Modeling the Effects of Parameter Changes on the Spiking Activity of Serotonergic Neurons

Valliappa Chockalingam, Thai-Son Nguyen, Vibin Parakkattu
University of Michigan
Ann Arbor, MI 48109
{valli, tsnguyen, vibinp}@umich.edu

I. Background and Motivation

Serotonin, or 5-hydroxytryptamine (5-HT), is a monoamine neurotransmitter that is biochemically derived from tryptophan, an aromatic aminoacid that is used in the biosynthesis of proteins [1]. It is primarily found in the gastrointestinal tract, blood platelets and the central nervous system of animals, including humans. The neurotransmitter has been extensively studied owing to its role in regulating mood and behavior and the sleep-wake cycle [1].

Depression, defined as "a state of low mood and aversion to activity or apathy that can affect a person's thoughts, behavior, feelings and sense of well-being" in [2], is a topic that has been strongly debated about [3], [2]. A few decades ago, some evidence for a relation between depression and serotonin was found. In particular, studies have shown that, in humans, the levels of 5-HT1A receptor activation in the brain is negatively correlated with aggression. Additionally, a mutation in the gene that codes for the 5-HT2A receptor may double the risk of suicide in those with the genotype [4], and nearly 10% of total variance in anxiety-related personality depends on variations in the description of where, when, and how many serotonin transporter neurons deploy [5]. This lead to Selective Serotonin Reuptake Inhibitors (SSRIs), the largest class of antidepressants, which increase the extracellular level of serotonin (particularly in synaptic clefts) by limiting the reabsorption into presynaptic cells and hence increasing the level of serotonin available to bind to postsynaptic receptors.

Being concerned with serotonin, we now turn to the parts of the nervous system where serotonin is involved. The Dorsal Raphe Nucleus (DRN) in the midbrain reticular formation is the largest serotonergic (serotonin producing) nucleus in the brain (the general region is shown in Figure 1 with the label "Raphe Nuclei"). As the phrase implies, the DRN serotonergic nucleus is the principal source of serotonin. The serotonergic neurons of the DRN will be henceforth denoted DRN SE at times for brevity (following past work like [6]).

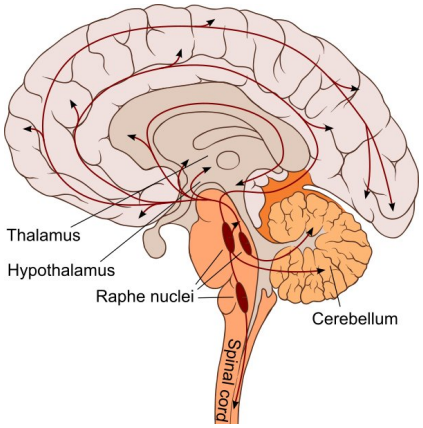

Figure 1: Serotonergic projections of the DRN extend throughout the central nervous system *(Patrick J. Lynch, medical illustrator; C. Carl Jaffe, MD, cardiologist.)*

The functions of the DRN include encoding reward signals, influencing learning, controlling emotions, and regulating neuroplasticity. [6]

Serotonergic neurons in the DRN typically fire in a slow and tonic pattern. Its action potentials are characterized by a long after-hyperpolarization followed by a plateau phase. However, it should be noted that some serotonergic neurons display bursts of spiking with small depolarizing currents. [6] Studies that record spiking activity of the neurons in vivo have produced variable results because the cells, in vivo, have a complex electrophysiological and neurochemical environment [6].

Now, as with serotonin, the DRN is implicated in depression, and studies have shown that the DRN is smaller in people with depression, but somewhat paradoxically, is higher in density in people who commit suicide [7], [8], [9]. Furthermore, it has been shown that the spiking frequency of serotonergic neurons in depressed rats is 35.4% lower than the frequency of serotonergic neurons in non-depressed rats [10]. Modeling how changes in the physiological parameters of a DRN SE neurons

affects spiking activity may give insight into how depression changes the physiological properties of an actual serotonergic neuron.

With that said, it is noted here again that there is indeed debate about whether depression and related mental disorders have just a physiological or genetic aspect, and what that may be, or involve just environmental aspect or some mixture of both [3], [8], [7], [9]. Furthermore, seeing the growth in the cases of depression [11], some have questioned whether depression is really an epidemic or "pseudo-epidemic" [12] and others have brought up the possibly skeptical nature of SSRIs and stated that SSRIs are largely a marketed myth [3].

So, while analyzing DRN SE might benefit research into depression and anxiety related disorders, the motivation for such an analysis becomes more clear from recent research into how DRN SE related to reward, punishment, and reward delay. [13] showed that, upon measuring the activity of single DRN SE neurons in primates given saccade tasks to obtain varying amounts of rewards, DRN SE neuronal activity was characterized by tonic modulation that was altered by the expected and received reward value. [14] also show how the firing rate of DRN SE neurons change as mice engage in a cue-association type task and note that "the activity of DRN neurons exhibits diverse behavioral correlates in reward-related tasks." Finally, [15] suggested that the DRN SE neurons seems to play the role of the discount factor, of the standard reinforcement learning setting [16], which controls for how much immediate rewards matter as compared to distal reward. In all of these works, the frequency of spikes of DRN SE neurons seems to about double in the delay period between a cue and the final reward. Taking this period to be one of temporary anxiety or stress (as some of the authors of the above works do), we thus have from [10] and the above that in general, depression seems to lead to lower firing rates (up to about 30% experimentally) of the DRN SE neurons and anxiety or stress seems to increase the firing rate (up to about 100%.)

Therefore, in summary, the motivation of this paper is essentially, given that DRN SE seem to play a role in depression and/or reward-signaling, and the complex in-vivo conditions for DRN SE neurons, to simulate a DRN SE model that shows most of the observed behaviors experimentally of these neurons and see how their firing rates are affected based on the different parameters. The firing rates are of particular importance, because, as noted before, the firing rate is what seems to be quite correlated with emotional or physical state. Having gained some insights into the workings of the model and seeing how the firing rates vary as a function of the different parameters, it is our hope that future research into the role of Serotonin and DRN SE neurons in various biological processes and mental disorders becomes more clear.

II. Model and Methods

To model DRN SE neurons, we use a single compartmental model where the membrane voltage is given by the following general form:

$$C\frac{dV}{dt} = -I, V(0) = V_0 \tag{1}$$

Here, C is membrane capacitance, I is the sum of all constituent currents (current density, i.e., current per unit area), V_0 is the initial value for V, which we take as the resting membrane potential unless otherwise noted. With this formulation, negative currents are depolarizing.

Denoting I as a sum, $I = \sum_i I_i$, writing the constituent currents explicitly, and writing the currents as a product of a maximal conductance, $g_{i,max}$, a driving force, $V - V_i$ where V_i is usually at or near the Nernst equilibrium potential, and activation and inactivation variables for voltage-gated channels, we get the Hodgkin Huxley model:

$$\begin{aligned} C\frac{dV}{dt} &= -[I_{Na} + I_K + I_{Leak} + \mu] \\ &= -[g_{Na,max}m^3h(V - V_{Na}) + \\ &\quad g_{K,max}n^4(V - V_K) + \\ &\quad g_{Leak,max}(V - V_{Leak}) + \mu] \end{aligned} \tag{2}$$

where μ corresponds to the applied current, I_{Na} corresponds to the fast transient sodium current, I_K corresponds to the delayed potassium current and I_{Leak} corresponds to the leak current, and n, m, and h are dimensionless quantities between 0 and 1 that are associated with potassium channel activation gating, sodium channel activation gating, and sodium channel inactivation gating, respectively. The full model including the differential equations for the gating parameters and the steady state activation and inactivation equations can be found in [17].

Modeling a DRN SE neuron in the DRN involves modifying the Hodgkin-Huxley equation to account for approximately eleven ion currents. The eleven ion currents and their physiological parameters were taken from a multitude of physiological studies concerning serotonergic neurons [6].

The modified differential equation for the change in the voltage over time is shown below:

$$\begin{aligned} C\frac{dV}{dt} = -[&I_{Na} + I_{KDR} + I_A + I_M + \\ &I_H + I_T + I_N + I_L + \\ &I_{BK} + I_{SK} + I_{Leak} + \mu] \end{aligned} \tag{3}$$

μ, I_{Na} and I_{Leak} remain as is from the Hodgkin Huxley model (henceforth abbreviated HH). On the

other hand, I_K of the HH model is now named I_{KDR} to distinguish the current from the other potassium channel currents. In addition, we now have 8 more currents: (1) I_A, a transient potassium current, (2) I_M, an M-Type potassium current, (3) I_H, a hyperpolarization activated cation current, (4) I_T a transient calcium current, (5) I_N, N-Type calcium current, (6) I_L, long lasting calcium current, (7) I_BK, a large conductance calcium-dependent potassium current, and (8) I_SK, a small conductance calcium-dependent potassium current. We now note some general equation forms that are used unless otherwise noted.

For non-inactivating currents, an activation variable, m, raised to a certain power $p \geq 1$ (not necessarily an integer) is often used so that:

$$I_i = g_{i,max} m^p (V - V_i) \tag{4}$$

If however, the current in question inactivates, we also use an inactivation variable h, which is usually raised to the power of 1, giving:

$$I_i = g_{i,max} m^p h (V - V_i) \tag{5}$$

Sometimes the activation or inactivation variables depend on the calcium ion concentration. This will be clearly noted.

At this point it should be noted that, as described in the background and motivation, DRN SE neurons have a very complex electrophysiological and biochemical environment. The model we use is one that, while simple, is a working model that demonstrates the behavior of DRN serotonergic (SE) neurons. This not only allows for easier implementation and discussion, but also easier analysis. In particular, following what was implemented by Tuckwell et. al. (2014) [6], we only included a calcium ion concentration dependence if it was absolutely crucial to getting a model that shows most of the experimentally observed properties of DRN SE neurons. Namely, in the model that follows, only I_{SK} depends on the calcium ion concentration.

Activation and inactivation variables are determined by differential equations which are generally written in the following forms:

$$\frac{dm}{dt} = \frac{m_\infty - m}{\tau_m} \tag{6}$$

for the activation variables, and,

$$\frac{dh}{dt} = \frac{h_\infty - h}{\tau_h} \tag{7}$$

for the inactivation variables,

where m_∞ and h_∞ are steady state values which depend on voltage and τ_m and τ_h are time constants may depend on voltage and/or calcium ion concentration.

To explain the model in more depth, a brief description of each of the currents, along with parameters and equations follows.

A. *Fast transient sodium current, I_{Na}*

The only sodium current included is the transient I_{Na} which, when blocked by TTX in DRN SE neurons, reduces spike amplitude by about 60 mV [6]. Thus, the Nernst or reversal potassium, V_{Na}, is taken to be $60mV$.

The current itself is given by the classical form from the HH model [17]:

$$I_{Na} = h_{Na,max} m_{Na}^3 h_{Na} (V - V_{Na}) \tag{8}$$

with activation variable m_{Na} and inactivation variable h_{Na}. The steady state activation is given by:

$$m_{Na,\infty} = \frac{1}{1 + e^{-(V - V_{Na_1})/k_{Na_1}}} \tag{9}$$

with the corresponding time constant:

$$\tau_{m,Na} = a_{Na} + b_{Na} e^{-\left((V - V_{Na_1})/k_{Na_2}\right)^2} \tag{10}$$

following the forms used by [18].

Similarly, the steady state inactivation is given by:

$$h_{Na,\infty} = \frac{1}{1 + e^{(V - V_{Na_3})/k_{Na_3}}} \tag{11}$$

and the corresponding time constant by:

$$\tau_{h,Na} = c_{Na} + d_{Na} e^{-\left((V - V_{Na_4})/k_{Na_4}\right)^2} \tag{12}$$

B. *Voltage-dependent potassium currents*

As stated in [6], there is evidence for three types of voltage-gated potassium currents in DRN SE neurons. These are the transient I_A, and two which are usually considered to be non-inactivating or very slowly inactivating, being the delayed rectifier, I_{KDR}, and the M-current, I_M.

1) Delayed rectifier potassium current, I_{KDR}: Evidence for a delayed rectifier potassium current in DRN SE neurons has been given in [19], [20]. However, there seems to be no explicit data on the properties of I_{KDR} in DRN SE neurons [6]. Noting this, we follow [6] and use the original squid axon HH formulation for I_K:

$$I_H = g_{KDR,max} n^{n_k} (V - V_{KDR}) \tag{13}$$

where V_{KDR} is the reversal potential, n_k is an integer between 1 and 4, and n is an activation variable notated so following the traditional notation for the activation variable for the I_K current which satisfies equation 6 with steady state activation:

$$n_\infty = \frac{1}{1 + e^{-(V - V_{KDR_1})/k_{KDR_1}}} \tag{14}$$

and corresponding time constant:

$$\tau_n = a_{KDR} + \frac{b_{KDR}}{cosh((V - V_{KDR_2})/k_{KDR_2})} \quad (15)$$

2) Transient potassium current, I_A: The transient potassium current I_A was documented in early studies of DRN SE neurons by, for example, [21]. While there have been conflicting ideas about the role of I_A, the current has been show to play an important role in determining the cell's firing rate [6]. Following [18], we have that the current is given by:

$$I_A = g_{A,max} m_A^4 h_A (V - V_A) \quad (16)$$

with activation variable m_A and inactivation variable h_A satisfying equations 6 and 7 respectively and the activation steady state given by:

$$m_{A,\infty} = \frac{1}{1 + e^{-(V - V_{A_1})/k_{A_1}}} \quad (17)$$

with the corresponding time constant given by:

$$\tau_{m_A} = a_A + \frac{b_A}{cosh\left((V - V_{A_2})/k_{A_2}\right)} \quad (18)$$

and the inactivation steady state given by:

$$h_{A,\infty} = \frac{1}{1 + e^{(V - V_{A_3})/k_{A_3}}} \quad (19)$$

with the corresponding time constant:

$$\tau_{h_A} = c_A + \frac{d_A}{cosh\left((V - V_{A_4})/k_{A_4}\right)} \quad (20)$$

3) M-type potassium current, I_M: M-type potassium currents are considered to play a significant role in adaptation [22], [23]. However, such currents are associated with extremely small conductance densities, being of the order 1000–4000 times less than that of the usual delayed rectifier. In addition, not all DRN SE cells seem to have an associated I_M current [6]. Thus, we omit I_M from our model. Nevertheless, to maintain consistency, we note the equations that correspond to this M-Type potassium current from [6].

The current I_M is given by:

$$I_M = g_{M,max} m_M (V - V_M) \quad (21)$$

with the activation variable m_M following equation 6 with steady-state activation given by:

$$m_{M,\infty} = \frac{1}{1 + e^{-(V - V_{M_1})/k_{M_1}}} \quad (22)$$

and the corresponding time constant by:

$\tau_{m_M} = \tau_{m,M_c}$

Parameters for this current can be found in [6].

C. Hyperpolarization activated cation current, I_H

This current, which is elicited by hyperpolarizations relative to rest, is slow to activate and does not inactivate [18], [6]. In DRN SE neurons a similar current activating below $-70mV$, which we notate as I_H, was described in [24], [25]. Being a non-specific hyperpolarization activated cation current, the effect of this current is generally understood to be to prevent excessive hyperpolarization and thus increase firing rates [18], [6].

Following [18], we use:

$$I_H = G_{H,max} m_H (V - V_H) \quad (23)$$

where V_H is the reversal potential (around -40 mV) and m_H follows the general formula for an activation variables (given in equation 6.) with steady state activation:

$$m_{H,\infty} = \frac{1}{1 + e^{(V - V_{H_1})/k_{H_1}}} \quad (24)$$

and time constant well fitted by:

$$\tau_{m_H} = \frac{a_H}{cosh((V - V_{H_2})/k_{H_2})} \quad (25)$$

D. Calcium Currents

Calcium currents are found in all excitable cells and have been generally divided into the two main groups of low-voltage activated (LVA) and high-voltage activated (HVA). The former group contains only the T-type (T for transient) while the latter group consists of the types L, N, P and R (L for so called long-lasting, N, either for neither T nor L, or neuronal, P for Purkinje, and R for resistant). For the DRN SE, looking at the L, N and T types suffices [6].

1) Transient Calcium T-type current, I_T: The T-type (low threshold) calcium current has been implicated in pacemaker activity in some cells and also in bursting activity [26], [27] and amplification of dendritic inputs [28].

Additionally, experimental studies have pointed out that spike generation and the pacemaker cycle in DRN SE neurons seem to be triggered by T-type currents [29], [30].

The mathematical form for the T-type current is chosen according to the simpler model in [6] (as opposed to the more complex constant field model):

$$I_T = g_{T,max} m_T^2 h_T (V - V_{Ca,rev}) \quad (26)$$

With voltage clamp data from [26], [27], we have the steady state activation, m_T, and steady state inactivation, h_T as being given by:

$$m_{T,\infty} = \frac{1}{1 + e^{-(V - V_{T_1})/k_{T_1}}} \quad (27)$$

$$h_{T,\infty} = \frac{1}{1 + e^{(V - V_{T_3})/k_{T_3}}} \quad (28)$$

For the time constants, we follow [18] for the activation variable and [31] for the inactivation variable as done in [6]:

$$\tau_{m_T} = a_T + \frac{b_T}{cosh\left((V - V_{T_2})/k_{T_2}\right)} \tag{29}$$

$$\tau_{h_T} = c_T + d_T e^{-\left((V - V_{T_4})/k_{T_4}\right)^2} \tag{30}$$

2) Calcium N-Type current, I_N: In voltage clamp experiments on DRN SE neurons, [32] found evidence that among high-voltage activated (HVA) calcium currents, N-type channels contributed about 40% of total calcium current in dissociated cells. Most of the remaining fraction was not blocked by ω-conotoxin and was called N-like. These two components are combined together as N-type as in [6].

We use the simple model in [6] for I_T (as opposed to the constant field model) with N replacing T throughout.

Here we note that we found that removing the N-Type current for some experiments lead to very similar results, and hence excluding this current might be fine (along with the previously mentioned I_M current.)

3) Long lasting Calcium L-Type current, I_L: As done for both I_T and I_L, we use the simple model in [6] (as opposed to the constant field model). Thus, the equations for L-Type current are the same as those of the T- and N-Type currents with the exception that L replaces T (or N) throughout.

With that said, assumptions about I_L are not expected to have major consequences for the spiking dynamics because the contributions from the L-type current are presumed to be less than about 10% of the whole DRN SE cell calcium currents, based on the observations of [32].

E. Calcium-dependent Potassium Currents

Calcium entry into neurons can activate certain calcium-dependent potassium ion channels which usually leads to hyperpolarizing effects. As described in [6], there are 4 main types of such channels in neurons: the large conductance BK channel (or $K_{Ca}1.1$) and the small conductance SK channels, SK1, SK2 and SK3 ($K_{Ca}2.1$, $K_{Ca}2.2$ and $K_{Ca}2.3$, respectively).

Apart from the magnitudes of their conductances,the BK and SK types have differing activation properties and pharmacology [6]. The activation of SK channels is purely calcium-dependent whereas that of BK channels depends both on calcium ion concentration and membrane potential. SK channels are selectively blocked by apamin from bee venom whereas BK channels are blocked by micromolar concentrations of TEA and certain scorpion-derived toxins such as iberiotoxin.

Now, calcium-dependent potassium currents have long been implicated as the basis of the long (several hundred milliseconds) after-hyperpolarization (AHP) following spikes in DRN SE neurons and hence are a major component of pacemaker-like activity in these cells [29], [30], [19], [6].

More specifically however, [33] show clearly the inhibiting effect of apamin on the afterhyperpolarization in DRN SE neurons. Since only SK channels are blocked by apamin, it is clear that the AHP is mainly due to SK channel activation. This is primarily the reason we use the simple voltage-only dependent model for BK from [6] (i.e., we ignore the calcium ion concentration dependence for BK.)

1) Large Conductance, BK Channel: As noted before, while we do classify the BK channel as part of the calcium dependent potassium channels (following [6]), we use the simpler voltage-dependent model for ease of analysis and the fact that we get similar results and use the fact that the SK channel plays a larger role in the DRN SE firing pattern (at least in the AHP sense). [34] ignore the Ca^{2+} dependence for a simplified model of the BK current where the current is given by:

$$I_{BK} = g_{BK,max} m_{BK} (V - V_K) \tag{31}$$

with the activation variable m_{BK} following equation 6, with steady-state activation:

$$m_{SK,\infty} = \frac{1}{1 + e^{-}(V - V_{BK})/k_{BK}} \tag{32}$$

and where $\tau_{m_{BK}}$ is a constant.

2) Small Conductance, SK Channel: As noted before, this current is dependent only on the internal Calcium concentration Ca_i. Following [6], we will assume that there is only one kind of SK channel, SK3, which was noted to be prevalent in the DRN. We then have:

$$I_{SK} = g_{SK,max} m_{SK} (V - V_K) \tag{33}$$

where m_{SK} follows the general equation for activation variables, i.e., equation 6, and without an explicit inactivation process, the decay of I_{SK} is governed by Ca^{2+} dynamics, modeled by a steady state activation that is steeply dependent on the internal calcium concentration, Ca_i:

$$m_{SK,\infty} = \frac{Ca_i^n}{Ca_i^n + K_c^n} \tag{34}$$

where n is the Hill coefficient and K_C is the EC_{50} (the value of Ca_i at which $m_{SK,\infty} = 0.5$.)

F. Leak current, I_{Leak}

In the HH model [17], a leak current was inserted in the differential equation for V with its own equilibrium potential and conductance, and was stated to be composed of chloride and other ions. One motivation for including a leakage current is to take account of ion flows by pumps.

However, based on the properties of DRN SE neurons, some of which are discussed above, there is usually not expected to be a zero ion flux at rest because many of the DRN SE neurons fire spontaneously without any applied current. Nevertheless, a leak current is inserted. In [6], a simple HH inspired model and a more complex model that separates the contributions by the sodium and potassium channels, which takes into account evidence for specific leak currents associated with the potassium [35] and sodium [36], are used. However, the authors of [6] note that both models give very similar results, and following Occam's razor [37] and the previously described motivation for a simpler model when possible, we use the HH inspired model, given below:

$$I_{Leak} = g_{Leak}(V - V_{Leak}) \tag{35}$$

G. Calcium Ion Dynamics

Finally, in the description of our model, we conclude with the Calcium ion concentration dynamics. One of the simplifications in [6] for making analysis easier is to make the Calcium ion concentration Dynamics simple. Following that, we use:

$$\begin{aligned}\frac{dCa_i}{dt} =& -CSF \cdot (I_L + I_N) \cdot \frac{1 - PB(t)}{2Fv} \\ & - K_s \cdot \frac{Ca_i}{Ca_i + K_m}\end{aligned} \tag{36}$$

H. Varying Physiological Parameters

The physiological parameters of the maximum conductances, gating functions, and time constants in the modified Hodgkin-Huxley model for the DRN neuron were varied away from their default values (.5 - 1.5 x physiological average) to investigate how changes in the parameters affected the firing activity of the serotonergic neuron. However, the ranges were truncated at times to ensure that there is always repetitive firing of action potentials for a given setting of the parameter at hand. The parameters varied are listed in Tables I, II, and III. The default values for each parameter may be found in Tables 17, 18, 19 and 20 in Tuckwell et. al. (2014) [6].

g_{Na}	g_{KDR}
g_{Leak}	g_T
g_L	g_{BK}
g_{Na}	g_A
g_H	g_{SK}

Table I: Maximum Conductance Parameters.

V_{Na1}	k_{Na1}	V_{Na2}	k_{Na2}
V_{Na3}	k_{Na3}	V_{Na4}	k_{Na4}
V_{KDR1}	k_{KDR1}	V_{KDR2}	k_{KDR2}
V_{T1}	k_{T1}	V_{T2}	k_{T2}
V_{T3}	k_{T3}	V_{T4}	k_{T4}
V_{L1}	k_{L1}	V_{L2}	k_{L2}
V_{L3}	k_{L3}	V_{N1}	k_{N1}
V_{N2}	k_{N2}	V_{N3}	k_{N3}
V_{A1}	k_{A1}	V_{A2}	k_{A2}
V_{A3}	k_{A3}	V_{A4}	k_{A4}
V_{H1}	k_{H1}	V_{H2}	k_{H2}
V_{BK}	k_{BK}		

Table II: Gating Activation Parameters.

a_{Na}	b_{Na}	c_{Na}
d_{Na}	a_{KDR}	b_{KDR}
a_T	b_T	c_T
d_T	a_L	b_L
tau_{hL}	a_N	a_N
b_N	tau_{hN}	a_A
b_A	c_A	d_A
a_H	tau_{mSK}	tau_{BK}

Table III: Time Constant Parameters.

III. Results

Before we delve into an analysis of the model with respect to various parameters and a discussion, we start with a replication of the results in [6]. In particular, we are looking for some of the characteristics of DRN SE firing:

- Spontaneous firing without any applied current, i.e, tonic firing
- A long after-hyperpolarization (AHP), with evidence that the SK current plays a major role in this.
- Plateaus after AHP

Furthermore, quantitatively, looking at figure 20 of [6], we are looking to verify action potential firing with an inter-spike interval (ISI) of about 700 milliseconds or equivalently a frequency of $\frac{1000}{800} \approx 1.25$ Hertz.

Running the experiment, we get the graphs on the following page for the voltage-time trace and ion currents, with no applied current. These plots demonstrate successful model replication.

Taking the difference of the last two spikes (since that gives us a good estimate for the ISI as opposed to say, the mean), we get 854.5 milliseconds, or, equivalently, a frequency of about 1.17 action potential spikes per second.

Performing a frequency analysis as a function of the applied current, as shown in figure 6, overall, DRN neurons appear to demonstrate Type 2 behavior [17] where neurons aren't necessarily able to exhibit arbitrarily slow frequencies as injected current levels are reduced (since, in particular, we have tonic firing meaning that no applied current is needed for firing action potentials.) In the plots that follow, a red star represents physiologically average

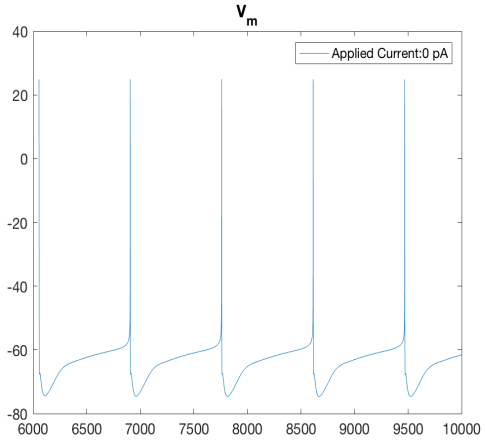

Figure 2: Voltage vs. Time Plot, Tonic Firing

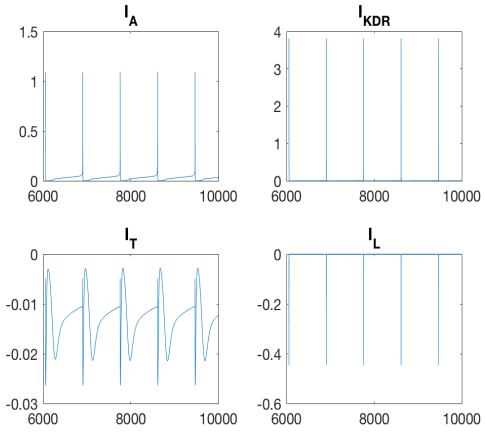

Figure 3: Clockwise from top left to bottom left: Current-time traces for I_A, I_{KDR}, I_T and I_L

values used by the authors in Set A.

Now, we discuss the effects of changing various parameters around the defaults. We, in particular, focus on the maximum conductances for the different currents as they give us a good sense of the "contribution" of each of the currents to the firing of action potentials, and the firing rate in turn.

As the maximum g_{Na} is increased, firing frequency seems to increase then level off. This behavior is expected for a depolarizing current. Small changes in maximum g_{Na} seem likely to produce moderate changes in firing frequency. As the maximum g_{KDR} is increased, firing frequency seems to gradually decrease, until it eventually drops drastically. There are some outlying values of firing frequency, likely in non-physiological ranges for g_{KDR}. This behavior would be expected for a hyperpolarizing potassium current. Small changes in maximum g_{KDR} from physiological conditions do not seem likely to produce great changes in firing frequency. As the maximum g_A is increased,

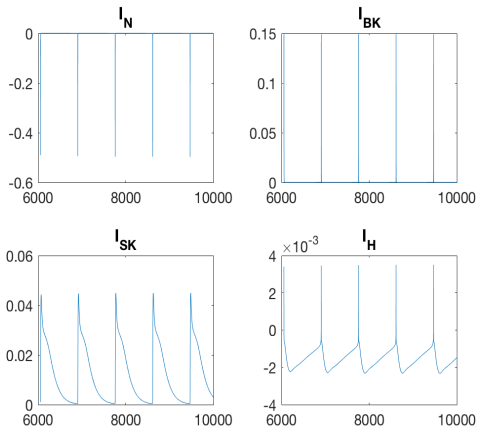

Figure 4: Clockwise from top left to bottom left: Current-time traces for I_N, I_{BK}, I_{SK} and I_H

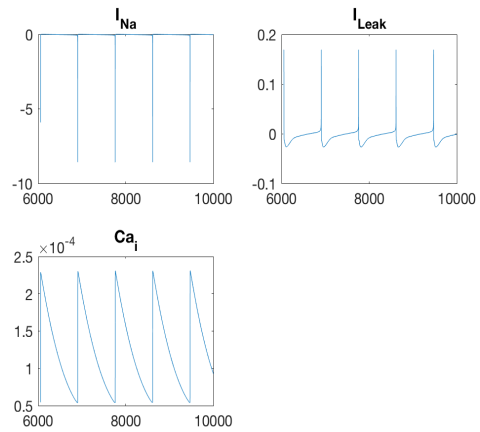

Figure 5: Current-time traces for I_{Na} (top left), I_{Leak} (top right) and Concentration-time trace for Ca_i (bottom left)

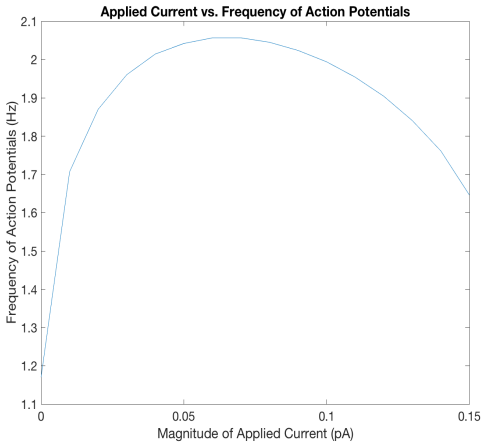

Figure 6: Frequency of Action Potentials as a function of Applied Current

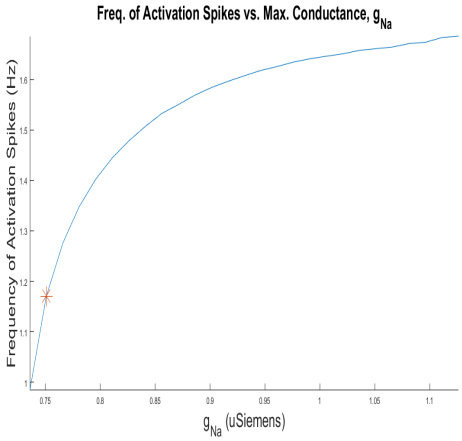

Figure 7: Frequency of Action Potentials as a function of I_{Na}

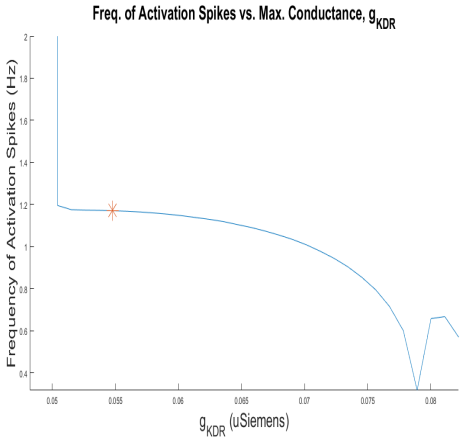

Figure 8: Frequency of Action Potentials as a function of I_{KDR}

firing frequency seems to decrease gradually. This behavior would be expected for a hyperpolarizing potassium current. Small changes in maximum g_A from physiological conditions would likely produce great changes in firing frequency. Similarly, as the maximum g_{Leak} is increased, firing frequency seems to decrease gradually. This behavior would be expected for a hyperpolarizing current. Small changes in maximum g_{Leak} from physiological conditions do not seem likely to produce great changes in firing frequency. As the maximum g_H is increased, firing frequency seems to increase linearly. As I_H is a current that is activated during hyperpolarization and serves to depolarize the cell towards baseline, it follows that increasing its maximum conductance would lead to an increase in firing frequency. Small changes in maximum g_H from physiological conditions likely will produce moderate changes in firing frequency. As the maximum g_L is increased, firing frequency seems to decrease gradually. This behavior would

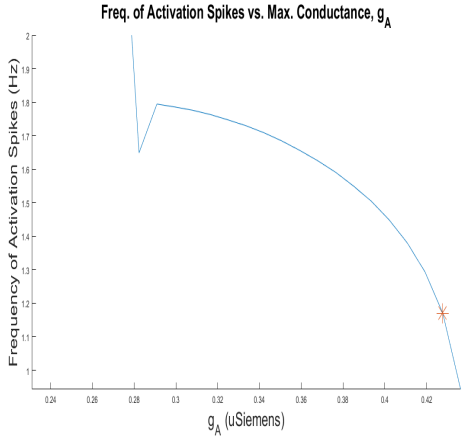

Figure 9: Frequency of Action Potentials as a function of I_A

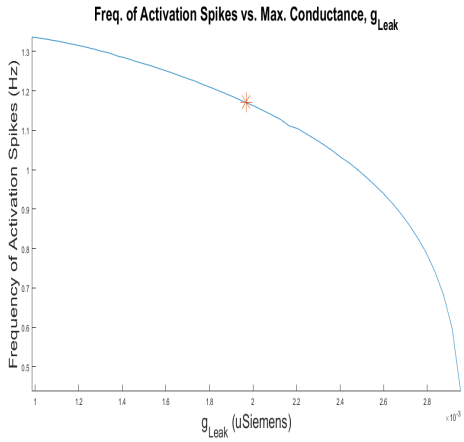

Figure 10: Frequency of Action Potentials as a function of I_{Leak}

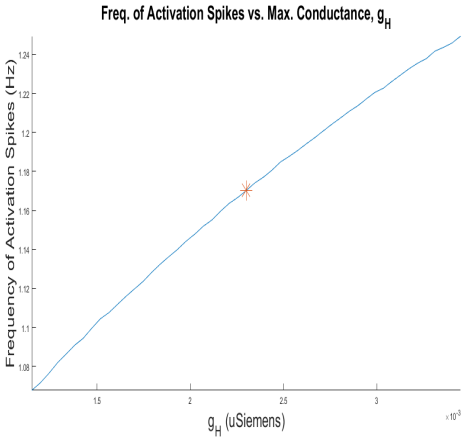

Figure 11: Frequency of Action Potentials as a function of I_H

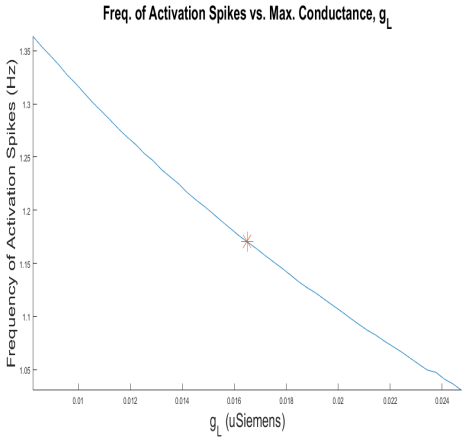

Figure 12: Frequency of Action Potentials as a function of I_L

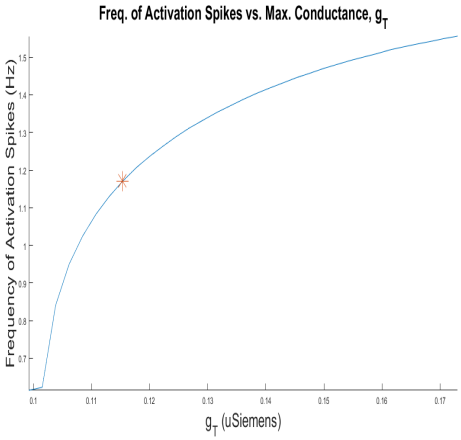

Figure 14: Frequency of Action Potentials as a function of I_T

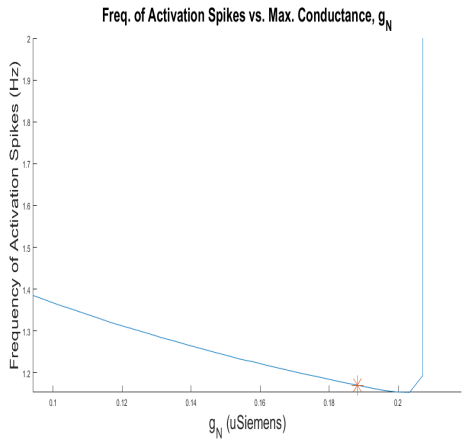

Figure 13: Frequency of Action Potentials as a function of I_N

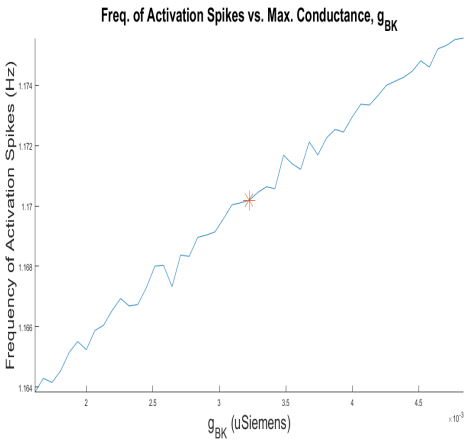

Figure 15: Frequency of Action Potentials as a function of I_{BK}

be expected for a hyperpolarizing current. Small changes in maximum g_L from physiological conditions likely will produce moderate changes in firing frequency. As the maximum g_N is increased, firing frequency seems to decrease gradually. This behavior would be expected for a hyperpolarizing current. There are some outlying values of firing frequency, likely in non-physiological ranges for g_N. Small changes in maximum g_N from physiological conditions likely will produce only minor changes in firing frequency, unless it is increased enough to trigger very non-physiological behavior. As the maximum g_T is increased, firing frequency seems to increase gradually before leveling off. This behavior would be expected for a depolarizing current. Small changes in maximum g_T from physiological conditions likely will produce moderate changes in firing frequency. As the maximum g_{BK} is increased, firing frequency seems to increase mostly linearly. This behavior is unexpected for a hyperpolarizing current. However, small changes in maximum g_{BK} from physiological conditions only produce small changes in firing frequency. This plot has a much less smoother increase with increasing g_{BK} because this current has a complex dependency on calcium concentration which is not accounted for here. As the maximum g_{SK} is increased, firing frequency seems to decrease almost exponentially. This behavior is expected for a hyperpolarizing current. Small changes in maximum g_{SK} from physiological conditions only produce small changes in firing frequency. Just as with g_{BK}, this plot has a much less smoother increase with increasing g_{SK} because this current also has a complex dependency on calcium concentration which is not accounted for here.

A. Clinical Implications: A simple experiment

A previous study showed that depressed DRN SE neurons fired at a 35.4% lower firing rate than non-depressed SE neurons in mice [10]. Non-depressed SE neurons have a firing frequency of 1.17 Hz as described previously in this section.

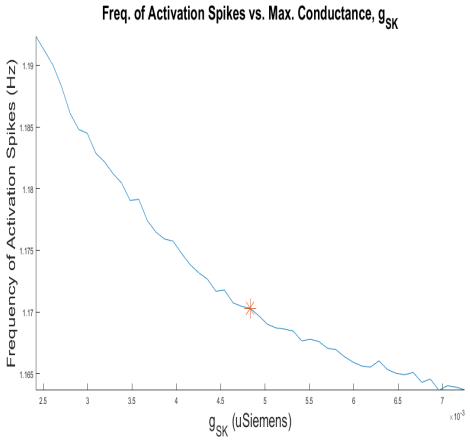

Figure 16: Frequency of Action Potentials as a function of I_{SK}

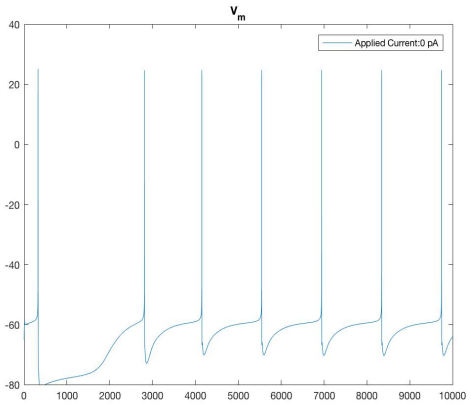

Figure 17: DRN SE neuron Voltage-Time trace with modified Leak Conductance (35.4% firing rate)

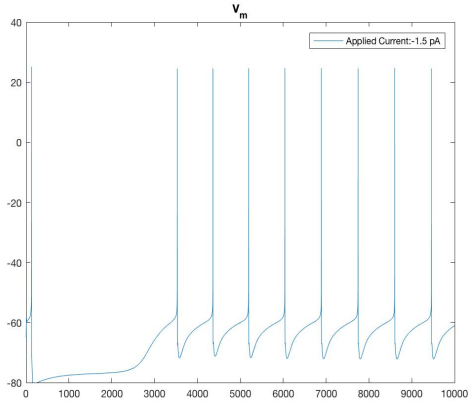

Figure 18: DRN SE neuron Voltage-Time trace with modified Leak Conductance back at baseline firing rate

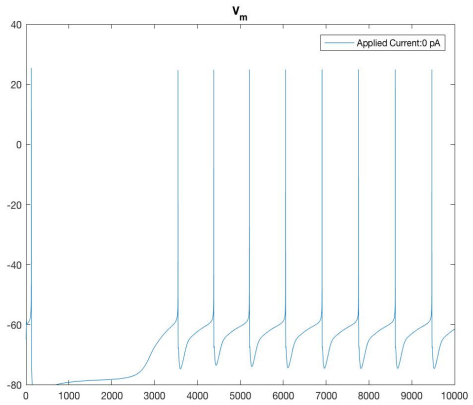

Figure 19: DRN SE neuron Voltage-Time trace without modified Leak Conductance (baseline)

Past work has shown that deletion of TREK-1 channels (K+ channels that contribute to the leak current) in mice causes depression resistance in DRN SE neurons [38]. The authors of the work explained that with the deletion of the TREK-1 channels, there appeared to be an increased efficacy of serotonin neurotransmission, the usual elevated corticosterone response to stress reduces and the change mimics SSRIs. Thus, to model a depressed SE neuron, we did the opposite. Namely, the g_{Leak} conductance was increased by 45%. This resulted in the modeled SE neuron firing at 0.756 Hz, which is approximately 35.4% lower than 1.17 Hz. We demonstrated in Figure 18 and Figure 19 that an input current of 1.5 pA (in magnitude) can be used to return the depressed neuron back to a firing frequency of 1.17 Hz.

IV. Summary and Conclusions

This study sought to create a robust model for dorsal raphe nuclei, the main source of serotonin in the central nervous system. Given the major role of dorsal raphe nuclei and serotonin in stress and pathological conditions like depression, accurate models of these neurons would be tremendously valuable clinically and academically. To model the DRN, the a modified Hodgkin-Huxley model was used. Besides the canonical fast transient sodium current, the leak current, and the delayed rectifier potassium current, this model included two potassium currents (fast transient A-type, M-type potassium), three calcium currents (low threshold T-type, high threshold L-type, high threshold N-type), two calcium-activated potassium currents (large conductance and small conductance), and a hyperpolarization-activated cation current.

To probe the model, various parameters were modified along a spectrum to determine the effect on firing frequency. One such parameter was the maximal conductance of each current. Overall, besides I_{BK}, all currents mostly behaved as expected: increasing the conductance of depolar-

izing currents increased firing rate, while increasing the conductance of repolarizing currents decreased firing rate. Changes in some maximal conductances (g_{KDR},g_A,g_{Leak},g_T) produced logarithmic changes in firing frequency, while others (g_H,g_L,g_N,g_{BK},g_{SK}) produced linear changes in firing frequency. Small changes in certain conductances (g_A) from physiological values produce large changes in firing frequency, while changing other conductances (g_{Na},g_H,g_L) produces moderate changes in firing frequency and changing other conductances still (g_{KDR},g_{leak},g_N,g_{BK},g_{SK}) only resulted in small changes in firing frequency.

Overall, it seems the repolarizing currents, such as the potassium A current and the leak current, would be good pharmacological targets for future serotonin-based antidepressants. Small decreases in these currents could cause large increases in the firing of DRN, thus causing large increases in serotonin release downstream to DRN projections.

V. Response to Questions

Question 1: Depression is much more related to how someone feels as opposed to caused behavior in things like epilepsy. Is there speculation that the cause of depression isn't entirely physiological?

A lot of the scientific debate is talked about in section I. In particular it is noted that there is a lot of debate about the role of Serotonin in depression, and more general about the cause of depression, and even more generally, about what a diagnoses of depression constitutes. This will be summarized again at the end of the answer to the question posed above. However, now, a brief look at the sociological and psychological aspects follows first.

Depression has increasingly been shown to have a biological basis, as have many other psychiatric conditions, however, there is a sociological aspect as well. In the past few decades, there has been a lot of discussion about the stigma that follows mental illness [39]. Apart from public stigma arising from, for example, the wide-spread perception that mental illness is associated with violence [40] or failure of self-control, self-stigma among those with mental illnesses that largely stems from the public stigma is also another concern [39]. Additionally, there is also the less talked about stigma that health professionals themselves face; "In a questionnaire done in 2000, 67% percent of psychiatrists reported that they were laughed at for working with psychiatric patients while 29% reported that their family discouraged them from joining the profession." [41]

The attribution theory says "there should be less stigma and discrimination as a result of less blame due to chromosomal or genetic alterations causing the mental illness." [39] While there have been conflicting opinions about whether certain mental illnesses are caused by certain genetic mutations or chemical imbalances, as we have increasingly found more genetic or biochemical causes for certain mental illnesses, studies reveal that the attribution theory does not seem to hold in general [42]. Namely, this seems to vary depending on the mental illness.

With some studies into the effects of chemical imbalance and neuronal firing activity analyzed in people with depression showing possibly genetic causes for depression, [43] note about the attribution theory that "... when applied to depression, genetic arguments have very different connotations: they are associated with social acceptance. If you imagine that someone's depression is a genetic problem, the condition seems more real and less blameworthy: it's in their genes, they're not weak, so I should accept them for who they are." This could possibly lead to an increase in research into the biological aspects of the disease and could also very well be one of the reasons that depression, a common mental disease, seems to be more widely prevalent given the stigma has decreased and it is increasingly recognized as mental illness across different cultures [11].

While the above sociological considerations and related biases might have little to do with the causes of depression, they are important considerations to keep when talking about a mental illness like depression where apart from a possible biological cause, there is also the environmental and social factors that affect the emotion and social aspects of the disease. That said, from the scientific viewpoint, as noted in section I, there is still considerable debate about the causes of depression (the largely un-understood SSRIs for example) and whether a diagnoses of depression is even sound [3], [8], [7], [9].

Question 2: How did the evoked calcium current change the overall behavior of spiking in the DRN? Calcium concentrations trigger various calcium currents, namely the I_{SK} currents. Action potentials in the DRN trigger an influx of calcium from the external environment into the cell, prolonging the action potential peak. The heightened calcium concentration then activates these repolarizing I_{SK} current, which then closes the calcium channels. Eventually, through other physiological mechanisms, this leads to a decrease in intracellular calcium levels and a restoration of the resting potential calcium gradient. This would be aided by the deactivation of the I_{SK} currents as the calcium concentration decreases. Overall, calcium currents and calcium dependent currents in this DRN model led to a wider action potential and a long after-hyperpolarization region. They also played a role in the spontaneous firing of action potentials through coupled dynamics of the I_{SK} with the I_L and I_N currents for example.

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CODE

Two codes were used in this project, a modified Hodgkin-Huxley model and a frequency plotting script. Both were written in MATLAB. The modified Hodgkin-Huxley model uses a differential equation solver and functions to model the spiking activity of a serotonergic neuron in the DRN. The modified Hodgkin-Huxley model is similar to the Hodgkin-Huxley model used in previous homework assignments with the exception of the additional ion currents and their respective steady-state and time constant equations from Tuckwell et. al. (2014) [6]. The frequency plotting code was designed to plot a graph with a selected physiological parameter acting as the independent variable and the frequency of spiking activity acting as the dependent variable. The frequency plotting code took in our selected parameter the and looped the modified Hodgkin-Huxley model for each parameter to create the frequency graphs. The amount of time it took to run the entire code depended on the number of parameters selected to be the independent variable. In one instance it took around ninety minutes to the plot frequency graphs for twenty-three selected parameters. This comes out to about four minutes per parameter.