April 18, 2016
Snail CPG due today
Snail Pharmacology
Results Snail 1 & 2 due
Thursday April 28

H&H 2, Snail Pharmacology

Prize: "for their discoveries concerning the ionic mechanisms involved in excitation of the nerve cell membrane"

Alan Hodgkin Andrew Huxley Sammy Squid

Some general and specific points for midterm papers:
Review the resource material for background on what each specific section of a paper should contain.
Consider the references offered for each lab exercise.
Refer to the example paper I sent out for paper organization and consistent reference style.
Always cite all references for facts or ideas not your own.
Always describe fully what a figure shows, and always describe all figures in the text.

More specific for certain paper topics:
1. Don’t connect a graphs data points unless it is continuous data (for example, intracellular recording trace or extracellular recording trace). Plot the data points as dots for most cases.
2. When fitting your data with an equation, explain EVERY SINGLE TERM of the equation. For example, if you fit data with polynomial ax^2+bx+c, explain what a, x and c means specifically. Cite literature and theories that support your fitting equation in this scenario. Don’t just use whatever function that fits your data well. It’s meaningless if you cannot find a theory to support and explain it, even if you get R^2=0.99999.
   The purpose of fitting is to get useful information. For example, the adaptation rate for MROs.
3. Always show the fitting equation and R^2 along with fitting curve.
4. Make sure you explain your analysis procedure and how you get parameters from your raw data. Show the raw traces before showing analytic graphs can be helpful for your readers to understand your analysis.
5. Be as quantitative as possible. “MRO2 is higher in amplitude than MRO1” is too general. Instead, “MRO2 is 0.7uV higher in amplitude than MRO1 (0.3uV) ”.

This paper was concerned with:
1) Providing some quantitative evidence about the influence of membrane potential on the process responsible for inactivation.
2) Quantifying the rate at which repolarization restores the ability of the membrane to respond with its characteristic increase in Na⁺ permeability.

J. Physiol. (1952) 116, 497–506
THE DUAL EFFECT OF MEMBRANE POTENTIAL ON SODIUM CONDUCTANCE IN THE GIANT AXON OF LOLIGO

By A. L. Hodgkin and A. F. Huxley
From the Laboratory of the Marine Biological Association, Plymouth, and the Physiological Laboratory, University of Cambridge

"Share the prize!"
Changing conditioning pulse time:

- **Depolarizing duration**
  - Pre-pulse > 20 ms, 40% reduction of $I$.

- **Hyperpolarizing duration**
  - $I_{\text{inactivation at rest!}}$

**Inactivation and recovery exponential**
- Reached steady state
- Faster at larger V steps

**Changing conditioning pulse amplitude**
- Time is constant, pre-step is changed
**Description of \( h \)**

**Modeling \( I_{Na} \)**

\[
g_{Na} = m^3 h g_{Na}
\]

3 states of Na channel:
- closed
- open
- inactivated

**Twin pulse recovery experiments**

Explains the refractory period!

**Activation/inactivation parameters**

What is the state of the Na channel?

Backwards

\( h \) = ability of membrane to undergo a change in Na permeability

40% inactivation at rest!

0 = -55 mV
Modeling 1:

\[ g_K = g_K n^4 \]

A status of K-channel:
- closed
- open

Model prediction and conductances

These experiments explain:
1) the shorter latency of the AP with a large depolarizing stimulus.
2) Refractory period
3) Accommodation.

These experiments set the stage for the major paradigms we still use today:
- Identifying ionic currents by:
  - ion substitution
  - reversal potential
description of I/V curves
activation and inactivation parameters
Modelling

Real neurons have many different currents distinguished by:
- Conducting ions
- Time course (activation/inactivation)
- Sensitivity to membrane potential
- Sensitivity to neuroactive compounds

First high profile computational work

Real

Simulated
Na AP vs. Heart AP

Cardiac AP currents

<table>
<thead>
<tr>
<th>Ion</th>
<th>Response to depolarization</th>
<th>Speed of repolarization</th>
<th>Inactivation</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na</td>
<td>Opens, Rest, but incomplete</td>
<td>Slow</td>
<td>None, Inward</td>
<td>Initial depolarization</td>
</tr>
<tr>
<td>K</td>
<td>Closes, Rest, None</td>
<td>Slow</td>
<td>None, Inward</td>
<td>Maintenance of resting potential</td>
</tr>
<tr>
<td>K</td>
<td>Closes, Slow</td>
<td>Slow</td>
<td>None, Inward</td>
<td>Repolarization</td>
</tr>
<tr>
<td>Ca</td>
<td>Opens due to Ca influx</td>
<td>Slow</td>
<td>None, Inward</td>
<td>Maintenance of resting potential</td>
</tr>
</tbody>
</table>

Snail week 2. Ionic mechanisms of excitability

Reduced Na

Reduced Ca

K+ Channel block with TEA/Cs for CaAP

Figures 1-4: Various events of cardiac AP. These figures demonstrate the effects of various ions on the AP. The blue curve shows an example of the control AP, while the red and green curves show the effects of Na and Ca channel blockers, respectively.
TEA/CS block progressing over time (5 minutes)

IK_Ca Channel “block” with barium