Action Potentials I
Generation

Reading:
BCP Chapter 4
Action potentials (AP’s) aka
- *Spikes* (because of how they look in an electrical recording of $V_m$ over time).
- “*Discharges*” (descriptive of their gunshot-like explosiveness).
- *Impulses*.

An AP is a **brief reversal of the resting membrane potential**: the inside briefly becomes positive relative to the outside.

**Propagation:**
- APs are **self-regenerating**...
- ...and **propagate** along excitable membranes.
- **AP’s usually generated in axons**, not soma or dendrites (there are exceptions).
Membranes that generate APs are called “excitable” (found mostly in neurons and muscle fibers).

Voltage-gated ion channels underlie AP activity.

Action potential, squid giant axon (Hodgkin & Huxley 1939)
Characteristics of Action Potentials

- **AP** an *all-or-nothing* event:
  - AP amplitude essentially *constant* at all points on a membrane (as long as ion gradients remain stable).
  - No such thing as a “partial” or “fractional” AP.

- AP duration *very brief*: 0.5 – 2.0 ms.

- **AP** does not require energy: *Potential* energy, i.e. separation of charge across the resting membrane, is converted to *kinetic* energy, i.e. ion currents, when channels open to generate AP.
Action Potential Generation
Phases of a “Spike”

- Resting Potential ($V_{rest}$)
- Threshold
- Rising Phase
- Overshoot
- Falling Phase
- Undershoot
- $V_{rest}$
Imagine a membrane at rest, only resting $K^+$ ($K_{\text{rest}}$) and Na$^+$ channels open ($Na_{\text{rest}}$), voltage-gated Na$^+$ ($Nav$) and K$^+$ channels closed:

When $V_m$ below threshold for opening Nav channels:
- “Electrotonic” (steady-state) currents are carried mainly by resting $K$ channels, i.e. $g_K >> g_{Na}$. Result: $V_m = -65 \text{ mV}$
- Nav channels closed when $V_m = -65 \text{ mv.}$
Threshold to open Nav channels is more positive (less negative) than $V_{rest}$.

When depolarized to Nav threshold, *inward* current through Nav channels just exceeds *outward* “leakage” current via open resting K channels.

Inward current depolarizes membrane further, opening even more Nav channels, causing *explosive amplification* of inward depolarizing current (*positive feedback* process)

**Inward Nav channel current creates rising phase** of the AP

<table>
<thead>
<tr>
<th>REST</th>
<th>THRESHOLD</th>
<th>RISING PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{Na} \ll g_K$</td>
<td>$g_{Na} \sim g_K$</td>
<td>$g_{Na} \gg g_K$</td>
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AP is terminated by following mechanisms:

- **Nav “inactivation”:** At positive membrane potentials, Nav channels close, terminating depolarizing inward Na$^+$ current through these channels.
- Net outward leakage current via resting K channels
- Net outward currents via Kv channels
- **Falling phase:** $g_K >> g_{Na}$, so $V_m$ rapidly repolarizes toward $V_{rest}$
Hodgkin & Huxley showed that outward currents are also activated by depolarization, attributed to voltage-gated $K^+ (K_v)$ channels.

$K_v$ channel activation is slower and briefly delayed ($\sim 1$ ms) relative to $Nav$ channel activation (hence referred to as the “delayed rectifier” $K_v$ channel).

Combined with K leakage through $K_{rest}$ channels, outward (+) current moving through $K_v$ channels accelerates repolarization of the membrane back toward $V_{rest}$ during falling phase.

$K_v$ channels slow to inactivate, so outward current persists for a while, creating the AP “undershoot”.

$K_v$ channels de-inactivate when membrane repolarizes (like $Nav$ channels).
Currents Shape Time Course of AP

- **Summed activity** of thousands of rapidly opening *Nav* channels and slowly opening *Kv* channels results in large **inward** and **outward** currents that are **out of phase** in time, shaping the biphasic voltage change of the AP.
Refractory Period

- Brief period (1-2 ms) *during* and *after* generation of the AP when membrane is unable, or less able, to generate another AP.

- Importance:
  - Affects the *duration* of the AP.
  - Sets upper limit of *firing rate*.
  - Prevents the AP from re-invading membrane that has just discharged, so that *AP propagates away from site of initiation*. 
Absolute Refractory Period

- ARP is the time during AP overshoot when all available Nav channels are either open or inactivated.
- Threshold for generating another AP is effectively infinite.
Relative Refractory Period 1

- *Follows* the absolute refractory period.
- Associated with AP *falling phase* and *undershoot*.
- Caused by *prolonged outward K currents* through *Kv* channels (high-threshold, slow inactivating *Kv3.1* channels).
During RRP, threshold is elevated but not infinite.

Initiation of another AP during the RRP requires stronger supra-threshold depolarization that can open more Nav channels to overcome outward K currents causing the afterpotential (undershoot of $V_{rest}$).
Stimulus Strength and Firing Rate

- **Sub-threshold** inward currents are “graded”, i.e. proportional to the strength of the stimulus.
  - $V_m$ depolarizes to a new steady state proportional to the magnitude of stimulus current (Ohm’s law in action).
  - Graded potentials can summate.
- **Supra-threshold inward currents** (via resting ion channels) may result in repetitive generation of APs.

![Diagram of neuron with injected current and membrane potential](image-url)
• *Supra*-threshold depolarization elicits AP due to activation of enough *voltage-gated* channels to exceed outward currents through resting channels.

• If depolarization is sustained above threshold, then *AP’s may repeat* as channels repeatedly cycle between open and closed states.
Stronger stimulus $\rightarrow$ greater depolarizing current $\rightarrow$ faster membrane reaches threshold to initiate another AP.

Firing rate increases with stimulus strength.

Firing rate is limited by the duration of the absolute refractory period.
Review

- An AP is a *brief reversal of the resting membrane potential*: the inside briefly becomes *positive* relative to the outside.
- AP an *all-or-nothing* event.
- AP phases are the result of differential activation of voltage-gated sodium and potassium (delayed rectifier) channels.
- There is a brief refractory period (1-3 ms) *during* and *after* generation of the AP when membrane is unable (absolute refractory period), or less able (relative refractory period), to generate another AP.
- Stimulus strength affects the firing rate of neurons.