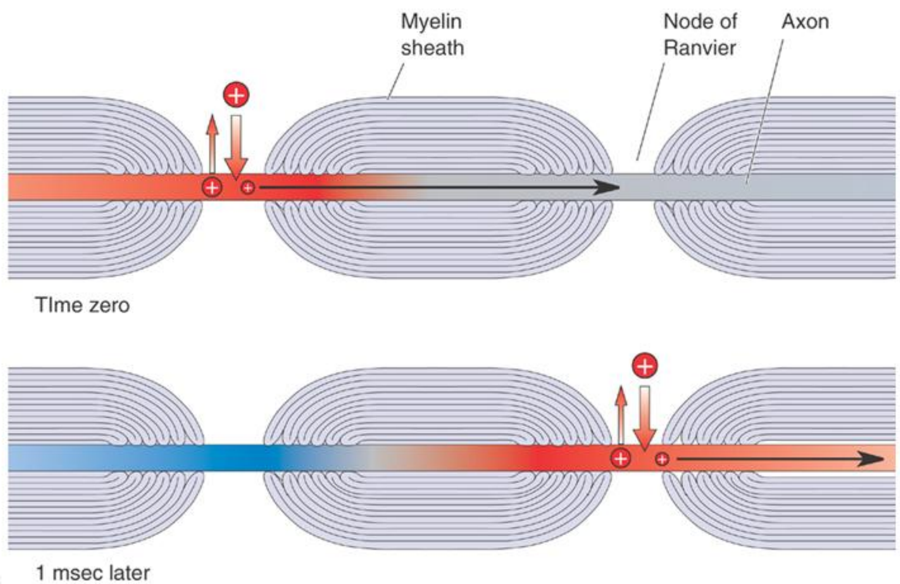
Action Potential Conduction

- Factors Influencing Conduction Velocity
  - Saltatory conduction at Nodes of Ranvier
  - Voltage gated sodium channels concentrated at nodes



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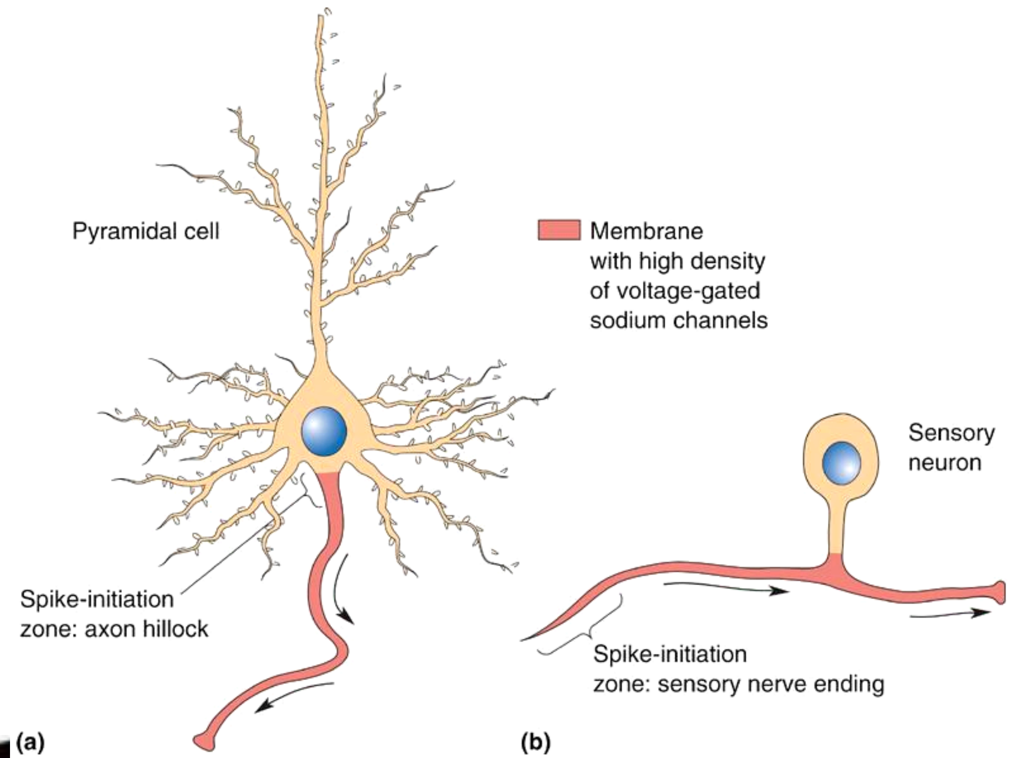
Action Potentials, Axons, and Dendrites

- Spike-initiation zone
  - Sensory nerve endings
  - Axon hillock



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Concluding Remarks

- Neuronal signal transmitted as the generation and regeneration of APs
  - e.g.,: Puncture the skin→ nerves stretch→ Na^{+}-channels open→ AP initiated and propagated→ information is "communicated" to next neuron across the membrane (synaptic transmission)
  - Emerging picture: The brain as an interconnected mesh of membranes
- Next: Synaptic transmission-information transfer