Computational Neuroscience Project Paper (CSD332)

Inhibitory Control

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1. **Motivation**

   I was born with an eye disorder, a rare variant of Amblyopia or popularly known as the lazy eye condition which rendered me effectively blind in my left eye. The reason wasn't deformed organs but rather the refusal of my optic nerve to relay the signals from my eye to my brain. I later learnt that this is a form of lopsided inhibitory control. The treatment I underwent to gain sight was largely experimental and boiled down to using brute force to make the optic nerve work. This piqued my interest in research related to Inhibitory Control.

2. **Literature Review**

   - *Inhibitory control* has multiple definitions depending on various factors such as the nature of control viz voluntary or involuntary, general or specific and large scale effect or cellular scale.
   - *Response inhibition* is a cognitive process and more specifically, an executive function – that permits an individual to inhibit their impulses and natural, habitual, or dominant behavioral responses to stimuli in order to select a more appropriate behavior that is consistent with completing their goals. [1]
   - Voluntary decisions to inhibit happen in the Prefrontal Cortex. Voluntary or involuntary, how this is achieved on a cellular level is explained by understanding Inhibitory Postsynaptic Potential (IPSP)
   - IPSP is a kind of synaptic potential that makes a postsynaptic neuron less likely to generate an action potential.
   - As an example of inhibitory postsynaptic action, consider a neuronal synapse that uses GABA as its transmitter. At such synapses, the GABA receptors typically open channels that are selectively permeable to Cl-. When these channels open, negatively charged chloride ions can flow across the membrane.
   - Assume that the postsynaptic neuron has a resting potential of -60 mV and an action potential threshold of -40 mV. If E-Cl is -70 mV, transmitter release at this synapse will inhibit the postsynaptic cell. Since E-Cl is more negative than the action potential threshold. It reduces the probability that the postsynaptic cell will fire an action potential.
   - Some types of *neurotransmitters*, such as glutamate, consistently result in EPSPs. Others, such as GABA, consistently result in IPSPs.The EPSPs and IPSPs can last as long as 5 to 10 msec. This allows the effect of one postsynaptic potential to build upon the next and so on.

3. **Future Prospects in Cancer Research - Neural Regulation**

The far reach of the Nerves

- Nerves permeate the human body, branching and tapering extensively from a central trunk to form microscopic contacts within tissues.
- These many nerves are integrated together with the brain and spinal cord into a functioning nervous system, which is uniquely capable of executing diverse programs from cognition to movement.
- They also critically regulate stem cell niches throughout the body.

Genetic Basis and Nervous System

- The nervous system is an integral and understudied force capable of shaping the initiation and growth of a variety of cancers such as brain, gastric, pancreatic, prostate, and skin malignancies. These recent conceptual advances regarding the neural regulation of cancer build upon decades of research firmly establishing the fundamental importance of genetic abnormalities to cancer.
- The etiology of nearly all cancers can be attributed, at least in part, to the influence of tumor-suppressor gene and oncogene mutations or other genetic/epigenetic aberrations.

Normal Stem Cell Niches

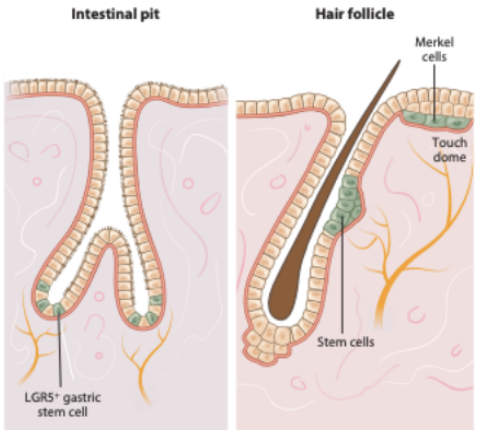

Fig 3.1. Stem Cell Niches

- While each stem cell niche is unique in terms of form and function, one common motif is the presence of nerve terminals.
- Nerves actively participate in shaping stem cell niche development, homeostasis, plasticity, and regeneration throughout the body.
- For many stem cell types, progrowth signals emanating from local nerve terminals are integral to maintenance of homeostatic stem cell population density. It now appears that this system of neural regulation is one of the first to be co-opted by incipient cancer cells on the journey to malignant transformation.
- Peripheral Nerves play diverse roles in promoting cancer initiation, spread and associate pain.

Modelling

- Computational models of the feedback loop between the Central Nervous System and the Mapped tumour growth could help with regulation of doses of inhibitory compounds introduced to the system, determining points of entry, and efficient means of introducing them.
- This is the closest to a "cure" that some scientists think is possible.

4. Experiment

An inhibitory control test is a neuropsychological test that measures an individual's ability to override their natural, habitual, or dominant behavioral response to a stimulus in order to implement more adaptive goal-oriented behaviors. Some of the neuropsychological tests that measure inhibitory control include the Stroop task, go/no-go task, Simon task, Flanker task, antisaccade tasks, delay of gratification tasks, and stop-signal tasks. [2]

Stroop Task

- *The Stroop effect* is the delay in reaction time between congruent and incongruent stimuli.
- The effect was named after John Ridley Stroop, who published the effect in English in 1935 in an article in the Journal of Experimental Psychology entitled "Studies of interference in serial verbal reactions" that includes three different experiments. [3]
- In his experiments, Stroop administered several variations of the same test for which three different kinds of stimuli were created:
    - Names of colors appeared in black ink
    - Names of colors in a different ink than the color named
    - Squares of a given color.

Observations

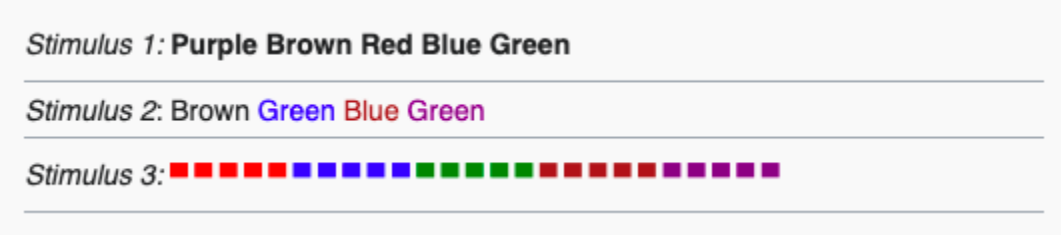

Fig 4.1. Examples of the three stimuli and colors used for each of the activities of the original Stroop article

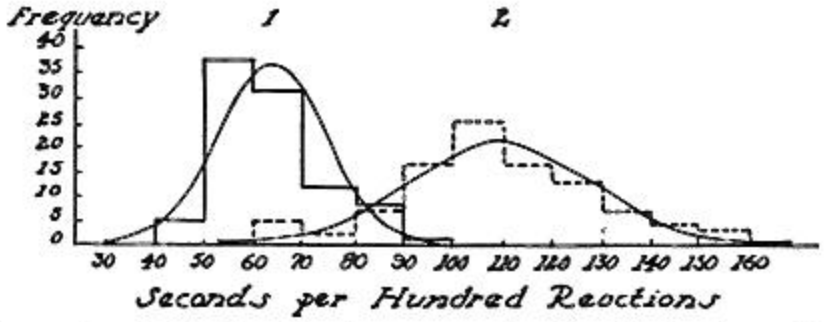

FIG. 1. Showing the effect of interference on naming colors. No interference (1); interference (2).

Fig 4.2. Experiment 2 of the original description of the Stroop Effect (1935).
1- the time that it takes to name the color of the dots
2 - the time that it takes to say the color when there is a conflict with the written word

Results

- Stimuli in Stroop paradigms can be divided into 3 groups: neutral, congruent and incongruent.
- Neutral stimuli are those stimuli in which only the text (similarly to stimuli 1 of Stroop's experiment), or color (similarly to stimuli 3 of Stroop's experiment) are displayed.
- Congruent stimuli are those in which the ink color and the word refer to the same color (for example the word "pink" written in pink).
- Incongruent stimuli are those in which ink color and word differ.
- Three experimental findings are recurrently found in Stroop experiments. A first finding is semantic interference, which states that naming the ink color of neutral stimuli (e.g. when the ink color and word do not interfere with each other) is faster than in incongruent conditions. It is called semantic interference since it is usually accepted that the relationship in meaning between ink color and word is at the root of the interference.
- The second finding, semantic facilitation, explains the finding that naming the ink of congruent stimuli is faster (e.g. when the ink color and the word match) than when neutral stimuli are present (e.g. stimulus 3; when only a coloured square is shown).
- The third finding is that both semantic interference and facilitation disappear when the task consists of reading the word instead of naming the ink color. [4]

5. Model

A single neuron is already a complex biological object. But, basically, neurons are electrically excitable cells that are composed of a soma (cell body), a dendrite tree and an axon. Dendrites and axons connect to each other (through synapses) to create a neural network. Thus, to make a model, we can, for example, choose geometry and some rules that produce the rule of connection between neurons. This simulation is built as follows. First, define the constant current in n, Membrane Capacitance C and resistance R. Here, the ultimate focus is on observing the effect of the IPSP signal on the membrane potential.

Matlab Code

```
% Basic integrate-and-fire neuron with IPSP
clear
% input current
I_1 = 4; % nA
I_2 = 4;
I_3 = 4;
I_4 = 4;

I_1_start      = 10;
I_2_start      = 30;
I_3_start      = 50;
I_4_start      = 70;
I_1_duration   = 2;
I_2_duration   = 2;
I_3_duration   = 2;
I_4_duration   = 2;

IPSP_start     =  72;
IPSP_duration  =  2;
R_IPSP         =  1;

% capacitance and leak resistance
C = 1; % nF
R = 20;  % M ohms
% I & F implementation dV/dt = - V/RC + I/C
% Using h = 1 ms step size, Euler method
V = 0;
tstop = 200;
abs_ref = 15; % absolute refractory period 5
ref = 0; % absolute refractory period counter
V_trace = []; % voltage trace for plotting
V_th = 10; % spike threshold  10
V_spike = 50;
time = 1:tstop;
input = I_1*(time>=I_1_start).*(time<(I_1_start+I_1_duration)) + I_2*(time>=I_2_start).*(time<(I_2_start+I_2_duration)) +
I_3*(time>=I_3_start).*(time<(I_3_start+I_3_duration)) + I_4*(time>=I_4_start).*(time<(I_4_start+I_4_duration));
R_time = R - (R-R_IPSP)*(time>=IPSP_start).*(time<(IPSP_start+IPSP_duration));

for t = 1:tstop
  if ~ref
    V = V - (V/(R_time(t)*C)) + (input(t)/C);
  else
    ref = ref - 1;
    V = 0.2*V_th; % reset voltage
  end

  if (V > V_th)
    V = V_spike;  % emit spike
    ref = abs_ref; % set refractory counter
  end
  V_trace = [V_trace V];
End

figure(3);
j=subplot(311); set(j,'FontSize',10);
plot(V_trace, 'LineWidth', 3);
axis([0 tstop 0 V_spike]);

ylabel('Voltage', 'FontSize', 10);
j=subplot(312); set(j,'FontSize',10);
plot(input, 'LineWidth', 3);
axis([0 tstop 0 10]);
```

```
ylabel('Input Current', 'FontSize', 10);
j=subplot(313); set(j,'FontSize',10);
plot(R_time, 'LineWidth', 3);
axis([0 tstop 0 40]);

xlabel('Time (ms)', 'FontSize', 10);
ylabel('Leak Resistance', 'FontSize', 10);
```

Observations

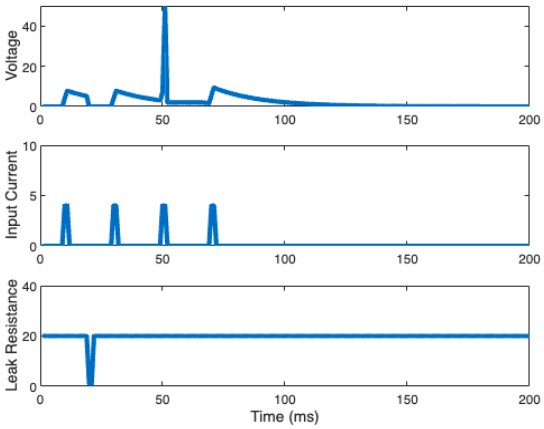

Fig 5.1. Effect of Leak Resistance on Voltage at IPSP_start = 20

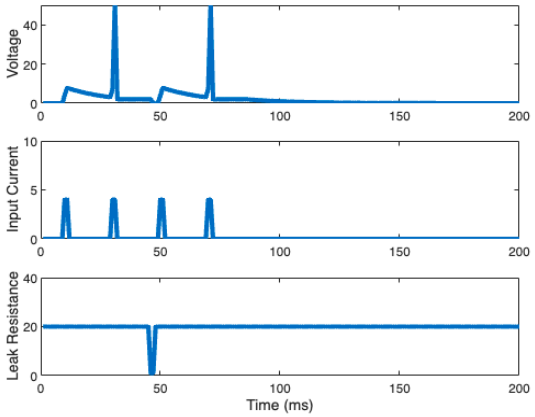

Fig 5.2. Effect of Leak Resistance on Voltage at IPSP_start = 46

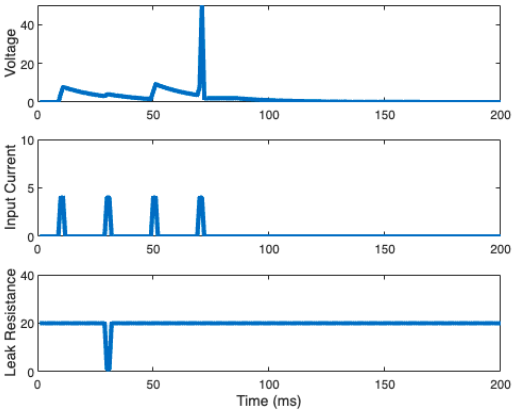

Fig 5.3. Effect of Leak Resistance on Voltage at IPSP_start = 30

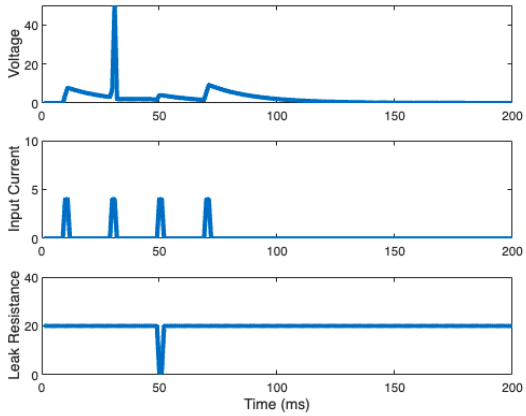

Fig 5.4. Effect of Leak Resistance on Voltage at IPSP_start = 50

Results

The start time of an IPSP signal determines the successive effect on membrane potential. Here, the effect of IPSP on an initiation potential or the successive booster potential completely curbs any chance at transmission.

6. Acknowledgements

I thank Prof. Ketan Bajaj for providing me with the opportunity to work on this project and take away valuable applied learnings in the field of Computational Neuroscience. I extend my gratitude and appreciation to the numerous researchers whose research I have cited in this paper. I am grateful to my batch mates who listened to my ideas and helped me implement them.

7. References

1. Ilieva IP, Hook CJ, Farah MJ (2015). "Prescription Stimulants' Effects on Healthy Inhibitory Control, Working Memory, and Episodic Memory: A Meta-analysis". J Cogn Neurosci.
2. Diamond A (2013). "Executive functions". Annu Rev Psychol. 64: 135–168
3. Stroop, John Ridley (1935). "Studies of interference in serial verbal reactions". Journal of Experimental Psychology.
4. Van Maanen L, Van Rijn H, Borst JP (December 2009). "Stroop and picture-word interference are two sides of the same coin". Psychon Bull Rev.