

Simulations: Thalamic Relay Neurons

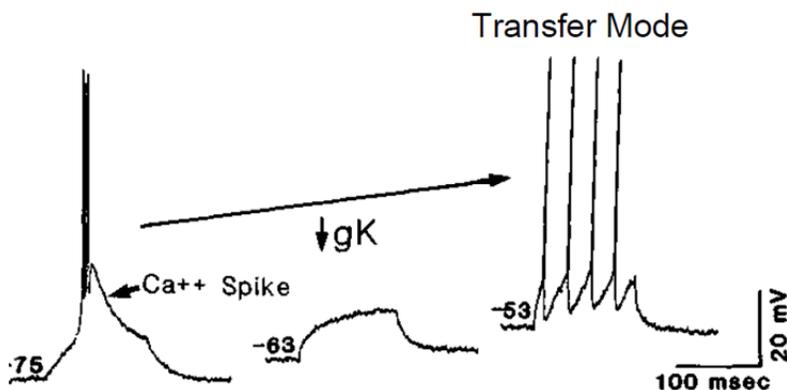
Key questions you should be able to answer based on this exercise:

1. How do certain calcium channels help to create transient bursts of action potentials at low resting membrane potentials?
2. Why are these transient bursts of action potentials absent at more depolarized resting potentials?
3. What general strategy can neurons use to create different patterns of activity depending on their resting membrane potential? (I.e., what kinds of ion channels help to achieve this?)

About Thalamic Relay Neurons

The first investigators to record from neurons in the brains of sleeping animals made a remarkable discovery. Instead of being silent during non-dream sleep (slow-wave sleep) as one might expect, Herbert Jasper, David Hubel, and Edward Evarts independently found that many cells were discharging in bursts of action potentials instead of the more independent series of single spikes typical of the waking animal (e.g., Jasper, Rici, & Doane, 1958). Indeed, intracellular recordings during slow-wave sleep from the thalamic relay cells that transmit information from the retina to the visual cortex revealed intermittent bursts of action potentials interspersed with periods of inactivity. The transition to either waking or dreaming sleep was associated with depolarization of the membrane potential, a lack of these burst discharges, and the generation of action potentials in a more regular manner (dreaming sleep is also known as REM sleep for the rapid eye movements associated with the eyes darting back and forth during dreams). Additional intracellular investigations, both *in vivo* and *in vitro* by Mircea Steriade, Martin Deschenes and colleagues, and Henrik Jahnsen and Rodolfo Llinas revealed the ionic mechanisms of this striking and important change in neuronal activity underlying the transition from sleep to waking (Steriade & Deschenes, 1984; Jahnsen and Llinas, 1984a, 1984b). *Intracellular recordings from thalamic relay cells reveal that they have two modes of action potential generation.*

At relatively hyperpolarized membrane potentials, intracellular injection of a depolarizing current pulse results in the activation of a low-threshold Ca^{++} spike that then activates a burst of 3 to 5 action potentials (next figure; Burst Mode). Interestingly, if the cell is at -63 mV, intracellular injection of the same current pulse now results in only the passive response of the cell (next Figure), which is shaped by the resistive and capacitive properties of the cell. Even more surprising, if the cell is further depolarized to -53 mV, then the same current pulse results in a train of action potentials that, unlike those in cortical pyramidal cells, *does not* exhibit a marked slowing of the rate of action-potential discharge (Next Figure; transfer mode).



In this manner, even single neurons exhibit changes in activity in relation to the sleep and wake cycle. The presence in thalamic cells of an extra mode of action-potential generation, the burst mode, during slow-wave sleep is due to the properties of a special type of Ca^{++} current known as the low-threshold, or transient, Ca^{++} current (also known as the T-type Ca^{++} current).

To examine the properties of this current, run SimCC then load and run the ThalamicRelay.CC5 file. In this cell with a resting potential of -85 mV, depolarizing the model cell with a current step results in the generation of a burst of action potentials riding on top of a depolarization that begins slowly and ends slowly. The amplitude and time course of the current underlying this slow depolarization, the T-current, can also be seen at the bottom of the screen.

Now, depolarize the neuron to -65 mV by navigating to the Parameters | Conductances menu and changing pK_{Leak} from 0.45 to 0.1 (bonus round: Why does this depolarize the neuron?) Run the protocol and you will see that the cell generates a steady train of action potentials and no burst discharges. Note especially that the T-type Ca^{++} current has disappeared! The lack of burst firing at depolarized membrane potentials indicates that the current underlying the burst is highly voltage dependent and is inactivated by depolarization.

To examine this a bit more, let's isolate the slow depolarization from action-potential generation by applying tetrodotoxin (TTX) to the cell.

- Re-load ThalamicRelay.CC5 and choose Run | Begin to run the cell in burst mode.
- Now, change g_{Na} from 15 to 0 in the Parameters | Conductances menu, thereby blocking the voltage-dependent Na^+ conductance (this is what TTX does in experimental setups).
- Choose Run | Begin to repeat the current pulse without Na^+ current and note the slow spike (membrane depolarization) on top of the passive membrane response.

The kinetics of the current underlying this slow spike are substantially slower than those underlying the fast action potential, thereby giving rise to this prolonged depolarization of the cell. Now you experiment with the ion concentrations in the bathing medium and find that when you reduce $[\text{Ca}^{++}]_o$ to 0.1 mM the slow spike disappears. This indicates that the slow spike is generated by the entry of Ca^{++} into the cell. In fact, this spike is generated by a Ca^{++} current known as the transient current, or T-current.

Like the Na^+ current underlying action-potential generation, the T-current inactivates with depolarization; therefore, steady depolarization of the cell results in complete inactivation of this current and a loss of these slow spikes. This property of the T-current underlies the ability of thalamic neurons to change from a pattern of burst firing during sleep to one of normal action-potential generation during wakefulness.

How is this depolarization naturally achieved? Thalamic neurons are depolarized by the release of neurotransmitters from the brain stem systems that are responsible for keeping us awake during the day. The release of these neurotransmitters, such as acetylcholine, reduces the resting conductance of the membrane to K^+ ions, thereby resulting in a maintained depolarization of thalamic cells during wakefulness (see McCormick, 1992). Interestingly, some drugs that have sedative side effects, such as antihistamines, block the receptors involved in maintaining this depolarization of central neurons. For example, activation of the H1 subtype of histaminergic receptors on thalamic relay cells reduces pK_{Leak} , resulting in a tonic *depolarization* of these cells. The active ingredient in over-the-counter sleeping pills is an H1 receptor antagonist and, by blocking the depolarizing actions of histamine, hyperpolarizes your thalamic neurons back into the sleep mode! (McCormick & Williamson, 1991)