Modeling Dopamine Circuitry in Learning and ADHD

Subhashini Arumugam, Priyan Kapoor, Arthur Lefebvre, Giuditta Monti,
Juan De La Torre Mosquera, Sahand Salari-Namin
University of California, San Diego

December 6. 2022
BENG260 Neurodynamics Fall 2022
Professor Henry Abarbanel

Abstract

Attention-Deficit Hyperactivity Disorder (ADHD) affects a growing portion of the population, with diagnoses increasing every year. Some of the symptoms include difficulty focusing, restlessness, and impatience. Depending on the degree of the symptoms ADHD can be mild, allowing for a relatively normal function of the affected individuals, to severe, which can result in social and academic impairments. Despite being a common disorder, the treatment options are limited. The most commonly prescribed treatments include chemical stimulants, which only target the symptoms (e.g. difficulty focusing) rather than addressing the root causes behind them. Furthermore, they can have adverse side effects including long term addiction. Even though the full mechanistic picture driving this disorder is far from being elucidated, the neurotransmitter dopamine seems to have a significant role in disease progression. Dopamine binds to dopamine receptors on the post-synaptic neuron and can stimulate it to propagate an action potential. Computational modeling is a powerful tool to reproduce and analyze complex physical and biological systems without undergoing complex (or potentially infeasible) experiments. Despite the intrinsic reliance on educated simplifications and assumptions, modeling can provide a unique outlook on biophysical phenomena and support both the understanding of a disorder and the design of *in vitro* and *in vivo* experiments. As part of this project, we aim to 1) review and summarize the current understanding of ADHD, including its biological basis, and 2) use a computational model to analyze and reproduce the mechanisms underlying ADHD and the effects of chemical stimulants. Given the impossibility of recreating the complexity of all the neural connections, our Python-based model will be centered around the inhibitory interaction between two dopaminergic neurons, with a particular focus on the concentration of dopamine in the synaptic cleft and its effects on the transmission of an action potential. The implementation of this model will help provide a more complete understanding of the biophysical mechanisms that result in ADHD and the extent to which chemical stimulants can reverse the effects of this disorder within our computational framework.

1. Background

1.1 Physiology of Learning Circuitry in the Brain

Learning is a complex process generally described as a change in an organism's behavior as a result of accumulated experience (Seger, 2010). Theories on how learning occurs in the brain are myriad, and learning has been a subject of intense scientific inquiry for decades. Recent advances in artificial intelligence aspire to harness, if not mimic, the basic principles of learning in humans to endow machines with the ability to similarly modulate their decision-making processes. While the exact mechanisms of learning remain elusive, neuroscience has come a long way in identifying neural activity correlated with such observable changes in behavior.

The essential functional unit of the brain is the neuron, a type of cell that is able to communicate with other neurons as well as cells throughout the body to convey messages and affect behavior. These messages are propagated via action potentials, which are electrical impulses carried along the length of the neuron's axon, a long cable-like projection extending away from the cell body. At the end of the axon, the action potential can elicit the release of neurotransmitters which can traverse the neural synapse - the gap between neurons - to produce an effect in the postsynaptic neuron, the neuron receiving the signals on the other end of the synapse. The summation of the impulses that arrive at the postsynaptic neuron drives the postsynaptic neuron's subsequent electrical activity.

Neurons are not necessarily uniform in their function and can vary spatially depending on the region of the brain in which they reside. Learning itself can be classified into several other subprocesses, including categorical learning, recall, and memory formation, to name a few (Seger, 2010). Thus, unsurprisingly it is a process that relies on the concerted efforts of several different brain regions, including the basal ganglia, hippocampus, limbic system, prefrontal cortex, and temporal lobes to name a few (Rajmohan, 2007). Many neural network models aim to recapitulate the activity of the basal ganglia neurons as they are responsible for habit formation and instrumental behaviors - behaviors that are modified in response to feedback (Yin, 2006).

1.2 Neuroplasticity

Over time, certain synaptic connections between neurons can be strengthened while others can be diminished in phenomena referred to as either Long Term Potentiation or Long Term Depression respectively (Johnston, 1994). Neuroplasticity thereby constitutes the quantitative basis of learning in the brain by describing the process by which neural circuits are modified over time as a result of experience. Hebbian learning or Hebbian plasticity refers to work published by neuroscientist Donald Hebb in the 1940s in which he describes how a presynaptic neuron that repeatedly fires to stimulate a postsynaptic neuron becomes more efficient at stimulating that postsynaptic neuron over time. In his own words, "When an axon of cell A is near enough to excite a cell B and repeatedly or persistently takes part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency, as one of the cells firing B, is increased."(Keysers, 2014) Notably, Hebb alludes to two important features of his theory: one, that the behavior of both the presynaptic and postsynaptic neurons

dictate changes in the synaptic connection; second, that the temporal nature of the firing pattern i.e, the repeated firing of the presynaptic neuron to stimulate the postsynaptic neuron underlies the modification of synaptic transmission. In other words, it is not simply neurons repeatedly firing together that evoke changes in the synapse, but more specifically one neuron firing to stimulate another neuron in a time-dependent manner that drives plasticity (Steratt, 2012). This idea is also referred to more specifically as spike-timing-dependent plasticity and accounts for the phenomenon by which the timing of individual spikes alters the direction and magnitude of plasticity at a synapse (Shouval, 2010). The observations of long-term potentiation/depression in future decades later established the neurophysiological basis for these Hebbian principles. Building upon the principles of spike-timing-dependent plasticity, long-term potentiation is observed when a presynaptic spike precedes a postsynaptic spike, whereas long-term depression is observed when the order of the spikes is reversed (Shouval, 2010).

1.3 The Role of Dopamine in Learning

Dopamine is produced by dopaminergic neurons within the ventral tegmental area (VTA) of the midbrain and orchestrates many pathways (Volman, 2013). In the mesolimbic pathway, dopamine is projected from the VTA to the nucleus accumbens (NAc) of the forebrain (part of the basal ganglia) and medial prefrontal cortex (mPFC) (Volman, 2013). Together these regions work to control decision-making and behaviors in regard to rewards and motivation (Volman, 2013). However, more recent work has demonstrated that dopamine is not only released in response to reward or pleasurable stimuli but also in response to aversive stimuli which may suggest the role of dopamine in reinforcement learning (Volman, 2013). Dopamine release from the presynaptic neurons is mediated by the Dopamine Transporter DAT1, which also is involved in dopamine reuptake. On the other end of the synaptic cleft, a variety of dopamine receptors on the postsynaptic neuron respond to dopamine. Unlike other common neurotransmitters, dopamine does not conform to producing exclusively excitatory or inhibitory signals. Due to its spatially and temporarily variable effects, dopamine is often better described as a neuromodulator. A total of 5 dopamine receptors - D1, D2, D3, D4, and D5 - have been identified, and each exhibits different dopamine binding/signaling activity and is localized to different regions within the brain (Bhatia, 2022). D1 and D5 receptors generally have an excitatory effect on the neuron when stimulated, whereas D2-D4 generally exhibit an inhibitory effect (Davidson, 2004).

1.4 Attention-Deficit Hyperactivity Disorder (ADHD)

A host of neurological disorders have underpinnings in dopamine transmission or availability, including Parkinson's, major depressive disorder, schizophrenia, and Attention Deficit Hyperactivity Disorder. In this project, we aim to explore dopamine dynamics specifically within the context of ADHD. Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders usually appearing during childhood (Centers For Disease Control and Prevention, 2022). It is mainly characterized by an ongoing pattern of impairing hyperactivity, impulsivity, and inattention that obstructs functioning or development (National Institute of Mental Health, 2022). Some of the symptoms linked to ADHD are inattention, distraction, hyperactivity, impatience, and impulsivity. Its epidemiologic research has been hampered (Rowland A, 2002) by difficulties in achieving a reliable diagnosis which

currently requires several steps. Over the years, links between ADHD and decreased literacy rates have contributed to making the disease a public health concern, with large numbers of school-age children now being regularly identified and treated for ADHD. Between 1990 and 1995, the number of children treated for the condition grew more than twofold. According to many literacy evaluations, rates among school-age children vary greatly over the world, from as little as 1% to as high as nearly 20% (Polanczyk, 2007).

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), published in 1994, the prevalence of ADHD is around 3-5% among schoolchildren (Rowland A, 2002). However, this study is poorly documented and unclear. Furthermore, according to a study performed by Guilherme Polanczyk, M.D. et al. (Polanczyk, 2007), the worldwide-pooled prevalence of ADHD was 5.29%. Both age and gender are contributing factors to prevalence rates, with males and younger children showing considerably higher diagnosis rates than females and adolescents respectively (Figure 1). Variability in prevalence also exists between studies of populations in North America, Africa, and the Middle East. However, no significant differences exist between populations in North America and Europe (Polanczyk, 2007).

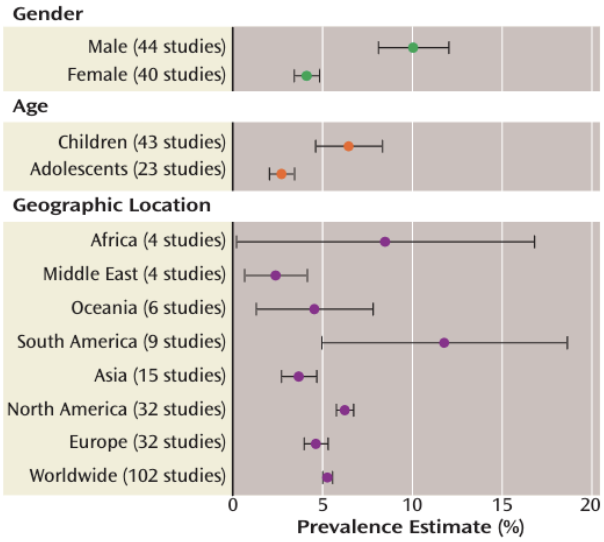

Figure 1: Prevalence estimation according to gender, age, and geographic location (Polanczyk, 2007)

1.5 Pathology of ADHD

Many of the clinical manifestations of ADHD - inattentiveness, hyperactivity, impulsivity - can be traced back to functions of several different brain regions including the frontal cortex, limbic system, and basal ganglia. The frontal cortex is responsible for higher-level cognition such as attention, decision-making, and organization. The limbic system refers to a collection of brain regions - the hippocampus, amygdala, and hypothalamus - generally associated with the processing of emotions. However, it is also essential for the development of attention (Rajmohan, 2007). The basal ganglia are also most often associated with movement patterns but it has also been implicated in the development of voluntary behaviors in response to rewards (Yin, 2006). Furthermore, many of the symptoms of ADHD are also attributed to malfunctioning of the reward pathways in our brains that allow for reinforcement learning and impulse control. Notably, children with ADHD do not exhibit the appropriate behavioral changes in response to

changing reward conditions (Volkow, 2009). Since dopamine is an integral neurotransmitter in these pathways, it was closely studied for many decades in patients with ADHD.

1.6 Dopamine Dynamics in ADHD

D2, which is localized in the NAc (as well as the hypothalamus, hippocampus, and amygdala), is particularly of interest in the study of ADHD as it has been shown to exhibit distinct variations observable in those with ADHD (Blum, 2008, Volkow, 2009, Ford, 2014). Variations in both the DAT1 gene and the DRD2 gene which gives rise to the D2 receptor protein have been correlated with the prevalence of ADHD symptoms (Volkow, 2009). Certain mutations seem to decrease the efficacy of dopamine signaling and reduce the response of the postsynaptic neuron to the dopamine in the synapse. Furthermore, lower availability of DAT1 as well as D2 and D3 were found in the NAc and midbrain regions of individuals with ADHD, supporting claims that lower dopamine activity within the reward pathway contributes to ADHD symptoms (Volkow, 2009). Thus increasing dopamine activity/availability in the synapse is the focus of several treatments for ADHD.

Stimulants are currently the most common treatment for ADHD and target some of the main symptoms of ADHD (e.g. impulsivity, fidgeting, and hyperactivity). They work to increase the overall concentration of dopamine in the synaptic cleft in the prefrontal cortex through a variety of mechanisms. These include increasing the production of dopamine, acting as competitors for dopamine receptors and transporters (thereby inhibiting the uptake of dopamine), increasing the DAT-mediated reverse transport, and maximizing the rate at which dopamine is released in the cytoplasm. The most commonly prescribed stimulant medications are Adderall (amphetamine salts) and Ritalin (methylphenidate).

1. 7 Dopamine Transmission Dynamics

After being produced in the dopaminergic neuron (DAT), dopamine is encapsulated in vesicles and transported to the membrane of the dendrite to be released in the space between the pre and post-synaptic neurons (synaptic cleft). The release of the neurotransmitter in the cleft can either be continuous and sustained (tonic release) or in a spike (phasic release). Once in the synaptic cleft, dopamine binds to the post-synaptic receptors and activates the neuron (given that the concentration is sufficient to generate an action potential) or autoreceptors on the DAT (to regulate the concentration of dopamine). Finally, the neurotransmitter is removed or recaptured by the DAT (Figure 2)(Véronneau-Veilleux, 2022).

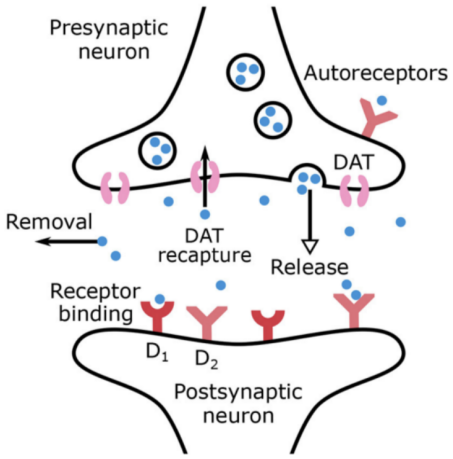

Figure 2: Dopamine transmission in the synaptic cleft (Véronneau-Veilleux, 2022)

In this model, ADHD is linked to a larger uptake of dopamine, which leads to a lower tonic dopamine level.

The dopamine dynamics model described by Véronneau-Veilleux et al. characterizes the temporal dopamine concentration and accounts for tonic and phasic releases (as described in Section 2.1.1). Equation 1 below describes the mechanisms behind dopamine regulation in a neuron:

$$\underbrace{\frac{dC_{DA}(t)}{dt}}_{\text{Dopamine concentration}} = \underbrace{(I_{DA}^{tonic} + I_{DA}^{phasic}(t))}_{\text{Dopamine Release}} - \underbrace{\frac{V_{max}C_{DA}(t)}{(k_m + C_{DA}(t))}}_{\text{Recapture by DATs}} - \underbrace{k_{rem}C_{DA}(t)}_{\text{Removal}}, \quad \textbf{(1)}$$

Based on Equation 1, the change in dopamine concentration over time is equal to the amount of dopamine released in the synaptic cleft (via both phasic and tonic release) minus the dopamine removed (assumed to be linear) and the dopamine that is recaptured by DATs (as described by the Michaelis-Menten equation).

Subsequently, the tonic dopamine release term, which is independent of autoreceptors, is expressed as

$$I_{DA}^{tonic} = \rho \frac{P_r^{tonic} n_0}{\alpha_{vf} N_A} \upsilon_{tonic}, \quad \textbf{(2)}$$

where ρ is the terminal density, α_{vf} the extracellular volume fraction, N_A the Avogadro's number, P_r^{tonic} the tonic release probability, n_0 the number of molecules released per vesicle fusion, and v_{tonic} the tonic firing rate.

Contrary to the dopamine tonic release, the dopamine phasic release term varies across three scenarios:

- If there is no response and no prediction error signal: $I_{DA}^{phasic}(t) = 0$.

- If there is a reward prediction error signal at a certain t_{reward}:

$$I_{DA}^{phasic}(t) = \rho \frac{\left(P_r^{phasic} \cdot \frac{0.334}{AR(t)}\right) n_0 |RPE|}{\alpha_{vf} N_A} \left(\upsilon_{phasic} \cdot \frac{0.334}{AR(t)}\right),$$

$$\text{for } t_{reward} + 0.1 \leq t \leq t_{reward} + 0.1 + 0.05, \quad \textbf{(3)}$$

- If there is a punishment prediction error at $t_{punishment}$:

$$C_{DA}(t) = 0,$$

$$\text{for } t_{punishment} + 0.1 \leq t \leq t_{punishment} + 0.1 + 0.05. \quad \textbf{(4)}$$

where the parameters are equivalent to the tonic ones and the only ones dependent on autoreceptors are the vesicular release probability and the phasic firing rate. Also, phasic release is proportional to the reward prediction signal (RPE) which establishes the difference between the predicted and received rewards (Véronneau-Veilleux, 2022).

1.8 Modeling Dopamine Circuits

To understand psychiatric disorders such as ADHD it is important to determine which neurocognitive processes go awry, and how. Psychiatry has traditionally suffered an explanatory gap between neurobiological mechanisms and symptom-level behaviors. Despite considerable research, pinpointing the molecular/environmental factors responsible for ADHD, and the mechanisms by which they operate remains challenging. This limited understanding is best exemplified by the fact that one-third of patients with ADHD do not respond to any medical treatments. To help overcome obstacles associated with approaching ADHD from a strictly cognitive lens, neuroscientists have turned to computational modeling approaches. These techniques seek to develop and test mathematical theories that explain how our brains operate within the context of the disorder. By using computer simulations with adjustable parameters to validate theoretical approaches, researchers can elucidate a wider range of potential mechanisms contributing to ADHD than otherwise possible. In one prominent recent study, computational models were used to confirm that ADHD contributed to reduced choice sensitivity during reinforcement learning, but not an altered learning rate (Ziegler, 2016). Eventually, by incorporating computational models into a diverse toolkit for tackling neurological disorders like ADHD, scientists will have the information required to develop superior treatment approaches than currently available.

Neurocomputational models of cognition have proven to be insightful among the many current modeling approaches. By using this computational framework, predictions are made about how ADHD causes cognitive and motivational deficits. In these models, dynamic interactions between dopamine (DA) and circuits linking the basal ganglia (BG) with the frontal cortex are simulated and examined in relation to action selection, reinforcement learning, working memory, and decision-making. Neural interactions are explicitly described in these models , and cognitive and motivational processes are illustrated through network dynamics. A reinforcement learning task and a working memory task were used to test model predictions in ADHD patients who were on and off stimulant medications. Motivating and working memory

deficits can both be explained by a reduced DA in the striatum, whereas other behaviorally independent aspects may be accounted for by another mechanism (like noradrenergic). Researchers can test the accuracy of their theoretical predictions and fine-tune them by linking models to real-life data from human or animal subjects. The potential of computational modeling for the understanding of neurological diseases, including ADHD, is illustrated by such approaches (Frank, 2007)

1.8.1 Hodgkin-Huxley Models

In the 1950s, scientists Alan Hodgkin and Andrew Huxley introduced their mathematical model of the neuron, which would go on to become the canonical biophysical model of a neuron. The principal equation of the model relates currents across sodium, potassium, and leak channels to provide an overall direction of the flow of current through a neuron, thereby describing the generation and propagation of an action potential (Steratt, 2012).

$$I_c = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} \quad \textbf{(5)}$$

The current flow of ions through a neuron's lipid bilayer is shown in (5). Here, C_m represents the capacitance of the lipid bilayer that makes up the cell membrane and V_m represents the membrane potential. The product of the differential change in potential over time and the capacitance accounts for current flow of ions through the membrane.

$$I_i = g_i(V_m - V_i) \quad \textbf{(6)}$$

(6) represents the contribution of facilitated diffusion to ion flow across the lipid bilayer. This process relies on the various ion channels embedded between the phospholipids and has a conductance represented by g_i. This conductance is a product of the maximum possible conductance and the fraction of open ion-gated channels as a function of voltage and time. Multiplying this quantity by the driving potential for the specific ion, or the difference between the membrane potential and the channel's reversal potential (V_i), we can assess the ion current flowing through the channel. This calculation can be repeated for all the various types of ion channels present in the lipid membrane. In the Hodgkin-Huxley model of the neuron, the contributions of sodium, potassium, and leak channels are accounted for. Leak channel ion flow represents the contribution of simple diffusion of ions through the lipid bilayer at a basal level throughout cellular processes to the overall ion current. In the case of leak channels, V_i represents the reversal potential of the membrane itself, and the conductance has no relation to the number of open channels, since channels are not facilitating the leakage.

By combining (5) and (6) we arrive at the final form of the Hodgkin-Huxley equation, that defines I, the total membrane current per unit area (7):

$$I = C_m \frac{\mathrm{d}V_m}{\mathrm{d}t} + g_K(V_m - V_K) + g_{Na}(V_m - V_{Na}) + g_l(V_m - V_l) \quad \textbf{(7)}$$

By building off the structure and intuitions used in this transformative model, researchers in the field of neuroscience have been able to generate far more complicated models for other types of neuron phenomena, including neurotransmitter release and subsequent action potential propagation.

1.8.2 Dopamine Neuron

Dopamine neurons refer to a specific subset of cells in the midbrain that control a range of neurological functions including voluntary movement and cognitive/emotive processes such as mood and reward (Chinta, 2005). Modeling the firing of this class of neurons has been a growing topic of exploration for researchers predicting a broad class of psychiatric and neurological conditions (Powell, 2021). Detecting irregularities or changes in these trademark bursts may provide clues regarding disease progression or drug efficacy in patients. To this effect, equations such as equation 8 serve as a template for midbrain dopamine neurons and illustrate the relationship between firing patterns and specific signaling currents they encounter (Yu, 2015).

$$C_{\mathrm{m}}\frac{dv}{dt} = -I_{\mathrm{Na}} - I_{\mathrm{Ca,L}} - I_{\mathrm{K,DR}} - I_{\mathrm{K,A}} - I_{\mathrm{K,ERG}} - I_{\mathrm{K,SK}} - I_{\mathrm{H}} - I_{\mathrm{Leak}} + 0.1I_{\mathrm{stim}}/\pi dL. \quad \textbf{(8)}$$

While sharing many similarities with the fundamental Hodgkin-Huxley model described earlier, models such as the one described above incorporate a greater specificity with regards to their ion channels, producing more accurate approximations of the net ion flux through the membrane of the neuron. Here, I_{Na} refers to the fast-spiking sodium current, while $I_{Ca,L}$ describes an L-type calcium current. Additionally, 3 different types of potassium currents (DR, A, ERG) are presented which encapsulate a much more complete spectrum than what is described in the H-H model. I_H accounts for a nonspecific cation current that occurs during hyperpolarization, while the leak current remains the same as earlier. These additional terms provide a level of complexity that gives researchers additional insight when conducting simulations.

1.8.3 Spiking Neuron Models

Spiking neuron models attempt to recapitulate the relevance of spike timing and rules of spike timing dependent plasticity in their algorithms. Thus they are more physiologically relevant/neuromorphic, and often more efficient in their computing than other existing deep neural networks (Kim, 2021). They are built from spiking neuron models of which there are two primary classes: the integrate-and-fire model and spike response models. In spiking neuron models spikes are treated as events fully characterized by their firing time, and occur when the membrane potential μ of the neuron exceeds some threshold (Gerstner, 2002). A refractory period during which no amount of stimulation can produce an effect in a postsynaptic neuron after it fires is considered in these models. At its foundation, an integrate-and-fire circuit relates the neuron to a circuit consisting of a resistor *R* and capacitor *C* in parallel driven by a current *I*.

The most useful integrate-and-fire models incorporate a "leakiness" component, which relates a time constant τ to the resistance and capacitance of the circuit. Thus the neuron itself is defined by the membrane potential μ and time constant τ, and described by its standard form:

$$\tau_m \frac{du}{dt} = -u(t) + RI(t) \qquad \textbf{(9)}$$

Action potentials are not explicitly handled by this model; instead a firing time variable $t^{(f)}$ is used to to formally define spikes that occur when the membrane potential exceeds a threshold criterion. Immediately after $u(t^{(f)})$, u resets to some value below the threshold criterion, and is defined by Equation 9 again until the next crossing. Thus the model's behavior is dictated by the reset and leakiness parameters. Additionally an absolute refractory period can be built into the model at points where $t = t^{(f)}$ (Gerstner, 2002).

In contrast, spike response models of neurons are concerned more with the timing of the last spike as opposed to the membrane potential and express the membrane potential as an integral over time (Gerstner, 2002). Thus the refractory period becomes defined by three components: a reduced responsiveness after an output strike, an increase in membrane threshold after spike firing, and a hyperpolarizing spike after-potential (the electrical activity following an action potential) (Gerstner, 2002). Since membrane potential is defined as an integral over time, neurons of spike response models are solely defined by their membrane voltage μ. At rest μ=0, and incoming spikes perturb μ_{rest}. If the summation of incoming spikes exceeds a certain threshold, a spike is triggered.

For this project, we focused on the model by Ribar et al., which analyzes the inhibitory interaction between two neurons (Figure 3). As the first neuron fires (blue), the second one is inhibited and there is no firing (anti-phasic activation). Then, as the action potential in the first one (red) decays, the second neuron is activated, further inhibiting the first neuron. Both neurons are stimulated by an external current Iapp (Ribar, 2019; Ribar 2021).

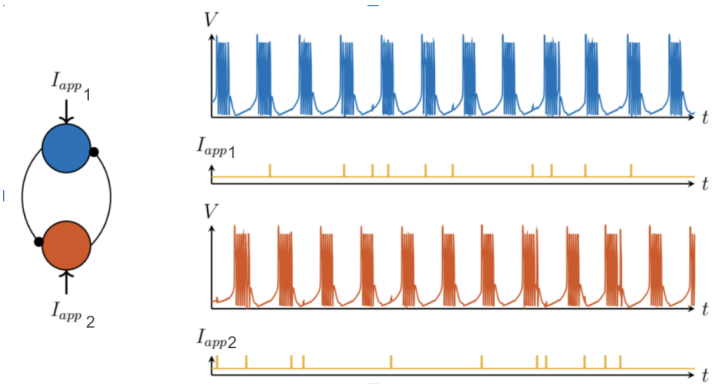

Figure 3: Inhibitory connection between two neurons (Ribar, 2019)

This inhibitory interaction can be also schematically represented by a circuit with a passive component, including a capacitor and a resistor that mimic the dissipation through the membrane, and feedback currents (e.g. the potassium outward current, the sodium inward current, and the leak current) (Figure 4).

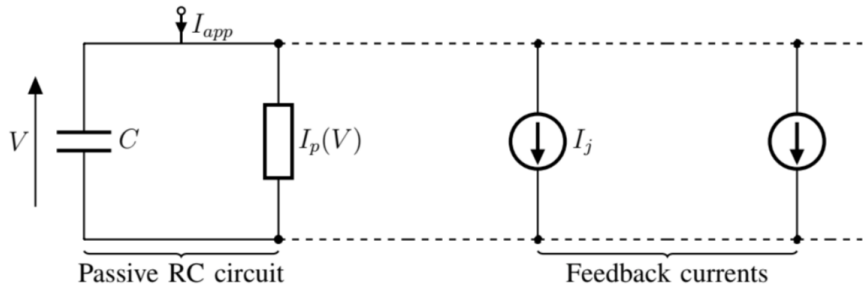

Figure 4: Circuit diagram of the inhibitory connection between 2 neurons (Ribar, 2019)

2. Methods

Our model is a combination of three preexisting models: Hodgkin-Huxley's, the dopamine neuron, and the biophysical neuron model. In particular, we employed the code and circuit representation from Ribar et al. as a starting point for the development of our computational model. Hodgkin-Huxley's model provided us with some of the equations employed to map the neurons.

2.1. Theoretical Model

Before starting the coding process, we wanted to understand how to represent ADHD from a biophysical point of view by mapping the interaction between two neurons with a simple circuit (Figures 3, 4). However, the model from Ribar et al. only represents two general neurons, and our goal was to make dopamine the main player of our model.

After extensive literature research, we identified D2 inhibitory receptors and DATs to have key roles in regulating the synaptic concentration of dopamine and in modulating the action potentials through those neurons (Schmitz, 2003; Ford, 2014). In a healthy brain, after the release of dopamine in the synaptic cleft from the presynaptic neuron, dopamine binds to the D2 receptors, which initiates a cascade in the postsynaptic neuron which results in an inhibitory action potential to occur (Figure 5). After the completion of the action potential, DATs reuptake the dopamine into the presynaptic neuron to prevent the excessive stimulation of the postsynaptic neuron and a prolonged action potential. However, in the brain of someone with ADHD, this process is impeded by the higher-than-normal density of DATs, which results in an increased reuptake of dopamine before it can bind to the D2 receptors (Figure 6). The lower-than-normal binding of dopamine to the D2 receptors results in the potassium channel not opening. This results in a malfunctioning of the action potential.

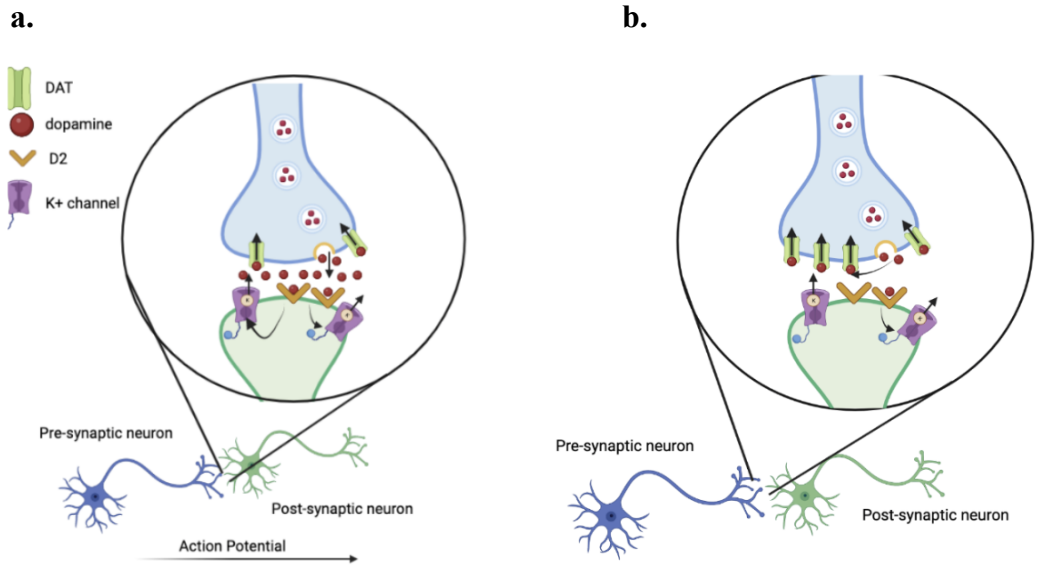

Figure 5a: Dopamine binding in the presynaptic cleft in a healthy individual. **5b:** Dopamine binding in the presynaptic cleft in an ADHD individual. The concentration of dopamine is lower due to a higher reuptake from the DATs.

These processes are relevant to ADHD due to the impact that the malfunctioning of action potential activation has on the reward mechanism in the brain. If action potentials are not started as a consequence of a given action, then there will be a lack of signal to the brain to continue that specific action (reward mechanism). In a healthy brain, when one is doing an activity that requires attention or is pleasant, then dopamine is released and starts action potentials that will eventually contribute to that action being continued (positive feedback loop). However, in ADHD, the lack/inefficiency of this mechanism results in the individual with ADHD struggling to pay attention to that activity and feeling the urge to move to something else.

2.2. Assumptions

To reduce the complexity of the model, we had to make some educated assumptions based on the existing literature. In particular, we know that DATs modulate the dopamine synaptic concentration by reuptake dopamine from the synaptic cleft, thereby preventing them from binding D2, and subsequently opening the potassium channels. As a consequence, we assumed that:

1. The reversal potential of the synaptic current $E_{Inhibitory}$ would be equal to the reversal potential of potassium (-75 mV) because of the primary role that potassium plays in this process.
2. The density of the DATs affects the potassium conductance LINEARLY. (Schmitz, 2003; Ford, 2014)
    a. Based on the work by Millichap et al., we learned that the density of DATs is 70% higher in brains with ADHD (Millichap, 2000). Therefore, we assumed that the potassium conductance will decrease by 70% in the synaptic clefts of these neurons.

b. Based on the paper by Fusar-Poli et al., chemical stimulants (e.g. methylphenidate) result in a 70% increase in the synaptic concentration of dopamine (Fusar-Poli, 2012). Hence, we assumed that the potassium conductance would also increase linearly in accordance with the synaptic dopamine concentration.

3. In order to simplify our model, we have assumed that g(t) is a constant over time. In practice, it can vary in time depending on the circumstances. Indeed, g(t) depends on a certain network activity and is characterized by a channel conductance. Therefore, g(t) can potentially vary over time in the context of more complex simulations.

2.3. Equations

There are two main equations at the core of this model. In class we learned that the synaptic current depends on the channel conductance *g(t)*, the difference between the reversal potential $E_{inhibitory}$ and the postsynaptic voltage V_{post}, and the binding and unbinding rate of NTs $S(V_{pre}(t))$, which is a function of the presynaptic voltage (Equation 10).

$$I_{synapse}(t) = g(t) * [E_{inhibitory} - V_{post}(t)] * S(V_{pre}(t)) \quad \textbf{(10)}$$

The binding and unbinding function S can be calculated using the hyperbolic tangent function on the ratio of the difference between the presynaptic voltage and V_0 and the dV_0 (Equation 11).

$$S(V_{pre}(t)) = 0.5 * [1 + tanh(\frac{Vpre - Vo}{dVo})] \quad \textbf{(11)}$$

Successively, we found the values for some of the constants involved in these equations. Based on Assumption 1 (Section 2.2), we assumed $E_{inhibitory}$ to be -0.075 V. Similarly, based on Assumption 2 (Section 2.2), we treated the conductance *g(t)* as being time-independent and to be equal to that of the potassium channel, 2.29 nS. Typical values for V_0 range from -5 to +5mV and dV_0 from 5 to 10mV. For our simulations, we assigned V_0 and dV_0 5 and -5mv respectively (Hill, 2014; Seutin, 2021).

2.4. Implementation

The simulations were done using python 3.9 and required the use of the following packages: numpy 1.23.3, matplotlib 3.6.2 and scipy 1.9.3. The original code comes from https://github.com/lukaribar/Circuit-Neuromodulation and our modified version can be found here https://github.com/Turelure13/BENG260_Circuit_Neuromodulation.

3. Results

In this section, the results of the previously explained methods in the context of a connection of two synaptic neurons are posited. We start with a simulation of a dopamine-inhibiting synaptic connection. Next, we have the synaptic connection change in the model due to external or internal network activity and simulate the output current of the synaptic connection. Then, we reproduce how the synaptic connection is affected in ADHD patients by

changing the conductance. Finally, we simulate how this conductance is increased when ADHD patients receive chemical stimulants.

3.1. Simulating a Synaptic Connection

Firstly, we analyzed the interaction between the presynaptic and the postsynaptic neurons by plotting their voltages with respect to time in the case of an excitable behavior called bursting. Bursting is a common signaling mechanism in neurons and has crucial consequences on their synchronization properties as well as on their information processing capabilities. From Figure 6 , it can be inferred that neurons have an inhibitory effect on each other as when the presynaptic's voltage lowers, i.e. it is inhibited, the postsynaptic's one increases, i.e. it is fired.

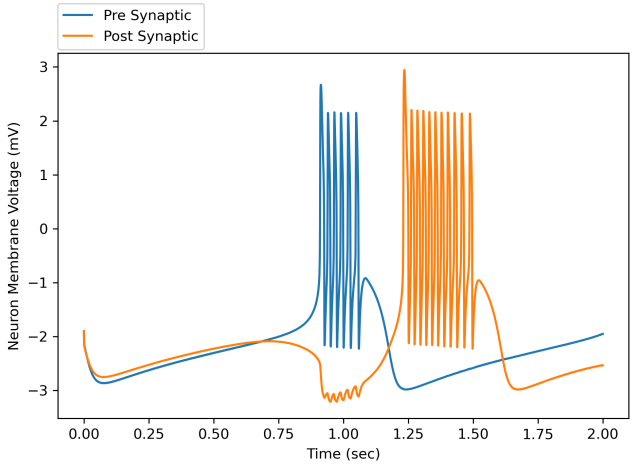

Figure 6: Presynaptic vs postsynaptic voltage vs time.

3.2. Simulating the Synaptic Connection Changes Due to Network Activity

Secondly, we focused on modeling the synaptic currents in three different t patient groups: healthy/non-diseased, with ADHD, and with ADHD after the use of chemical stimulants. Because ADHD causes a 70% higher DAT density, we assumed that conductance decreases by 70% in these neurons. Next, from the literature, we know that chemical stimulants cause a 70% decrease in DAT density in ADHD patients, so we assumed that conductance increases accordingly. We used the conductance value for the methylphenidate as described in the assumptions section to simulate the current of the synaptic connection.
We can visualize in Figure 7 the synaptic current between 0 and 9 seconds showing just one burst of the full frame, reaching a maximum value of approximately 6 nA.

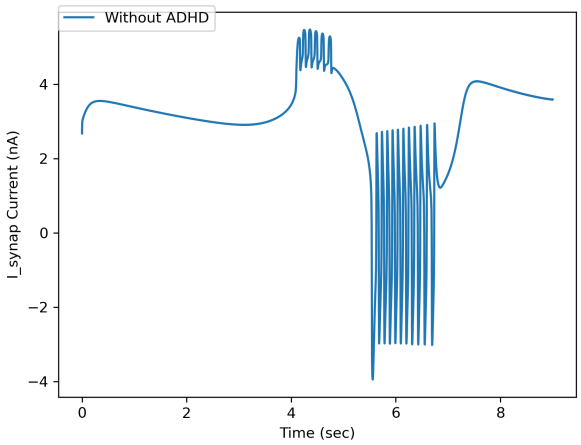

Figure 7: Synaptic current in healthy patients.

Then, we added the synaptic current of a model ADHD patient. It can be seen that there is a considerable difference between both cases. Current from the ADHD patient group appears much more linear and flatter than the original current, reaching a maximum of only 2 nA, three times less than healthy patients.

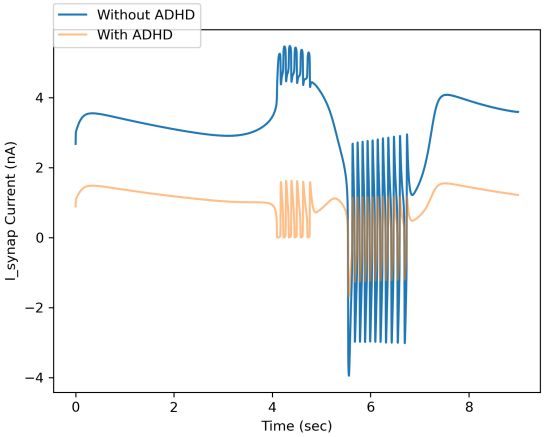

Figure 8: Comparison of synaptic current in healthy patients vs ADHD patients.

Finally, the use of chemical stimulants has been incorporated and according to our premises, we saw that they increase the power of the synaptic current. However, these currents do not approach values similar to the healthy patient models. However, we still observe a slight improvement with the synaptic current achieving almost 3 nA.

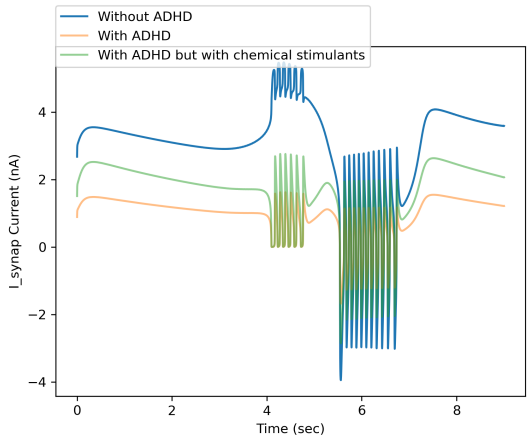

Figure 9: Comparison of synaptic current vs. time in healthy patients vs ADHD patients vs ADHD patients with stimulants.

Finally, Figure 9 illustrates how the current varies with respect to voltage. It gives an overview of the quality of the synaptic connection in the case of a healthy patient, a patient with ADHD and finally a patient with ADHD but with chemical stimulants. Again, we can clearly observe that the patient without ADHD is the patient with the best synaptic connection, while the patient with ADHD obtains lower current values, thus a worse synaptic connection. This synaptic connection can be enhanced by the use of chemical stimulants that results in a higher conductance and thus a higher current.

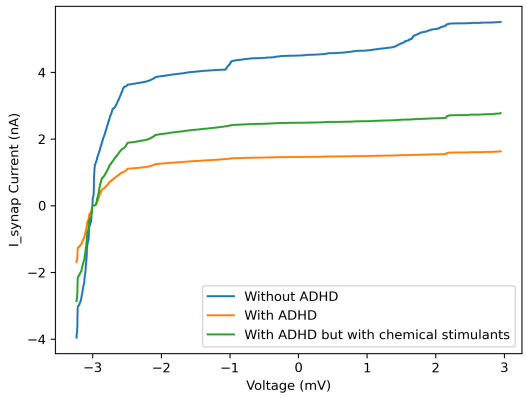

Figure 10: Comparison of synaptic current vs. voltage.

4. Future Scope

Despite the promising initial results we have presented, our modeling techniques could still be significantly improved in order to develop a more complete and physiologically accurate recapitulation of dopamine transmission in the ADHD brain. More complex models will need to take into account additional parameters that impact dopamine concentrations in the synaptic cleft. Incorporating more channels in addition to potassium (K^+) channels, such as sodium (Na^+) channels, would be critical in accomplishing this since membrane conductance is a function of several variables beyond K^+ channels. Additionally, including neurotransmitters besides

dopamine in the model (e.g. norepinephrine) would more accurately represent a real neurological landscape laden with various neurotransmitters, and elucidate any effects these neurotransmitters have on action potentials and the concentration of dopamine within the synaptic cleft. While incorporating these additional parameters we should also avoid exceeding a threshold number of variables that will cause overfitting problems and a lack of trainability in our model.

The lack of homogenization regarding dopamine modeling is a significant obstacle we encountered throughout our project. The sheer number of models available and their vastly different parameters present an issue when comparing results between various models, and when attempting to verify previous works. Therefore, it could be advantageous to develop a standardized model exclusively for dopamine control and its related dynamics. Machine learning (ML) algorithms could play an important role in achieving this objective, as their tunability, accuracy, and automated nature could eliminate many of the drawbacks associated with current dopamine modeling. Starting from such standardized models would give researchers a platform to quickly and easily observe the effects of novel drugs and potential treatment plans in a theoretical space, lowering the experimental and administrative costs normally required for such endeavors.

To effectively customize and adapt most software, a large volume of training data is typically required. The field of dopamine dynamics in neurological modeling is no different in this regard. Creating databases of accurate dopamine concentrations given different parameters/experimental setups will ensure researchers can better train their algorithms and produce models with more robust prediction capabilities. In our investigations, we were not able to find any reliable sources for such data, particularly not in the numbers required for training a robust ML algorithm. Filling this gap will provide neuroscientists with a useful tool capable of significantly speeding up new modeling investigations without sacrificing accuracy.

By combining such advances, we could achieve a much more diverse and robust modeling toolkit for dopamine dynamics capable of distinguishing between various levels of ADHD severity if given the appropriate user inputs. This longer-term goal would provide incredible insight to clinicians particularly as they track patient progression and determine the efficacy of their treatment plans. Such an advance could potentially revolutionize the field and pave the way for similar modeling aimed at tackling diverse neurological phenomena.

5. Conclusions

The most common neurodevelopmental disorder in children is Attention Deficit Hyperactivity Disorder (ADHD). Stimulants such as methylphenidate block more than 70% of dopamine transporters (DAT) in the striatum when administered in therapeutic doses and are used as the first line of treatment (Millichap, 2000) in children and adults alike.

Several previously established models attempt to account for dysfunctional dopamine dynamics in ADHD, resulting in a lack of homogeneity across modeling parameters. To better understand how computational models play a crucial role in simplifying biology and planning experiments/treatments, we explored a number of existing models (i.e. Hodgkin-Huxley, Dopamine Neuron, Biophysical Neuron, and Ribar et al.'s models). From these models, class material, and extensive literature research, we introduced a more complex, dopamine-specific model. Since DATs affect dopamine-mediated signaling by modulating dopamine synaptic

concentration, we created a model to describe DAT activity. Previous work suggests that dopamine signaling most directly affects potassium conductance. Assuming that DAT density is linearly related to potassium conductance, we were able to build a model that describes dopamine signaling in D2 receptor neurons. From our model, we observed that the synaptic current of ADHD patients is typically lower than that of the healthy population. The model also demonstrated an increase in the synaptic current in ADHD brains with the use of chemical stimulants. However this improvement did not fully restore the synaptic current ranges to ranges consistent with the non-diseased population. Thus, while medication may result in a significant improvement of ADHD symptoms via improvements in synaptic transmission of dopamine, there is still scope for improvement. It is clear from our research that creating a robust model that can accurately predict the changes in dopamine dynamics that occur in diseases like ADHD is a useful tool for both neuroscientists and physicians alike. By continuing to add layers of complexity to the model we have introduced, we will be able to provide the scientific community at large with mechanistic insights for a highly complex neurological process that affects millions.

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