Excitability of Type III Neuron

Physics 178

Erik Amundson, Tharindu Fernando, Joanne Ting-Yu Hsu, Benjamin Shifflett

I. Introduction

This paper will explore an attempt to reproduce the results of a paper by Huguet et al.: *Phasic Firing and Coincidence Detection by Subthreshold Negative Feedback: Divisive or Subtractive, or Better, Both* [1]. Huguet et al. model phasic neurons, which fire after activation by presynaptic input (which contrasts with tonic firing*). Phasic neurons have high temporal precision for phase locking and coincidence detection, and are classified as Type III neurons. Type III neurons are fired at most once or twice (or not at all) regardless of stimulus intensity or duration; typically due to a fast-rising input (such as a step current) [1].

What controls phasicness is dynamic, voltage-gated negative feedback that can happen at subthreshold levels. This prevents neurons from spiking if increasing input doesn't rise fast enough. There are two such negative feedback mechanisms that are responsible for phasicness: Subtractive (S) and Divisive (D). A combination of both S and D, the Combined mechanism (C), could be considered as well. The Subtractive mechanism results from an outward, low-threshold, Potassium current; while the Divisive mechanism results from an inward Sodium current with subthreshold inactivation. The Combined mechanism integrates both S and D into a mechanism that draws from both S and D. The general idea behind all mechanisms is that if a neuron depolarizes slowly, an activation/inactivation process develops faster than the depolarization so that it does not fire (and so is maintained at subthreshold levels).

A version of the Hodgkin-Huxley model modified for Type III neurons was used to model the S, D and C mechanisms (see section *II. Method*). Performance was assessed per the precision of phase-locking and coincidence detection given by the models' responses to repetitive packets of excitatory synaptic inputs with varying temporal coherence.

** which is often characterized by a steady action potential firing at a constant frequency, i.e. without presynaptic input*[4]

II. Method

A. Neuron Models:

We use three modified Hodgkin-Huxley models developed by Huguet et al[1]. (2017), and solve the coupled ordinary differential equations using Mathematica. The three models are the subtractive, divisive, and combined models. All three models have type III excitability but each has its own characteristics due to modified parameters and constant values.

1. Subtractive Model (S) *[the inactivation variable for the Sodium current I_{Na} is frozen; is a 2-variable model]*

$$C(dV/dt) = -2(g_{Na}m_\infty(V)^3 h_0(V-E_{Na}) + g_{KLT}w^4 z_0(V-E_K) + g_I(V-E_I)) + I$$

$$dw/dt = 3(\frac{w_\infty(V) - w}{\tau_w(V)})$$

2. Divisive Model (D) *[the conductance of the low-threshold Potassium current I_{KLT} is frozen; is a 2-variable model]*

$$C(dV/dt) = -2(g_{Na}m_\infty(V)^3 h(V-E_{Na}) + g_{KLT}w_0^4 z_0(V-E_K) + g_I(V-E_I)) + I$$

$$dh/dt = 3(\frac{h_\infty(V) - h}{\tau_h(V)})$$

3. Combined Model (C) *[includes modifications to both S and D above; and is a 3-dimensional model]*

$$C(dV/dt) = -2(g_{Na}m_\infty(V)^3 h(V-E_{Na}) + g_{KLT}w^4 z_0(V-E_K) + g_I(V-E_I)) + I$$

$$dh/dt = 3(\frac{h_\infty(V) - h}{\tau_h(V)})$$

$$dw/dt = 3(\frac{w_\infty(V) - w}{\tau_w(V)})$$

For the most part, values for constants in the equations above were taken directly from Huguet et al.[1] The action potential of the models are -40 (mV).

B. Input Stimulation

The models were fed with the following input current functions:

1. Step Input

   $I(t) = \frac{1}{1+Exp((t-5)/0.01)}\ (nA)$

   This is an approximation of the Heaviside step function. We vary the amplitude of the step input in order to see the its influence on the voltage output for different mechanisms.

2. Ramp Input

   $I(t) = \frac{1}{1+Exp((t-5)/k)}\ (nA)$

   By varying the parameter k from 0.01 to 1, the input change from a step function to a gradually increased ramp function.

3. Constant Slope Input

   $I(t) = m\ t\ (nA)$

   By varying the slope (m) of the input, we try to observe the threshold slope that trigger the output voltage.

4. Sinusoidal Input:
   $I(t) = Abs(Sin(\omega t))\ (nA)$

   In the above equation, the only constant is ω, which is just the frequency at which the sine function oscillates. We chose to take the absolute value of the sine function because it does not make sense for an input current to be negative.
5. Noisy, Constant Mean Input

   $I(t) = m + \sigma\ \eta(t)\ (nA)$
   In the above equation, m is the mean of the input, $\eta(t)$ is the white noise process, and σ is the standard deviation of the white noise process. We interpolate a set of random data distributed according to the white noise process with the constant mean (m) ranging from -1 to 2.5 (nA).

6. Spike Train Input
   $I(t) = \frac{exp(b\ Cos(t-a))}{2\ \pi\ Bessel(0,b)}\ (nA)$

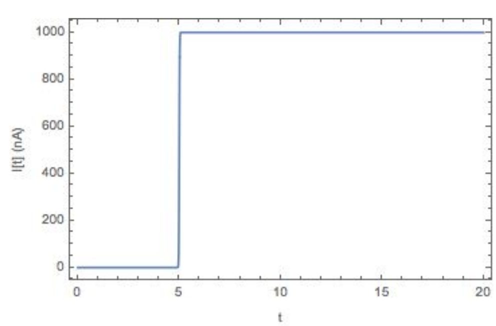
   The above equation is called the von Mises Distribution, and represents coincident input. The parameter b is the temporal coherence, which is inversely proportional to the width the spikes. We vary b from 0 to 20, which produces input varying from a uniform distribution to a spike train.

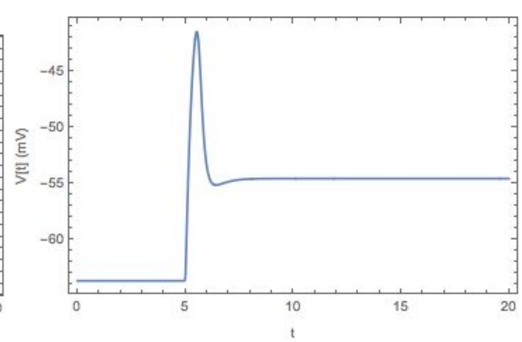
III. Result

A. Step Input

The step input is the most basic input for this model. It represents a constant current suddenly being induced upon the neuron. We decided to animate the step function over a range of 0 to 2 nA to show that there is a spike threshold around 1 nA for the values we used to set up the model.

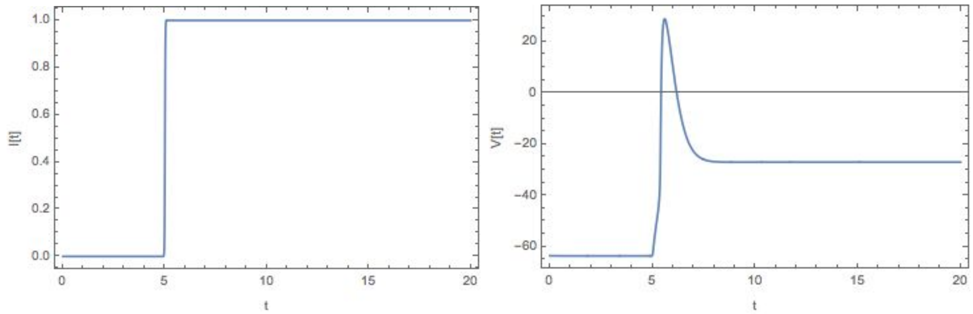
1. Subtractive Model





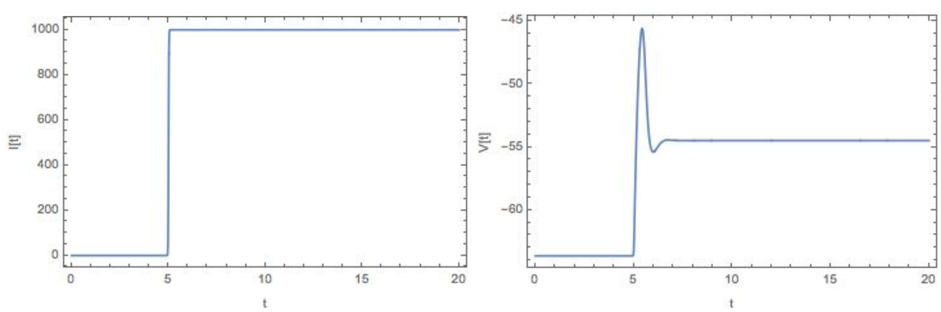
The subtractive model has the most thinnest spike of the three models. When the current reaches 1 nA, the output voltage spikes to 0 mV, then comes down very fast to nearly the initial condition. This is because the subtractive model has the most temporal precision, but does not provide robustness in the same way that the divisive and the combined models do.

2. Divisive Model



The divisive model, contrary to the subtractive model, spikes very smoothly. There is still a jump at the threshold current from below the threshold voltage to above it, however as the step size increases the voltage output is more smooth than the extreme subtractive model. An interesting thing to note here is that as the current gets high above the threshold current, the voltage after the spike indicates that the neuron would continuously fire as the voltage is above the threshold. This is not consistent with the phasic properties of a Type III neuron. It is, however, consistent with the prior knowledge that the divisive model is not as accurate as the subtractive or the combined models. It's purpose is mostly to model the robustness of a type III neuron.

Combined Model

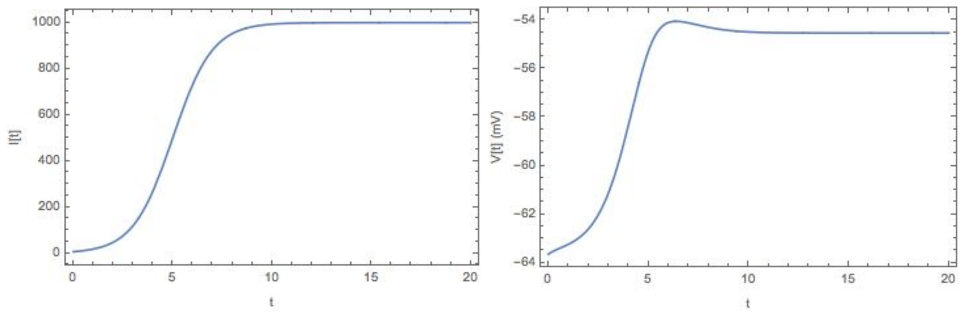


The combined model here shows properties of both the subtractive and the divisive models. It has the steep spike of the subtractive model and the smooth downspike of the divisive model. The combined model is clearly the superior option. It allows to have the accuracy of the subtractive model and the robustness of the divisive model. It is also worth noting that the constant voltage after the spike is in between that of the subtractive and divisive. It is still, however, below the threshold voltage and thus maintains the phasic properties of a Type III neuron.

B. Ramp Input

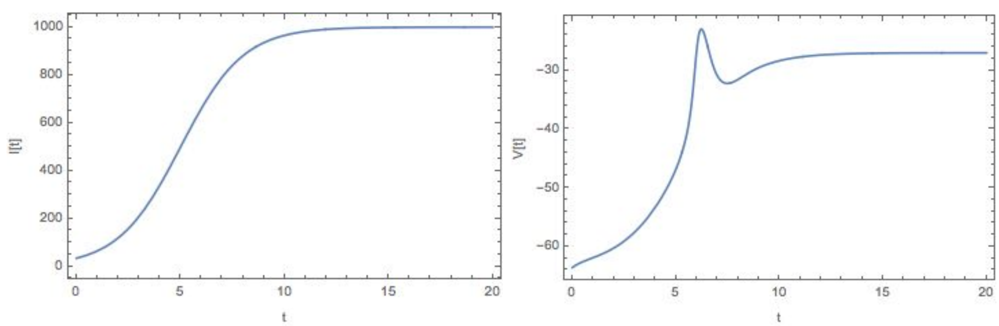
For this model, we again use the basic step function as voltage. This time, however, instead of evolving the input over its amplitude, we evolved it over its step time. As a result, the input transforms from a step function into a slowly increasing ramp function, and we can observe its effect on the different models. This form of input is an effective tool for testing the robustness of properties.

1. Subtractive Model



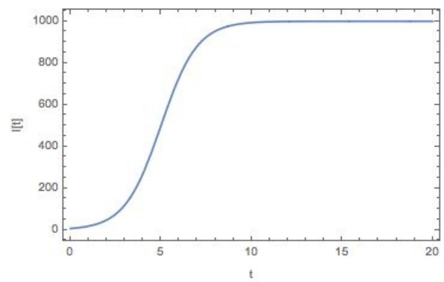
The subtractive model is affected drastically by smoothing out the step function. As soon as the ramp begins to have a slope, the spike size decreases significantly, eventually disappearing entirely. The rapidity at which the spike decreases exemplifies the non-robust property of the subtractive model. If the input changes slightly from a step function, it no longer spikes and thus no longer upholds the phasic properties that define a Type III neuron.

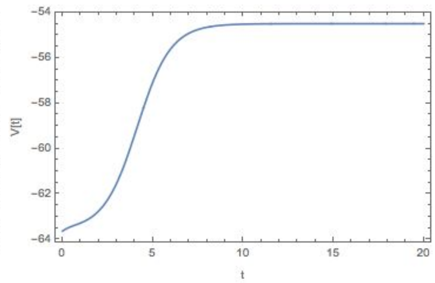
2. Divisive Model



The divisive model exhibits similar properties when compared to the subtractive model. However, the slope it takes for the divisive model to lose its spike is much larger than for the subtractive model. As a point of reference, we evolved the subtractive model over a range of $0 < k < 100$, while we evolved the divisive model over a range of $0 < k < 400$. The two animations look similar to each other despite the difference in range, so we can conclude that the divisive model exhibits much more robustness with regard to the phasic properties of a Type III neuron.

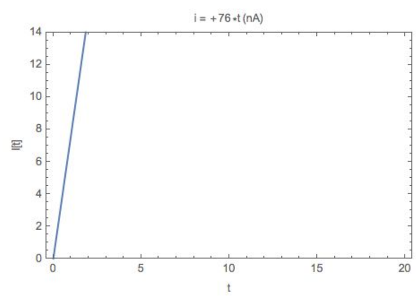
3. Combined Model

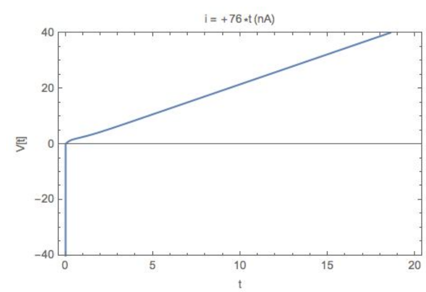




The combined model in this case more closely mirrors the subtractive. It is slightly slower to lose its spike, which is due to the influence of the divisive model. However, unlike with varying amplitude of the current when the combined model was halfway between the two other models, in this case it is much closer to the subtractive model. The most important phenomena that we observe in all three models is that there is a relationship between the slope of the input and the probability of firing. Essentially, if the slope is not steep enough and the amplitude of the input current doesn't overload the model, the neuron will not fire.

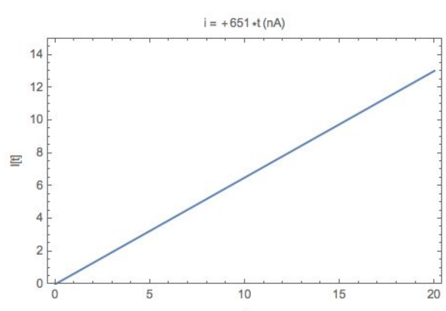
C. Constant Slope Input
   1. Subtractive Model

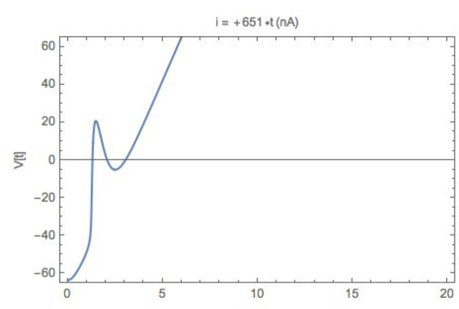




There is little response of the subtractive mechanism to the constant slope input. This is most likely related to the fact that the subtractive model operates within a restricted parameter range and so it only attempts to fire an action potential rarely and when it does it is quickly overtaken by the increasing current values of the input.

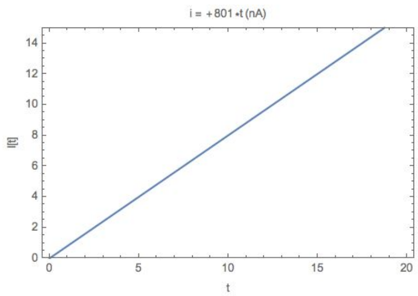
   2. Divisive Model:

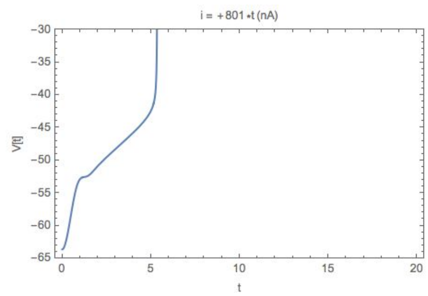




The divisive model’s response to the changing slope input most closely resembles that of an action potential. A peak forms, rises, and reaches the peak voltage characteristic of action potentials (20mV) as the slope function of the current changes. However, the voltage does not go back to equilibrium since the input current is increasing with time and soon overloads the system and causes the voltage to increase in a manner directly proportional to the change in slope of the current. From this graph, it appears the divisive model responds best to input currents with constant slopes.

3. Combined Model:



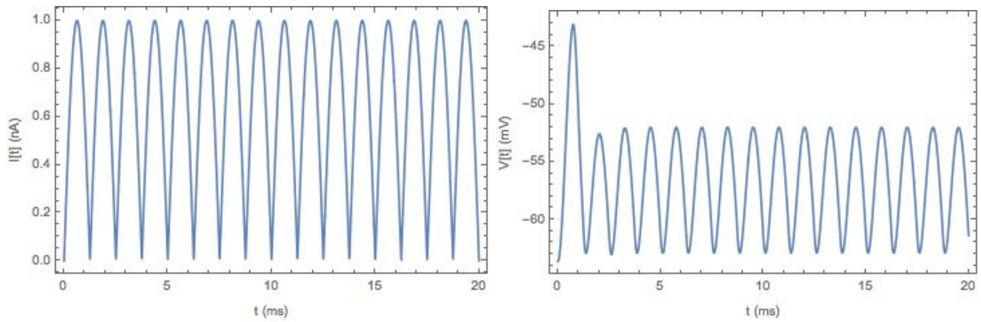


The rapid increase in the voltage that occurs around 16 seconds and decreases in time of its onset begins at around the same point of the small fluctuation in the subtractive model. The combined model, like the subtractive model, is generally heavily influenced by the monotonically increasing slope function and only achieves some points where the voltage graph resembles that of an action potential. There is a resemblance of a peak around where the divisive model experiences its change in voltage thats is reminiscent of an action potential (minus reestablishment of equilibrium). These properties show that the divisive model incorporates aspects of both models, making its degree of effectiveness vary on what model dominates at the time.

D. Sinusoidal Input

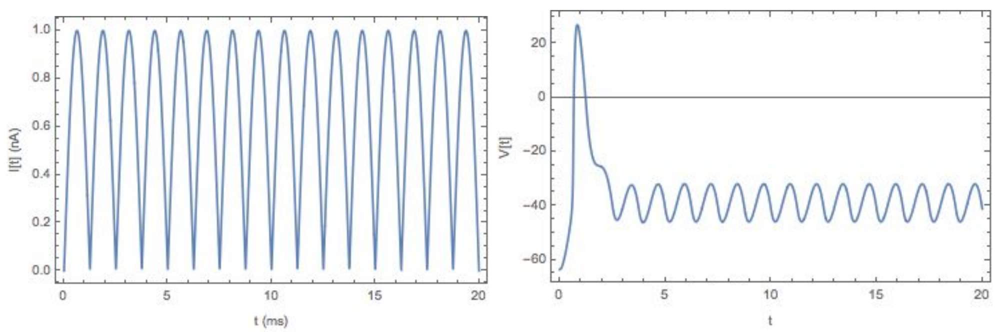
The sinusoidal input is perhaps the best example of phasic properties in a Type III neuron, and also in the three models. We chose to take the absolute value of the sine function for consistency with an input current. It would not make sense for the input current to leave the neuron. However, it is still an oscillating current with peaks both up and down.

1. Subtractive Model:



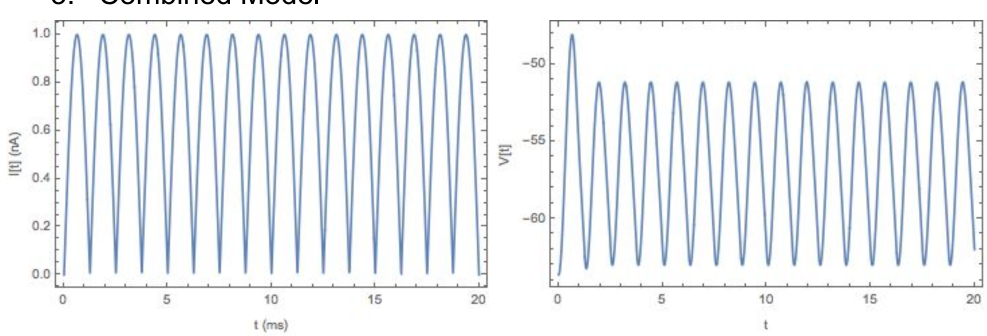
With a sinusoidal input, the subtractive model shows the least conservation of phasic properties. The initial spike is around twice as high as the subsequent spikes, but the subsequent spikes are still significant. With a lower activation threshold than -40 mV, it is possible that a combined model would indicate a spike train rather than a single spike. The reason that the subtractive model has such high subsequent spikes is that it is not strong in providing robustness to the phasic firing properties of a Type III neuron, but rather its strength comes in precision over a short range of currents.

2. Divisive Model



The divisive model, contrary to the subtractive model, clearly demonstrates phasic properties. The initial spike, rather than being twice as high as the subsequent spikes, is closer to four or five times as high. However, the divisive model's weakness in this situation is its precision. The subsequent spikes, while quite small, oscillate above and below the threshold voltage of -40 mV. These oscillations indicate an oscillating spike train rather than only one large spike. As a result, it does not fully model the behavior of a Type III neuron.

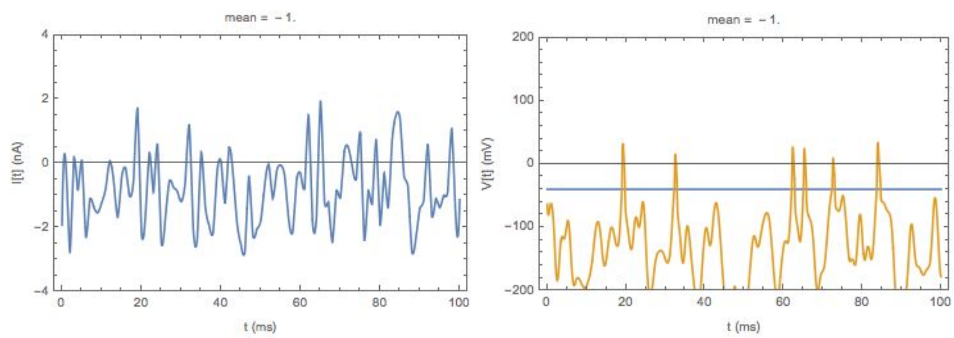
3. Combined Model



The combined model in this case looks closer to the subtractive model. Once again, the main spike is larger than the subsequent spikes. In this case however, the subsequent spikes are even closer to the size of the original spike. It is important to note, however, that according to this model the neuron does not spike at all, as the threshold voltage is -40 mV and the combined model barely reaches -45 mV. This could be a problem with our model, but it could also imply that the absolute value of a sinusoidal input is not a realistic input and would not cause a sufficient voltage spike in an actual Type III neuron.

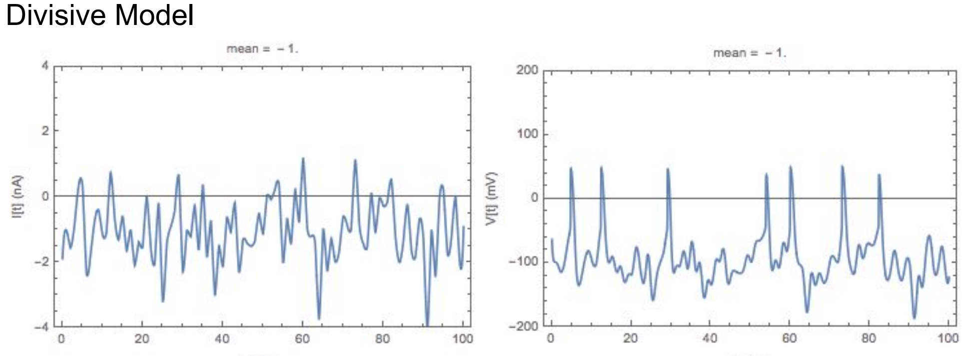
E. Noisy, Constant Mean Input

1. Subtractive Model:



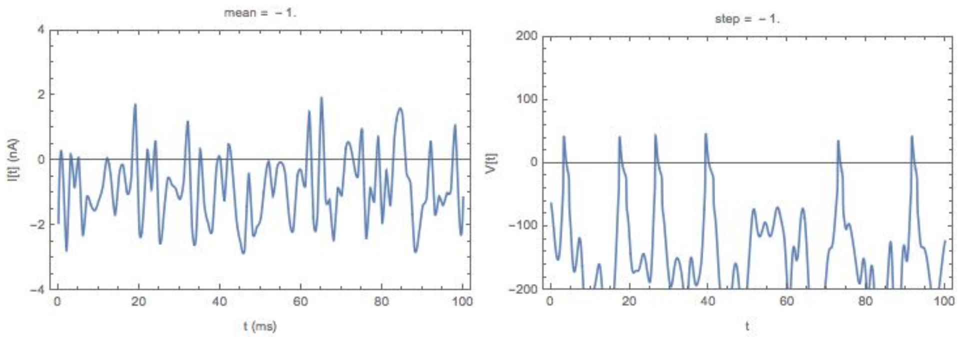
When the mean of the noisy input is between -0.5 to 1.2(nA), the voltage output spikes very precisely. The shape and timing of the voltage output are almost the same as the input current. However, outside of this range, the shape of the voltage output is distorted or there is little voltage spikes. This indicate that the subtractive model has great temporal precision within a small input range. Moreover, the subtractive model has less spikes compared to the other two models. This is because the reduced sodium conductance in the subtractive model requires stronger fluctuations to generate spikes.

2. Divisive Model



The voltage output of the divisive model ranges from -65 to 50 (mV). Its amplitude of the output spike is larger than the subtractive and combined models, which have the output range -65 to 0 (mV) and -65 to 40 (mV) respectively. The divisive model work well within the range of -1 to 2 (nA), which is a bigger range than the subtractive model. Although the divisive model guarantee the robustness of the phasic properties and can work for a wider range of input, it is less precise compared to the subtractive model. The shape and the timing of the voltage output is not as precise as the subtractive model.

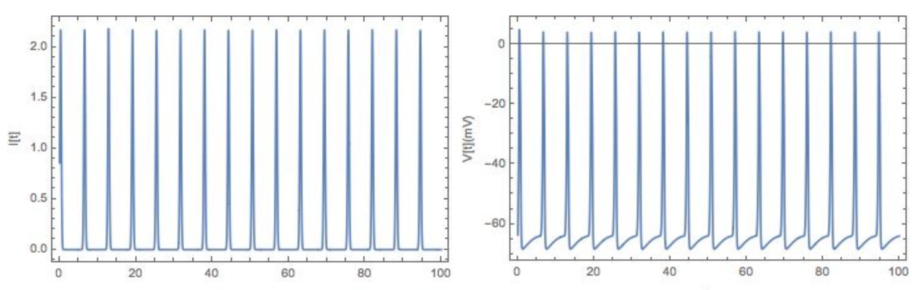
3. Combined Model



The combined model has the intermediate voltage output range (-65 to 40 (mV)) and works for an intermediate current input (-0.7 to 1.7 (nA)). It has a better precision than the divisive model, but has worse precision than the subtractive model.

F. Spike Train Input
The spike train input capture our neuron spike input most precisely. In this simulation, we observe that the subtractive model has the lowest output amplitude, the smallest parameter range to pass threshold, and the smallest output spike width, and vice verse for the divisive model. The result for the combined model lies in between the other two models. An interesting note is that the width of the combined model is very wide on the bottom but precise on the top (see plot). As long as the spike decrease fast enough at the threshold level (on the top), the output can represent a good temporal precision.

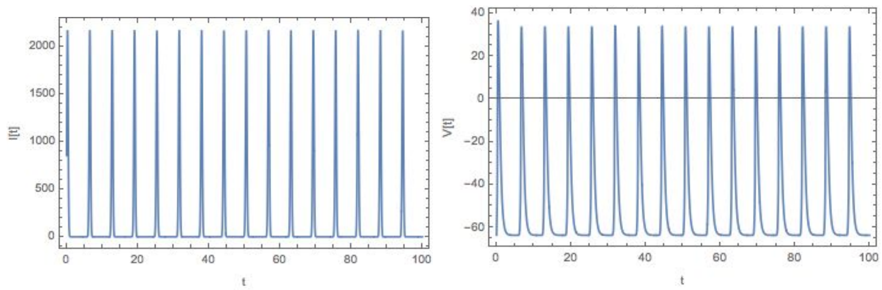
1. Subtractive Model:



a) Voltage Output Amplitude (b=20): 0 (mV)
b) Pass Threshold at: b=10

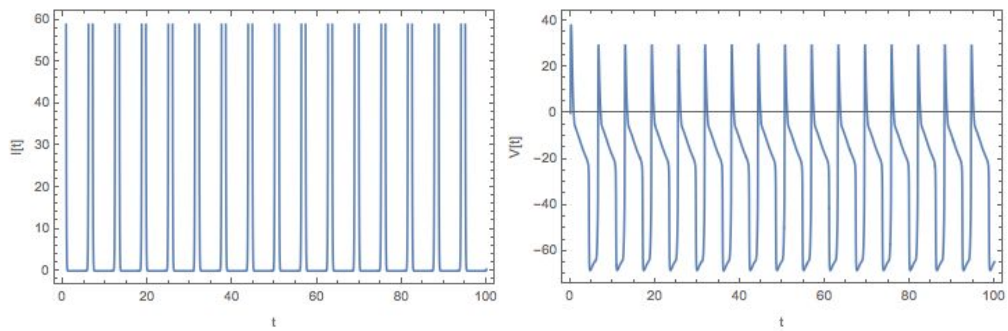
c) Output Spike Width: Small

2. Divisive Model



a) Voltage Output Amplitude (b=20): 40 (mV)
b) Pass Threshold at: b=4
c) Output Spike Width: Big

3. Combined Model

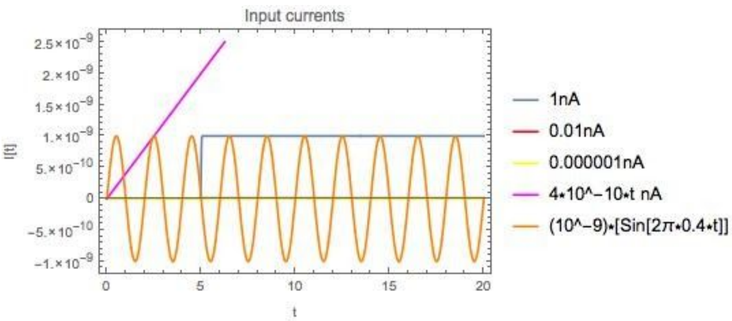


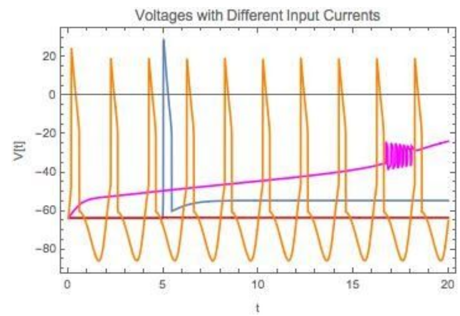
a) Voltage Output Amplitude (b=20): 20 (mV)
b) Pass Threshold at: b=8
c) Output Spike Width: Small on the top but big on the bottom

G. Exploration

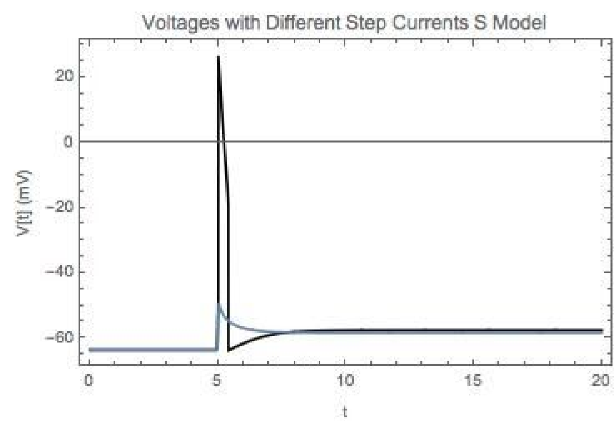
We tested the limitations and parameters of each of the models through the utilization of various current inputs with differing derivatives, maximum values, and other factors. For each model we tested five different types of inputs and plotted the resulting voltages on the same graph, making three graphs of five voltage responses each. The currents are as follows: 1nA step function (blue), 0.01nA step function (red), 0.000001 nA step function (yellow), a monotonically increasing function (magenta), and a Sine function (orange).

1. Subtractive Model

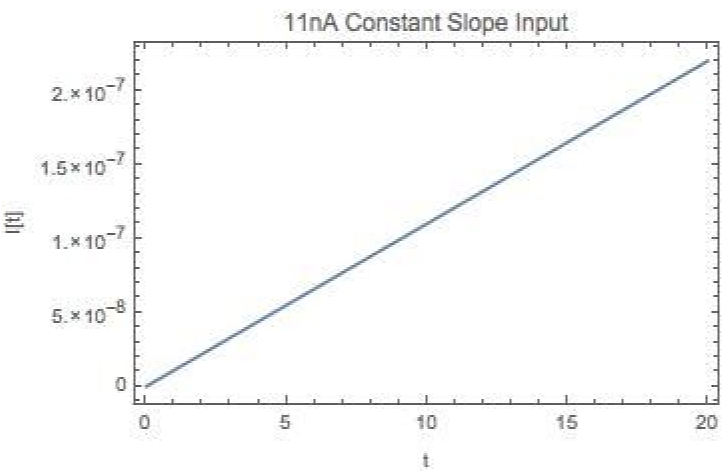


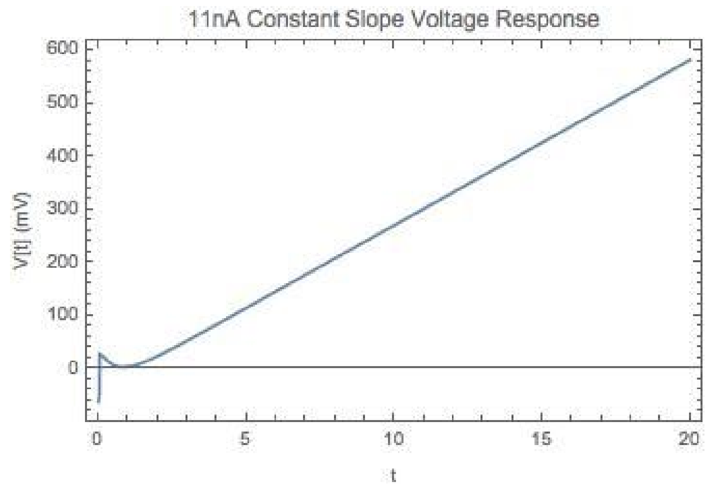


As evidenced by comparing the graphs of the inputs with the corresponding voltage outputs it is clear that only the 1nA step function (blue) and the sinusoidal input (orange) trigger action potentials in the subtractive model. The linearly increasing function (magenta) has a small range where the voltage fluctuates, as if attempting to fire an action potential yet being stifled repeatedly. This is possibly representative of the fact that the subtractive model operates best within a small parameter range as stated in Huguet et. al. This phenomena may also be related to the fact that the range in question is near -40mV which is near the plausible threshold voltage of the system, and so due to that the system attempts to fire yet is overcome by the subthreshold negative feedback mechanism. The 1nA voltage graph has a greater maximum than any of the voltage peaks of the sinusoidal voltage graph. This is due to the fact that Type III firing depends on the slope of the input, and the step function has a larger derivative than the Sine function (Step derivative: 15 nA/s; Sine derivative: 2.54 nA/s). The voltage response of the sinusoidal graph also showcases the temporal precision of the subtractive model, with spikes corresponding to near the exact moment the current increases.



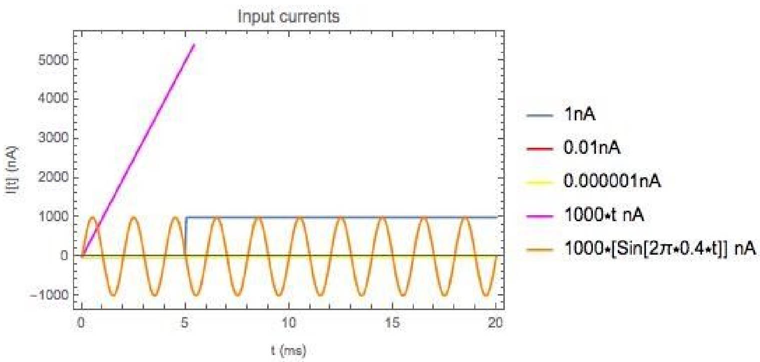
The above figure is a graph of voltage responses to two step function current inputs: the minimum needed to fire an action potential (0.44 nA; black) and the maximum step function that does not trigger an action potential (0.43 nA; blue). The 0.44nA step function has a slope (current derivative) of 11nA/s, while the 0.43 nA step function has a slope of 10.75nA/s. This small difference is enough to cause the subtractive model to fire or to not reach threshold. Due to the fact that the slope of the step functions are essentially infinite in theory the small changes in slope between the models may not be the only factor affecting action potential generation. The action potential generation for this model may also be dependent on the height of the step function/maximum current value aside from the slope of the current. This is evident due to the fact the Sine graph has a max value of 1nA while the step function that does not cause an action potential has a height of 0.43nA, yet the slope of the Sine graph is less than that of the step function (Sine: 2.54 nA/s; Step: 11nA/s).

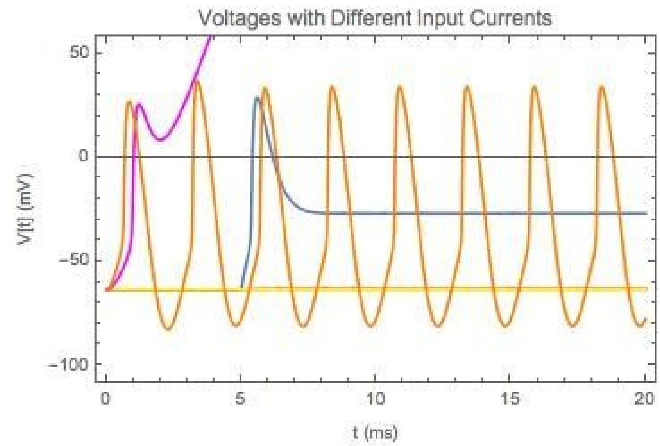


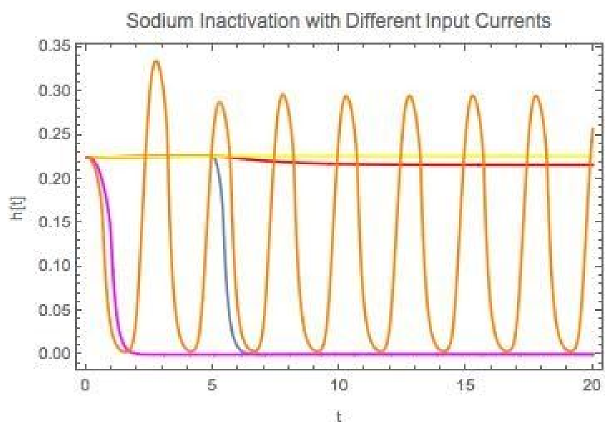


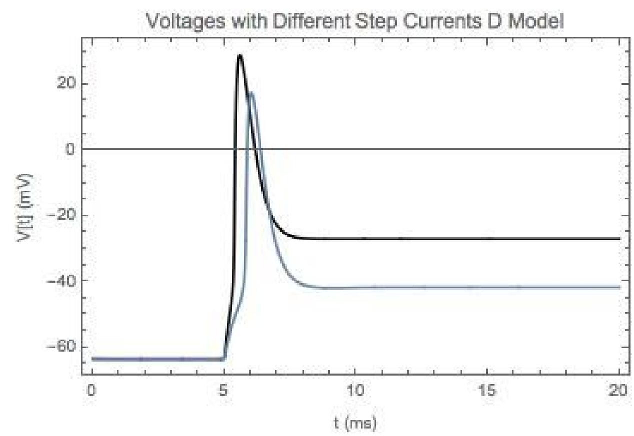
The above graphs show the response of a neuron to a constant current of slope of 11nA/s. The slope of this graph is equal to that of the above step function which fired an action potential, the fact that this line does not produce the same results showcases that current derivative is not the only factor which affects Type III excitability in the subtractive model. The voltage graph of the 11nA constant slope input gets near threshold at the beginning, meaning the slope is close to that which triggers an action potential in the system yet the neuron is quickly overloaded due to the increase in the current over time. It is possible that an action potential is not generated since the current leaves the operable range too quickly, firing also depends on the second derivative/concavity of the current, or some other criteria. The second derivative may play an important role since that can possibly explain the fact that the Sine function triggers an action potential yet has a smaller slope than the 11nA line function (Sine: 2.54 nA/s; Line: 11nA/s).

2. Divisive Model





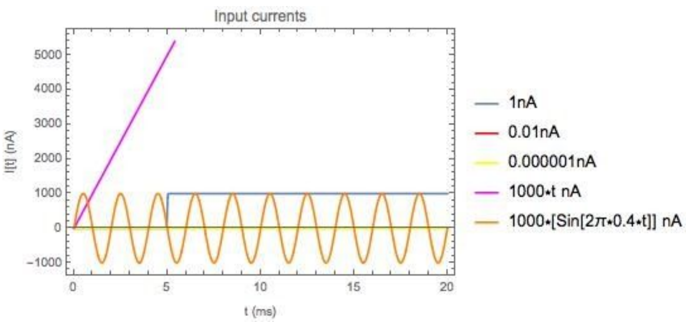


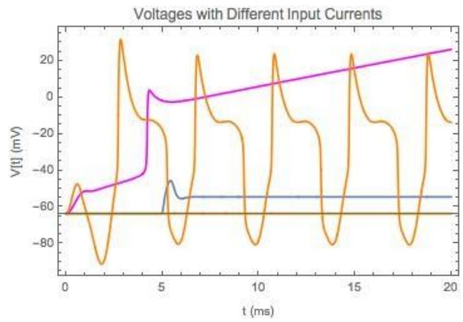


Note: The above graph of the input currents is scaled in picoAmperes, not nanoAmperes as indicated.

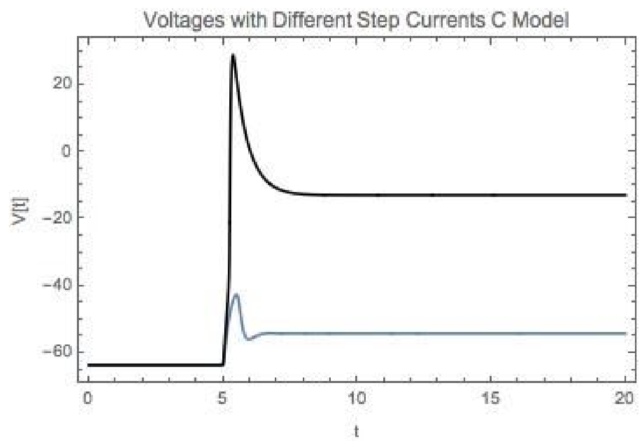
The divisive model fires for the sinusoidal and 1nA step function, same as the subtractive model, yet also experiences an action potential for the constant slope current. The spiking of the divisive model is slower than the subtractive model (Roughly 0.4 second delay versus 0.02 seconds) which shows how the subtractive model has a better degree of phase locking and temporal precision. The sinusoidal input having a greater voltage response compared to the 1nA step current is somewhat related to the inactivation of the sodium current (h variable) as evident from the above graph. This change in h is most likely characteristic of the system and is possibly due to the divisive model being more susceptible to oscillatory inputs (Gradual slope) in comparison to current injections (Infinite slope). The firing of the neuron in response to the constant slope current shows that the current value is critical for the divisive model. This is because at one second, when the action potential is generated, the current value is 1nA (Same as 1nA step which fires) and even with the lesser slope compared to the 1nA step function the neuron still fires. The graph of the voltages with different step functions (Black: 1nA; Blue: 0.58nA) shows how the lower maximum current values causes the divisive model to trigger an action potential at a slower rate.

3. Combined Model





Note: The above graph of the input currents is scaled in picoAmperes, not nanoAmperes as indicated.



The combined model only fires a proper action potential for the sinusoidal input, while the 1nA step function comes close to firing and achieves threshold voltage when at a larger maximum current value, say 1.7 nA. The combined model has a similar time delay to that of the divisive model and has a similar sharp voltage peak as that of the subtractive model. The fact that the divisive model fires for the sinusoidal input and not for the step function when the step function has a larger slope (Step: 42.5nA/s; Sine: 3.14nA/s) and same maximum value shows how the divisive model depends on other factors as well. The graph of the different step currents (Black: 1.7nA; Blue: 1nA) shows how the divisive model has strong phase locking and also has a characteristic difference in how it does not come back down to -60mV like the other models, this could provide the combined model less susceptibility to firing.

IV. Conclusion

- In order to answer the objective goals prescribed in the project assignment, the paper by Huguet et al.[1] will be used graciously as follows: Theoretically, varying input current frequencies and vector strengths are a measure of coincidence detection. Computing the output firing rate allows for a measure of entrainment while the vector strength is indicative of phase locking.

The S and D mechanisms both were shown to enhance vector strength (making phase locking more robust). However, spikers in the S model outperformed those of D when it came to temporal precision and coincidence detection; but within a strict parameter range. The D model, on the other hand, was found to be less sensitive to the arrival time of inhibitory inputs (in contrast to both S and C). While this guaranteed robustness of the system, it did so with less precision. Overall, however, it was concluded that phasic neurons with both negative feedback processes (i.e. from the C model) are more robust to changes in applied currents and conductance densities than models with just either S or D on their own. S and D synergize in C to enhance phasic properties.
Even though exact measures of coincidence detection**, entrainment and phase locking weren't made during our efforts to replicate the paper's results, we could reproduce the authors' results for different input current functions. Further exploration allowed us more insight into the models.

*** except in the last input current case, the von Mises distribution (which represents coincident input)*

- The further exploration of the models gave us insight into the conditions that each model performs best at and which properties of the input currents trigger the neuron to fire. Type III excitability is characterized by its phasic firing and response to the slope of the input. Both of these criteria were met by all three of the models, yet the models showed other criteria that influenced their activation. Other factors include the maximum current value of the input and the second derivative of the input. Certain minimum current values must be met for all of the models in order for firing to occur and in some cases, notably the subtractive model, the second derivative of the current seems to affect the height of the voltage output. Thus, slope of input current is important yet is not the only factor as evidenced by the fact that constant slope functions with slopes equal to that of step functions do not always correspond to the same voltage output (e.g. 11nA step versus 11nA constant slope for subtractive model). Overall, slope of input current is a crucial component of Type III excitability yet other factors such as maximal current values, intrinsic properties of the gating variables, and other factors also influence whether or not an action potential is generated.

V. References

1. Phasic Firing and Coincidence Detection by Subthreshold Negative Feedback: Divisive or Subtractive or, Better, Both, G. Huguet, X. Meng, and J. Rinzel, *Frontiers in Comp Neuroscience* 11 (2017): 3.
2. Rothman, J. S., and Manis, P. B. (2003). The roles potassium currents play in regulating the electrical activity of ventral cochlear nucleus neurons. *J. Neurophysiol.* 89, 3097–3113. doi: 10.1152/jn.00127.2002.
3. United States of America. National Institute of Health. *The Brain: Understanding Neurobiology*. U.S. Department of Health and Human Services, n.d. Web. 22 Mar. 2017.
4. Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia, Grace AA, *PubMed* PMID: 1676137.