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# Mathematical Modeling and Examination into Existing and Emerging Parkinson's Disease Treatments: Levodopa and Ketamine

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Mathematical Modeling & Examination into Existing and Emerging Parkinson's Disease Treatments: Levodopa and Ketamine

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## Abstract

Parkinson's disease (PD) is the second most common neurodegenerative disease across the world, affecting over 6 million people worldwide. This disorder is characterized by the progressive loss of dopaminergic neurons within the substantia nigra pars compacta (SNpc) due to the aggregation of α-synuclein within the brain. Patients with PD develop motor symptoms such as tremors, bradykinesia, and postural instability, as well as a host of non-motor symptoms such as behavioral changes, sleep difficulties, and fatigue. The reduction of dopamine within the brain is the primary cause of these symptoms. The main form of treatment for PD is levodopa, a precursor to dopamine that can cross the blood-brain barrier (BBB). Levodopa reduces PD symptoms by increasing dopamine levels. While L-Dopa is often used as the primary pharmaceutical for PD, it comes with many drawbacks with long-term use. 40% of patients develop complications with levodopa within five years of treatment. A new emerging Parkinson's treatment is ketamine, which has been shown to produce long-lasting benefits for PD patients. Ketamine reduces motor complications and produces neuroprotective effects within the brain. Using current neuroscience literature, a mathematical model created in CellDesigner depicts the neurological pathways of these medications within the brain. Using a biochemical system simulator, COPASI, these models investigate the effects of levodopa and ketamine on a diseased brain system. Model results aligned with current literature and highlighted key areas for future research.

# I. Introduction

## 1.1 Overview of Parkinson's Disease

Parkinson's Disease (PS) is a neurological disorder, affecting nearly 6.1 million people worldwide in the year 2016 (Bloem, et al., 2021). PD affects nearly 2% of the population over age 65 and is the second most common neurodegenerative disease, which has doubled in frequency from 1990 to 2016 (Vázquez-Vélez, et al, 2021). Only 3-5% of all cases have been shown to stem from genetics, leading scientists to believe environmental factors play a key role in the development of the disorder (Bloem, et al., 2021).

At the disease's core, it involves the breakdown of the nigrostriatal dopaminergic pathway and a reduction of dopamine in the brain (Raza, et al., 2019). The disorder begins when roughly 50% of the melanized dopaminergic neurons in the substantia nigra pars compacta (SNpc) have degenerated (Langley, et al., 2020). Neuromelanin is believed to be a neuroprotective agent against toxic iron species. The loss of these melanized neurons is not uniform, with the greatest area of loss shown to be in the lateroventral portion of the SNpc (Langley, et al., 2020). Additionally, PD is characterized by the accumulation of α-synuclein aggregates known as Lewy bodies (LB). The body cannot break down LBs leading to further accumulation and cell death. The majority of neuron death, during the beginning-to-middle stages of PD, occurs in the brain stem. It is thought that a lack of neuromelanin leads to toxic iron species being released and interacting with α-synuclein, further driving the degeneration process (Mochizuki, et al., 2020). Iron's role in the pathology of PD will be further explored later on in the mathematical models.

## 1.2 Symptoms

Following SNpc degeneration, the disorder begins to display many different symptoms. PD is known for its tell-tale motor symptoms which act as the hallmarks of the disorder. These symptoms are tremor, bradykinesia, rigidity, and postural instability. Bradykinesia is a term to describe the slowness of movement, which often appears as shuffling while walking, dragging feet, little to no facial expressions, and freezing (Berardelli, et al., 2001). Appearance of bradykinesia is required for a diagnosis of PD, alongside a second motor symptom. Despite tremor often thought of as a typical symptom of the disorder, only roughly 20% of PD cases display it (Bloem, et al., 2021). Overall, motor symptoms primarily stem from the loss of dopaminergic neurons in the SNpc (Lindestam Arlehamn, et al., 2020).

PD is not only characterized by motor symptoms but also by a swath of non-motor symptoms. These symptoms extend to various sensory abnormalities, behavioral changes, sleep difficulties, autonomic dysfunction, and fatigue (Pfeiffer, 2016). The non-motor symptoms can be divided into several categories: cortical manifestations, basal ganglia symptoms, brainstem symptoms, and peripheral nervous system (PNS) disturbances (Lee, et al., 2015). In cortical manifestations, symptoms include psychosis and cognitive impairment. Basal ganglia symptoms involve impulse control issues, apathy, and restlessness. Brainstem symptoms include depression, anxiety, and sleep disorders; PNS disorders include constipation, pain, and sensory disturbances (Lee, et al., 2015). Non-motor symptoms are thought to stem from the loss of catecholaminergic and cholinergic neurons outside the SNpc (Lindestam Arlehamn, et al., 2020).

In PD patients, at least one non-motor symptom was present in almost 100% of cases (Pfeiffer, 2016). The non-motor symptoms primarily contribute to the disability of PD patients. Due to the progressive nature of the disease, it can last decades depending on the individual patient. Often the earliest stages of PD begin ten years before any diagnosis is made. The

disorder presents an extreme burden on the patient as well as caregivers, who carry the socioeconomic burden surrounding the disorder. Despite PD prevalence in the human population, there is no cure. Current medications for PD aim to relieve the primary motor symptoms but often have limited effectiveness. As of today, there is only one main form of treatment for PD which is the medication levodopa. Although, in recent years, ketamine has proven to be a possible form of treatment for PD patients. Through mathematical modeling, the biochemical processes of levodopa and ketamine within the brain are examined, allowing for a better understanding of these medications.

## II. Levodopa

### 2.1 Levodopa Introduction

Since 1960, levodopa has been the primary form of treatment for PD. Levodopa belongs to the large neutral amino acids (LNAA) class. Levodopa, also known as L-dopa, is the precursor of dopamine and is used as a dopamine replacement treatment for those with PD. Currently, levodopa is considered the most successful drug for PD as it provides the best symptom control. While levodopa is not a cure for PD, it successfully reduces motor symptoms from the disease. The drug is primarily used to control bradykinetic symptoms, such as tremor and rigidity. Dopamine cannot pass through the blood-brain barrier, and thus cannot be administered as a treatment option. Levodopa does not have this issue, as it can readily cross the barrier. When taken orally, levodopa is absorbed by the small intestine and carried by the LNAA transport system. It has a short half-life of 90 minutes. Levodopa is administered alongside carbidopa or benserazide to prevent gastrointestinal metabolism by the enzyme L-amino acid decarboxylase (Contin, et al., 2010). These supplementary drugs prevent early breakdown and increase the absorbency of levodopa.

## 2.2 Side Effects

The beginning of levodopa treatment is often described as a “honeymoon” phase as there is an improvement in patient motor performance. At first, the drug helps patients gain better control over their movements and easily perform daily tasks. Levodopa increases the dopamine levels in the brain. Throughout the disease, the therapeutic window for levodopa shrinks, leading to complications. Within five years of treatment, 40% of PD patients are estimated to have complications (Boelens Keun, et al., 2021).

As the disease progresses, there are fewer benefits from the medication as patients begin to notice the return of PD symptoms faster before the next dose. Additional doses can help this issue at first, but over time the wearing-off periods become more frequent and respond less to levodopa (Thanvi, et al., 2004). Chronic levodopa treatment interferes with the tonic and phasic activity of dopaminergic neurons, leading to neuroadaptation (Voon, et al., 2017). There are several key side effects of levodopa: nausea and vomiting, hypotension, behavioral changes, and dyskinesia.

### 2.2.1 Nausea and Vomiting

Nausea is the most common side effect of levodopa and occurs in 30% of patients (Hälbig, et al., 2007). Typically, nausea and vomiting resolves itself within days or weeks of continued treatment. These side effects are significantly reduced or eliminated with carbidopa and benderizine, which are classified as peripheral dopa decarboxylase inhibitors (Thanvi, et al., 2004).

### 2.2.2 Orthostatic Hypotension

Another side effect of levodopa is orthostatic hypotension which occurs in roughly 30-50% of patients after 3-5 years of treatment (Hälbig, et al., 2007). Levodopa can induce or worsen this

condition. Orthostatic hypotension describes low blood pressure from sitting or lying down, followed by dizziness. The drop in blood pressure is distinct and does not happen within the first 10 minutes (Jost, et al., 2020). This side effect often leads to an increased risk of injury or death in patients as it increases their chance of stroke, falling, or accidental injuries. One post-mortem study found that 78% of PD patients had orthostatic hypotension (Liu, et al., 2023). It is debated whether PD or levodopa is the cause of orthostatic hypotension. It is hypothesized that the hypotension stems from the activation of postsynaptic D_1-receptors and sympathetic presynaptic D_2-receptors by dopaminergic agents in levodopa. These D_2-receptors lead to reduced vasoconstrictor response from norepinephrine inhibition (Hälbig, et al., 2007). Others hypothesize that levodopa does not trigger this side effect, but rather a deficient adaptation occurring under strain (Jost, et al., 2020). Levodopa can indeed affect blood pressure and blood pressure regulation, but its extent is contested.

### 2.2.3 Behavior

Levodopa also affects an individual's behavior. There is a spectrum of neuropsychiatric side effects, which include difficulties with impulse control and hallucinations (Beaulieu-Boire, et al., 2014). Many of the mechanisms surrounding behavioral symptoms are not understood. One hypothesis known as the "continuum hypothesis" has proposed that medication-induced neuropsychiatric conditions begin with sleep disruption and end in delirium (Holroyd, et al., 2001).

**Hallucinations.** Hallucinations are perceptions without external stimuli. Hallucination incidence numbers are low for PD patients, with a rate of only 3-5% during the first five years of levodopa treatment (Hälbig, et al., 2007). The issue primarily appears in the later progression of PD with the increase of levodopa dose. In later stages of PD, 30-50% of patients developed

levodopa-produced hallucinations and other psychiatric effects (Hälbig, et al., 2007). In 67% of hallucinating PD patients, hallucinations occurred at least once a week. In 33% of hallucinating patients, multiple forms of hallucinations occurred together (de Maindreville, et al., 2005).

Visual levodopa-induced hallucinations are the primary form of hallucination experienced in patients. Almost all hallucinations were of visual nature (Holroyd, et al., 2001). Often these hallucinations are complex and well-formed and often consist of children or animals (Beaulieu-Boire, et al., 2015). Additionally, they typically occur in dim environments in the evening hours.

Before levodopa treatment, hallucinations in PD patients were extremely rare. While this side effect has a large swarth of supporting data linking it to dopaminergic medications, only a portion of patients experience hallucinations, which suggests there may be other factors involved. One study found hallucinations to have an association with a history of depression and sleep disorders, which aligns with the "continuum hypothesis" (Holroyd, et al., 2001). Overall, hallucinations are a high contributor to permanent nursing home placements and high mortality rates for PD patients (Fénelon, et al., 2000).

**Impulse Control Disorders.** Another behavioral side effect of levodopa treatment is the development of impulse control disorders. Levodopa has been shown to produce reinforcing effects and display enhanced novelty-seeking behavior, which plays a key role in the development of these disorders. Impulse Control Disorders, also known as behavioral addictions, occur in 80% of patients after several years of chronic treatment (Voon, et al., 2017). The category of impulse control disorders includes gambling disorder, compulsive shopping, compulsive sexual behaviors, and binge eating disorder (Voon, et al., 2017).

Additionally, it includes other addictive behaviors such as compulsive medication use and punding. Punding is defined as a complex, repetitive, and non-goal-oriented activity, such as repeatedly adding up number tables for no purpose (Pouchon, et al., 2021). It is often associated with an intense focus and admiration of everyday objects, with the patient consistently examining, collecting, sorting, and storing these items. Prevalence of punding ranges from 1.4-14% of patients, however, this behavior is severely underdiagnosed and often not discussed (Rajalingam, 2023). Punding has been linked to hyperdopaminergic activity from dopaminergic agents, such as levodopa. Not all patients develop punding though, which leads researchers to believe it is caused by a complex interaction between habits, frontal lobe degeneration, basal ganglia dysfunction, and levodopa treatment (Rajalingam, 2023).

### 2.2.4 Levodopa-induced dyskinesia (LID)

Levodopa-induced dyskinesia (LID) is the most common side effect from levodopa treatment with roughly 80% of patients developing this symptom (Thanvi, et al., 2007). This symptom is even more likely in younger patients as well. LID consists of abnormal, involuntary movements. LID displays several different types of dyskinesia, such as diphasic, chorea, and athetosis (Gerlach, et al., 2011). Chorea may appear as “head bobbing”, while diphasic dyskinesia typically affects leg movement control (Espay, et al., 2018). Advanced levodopa treatment often appears with tremor and gait-freezing (Espay, et al., 2018). This side effect arises after long-term treatment of levodopa, with half of patients developing dyskinesia within the first 6 months of treatment (Thanvi, et al., 2007). The mechanisms behind LID are unclear, with the primary hypothesis stemming from hypersensitivity to dopamine and excessive levels of dopamine throughout the brain (Bezard, et al., 2001). Unfortunately, the development of LID is a general marker of levodopa treatment success, as those who do not display LID are often undertreated

(Espay, et al., 2018). Despite how common this side effect is for PD patients; it is the least managed levodopa complication. There are several approved medications aimed at reducing LID, the most promising is ketamine treatment which has been approved by the FDA for clinical studies.

## III. Ketamine

### 3.1 Ketamine Introduction

Ketamine, formal name (RS)-2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone, is a racemic mixture used clinically since 1970 as an anesthetic agent (Zanos, et al., 2018). Ketamine is a dissociative anesthetic, which is a form of anesthesia characterized by catatonia and amnesia.

Ketamine is popularly known as a drug of abuse due to its hallucinogenic and dissociative effects in subanesthetic doses. Recreational use of the drug often occurs in "rave" and "club" culture internationally, with subanesthetic doses leading to altered "psychedelic" mind states (Sassano-Higgins, et al., 2016). A low dose of the drug produces changes in mood and hallucinations. Ketamine is a derivative of phencyclidine (PCP), a popular hallucinogenic with many mind-altering effects including euphoria and illusions of extreme confidence. Currently, ketamine is classified as a Schedule III non-narcotic substance under the United States' Controlled Substances Act. Schedule III drugs are defined as drugs with low to moderate potential for abuse and dependence (Drug Scheduling, n.d.). While the Controlled Substances Act prevents community access to hazardous and addicting drugs, it hinders research exploring the therapeutic potential of many of these substances (Andreae, et al., 2016). Due to legal fear, drug stigma, and a lack of research funding, there are many barriers to the exploration of possible beneficial uses for ketamine. Only in recent years have researchers begun to explore the possible benefits of psychedelics.

Over the last 20 years, ketamine has emerged as a new treatment option for treatment-resistant depression (Singh, et al., 2016). For patients with depression, the typical treatment are antidepressants, but a reduction in symptoms are only seen after six to eight weeks of beginning the medication. Additionally, one-third of patients see no improvement even after multimodality treatment interventions (Corriger, et al., 2019). For the last 20 years, ketamine has been shown to produce rapid antidepressant effects after a single dose (Corriger, et al., 2019). In 2019, ketamine was approved to be used for treatment-resistant depression, preferably as a last-choice solution for patients.

Ketamine's anti-depressive effects stem from the drug's promotion of neural plasticity through synaptogenesis within the brain (Wu, et al., 2021). After a single dose of ketamine, the density of dendritic spines increased within a day and the drug has been shown to reverse stress-induced dendritic spine loss (Wu, et al., 2021). It is believed that the anti-depressant effects come from the growth of new dendrites within the brain, but this neural growth may benefit patients with neurodegenerative diseases by restoring synaptic pathways.

**3.2 Side Effects**

The side effects of ketamine vary depending on whether the substance is taken recreationally or clinically. Ketamine abuse is associated with a range of dangerous long-term side effects, but studies have shown these effects only apply to daily users of the drug (Singh, et al., 2016). Only 6-12% of patients who take medicinal ketamine experience side effects (Rosenbaum, et al., 2024). Overall, the most common negative side effects experienced by patients are nausea, vomiting, dizziness, dysphoria, and confusion (Rosenbaum, et al., 2024). In cases where ketamine was used to treat depression, there were several subtypes of symptoms: psychiatric, dissociative, cardiovascular, neurological, and other (Short, et al., 2018). The most

common psychiatric side effects are anxiety, irritability, elevated mood, delusions, panic, and apathy. It is uncertain if these side effects are a direct result of ketamine treatment or due to patients diagnosed with mental illnesses (Short, et al., 2018). The primary dissociative side effect is dissociation, followed by perceptual dis¬turbances. These effects only last in the short term (Short, et al., 2018). Common cardiovascular effects are an increase in blood pressure and bradycardia. These side effects do not present a significant threat to patients unless they have pre-existing conditions. Neurological side effects include confusion, delirium, and seizures.

Overall, many of these side effects are extremely uncommon. Ketamine is given at low doses and is shown to be safe, effective, and well tolerated (Sherman, et al., 2016).

**3.3 Parkinson's Disease Treatment**

In recent years, many studies have investigated ketamine's therapeutic ability in PD as the drug is used in long-term depression and chronic pain. Low-dose intravenous ketamine infusion has been shown to produce long-lasting benefits for PD patients (Sherman, et al., 2016). Ketamine increases cortical dopamine levels within the brain by 88-180% (Kokkinou, et al., 2018). Additionally, ketamine leads to a 62–180% increase in dopaminergic neuron activity (Kokkinou, et al., 2018). All of these facts make ketamine a promising treatment for PD.
In one study, mice received 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (20 mg/kg/d) to create PD pathology followed by ketamine treatment (8 mg/kg) (Fan, et al., 2017). The mice who did not receive ketamine showed clear neurobehavioral changes that reflected PD, such as tremor and hypokinesia. On the other hand, the mice who received ketamine infusions showed increased movement coordination and memory abilities compared to the control (Fan, et al., 2017). Not only did ketamine reduce motor symptoms associated with PD, but the drug produced neural protective effects within the mice. In these ketamine-infused mice, there were

significantly more nigra neurons than in the no-treatment group, suggesting ketamine reduced neuron apoptosis (Fan, et al., 2017). Ketamine's mechanism of action leads to the protection of dopaminergic neurons leading to the improvement of coordination and cognition within a diseased brain system (Fan, et al., 2017). This study highlighted the key neuronal benefits associated with ketamine.

Other animal studies have validated these findings and have shown ketamine successfully treats PD symptoms and reduces long-term motor complications, such as LID (Hallett, et al., 2004). In one human case, ketamine even alleviated dyskinesia immediately after infusion (Wright, et al., 2009). Currently, ketamine treatment is focused on reducing the complications associated with levodopa, in particular LID which is the most common and debilitating symptom of PD. While ketamine shows great promise in reducing chronic levodopa symptoms, this possible treatment also showcases major neuroprotective and neurorestorative effects within the brain. With mounting evidence of ketamine's neuroprotective effects, more clinical research is needed to ensure the drug's efficacy and long-term effects in PD patients. The exploration of ketamine's effects on the brain system is necessary to understand the mechanisms behind these therapeutic effects.

## IV. Methods

### 4.1 Cell Designer

Using the biochemical modeling software, CellDesigner 4.4.2, three computational models were created to showcase the pathways of Parkinson's disease, levodopa, and ketamine in the human brain. Arrows outline the specific processes and pathways within the neurological system. Colors have been utilized for better model comprehension.

### 4.2 Parkinson's Model

Parkinson's disease is theorized to stem from a variety of factors, from genetics to insecticides (Chade, et al., 2006). The Parkinson's Model serves a conceptual purpose. For modeling purposes, the form of PD will be idiopathic to simplify the pathway. Additionally, the Parkinson's Model showcases this cascade of cellular damage through simple arrows to signal each cellular process.

The Parkinson's Model begins with α-synuclein, which is a toxic protein consisting of 140 amino acid residues. α-Synuclein behaves like an unfolded protein but forms an α-helix that binds to artificial membranes (Bendor, et al., 2013). In the unbound form, α-synuclein is intrinsically disordered and results due to missense mutations in the α-synuclein gene (Breydo, et al., 2012). Due to mitochondrial impairment or oxidative stress, α-synuclein begins to aggregate which is the central pathogenesis behind PD (Breydo, et al., 2012). α-Synuclein aggregates are shown within the pathway as a complex titled "α-synuclein" which contains several α-synuclein proteins. These aggregates form within dopaminergic neurons within the SNpc. As shown within the model, the aggregation of α-synuclein creates the central feedback loop in PD.

α-Synuclein contains an unknown mitochondrial targeting signal, which leads to the reduction of mitochondrial multienzyme complex I activity within the electron transport chain (Devi, et al., 2008). α-Synuclein aggregates inhibit the proper redox coupling of protons, leading to an increase in superoxide ($O_2^{-\cdot}$) within neurons. The model uses an inhibition arrow to showcase the antagonistic action from α-synuclein aggregates. The redox reaction is shown through the oxidation of NADH to NAD+. This redox reaction is shown within the model through the two proteins "complex_I_ox" and "complex_I_red". Two arrows are used to show the oxidation of NADH to NAD+ and the reduction of H+ to superoxide. Additionally,

superoxide is represented with the symbol O2-. It is not certain why or how α-synuclein targets complex I, but studies have shown that aggregates lacking mitochondrial targeting signals will fail to produce any effect on the mitochondria (Devi, et al., 2008).

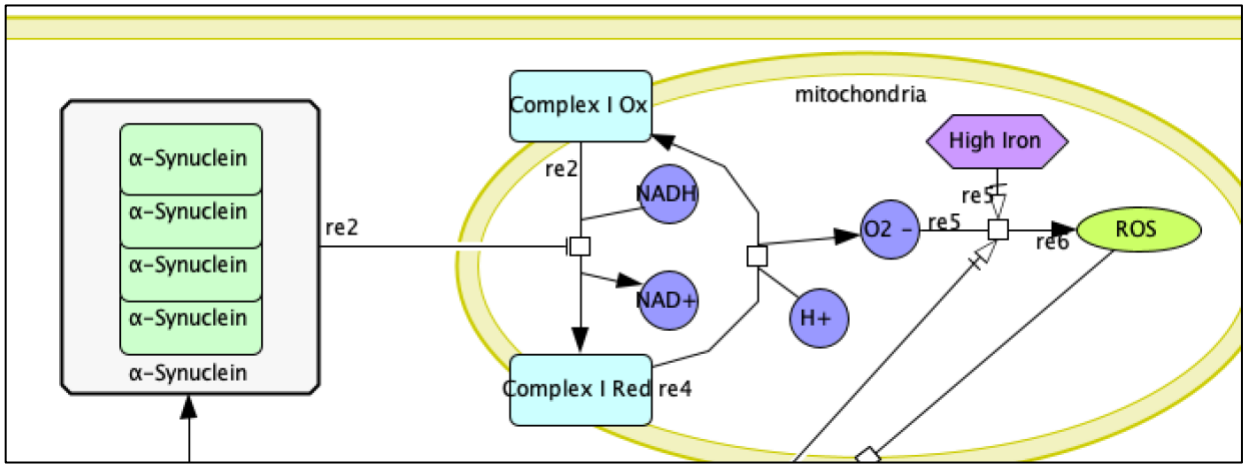



*Figure 1: Reactions 2, 4, 5, 6 in Parkinson's Model*

The superoxide produced then reacts to the high iron mitochondrial environment. Iron plays a key role in many physiological functions within the neuronal metabolism, except high levels lead to unbound or free iron within the cell (Sian-Hülsmann, et al., 2010). Iron plays a key role in the pathogenesis of PD. In patients with the disease, there is an increase in iron in several brain regions in PD. The mitochondria is a key player in iron homeostasis within the cell, and store and synthesize iron from the cytosol (Ben-Shachar, 2020). The electron transport chain normally produces hydrogen peroxide during normal metabolism. Through the Fenton reaction and Haber-Weiss reaction, hydrogen peroxide and superoxide are formed from the free iron to form hydroxide ($OH^-$) and hydroxyl radical ($OH\cdot$) (Sian-Hülsmann, et al., 2010). This reaction is simplified within the model and shown in reaction 5 ("re5") as "O2-" is catalyzed into "ROS" by the phenotype "high_iron." These two products are forms of reactive oxygen species (ROS).

ROS are normal cellular byproducts, but in high levels produce a state of oxidative stress within the cell. ROS is signified through the simple molecule “ROS” within the model.

Oxidative stress contributes to the cascade leading to dopaminergic neuron death (Jenner, 2003). Oxidative stress causes oxidative damage to lipids, proteins, and DNA, which all contribute to cell apoptosis and further inflammation within the brain (Jenner, 2003). Oxidative stress also furthers the production of ROS. PD is ultimately a feedback loop, with inflammation causing further oxidative damage and aggregation of α-synuclein. In the model, trigger arrows have been used to showcase the effects of oxidative stress and inflammation on this PD pathway.

**4.3 Levodopa Model**

Levodopa’s metabolism has a short pathway, with a short half-life and duration within the body. While not shown within the Levodopa Model, the medicine is taken alongside a peripheral dopa decarboxylase inhibitor to prevent early breakdown (Contin, et al., 2010). The model begins with levodopa crossing through the blood-brain barrier (“Blood_Brain_Barrier”). Levodopa is shown as a drug titled “Levodopa” within the model. Levodopa is transported by the LNAA transport system. Once passed through the barrier, levodopa is decarboxylated by aromatic L-amino acid decarboxylase (“AAAD”) into dopamine, which is shown through the catalyst arrow. The decarboxylation of levodopa produces the drug’s antiparkinsonian effects (Aldred, et al., 2010). AAAD is present in dopamine and serotoninergic nerve terminals, but enzyme levels are reduced in the brain in PD patients (Aldred, et al., 2010). Despite the reduction, there are high enough levels of AAAD in the brain to properly decarboxylate levodopa.

Through decarboxylation, levodopa becomes dopamine within the brain. Typically, the next step for dopamine within the brain is conversion into 3-methoxytyramine (“3-MT”) by

catechol-O-methyltransferase (“COMT”) and 3,4-Dihydroxyphenylacetaldehyde (“DOPAL”) by monoamine oxidase (“MAO”). There are two isoforms of MAO, MAO-A, and MAO-B. MAO-B is the dominant form of MAO in the brain and makes up 80% within the neurological system (Aldred, et al., 2010). While not stated outright, MAO-B is the primary isomer within the model. These compounds are further converted from 3-MT into 3-Methoxy-4-hydroxyphenylacetaldehyde (“homovanillin”) by aldehyde-dehydrogenase and DOPAL into 3,4-Dihydroxyphenylacetic acid (“DOPAC”). Then both compounds are converted into homovanillic acid (“HVA”). DOPAC is catalyzed by COMT and homovanillin is catalyzed by aldehyde-dehydrogenase (Aldred, et al., 2010 & Hälbig, et al., 2007). This pathway is shown in Figure 2, with enzymes utilizing catalysis arrows to show the conversion of dopamine to HVA.

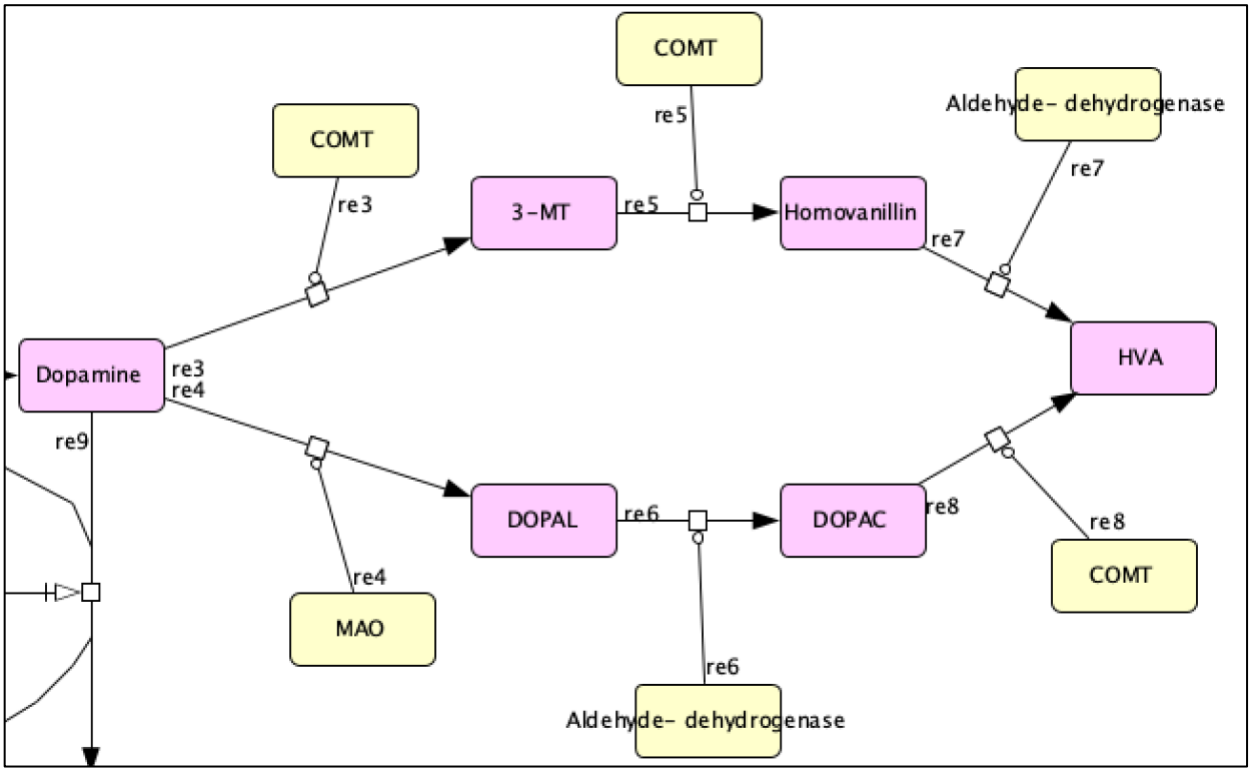



*Figure 2: Reactions 3, 4, 5, 6, 7, and 8 in Levodopa Model*

HVA is the major metabolite formed from the breakdown of dopamine and may act as an indicator of proper dopaminergic pathways in the brain (Sternberg, et al., 1983). While the formation of HVA results in a typical dopamine pathway, the auto-oxidation of dopamine produces a different outcome. As stated previously, PD patients possess increased mitochondrial iron stores, and these increased levels of iron lead to the increased oxidation of dopamine (Ben-Shachar, 2020). The auto-oxidation of dopamine is shown through reaction 9 ("re9"), as the dopamine auto-oxidizes into 3,4-Dihydroxyphenylacetaldehyde ("3,4_DOPAL"). Oxygen is represented as "O2" and becomes hydrogen peroxide, "H2O2" (Ben-Shachar, 2020). As stated within the Parkinson's Model, hydrogen peroxide is catalyzed by the Fenton reaction and Haber-Weiss reaction to form hydroxyl radicals ("·OH"). This catalysis is shown through reaction 10 ("re10") in the model. These radicals then cause an oxidative stress state ("Oxidative_Stress") after their accumulation (Ben-Shachar, 2020). Oxidative stress then leads to a cascade of negative effects which is shown in the Parkinson's Model, but to keep this model simple, these effects have been excluded.

High mitochondrial iron stores ultimately cause levodopa to work against the patient. The auto-oxidation of dopamine may be a key reason behind the issues associated with chronic levodopa use.

**4.4 Ketamine Model**

Ketamine is a non-competitive, glutamate N-methyl-D-aspartate receptor (NMDAR) antagonist (Kawatake-Kuno, et al., 2021). The Ketamine Model shows how the drug is metabolized within the brain to produce positive effects on the individual when taken at a medicinal dose (between 0.5mg/kg to 1.0mg/kg) (Fava, et al., 2020).

Ketamine binds to NMDARs (“NMDAR”) on GABA interneurons, which inhibits glutamatergic neurons from taking up glutamate into glutamate receptors (“GluR”). The inhibition of glutamate reuptake causes an increase in glutamate levels (“Increase_In_Glutamate”) within the synapse. The increase in glutamate leads to α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) activation (Kawatake-Kuno, et al., 2021). AMPARs are located on the post-synaptic neuron. AMPAR activation is shown in the model with a state transition from “AMPAR_Inactive” to “AMPAR_Active” triggered by increased glutamate. Active AMPAR then allows for voltage-gated calcium channels (“VDCC”) to open and allow the flow of calcium (“Ca2+”) into the post-synaptic neuron. Increased influx of extracellular calcium into the neuron leads to increased levels of brain-derived neurotrophic factors (BDNF), which is shown as the phenotype “Increase_in_BDNF_Levels” (Finkbeiner, 2000). BDNFs play a key role in the growth and survival of neurons and are involved in plastic changes in learning and memory (Miranda, et al., 2019). Since this mechanism and source behind BDNF is unknown, the model shows a simple state transition in reaction 14 (“re14”).

Due to increased BDNF levels, tropomyosin receptor kinase B (“TrkB”) becomes activated. TrkB is a receptor for BDNF and stimulates phospholipase Cγ1 (PLCγ1), resulting in calcium signaling activation which signal cascades to epigenetic and transcription modulators (Kawatake-Kuno, et al., 2021). There are many different modulators and the intracellular signaling pathway is extremely complex, therefore this cascade is represented by the phenotype “Activates_Intracellular_Signaling_Pathways.” The signaling pathways ultimately release an influx of calcium within the neuron and activate downstream synaptogenesis signaling pathways, in particular, the mammalian target of rapamycin (“mTOR”) (Aleksandrova, et al., 2017). The increase in calcium is represented by the phenotype “Increase_In_Ca2+.” Calcium is located at

the center of many of ketamine's neuronal activity and here the increased calcium further triggers the release of BDNFs into the neuron, as shown through reaction 18 ("re18") (Aleksandrova, et al., 2017). These synaptogenesis pathways ultimately modify gene expression leading to dendritic growth, synaptic expansion, and neuronal plasticity (Kawatake-Kuno, et al., 2021). This growth is expressed simply as "Soma_and_Dendritic_Growth" within the model. Additionally, mTOR further stimulates AMPAR activation, which is shown in reaction 4 ("re4").

Ketamine can also bind at a second location on NMDARs in post-synaptic neurons (Aleksandrova, et al., 2017). NMDARs on the post-synaptic neuron activate eukaryotic elongation factor 2 (eEF2) via eEF2 kinases to reduce BDNF levels in the neuron (Aleksandrova, et al., 2017). Ketamine inhibits NMDAR causing the deactivation and inhibition of the phosphorylation of eEF2 kinase ("eEF2K") as shown in reaction 24 ("re24"). Since eEF2K cannot be phosphorylated, there is an increased translation of BDNF, as shown by reaction 25 ("re25") (Aleksandrova, et al., 2017). Here, the model continues in the same manner as the other ketamine binding pathway. The Ketamine Model displays the key ways that the drug produces synaptic growth and plasticity within the brain.

**4.5 SBMLsqueezer**

Using the program SBMLsqueezer, kinetic rate equations were generated for each model. SBMLsqueezer generates kinetic equations based on stoichiometry, species types, and regulatory interactions between species (Dräger, et al., 2008). After the generation of kinetic laws for each model, they were imported into the program COPASI. All models possess accurate kinetic laws, but only the Levodopa and Ketamine Models will serve as experimental models, as the Parkinson's Model was created to conceptualize the disease.

**4.6 COPASI**

COPASI (COmplex PAthway SImulator) is a biochemical network simulator, which showcases model dynamics within cells. After the generation of kinetic laws from SBMLsqueezer from the mathematical models, the data is uploaded into COPASI. COPASI assigns each reaction a flux equation. Appendix B displays each differential equation created for the three models. Each equation represents a reaction ("re") within the model.

Parameters are then added to the program, assigning species an initial species concentration (M). These concentrations were calculated from brain tissue species abundances (ppm) from the Pax database and molecular weights (Da) from the UniProt database. The concentrations for each model are found in Appendix C. Models were then run within COPASI.

## V. Results

Results were obtained by running the "Time Course" task in COPSAI for 100 seconds, 100 intervals, with an interval size of 10. Species concentration (mol/l) were compared against time (s). Two main takeaways came from the model results. Firstly, the model results reflected current scientific literature on these medications. Secondly, these models provide insight into the biochemical pathways of the two drugs and can allow for future manipulation to better understand these treatments.

The Levodopa Model showcased typical and atypical dopamine pathways. Typical breakdown of dopamine results in HVA within the cells, while the atypical breakdown is the auto-oxidation of dopamine caused due to the high iron levels within the cells. The focus of this model is on the atypical pathway and outcome of levodopa on a high iron system.

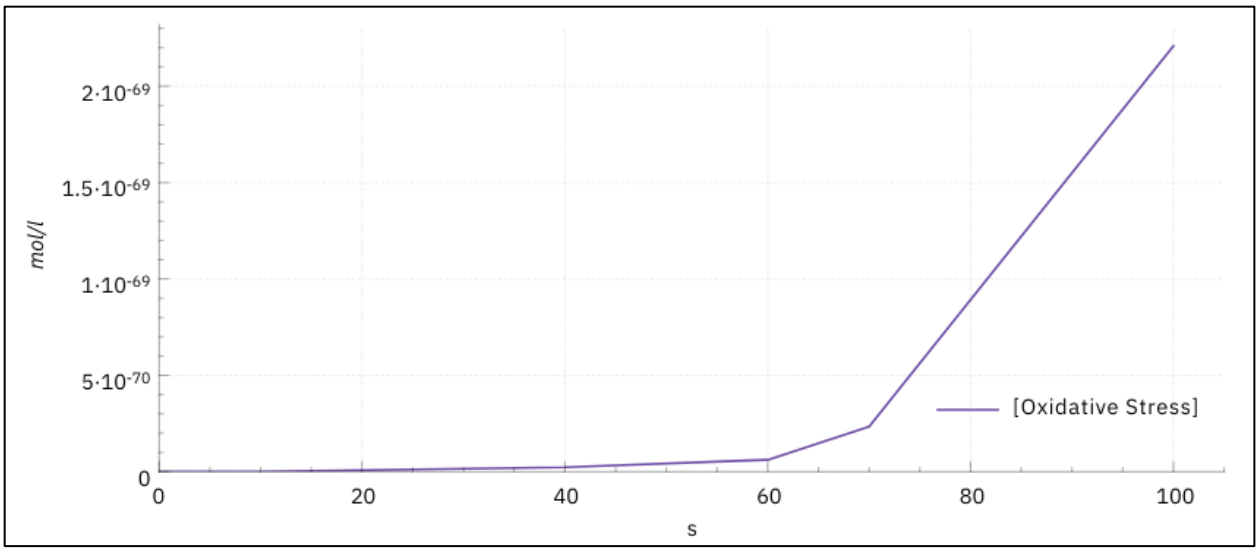



*Figure 3: Oxidative Stress Concentration vs. Time in Levodopa Model*

As discussed previously, the high iron storage levels within mitochondria cause the auto-oxidation of dopamine ultimately leading to the formation of hydroxyl radicals (·OH). (Ben-Shachar, 2020). The accumulation of these radicals then produces an oxidative stress state within the cell. This cellular process is clear in Figure 3, as oxidative stress exponentially increases over time due to radical production from levodopa. At t=0, the concentration of oxidative stress is also 0 mol/L. The slope starts small until t=60, where there is a small increase in concentration, then followed by a massive spike at t=70 with the concentration surpassing 2e-69 mol/L. This value is extremely small, but it represents the beginning of oxidative stress within the cells. The oxidative stress state begins in small concentrations, but over time leads to a massive oxidative stress state causing neuronal death. This cascade follows the progression and side effects from chronic levodopa treatment, as 40% of PD patients were estimated to have complications within 5 years (Boelens Keun, et al., 2021). While chronic levodopa inefficiency stems from neuroadaptation, the side effects associated could be a result of the increased levels of oxidative stress within the

body. This time course represents a single dose of the drug, showing that even one treatment can lead to an increase in oxidative stress within the cell.

Overall, the graph closely resembles an exponential function, which is explained by the gradual formation of hydrogen peroxide from dopamine auto-oxidation. These results follow the accumulation of hydroxyl radicals, as more species are formed, the levels of oxidative stress increase within the cell.

While in the Ketamine Model, the focus is on the effects of medicinal ketamine on post-synaptic neurons. Despite ketamine's history as a drug of abuse, the medicinal effects of the drug show promise in not only reducing levodopa-induced dyskinesia but also restoring neuron pathways.

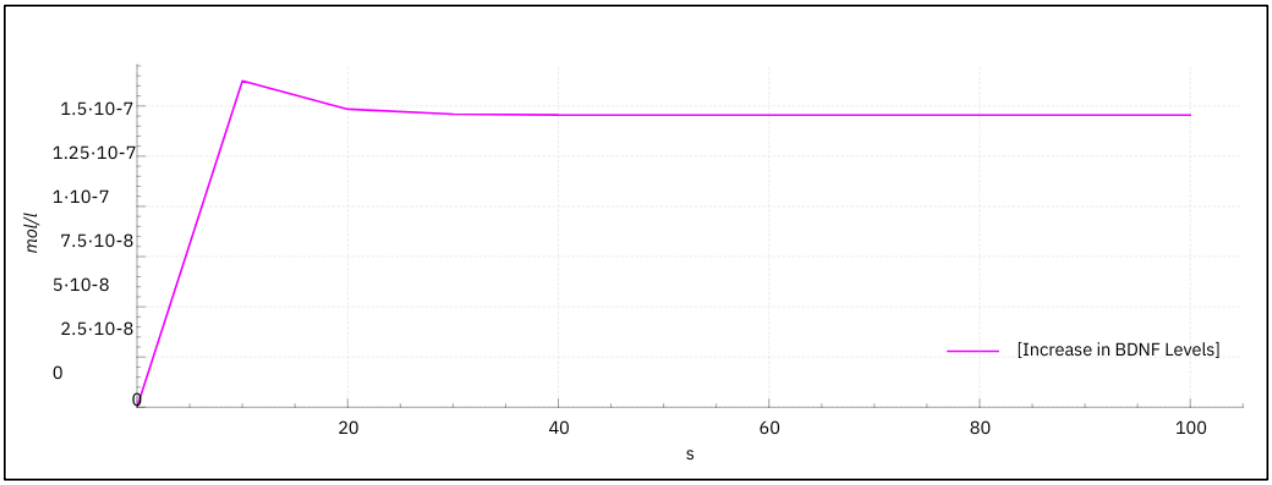



*Figure 4: Increase in BDNF Level Concentration vs. Time in Ketamine Model*

Figure 4 displays how ketamine induces further BDNF expression within a post-synaptic neuron. At t=0, the increase in BDNF levels remained at an initial concentration of 0 mol/L. While this initial concentration is zero, it does not mean there are no BDNFs within the post-synaptic neuron. This factor, "Increase_in_BDNF_Levels," simply describes the growth in the production of BDNFs. After the start of the time course trial, there is a sharp increase in slope

reaching above 1.5e-7 mol/L at t=10. The slope begins to stabilize and decreases to 1.5e-7 mol/L at t=20. For the rest of the time course, the slope levels out and very slightly steadily decreases.

Figure 4 shows that BDNK levels can only increase to a certain level before hitting a limit. Unlike oxidative stress in Figure 3, BDNF levels do not increase forever, rather it hits an expression ceiling. The cell can only produce BDNFs to a certain amount and this figure showcases that fact. These findings are shown in scientific literature, as ketamine has been shown to stimulate BDNF release (Deyama, et al., 2020). Currently, there is a lack of research on BDNFs and their effects. The pathway behind the stimulation of this factor is unknown.

Overall, BDNF is a neurotrophic factor that stimulates and controls the growth of new neurons (Bathina, et al., 2015). In PD, BDNF levels are decreased as a result of neuronal loss from the disease. Ketamine presents as a possible neuronal growth tool in the brain that could repair the dopaminergic neuron loss in the SNpc. BDNF's effects are further shown in figure 5, as the increase of these factors triggers soma and dendritic growth.

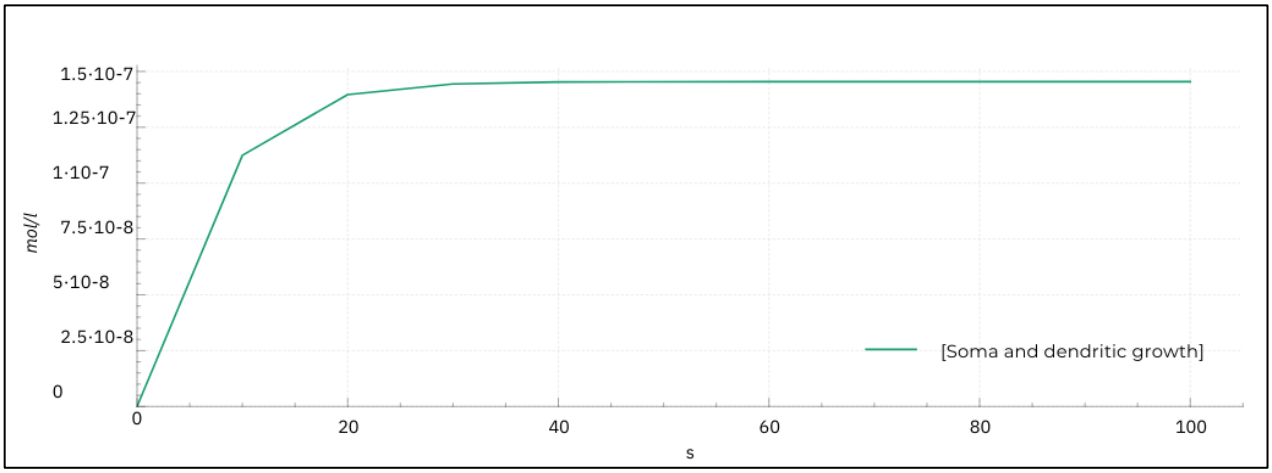



*Figure 5: Soma and Dendritic Growth Concentration vs. Time in Ketamine Model*

Soma and dendritic growth is defined as an increase in the total length, branching, and complexity of soma and dendrites (Okabe, 2008). This growth allows for increased connectivity,

plasticity, neuronal integration, and neuroprotection. With PD characterized by the progressive death of dopaminergic neurons, these increased factors may allow for neuronal adaptation to the changing environment. Figure 5 showcases the increased growth from the medicinal dose of ketamine. Even after one dose, ketamine can produce significant and lasting neurological changes to the brain (Corriger, et al., 2019).

Similarly to Figure 4, the factor "soma_and_dendritic_growth" describes the increase in dendritic growth and does not account for previous growth occurring in the neuron. The time course begins at t=0 with a growth concentration of 0 mol/L. Once again, the growth concentration at zero does not mean there is no dendritic growth at the beginning. At t=10, the growth concentration slope increases to roughly 1.1e-7 mol/L. Then, at t=20, the slope increases further to roughly 1.35e-7 mol/L. After t=30, the slope levels out just under 1.5e-7 mol/L and flattens out for the rest of the time course.

Soma and dendritic growth acts similarly to the increase in BDNF levels within the Ketamine Model. Soma and dendritic growth can only increase to a certain limit before stopping and remaining stable. Once again, ketamine can only produce a certain limit of growth before stopping. Soma and dendritic growth cannot continue forever and will level out.

Overall, these results reflected current scientific literature and highlighted further areas of exploration. There are many different avenues of possible exploration shown within the models. In the Levodopa Model, the results highlighted how levodopa may further harm neurons through the production of oxidative stress. The neurological environment of PD reacts with dopamine ultimately leading to neuronal death (Jenner, 2003). Chronic levodopa treatment in rats has not been associated with the destruction of the nigrostriatal pathway, highlighting that levodopa may only produce harm if the nigrostriatal tract is already damaged (Jenner, et al.,

1998). It is not exactly known if the auto-oxidation of levodopa produces the negative effects seen with chronic treatment, but it further harms the nigrostriatal pathway and causes neuron death. Further exploration of auto-oxidation over a longer period may provide key insights into this idea. The Levodopa Model time course only ran for 100 seconds and showcased a clear way levodopa could cause many different negative effects on a patient.

Within the Ketamine Model, the results supported current literature showcasing the effectiveness of medicinal ketamine. Ketamine is shown to increase BDNF production and lead to increased soma and dendritic growth. These findings suggest that ketamine produces neuroprotective and neurorestorative effects. This fact has major implications for PD, as ketamine-induced neuroplasticity and synaptogenesis may mitigate neuronal loss for patients. Further research is necessary to understand and explore this possibility.

Additionally, increasing the dose of ketamine may further alleviate symptoms of PD and promote neuronal expansion. For modeling purposes, a lower medicinal dose (0.5 mg/kg) was chosen, but an increased dose may cause a further increase in BDNF levels and soma and dendritic growth. Although, dosing too high may induce anesthetic effects with no beneficial changes to synaptic plasticity (Muscat, et al., 2021). Ensuring the dose is high enough to produce maximum effects, but not induce anesthesia is a challenge. Further modeling could produce a predicted peak therapeutic effect.

Overall, the results showcase a new treatment option for PD patients. While the results are promising, the model's focus on acute effects may not fully capture the long-term consequences of ketamine treatment. Future studies could focus on the long-term effects of ketamine treatment.

## VI. Discussion

With Parkinson's Disease affecting nearly 6.1 million people worldwide, it is necessary to explore new treatment ideas (Bloem, et al., 2021). Levodopa, the primary form of treatment for PD, has been shown to not be a long-term solution for those suffering from the disorder. Ketamine presents as a unique solution, that produces lasting changes to neuroplasticity and growth. In recent years, studies have shown that ketamine leads to a reduction in pain, depression, PTSD, and L-DOPA-induced dyskinesias (LID) in PD (Bartlett, et al., 2016). Ketamine is currently being investigated for its key reduction in LID, which is the most common and debilitating side effect of PD. A reduction of LID would allow for longer levodopa treatment (Bartlett, et al., 2016). While clinical research focuses on ketamine as an additional treatment to levodopa, it does not consider the neuroprotective and neurorestorative effects ketamine produces within the brain. Additionally, it overlooks the negative effects produced by levodopa in the PD environment. This project sought to accomplish three goals: understand the biochemical pathways of levodopa and ketamine within the brain, mathematically display and analyze these pathways through the programs CellDesigner 4.4.2, SBMLsqueezer, and COPASI, and examine model accuracy using species concentrations from the scientific literature. Time course data showcases how these goals were achieved, as levodopa increases oxidative stress within the neuron and ketamine induces high expression of BDNFs and increases soma and dendritic growth. The results reflect current scientific literature, which means these models could be used for further testing and examination.

The computational modeling of levodopa and ketamine provided valuable insights into the therapeutic effects of both medications. The models allowed for a detailed understanding and exploration of the biochemical pathways underlying both drugs. The Levodopa Model showcased how levodopa may exacerbate neuronal damage through the production of oxidative

stress. The high iron environment stimulates the auto-oxidation of dopamine, which is highlighted within the model as a keyway levodopa may lead to further neuronal death. Time course data showcases the increase in oxidative stress within the neurons in a short period of time. Further exploration of these long-term effects could provide crucial insights into the PD neurological environment and the development of more effective treatments.

The Ketamine Model highlighted the neuroprotective and neurorestorative effects of medicinal ketamine. The model provided evidence for ketamine's potential as a stand-alone therapeutic medication for PD. These findings suggest that ketamine-induced neuroplasticity and synaptogenesis may mitigate neuronal loss and offer promising avenues for further research and clinical exploration. The Ketamine Model focuses on the acute, short-term effects of ketamine treatment, thus further long-term research on the drug's effects is needed. Further exploration of ketamine therapy may allow for the drug to become a new treatment option for PD patients and significantly improve patient lives.

Overall, computational modeling offers new insights and understanding into PD and its treatments. While modeling is not the final step for clinical approval of ketamine as a treatment option, it has highlighted the key benefits that can come from the medication. Through the display of the biochemical pathways of levodopa and ketamine, these models provide a foundation for future research aimed at developing new treatment options for PD.

## References

Aldred, J., & Nutt, J. G. (2010). Levodopa. In *Encyclopedia of Movement Disorders*. 132-137. https://doi.org/10.1016/B978-0-12-374105-9.00340-3.

Aleksandrova, L. R., Phillips, A. G., & Wang, Y. T. (2017). Antidepressant effects of ketamine and the roles of AMPA glutamate receptors and other mechanisms beyond NMDA receptor antagonism. *Journal of psychiatry & neuroscience : JPN*, *42*(4), 222–229. https://doi.org/10.1503/jpn.160175

Andreae, M. H., Rhodes, E., Bourgoise, T., Carter, G. M., White, R. S., Indyk, D., Sacks, H., & Rhodes, R. (2016). An Ethical Exploration of Barriers to Research on Controlled Drugs. *The American journal of bioethics : AJOB*, *16*(4), 36–47. https://doi.org/10.1080/15265161.2016.1145282.

Bartlett, M. J., Joseph, R. M., LePoidevin, L. M., Parent, K. L., Laude, N. D., Lazarus, L. B., Heien, M. L., Estevez, M., Sherman, S. J., & Falk, T. (2016). Long-term effect of sub-anesthetic ketamine in reducing L-DOPA-induced dyskinesias in a preclinical model. *Neuroscience letters*, *612*, 121–125. https://doi.org/10.1016/j.neulet.2015.11.047.

Bathina, S., & Das, U. N. (2015). Brain-derived neurotrophic factor and its clinical implications. *Archives of medical science : AMS*, *11*(6), 1164–1178. https://doi.org/10.5114/aoms.2015.56342.

Beaulieu-Boire, I., & Lang, A. E. (2015). Behavioral effects of levodopa. *Movement Disorders, 30*(1), 90-102. doi:10.1002/mds.26121.

Ben-Shachar, D. (2020). The bimodal mechanism of interaction between dopamine and

mitochondria as reflected in Parkinson's disease and in schizophrenia. *Journal of neural transmission (Vienna, Austria : 1996)*, *127*(2), 159–168. https://doi.org/10.1007/s00702-019-02120-x.

Bendor, J. T., Logan, T. P., & Edwards, R. H. (2013). The function of α-synuclein. *Neuron*, *79*(6), 1044-1066. https://doi.org/10.1016/j.neuron.2013.09.004.

Berardelli, A., Rothwell, J.C., Thompson, P.D., Hallett, M. (2001). Pathophysiology of bradykinesia in Parkinson's disease. *Brain*, *124*(11), 2131–2146. https://doi.org/10.1093/brain/124.11.2131.

Bezard, E., Brotchie, J. M., & Gross, C. E. (2001). Pathophysiology of levodopa-induced dyskinesia: potential for new therapies. *Nature Reviews Neuroscience*, *2*(8), 577-588. https://doi.org/10.1038/35086062.

Bloem, B. R., Okun, M. S., & Klein, C. (2021). Parkinson's disease. *The Lancet, 397*(10291), 2284-2303. doi:10.1016/S0140-6736(21)00218-X.

Boelens Keun, J. T., Arnoldussen, I. A., Vriend, C., & van de Rest, O. (2021). Dietary approaches to improve efficacy and control side effects of levodopa therapy in parkinson's disease: A systematic review. *Advances in Nutrition, 12*(6), 2265-2287. doi:10.1093/advances/nmab060.

Botella, J. A., Bayersdorfer, F., & Schneuwly, S. (2008). Superoxide dismutase overexpression protects dopaminergic neurons in a drosophila model of parkinson's disease. *Neurobiology of Disease, 30*(1), 65-73. doi:10.1016/j.nbd.2007.11.013

Breydo, L., Wu, J. W., & Uversky, V. N. (2012). A-synuclein misfolding and parkinson's disease. *Biochimica Et Biophysica Acta (BBA) - Molecular Basis of Disease, 1822*(2), 261-285. doi:10.1016/j.bbadis.2011.10.002

Chade, A. R., Kasten, M., & Tanner, C. M. (2006). Nongenetic causes of Parkinson's disease. *Parkinson's disease and related disorders*, 147-151. https://doi.org/10.1007/978-3-211-45295-0_23.

Contin, M., Martinelli, P. (2010). Pharmacokinetics of levodopa. *J Neurol 257*(Suppl 2), 253–261. https://doi.org/10.1007/s00415-010-5728-8.

Corriger, A., & Pickering, G. (2019). Ketamine and depression: a narrative review. *Drug design, development and therapy*, 3051-3067. https://doi.org/10.2147/DDDT.S221437.

de Maindreville, A. D., Fénelon, G., & Mahieux, F. (2005). Hallucinations in Parkinson's disease: a follow-up study. *Movement disorders : official journal of the Movement Disorder Society*, *20*(2), 212–217. https://doi.org/10.1002/mds.20263.

Devi, L., Raghavendran, V., Prabhu, B. M., Avadhani, N. G., & Anandatheerthavarada, H. K. (2008). Mitochondrial import and accumulation of α-synuclein impair complex I in human dopaminergic neuronal cultures and Parkinson disease brain. *Journal of Biological Chemistry*, *283*(14), 9089-9100. https://doi.org/10.1074/jbc.M710012200.

Deyama, S., & Duman, R. S. (2020). Neurotrophic mechanisms underlying the rapid and sustained antidepressant actions of ketamine. *Pharmacology, biochemistry, and behavior*, *188*, 172837. https://doi.org/10.1016/j.pbb.2019.172837.

Dias, V., Junn, E., & Mouradian, M. M. (2013). The role of oxidative stress in Parkinson's disease. *Journal of Parkinson's disease*, *3*(4), 461-491. https://doi.org/10.3233/JPD-130230.

Dräger, A., Hassis, N., Supper, J., Schröder, A., & Zell, A. (2008). SBMLsqueezer: a CellDesigner plug-in to generate kinetic rate equations for biochemical networks. *BMC systems biology*, *2*, 39. https://doi.org/10.1186/1752-0509-2-39.

*Drug scheduling*. (n.d.). DEA. https://www.dea.gov/drug-information/drug-scheduling.

Espay, A. J., Morgante, F., Merola, A., Fasano, A., Marsili, L., Fox, S. H., Bezard, E., Picconi, B., Calabresi, P. & Lang, A. E. (2018). Levodopa-induced dyskinesia in Parkinson disease: current and evolving concepts. *Annals of Neurology*, *84*(6), 797-811. https://doi.org/10.1002/ana.25364.

Fan, J., Song, J., Wang, Y., Chen, Y., & Hong, D. (2017). Neuron-protective effect of subanesthestic-dosage ketamine on mice of parkinson's disease. *Asian Pacific Journal of Tropical Medicine, 10*(10), 1007-1010. doi:10.1016/j.apjtm.2017.09.014.

Fava, M., Freeman, M.P., Flynn, M. *(*2020*).* Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). *Mol Psychiatry, 25*, 1592–1603 https://doi.org/10.1038/s41380-018-0256-5.

Fénelon, G., Mahieux, F., Huon, R., & Ziégler, M. (2000). Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. *Brain: a journal of neurology*, *123 ( Pt 4)*, 733–745. https://doi.org/10.1093/brain/123.4.733.

Finkbeiner S. (2000). Calcium regulation of the brain-derived neurotrophic factor gene. *Cellular and molecular life sciences : CMLS*, *57*(3), 394–401. https://doi.org/10.1007/PL00000701.

Gerlach, M., Riederer, P., & Scheller, D. (2011). Mechanisms underlying and medical management of L-Dopa-associated motor complications. *Journal of Neural Transmission, 118*, 1659-1660. https://link.springer.com/article/10.1007/s00702-011-0728-0.

Hälbig, T. D., & Koller, W. C. (2007). Levodopa. *Handbook of Clinical Neurology, 84*, 31-72. doi:10.1016/S0072-9752(07)84032-2.

Hallett, P. J. & Standaert, D. G. (2004). *Pharmacology & Therapeutics, 102* (2), 155-174. doi:

10.1016/j.pharmthera.2004.04.001.

Holroyd, S., Currie, L., & Wooten, G. F. (2001). Prospective study of hallucinations and delusions in Parkinson's disease. *Journal of neurology, neurosurgery, and psychiatry*, *70*(6), 734–738. https://doi.org/10.1136/jnnp.70.6.734.

Jenner, P. (2003). Oxidative stress in Parkinson's disease. *Annals of Neurology: Official Journal of the American Neurological Association and the Child Neurology Society*, *53*(S3), S26-S38. https://doi.org/10.1002/ana.10483.

Jenner, P. G., & Brin, M. F. (1998). Levodopa neurotoxicity: experimental studies versus clinical relevance. *Neurology*, *50*(6), S39-S43. https://doi.org/10.1212/WNL.50.6_Suppl_6.S39.

Jost, W.H., Altmann, C., Fiesel, T., Becht, B., Rangwald, S., Hoppe, T. (2020). Influence of levodopa on orthostatic hypotension in Parkinson's Disease. *Neurol Neurochir Pol, 54*(2), 200-203. doi: 10.5603/PJNNS.a2020.0019.

Kawatake-Kuno, A., Murai, T., & Uchida, S. (2021). A Multiscale View of the Mechanisms Underlying Ketamine's Antidepressant Effects: An Update on Neuronal Calcium Signaling. *Frontiers in behavioral neuroscience*, *15*, 749180. https://doi.org/10.3389/fnbeh.2021.749180.

Kokkinou, M., Ashok, A. H., & Howes, O. D. (2018). The effects of ketamine on dopaminergic function: meta-analysis and review of the implications for neuropsychiatric disorders. *Molecular psychiatry*, *23*(1), 59-69. https://doi.org/10.1038/mp.2017.190.

Langley, J., Huddleston, D. E., & Hu, X. P. (2020). Chapter 20 - detecting parkinsonian degeneration in lateroventral tier of substantia nigra pars compacta with MRI. In C. R. Martin, & V. R. Preedy (Eds.), *Genetics, neurology, behavior, and diet in parkinson's disease* (pp. 313-325) Academic Press. doi:10.1016/B978-0-12-815950-7.00020-5.

Lee, H. M., & Koh, S. B. (2015). Many Faces of Parkinson's Disease: Non-Motor Symptoms of Parkinson's Disease. *Journal of movement disorders*, *8*(2), 92–97. https://doi.org/10.14802/jmd.15003.

Lindestam Arlehamn, C.S., Dhanwani, R., Pham, J. (2020). α-Synuclein-specific T cell reactivity is associated with preclinical and early Parkinson's disease. *Nat Commun 11*, 1875.https://doi.org/10.1038/s41467-020-15626-w.

Liu, Z., Su, D., Zhou, J., Wang, X., Wang, Z., Yang, Y., et al. (2023). Acute effect of levodopa on orthostatic hypotension and its association with motor responsiveness in parkinson's disease: Results of acute levodopa challenge test. *Parkinsonism & Related Disorders, 115*, 105860. doi:10.1016/j.parkreldis.2023.105860.

Miranda, M., Morici, J. F., Zanoni, M. B., & Bekinschtein, P. (2019). Brain-Derived Neurotrophic Factor: A Key Molecule for Memory in the Healthy and the Pathological Brain. *Frontiers in cellular neuroscience*, *13*, 363. https://doi.org/10.3389/fncel.2019.00363.

Mochizuki, H., Choong, C. J., & Baba, K. (2020). Parkinson's disease and iron. *Journal of neural transmission (Vienna, Austria : 1996)*, *127*(2), 181–187. https://doi.org/10.1007/s00702-020-02149-3.

Muscat, S. A., Hartelius, G., Crouch, C. R., & Morin, K. W. (2021). An integrative approach to ketamine therapy may enhance multiple dimensions of efficacy: improving therapeutic outcomes with treatment resistant depression. *Frontiers in Psychiatry*, *12*, 710338. https://doi.org/10.3389/fpsyt.2021.710338.

Okabe, S. (2008). Dendritic Growth. *Encyclopedia of Neuroscience*, 937–942. https://doi.org/10.1007/978-3-540-29678-2_1441.

Pfeiffer, R. F. (2016). Non-motor symptoms in parkinson's disease. *Parkinsonism & Related Disorders, 22*, S119-S122. doi:10.1016/j.parkreldis.2015.09.004.

Pouchon, A., Dondé, C., & Polosan, M. (2021). Punding Behavior as a Red Flag for Dementia in a Patient With Depression: Case Report. *Frontiers in psychiatry*, *12*, 637861. https://doi.org/10.3389/fpsyt.2021.637861.

Rajalingam, R., & Fasano, A. (2023). Punding in Parkinson's Disease: An Update. *Movement disorders clinical practice*, *10*(7), 1035–1047. https://doi.org/10.1002/mdc3.13748.

Raza, C., Anjum, R., & Shakeel, N. u. A. (2019). Parkinson's disease: Mechanisms, translational models and management strategies. *Life Sciences, 226*, 77-90. doi:10.1016/j.lfs.2019.03.057.

Reinert, A., Reinert, T., Arendt, T., & Morawski, M. (2022). High Iron and Iron Household Protein Contents in Perineuronal Net-Ensheathed Neurons Ensure Energy Metabolism with Safe Iron Handling. *International journal of molecular sciences*, *23*(3), 1634. https://doi.org/10.3390/ijms23031634.

Rosenbaum, S. B., Gupta, V., Patel, P., & Palacios, J. L. (2024). Ketamine. In: StatPearls [Internet]. https://www.ncbi.nlm.nih.gov/books/NBK470357/.

Sassano-Higgins, S., Baron, D., Juarez, G., Esmaili, N., & Gold, M. (2016). A review of ketamine abuse and diversion. *Depression and Anxiety, 33*(8), 718-727. doi:10.1002/da.22536.

Serafini, G., Howland, R. H., Rovedi, F., Girardi, P., & Amore, M. (2014). The role of ketamine in treatment-resistant depression: a systematic review. *Current neuropharmacology*, *12*(5), 444–461. https://doi.org/10.2174/1570159X12666140619204251.

Sherman, S. J., Estevez, M., Magill, A. B., & Falk, T. (2016). Case reports showing a long-term effect of subanesthetic ketamine infusion in reducing l-DOPA-induced dyskinesias. *Case Reports in Neurology*, *8*(1), 53-58. https://doi.org/10.1159/000444278.

Short, B., Fong, J., Galvez, V., Shelker, W., & Loo, C. K. (2018). Side-effects associated with ketamine use in depression: a systematic review. *The Lancet Psychiatry*, *5*(1), 65-78. https://doi.org/10.1016/S2215-0366(17)30272-9.

Sian-Hülsmann, J., Mandel, S., Youdim, M. B., & Riederer, P. (2011). The relevance of iron in the pathogenesis of Parkinson's disease. *Journal of neurochemistry*, *118*(6), 939-957. https://doi.org/10.1111/j.1471-4159.2010.07132.x.

Singh, I., Morgan, C., Curran, V., Nutt, D., Schlag, A., & McShane, R. (2017). Ketamine treatment for depression: opportunities for clinical innovation and ethical foresight. *The Lancet Psychiatry*, *4*(5), 419-426. https://doi.org/10.1016/S2215-0366(17)30102-5.

Sternberg, D. E., Heninger, G. R., & Roth, R. H. (1983). Plasma homovanillic acid as an index of brain dopamine metabolism: enhancement with debrisoquin. *Life sciences*, *32*(21), 2447–2452. https://doi.org/10.1016/0024-3205(83)90370-3.

Thanvi, B.R., Lo, T.C.N. (2004). Long term motor complications of levodopa: clinical features, mechanisms, and management strategies, *Postgraduate Medical Journal*, *80*(946), 452–458, https://doi.org/10.1136/pgmj.2003.013912

Thanvi, B.R., Lo, T.C.N., & Robinson, T. (2007). Levodopa-induced dyskinesia in Parkinson's disease: clinical features, pathogenesis, prevention and treatment. *Postgraduate medical journal*, *83*(980), 384-388. https://doi.org/10.1136/pgmj.2006.054759.

Vázquez-Vélez, G. E., & Zoghbi, H. Y. (2021). Parkinson's Disease Genetics and

Pathophysiology. *Annual review of neuroscience*, *44*, 87–108. https://doi.org/10.1146/annurev-neuro-100720-034518.

Voon, V., Napier, T. C., Frank, M. J., Sgambato-Faure, V., Grace, A. A., Rodriguez-Oroz, M., ... & Fernagut, P. O. (2017). Impulse control disorders and levodopa-induced dyskinesias in Parkinson's disease: an update. *The Lancet Neurology*, *16*(3), 238-250. https://doi.org/10.1016/S2215-0366(17)30102-5.

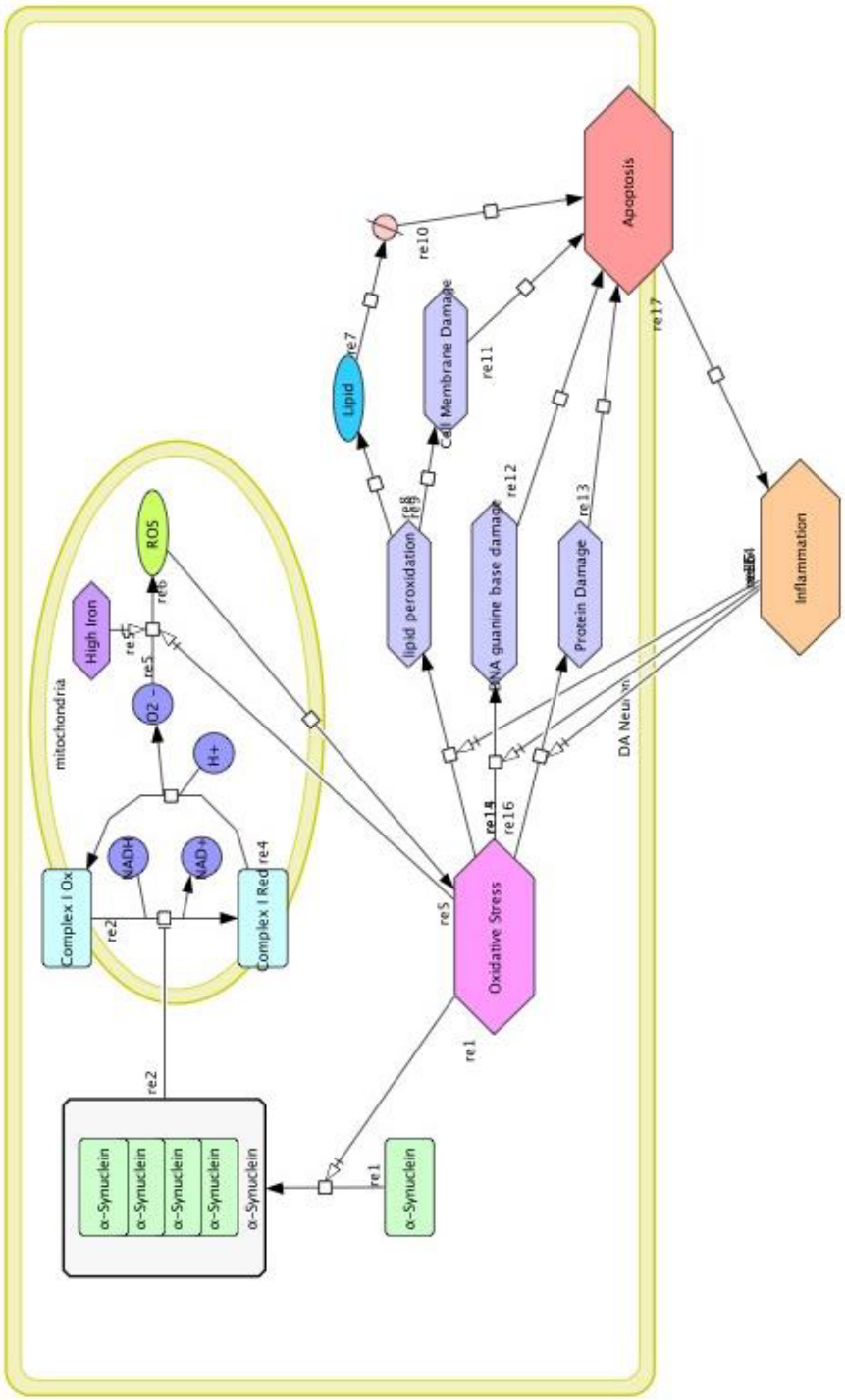
Wright, J. J., Goodnight, P. D., & McEvoy, M. D. (2009). The utility of ketamine for the preoperative management of a patient with Parkinson's disease. *Anesthesia and analgesia*, *108*(3), 980–982. https://doi.org/10.1213/ane.0b013e3181924025.

Wu, H., Savalia, N. K., & Kwan, A. C. (2021). Ketamine for a Boost of Neural Plasticity: How, but Also When?. *Biological psychiatry*, *89*(11), 1030–1032. https://doi.org/10.1016/j.biopsych.2021.03.014.

Zanos, P., Moaddel, R., Morris, P. J., Riggs, L. M., Highland, J. N., Georgiou, P., Pereira, E. F. R., Albuquerque, E. X., Thomas, C. J., Zarate, C. A., Jr, & Gould, T. D. (2018). Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacological reviews*, *70*(3), 621–660. https://doi.org/10.1124/pr.117.015198.

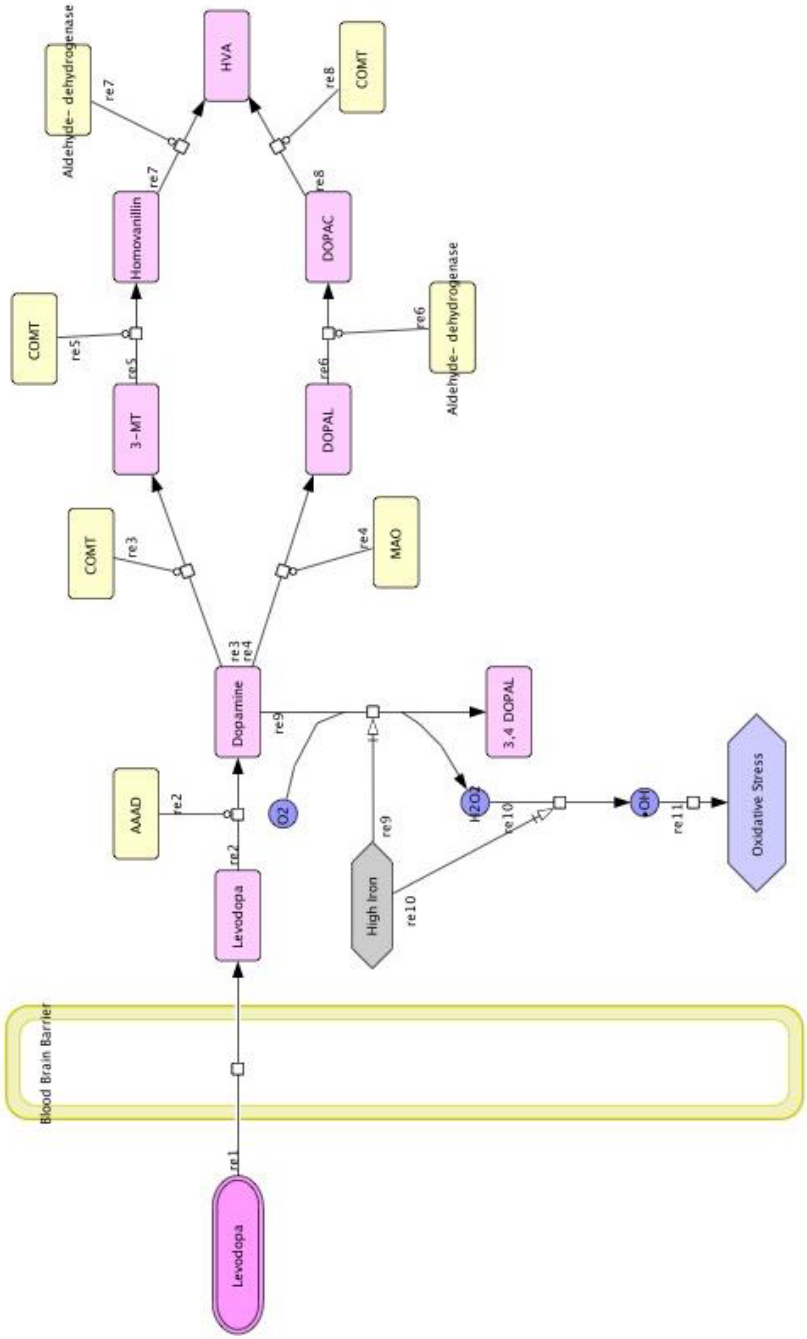
# Appendix A

Parkinson's Model



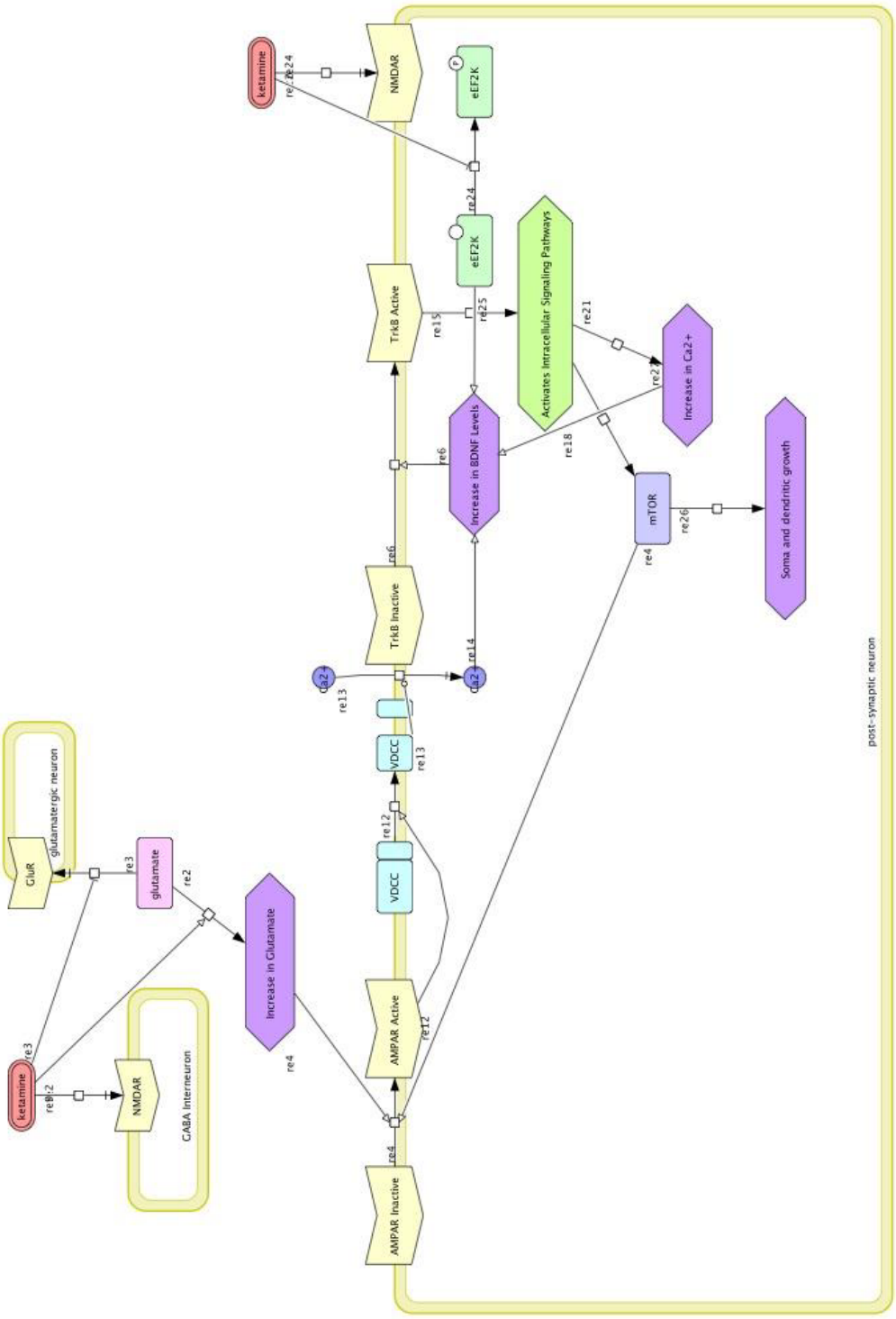
# Appendix A

Levodopa Model



# Appendix A

Ketamine Model



# Appendix B

## Parkinson's Model Differential Equations

$$\frac{d(["\alpha\text{-Synuclein}"]\cdot V_{"DA\ Neuron"})}{dt} = -V_{"DA\ Neuron"}\cdot\left(\frac{\frac{["Oxidative\ Stress"]}{kA\_1\_s12+["Oxidative\ Stress"]}\cdot kI\_1\_s12}{kI\_1\_s12+["Oxidative\ Stress"]}\cdot(kass\_1\cdot["\alpha\text{-Synuclein}"]-kdiss\_1\cdot["\alpha\text{-Synuclein\_2}"])}{V_{"DA\ Neuron"}}\right)$$

$$\frac{d(["\alpha\text{-Synuclein\_2}"]\cdot V_{"DA\ Neuron"})}{dt} = +V_{"DA\ Neuron"}\cdot\left(\frac{\frac{["Oxidative\ Stress"]}{kA\_1\_s12+["Oxidative\ Stress"]}\cdot kI\_1\_s12}{kI\_1\_s12+["Oxidative\ Stress"]}\cdot(kass\_1\cdot["\alpha\text{-Synuclein}"]-kdiss\_1\cdot["\alpha\text{-Synuclein\_2}"])}{V_{"DA\ Neuron"}}\right)$$

$$\frac{d(["Complex\ I\ Ox"]\cdot V_{mitochondria})}{dt} = -((kass\_2\cdot["Complex\ I\ Ox"]\cdot[NADH]-kdiss\_2\cdot["Complex\ I\ Red"]\cdot["NAD+"]))$$
$$+V_{mitochondria}\cdot\left(\frac{kass\_3\cdot["Complex\ I\ Red"]\cdot["H+"]-kdiss\_3\cdot["Complex\ I\ Ox"]\cdot["O2\ -"]}{V_{mitochondria}}\right)$$

$$\frac{d(["Complex\ I\ Red"]\cdot V_{mitochondria})}{dt} = +((kass\_2\cdot["Complex\ I\ Ox"]\cdot[NADH]-kdiss\_2\cdot["Complex\ I\ Red"]\cdot["NAD+"]))$$
$$-V_{mitochondria}\cdot\left(\frac{kass\_3\cdot["Complex\ I\ Red"]\cdot["H+"]-kdiss\_3\cdot["Complex\ I\ Ox"]\cdot["O2\ -"]}{V_{mitochondria}}\right)$$

$$\frac{d(["NADH"]\cdot V_{mitochondria})}{dt} = -((kass\_2\cdot["Complex\ I\ Ox"]\cdot[NADH]-kdiss\_2\cdot["Complex\ I\ Red"]\cdot["NAD+"]))$$

$$\frac{d(["NAD+"]\cdot V_{mitochondria})}{dt} = +((kass\_2\cdot["Complex\ I\ Ox"]\cdot[NADH]-kdiss\_2\cdot["Complex\ I\ Red"]\cdot["NAD+"]))$$

$$\frac{d(["O2\ -"]\cdot V_{mitochondria})}{dt} = -\left(\frac{\frac{\frac{["High\ Iron"]}{kA\_4\_s11+["High\ Iron"]}\cdot["Oxidative\ Stress"]}{kA\_4\_s12+["Oxidative\ Stress"]}\cdot kI\_4\_s11}{kI\_4\_s11+["High\ Iron"]}\cdot kI\_4\_s12}{kI\_4\_s12+["Oxidative\ Stress"]}\cdot(kass\_4\cdot["O2\ -"]-kdiss\_4\cdot[ROS])\right)$$
$$+V_{mitochondria}\cdot\left(\frac{kass\_3\cdot["Complex\ I\ Red"]\cdot["H+"]-kdiss\_3\cdot["Complex\ I\ Ox"]\cdot["O2\ -"]}{V_{mitochondria}}\right)$$

$$\frac{d(["H+"]\cdot V_{mitochondria})}{dt} = -V_{mitochondria}\cdot\left(\frac{kass\_3\cdot["Complex\ I\ Red"]\cdot["H+"]-kdiss\_3\cdot["Complex\ I\ Ox"]\cdot["O2\ -"]}{V_{mitochondria}}\right)$$

$$\frac{d(["ROS"]\cdot V_{mitochondria})}{dt} = +\left(\frac{\frac{\frac{["High\ Iron"]}{kA\_4\_s11+["High\ Iron"]}\cdot["Oxidative\ Stress"]}{kA\_4\_s12+["Oxidative\ Stress"]}\cdot kI\_4\_s11}{kI\_4\_s11+["High\ Iron"]}\cdot kI\_4\_s12}{kI\_4\_s12+["Oxidative\ Stress"]}\cdot(kass\_4\cdot["O2\ -"]-kdiss\_4\cdot[ROS])\right)$$
$$-((kass\_5\cdot[ROS]-kdiss\_5\cdot["Oxidative\ Stress"]))$$

$$\frac{d(["Oxidative\ Stress"]\cdot V_{"DA\ Neuron"})}{dt} = +((kass\_5\cdot[ROS]-kdiss\_5\cdot["Oxidative\ Stress"]))$$
$$-\left(\frac{\frac{[Inflammation]}{kA\_13\_s22+[Inflammation]}\cdot kI\_13\_s22}{kI\_13\_s22+[Inflammation]}\cdot(kass\_13\cdot["Oxidative\ Stress"]-kdiss\_13\cdot["lipid\ peroxidation"])\right)$$
$$-\left(\frac{\frac{[Inflammation]}{kA\_14\_s22+[Inflammation]}\cdot kI\_14\_s22}{kI\_14\_s22+[Inflammation]}\cdot(kass\_14\cdot["Oxidative\ Stress"]-kdiss\_14\cdot["DNA\ guanine\ base\ damage"])\right)$$
$$-\left(\frac{\frac{[Inflammation]}{kA\_15\_s22+[Inflammation]}\cdot kI\_15\_s22}{kI\_15\_s22+[Inflammation]}\cdot(kass\_15\cdot["Oxidative\ Stress"]-kdiss\_15\cdot["Protein\ Damage"])\right)$$

$$\frac{d(["lipid\ peroxidation"]\cdot V_{"DA\ Neuron"})}{dt} = -V_{"DA\ Neuron"}\cdot\left(\frac{kass\_7\cdot["lipid\ peroxidation"]-kdiss\_7\cdot[Lipid]}{V_{"DA\ Neuron"}}\right)$$
$$-V_{"DA\ Neuron"}\cdot\left(\frac{kass\_8\cdot["lipid\ peroxidation"]-kdiss\_8\cdot["Cell\ Membrane\ Damage"]}{V_{"DA\ Neuron"}}\right)$$
$$+\left(\frac{\frac{[Inflammation]}{kA\_13\_s22+[Inflammation]}\cdot kI\_13\_s22}{kI\_13\_s22+[Inflammation]}\cdot(kass\_13\cdot["Oxidative\ Stress"]-kdiss\_13\cdot["lipid\ peroxidation"])\right)$$

$$\frac{d\left(["\text{DNA guanine base damage}"]\cdot V_{"\text{DA Neuron}"}\right)}{dt} = -V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_11\cdot["\text{DNA guanine base damage}"]-kdiss\_11\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$
$$+\left(\frac{\frac{[\text{Inflammation}]}{kA\_14\_s22+[\text{Inflammation}]}\cdot kI\_14\_s22}{kI\_14\_s22+[\text{Inflammation}]}\cdot(kass\_14\cdot["\text{Oxidative Stress}"]-kdiss\_14\cdot["\text{DNA guanine base damage}"])\right)$$

$$\frac{d\left(["\text{Protein Damage}"]\cdot V_{"\text{DA Neuron}"}\right)}{dt} = -V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_12\cdot["\text{Protein Damage}"]-kdiss\_12\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$
$$+\left(\frac{\frac{[\text{Inflammation}]}{kA\_15\_s22+[\text{Inflammation}]}\cdot kI\_15\_s22}{kI\_15\_s22+[\text{Inflammation}]}\cdot(kass\_15\cdot["\text{Oxidative Stress}"]-kdiss\_15\cdot["\text{Protein Damage}"])\right)$$

$$\frac{d\left([\text{sa22\_degraded}]\cdot V_{"\text{DA Neuron}"}\right)}{dt} = +V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_6\cdot[\text{Lipid}]-kdiss\_6\cdot[\text{sa22\_degraded}]}{V_{"\text{DA Neuron}"}}\right)$$
$$-V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_9\cdot[\text{sa22\_degraded}]-kdiss\_9\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$

$$\frac{d\left([\text{Lipid}]\cdot V_{"\text{DA Neuron}"}\right)}{dt} = -V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_6\cdot[\text{Lipid}]-kdiss\_6\cdot[\text{sa22\_degraded}]}{V_{"\text{DA Neuron}"}}\right)$$
$$+V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_7\cdot["\text{lipid peroxidation}"]-kdiss\_7\cdot[\text{Lipid}]}{V_{"\text{DA Neuron}"}}\right)$$

$$\frac{d\left(["\text{Cell Membrane Damage}"]\cdot V_{"\text{DA Neuron}"}\right)}{dt} = +V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_8\cdot["\text{lipid peroxidation}"]-kdiss\_8\cdot["\text{Cell Membrane Damage}"]}{V_{"\text{DA Neuron}"}}\right)$$
$$-V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_10\cdot["\text{Cell Membrane Damage}"]-kdiss\_10\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$

$$\frac{d\left([\text{Apoptosis}]\cdot V_{"\text{DA Neuron}"}\right)}{dt} = -(kass\_16\cdot[\text{Apoptosis}]-kdiss\_16\cdot[\text{Inflammation}])$$
$$+V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_9\cdot[\text{sa22\_degraded}]-kdiss\_9\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$
$$+V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_10\cdot["\text{Cell Membrane Damage}"]-kdiss\_10\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$
$$+V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_11\cdot["\text{DNA guanine base damage}"]-kdiss\_11\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$
$$+V_{"\text{DA Neuron}"}\cdot\left(\frac{kass\_12\cdot["\text{Protein Damage}"]-kdiss\_12\cdot[\text{Apoptosis}]}{V_{"\text{DA Neuron}"}}\right)$$

$$\frac{d\left([\text{Inflammation}]\cdot V_{default}\right)}{dt} = +(kass\_16\cdot[\text{Apoptosis}]-kdiss\_16\cdot[\text{Inflammation}])$$

# Appendix B

Levodopa Model Differential Equations

$$\frac{d([\text{Levodopa}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{kass\_1\cdot[\text{Levodopa}]-kdiss\_1\cdot[\text{Levodopa\_2}]}{V_{default}}\right)$$

$$\frac{d([\text{Levodopa\_2}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{[AAAD]\cdot\left(\frac{kcatp\_2}{kM\_2\_s25}\cdot[\text{Levodopa\_2}]-\frac{kcatn\_2}{kM\_2\_s26}\cdot[\text{Dopamine}]\right)}{1+\frac{[\text{Levodopa\_2}]}{kM\_2\_s25}+\frac{[\text{Dopamine}]}{kM\_2\_s26}}}{V_{default}}\right) + V_{default}\cdot\left(\frac{kass\_1\cdot[\text{Levodopa}]-kdiss\_1\cdot[\text{Levodopa\_2}]}{V_{default}}\right)$$

$$\frac{d([\text{Dopamine}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_3}{kM\_3\_s26}\cdot[\text{Dopamine}]-\frac{kcatn\_3}{kM\_3\_s32}\cdot[\text{"3-MT"}]\right)}{1+\frac{[\text{Dopamine}]}{kM\_3\_s26}+\frac{[\text{"3-MT"}]}{kM\_3\_s32}}}{V_{default}}\right) + V_{default}\cdot\left(\frac{\frac{[AAAD]\cdot\left(\frac{kcatp\_2}{kM\_2\_s25}\cdot[\text{Levodopa\_2}]-\frac{kcatn\_2}{kM\_2\_s26}\cdot[\text{Dopamine}]\right)}{1+\frac{[\text{Levodopa\_2}]}{kM\_2\_s25}+\frac{[\text{Dopamine}]}{kM\_2\_s26}}}{V_{default}}\right) - V_{default}\cdot\left(\frac{\frac{[\text{"High Iron"}]}{kA\_9\_s40+[\text{"High Iron"}]}\cdot kI\_9\_s40}{kI\_9\_s40+[\text{"High Iron"}]}\cdot(kass\_9\cdot[\text{Dopamine}]\cdot[O2]-kdiss\_9\cdot[\text{"3,4 DOPAL"}]\cdot[H2O2])}{V_{default}}\right) - V_{default}\cdot\left(\frac{\frac{[MAO]\cdot\left(\frac{kcatp\_4}{kM\_4\_s26}\cdot[\text{Dopamine}]-\frac{kcatn\_4}{kM\_4\_s42}\cdot[DOPAL]\right)}{1+\frac{[\text{Dopamine}]}{kM\_4\_s26}+\frac{[DOPAL]}{kM\_4\_s42}}}{V_{default}}\right)$$

$$\frac{d([\text{"3-MT"}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_3}{kM\_3\_s26}\cdot[\text{Dopamine}]-\frac{kcatn\_3}{kM\_3\_s32}\cdot[\text{"3-MT"}]\right)}{1+\frac{[\text{Dopamine}]}{kM\_3\_s26}+\frac{[\text{"3-MT"}]}{kM\_3\_s32}}}{V_{default}}\right) - V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_5}{kM\_5\_s32}\cdot[\text{"3-MT"}]-\frac{kcatn\_5}{kM\_5\_s4}\cdot[\text{Homovanillin}]\right)}{1+\frac{[\text{"3-MT"}]}{kM\_5\_s32}+\frac{[\text{Homovanillin}]}{kM\_5\_s4}}}{V_{default}}\right)$$

$$\frac{d([DOPAL]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[MAO]\cdot\left(\frac{kcatp\_4}{kM\_4\_s26}\cdot[Dopamine]-\frac{kcatn\_4}{kM\_4\_s42}\cdot[DOPAL]\right)}{1+\frac{[Dopamine]}{kM\_4\_s26}+\frac{[DOPAL]}{kM\_4\_s42}}}{V_{default}}\right)$$
$$-V_{default}\cdot\left(\frac{\frac{["Aldehyde- dehydrogenase"]\cdot\left(\frac{kcatp\_6}{kM\_6\_s42}\cdot[DOPAL]-\frac{kcatn\_6}{kM\_6\_s2}\cdot[DOPAC]\right)}{1+\frac{[DOPAL]}{kM\_6\_s42}+\frac{[DOPAC]}{kM\_6\_s2}}}{V_{default}}\right)$$

$$\frac{d([Homovanillin]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_5}{kM\_5\_s32}\cdot["3\text{-}MT"]-\frac{kcatn\_5}{kM\_5\_s4}\cdot[Homovanillin]\right)}{1+\frac{["3\text{-}MT"]}{kM\_5\_s32}+\frac{[Homovanillin]}{kM\_5\_s4}}}{V_{default}}\right)$$
$$-V_{default}\cdot\left(\frac{\frac{["Aldehyde- dehydrogenase"]\cdot\left(\frac{kcatp\_7}{kM\_7\_s4}\cdot[Homovanillin]-\frac{kcatn\_7}{kM\_7\_s3}\cdot[HVA]\right)}{1+\frac{[Homovanillin]}{kM\_7\_s4}+\frac{[HVA]}{kM\_7\_s3}}}{V_{default}}\right)$$

$$\frac{d([DOPAC]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{["Aldehyde- dehydrogenase"]\cdot\left(\frac{kcatp\_6}{kM\_6\_s42}\cdot[DOPAL]-\frac{kcatn\_6}{kM\_6\_s2}\cdot[DOPAC]\right)}{1+\frac{[DOPAL]}{kM\_6\_s42}+\frac{[DOPAC]}{kM\_6\_s2}}}{V_{default}}\right)$$
$$-V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_8}{kM\_8\_s2}\cdot[DOPAC]-\frac{kcatn\_8}{kM\_8\_s3}\cdot[HVA]\right)}{1+\frac{[DOPAC]}{kM\_8\_s2}+\frac{[HVA]}{kM\_8\_s3}}}{V_{default}}\right)$$

$$\frac{d([HVA]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{["Aldehyde- dehydrogenase"]\cdot\left(\frac{kcatp\_7}{kM\_7\_s4}\cdot[Homovanillin]-\frac{kcatn\_7}{kM\_7\_s3}\cdot[HVA]\right)}{1+\frac{[Homovanillin]}{kM\_7\_s4}+\frac{[HVA]}{kM\_7\_s3}}}{V_{default}}\right)$$
$$+V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_8}{kM\_8\_s2}\cdot[DOPAC]-\frac{kcatn\_8}{kM\_8\_s3}\cdot[HVA]\right)}{1+\frac{[DOPAC]}{kM\_8\_s2}+\frac{[HVA]}{kM\_8\_s3}}}{V_{default}}\right)$$

$$\frac{d(["3,4\ DOPAL"]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{\frac{["High\ Iron"]}{kA\_9\_s40+["High\ Iron"]}\cdot kI\_9\_s40}{kI\_9\_s40+["High\ Iron"]}\cdot(kass\_9\cdot[Dopamine]\cdot[O2]-kdiss\_9\cdot["3,4\ DOPAL"]\cdot[H2O2])}{V_{default}}\right)$$

$$\frac{d([O2]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{["High\ Iron"]}{kA\_9\_s40+["High\ Iron"]}\cdot kI\_9\_s40}{kI\_9\_s40+["High\ Iron"]}\cdot(kass\_9\cdot[Dopamine]\cdot[O2]-kdiss\_9\cdot["3,4\ DOPAL"]\cdot[H2O2])}{V_{default}}\right)$$

$$\frac{d([H2O2]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{["High\ Iron"]}{kA\_10\_s40+["High\ Iron"]}\cdot kI\_10\_s40}{kI\_10\_s40+["High\ Iron"]}\cdot(kass\_10\cdot[H2O2]-kdiss\_10\cdot[\bullet OH])}{V_{default}}\right)$$

$$+V_{default}\cdot\left(\frac{\frac{["High\ Iron"]}{kA\_9\_s40+["High\ Iron"]}\cdot kI\_9\_s40}{kI\_9\_s40+["High\ Iron"]}\cdot(kass\_9\cdot[Dopamine]\cdot[O2]-kdiss\_9\cdot["3,4\ DOPAL"]\cdot[H2O2])}{V_{default}}\right)$$

$$\frac{d([\bullet OH]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{kass\_11\cdot[\bullet OH]-kdiss\_11\cdot["Oxidative\ Stress"]}{V_{default}}\right)$$

$$+V_{default}\cdot\left(\frac{\frac{["High\ Iron"]}{kA\_10\_s40+["High\ Iron"]}\cdot kI\_10\_s40}{kI\_10\_s40+["High\ Iron"]}\cdot(kass\_10\cdot[H2O2]-kdiss\_10\cdot[\bullet OH])}{V_{default}}\right)$$

$$\frac{d(["Oxidative\ Stress"]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{kass\_11\cdot[\bullet OH]-kdiss\_11\cdot["Oxidative\ Stress"]}{V_{default}}\right)$$

# Appendix B

## Ketamine Model Differential Equations

$$\frac{d([\text{Levodopa}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{kass\_1\cdot[\text{Levodopa}]-kdiss\_1\cdot[\text{Levodopa\_2}]}{V_{default}}\right)$$

$$\frac{d([\text{Levodopa\_2}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{[AAAD]\cdot\left(\frac{kcatp\_2}{kM\_2\_s25}\cdot[\text{Levodopa\_2}]-\frac{kcatn\_2}{kM\_2\_s26}\cdot[\text{Dopamine}]\right)}{1+\frac{[\text{Levodopa\_2}]}{kM\_2\_s25}+\frac{[\text{Dopamine}]}{kM\_2\_s26}}}{V_{default}}\right) + V_{default}\cdot\left(\frac{kass\_1\cdot[\text{Levodopa}]-kdiss\_1\cdot[\text{Levodopa\_2}]}{V_{default}}\right)$$

$$\frac{d([\text{Dopamine}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_3}{kM\_3\_s26}\cdot[\text{Dopamine}]-\frac{kcatn\_3}{kM\_3\_s32}\cdot[\text{"3-MT"}]\right)}{1+\frac{[\text{Dopamine}]}{kM\_3\_s26}+\frac{[\text{"3-MT"}]}{kM\_3\_s32}}}{V_{default}}\right) + V_{default}\cdot\left(\frac{\frac{[AAAD]\cdot\left(\frac{kcatp\_2}{kM\_2\_s25}\cdot[\text{Levodopa\_2}]-\frac{kcatn\_2}{kM\_2\_s26}\cdot[\text{Dopamine}]\right)}{1+\frac{[\text{Levodopa\_2}]}{kM\_2\_s25}+\frac{[\text{Dopamine}]}{kM\_2\_s26}}}{V_{default}}\right) - V_{default}\cdot\left(\frac{\frac{[\text{"High Iron"}]}{kA\_9\_s40+[\text{"High Iron"}]}\cdot kI\_9\_s40}{kI\_9\_s40+[\text{"High Iron"}]}\cdot(kass\_9\cdot[\text{Dopamine}]\cdot[O2]-kdiss\_9\cdot[\text{"3,4 DOPAL"}]\cdot[H2O2])}{V_{default}}\right) - V_{default}\cdot\left(\frac{\frac{[MAO]\cdot\left(\frac{kcatp\_4}{kM\_4\_s26}\cdot[\text{Dopamine}]-\frac{kcatn\_4}{kM\_4\_s42}\cdot[DOPAL]\right)}{1+\frac{[\text{Dopamine}]}{kM\_4\_s26}+\frac{[DOPAL]}{kM\_4\_s42}}}{V_{default}}\right)$$

$$\frac{d([\text{"3-MT"}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_3}{kM\_3\_s26}\cdot[\text{Dopamine}]-\frac{kcatn\_3}{kM\_3\_s32}\cdot[\text{"3-MT"}]\right)}{1+\frac{[\text{Dopamine}]}{kM\_3\_s26}+\frac{[\text{"3-MT"}]}{kM\_3\_s32}}}{V_{default}}\right) - V_{default}\cdot\left(\frac{\frac{[COMT]\cdot\left(\frac{kcatp\_5}{kM\_5\_s32}\cdot[\text{"3-MT"}]-\frac{kcatn\_5}{kM\_5\_s4}\cdot[\text{Homovanillin}]\right)}{1+\frac{[\text{"3-MT"}]}{kM\_5\_s32}+\frac{[\text{Homovanillin}]}{kM\_5\_s4}}}{V_{default}}\right)$$

$$\frac{d([DOPAL]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[MAO]\cdot\left(\frac{kcatp\_4}{kM\_4\_s26}\cdot[\text{Dopamine}]-\frac{kcatn\_4}{kM\_4\_s42}\cdot[DOPAL]\right)}{1+\frac{[\text{Dopamine}]}{kM\_4\_s26}+\frac{[DOPAL]}{kM\_4\_s42}}}{V_{default}}\right) - V_{default}\cdot\left(\frac{\frac{[\text{"Aldehyde- dehydrogenase"}]\cdot\left(\frac{kcatp\_6}{kM\_6\_s42}\cdot[DOPAL]-\frac{kcatn\_6}{kM\_6\_s2}\cdot[DOPAC]\right)}{1+\frac{[DOPAL]}{kM\_6\_s42}+\frac{[DOPAC]}{kM\_6\_s2}}}{V_{default}}\right)$$

$$\frac{d([\text{Homovanillin}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{[\text{COMT}]\cdot\left(\frac{kcatp\_5}{kM\_5\_s32}\cdot[\text{"3-MT"}]-\frac{kcatn\_5}{kM\_5\_s4}\cdot[\text{Homovanillin}]\right)}{1+\frac{[\text{"3-MT"}]}{kM\_5\_s32}+\frac{[\text{Homovanillin}]}{kM\_5\_s4}}}{V_{default}}\right)$$

$$-V_{default}\cdot\left(\frac{\frac{[\text{"Aldehyde- dehydrogenase"}]\cdot\left(\frac{kcatp\_7}{kM\_7\_s4}\cdot[\text{Homovanillin}]-\frac{kcatn\_7}{kM\_7\_s3}\cdot[\text{HVA}]\right)}{1+\frac{[\text{Homovanillin}]}{kM\_7\_s4}+\frac{[\text{HVA}]}{kM\_7\_s3}}}{V_{default}}\right)$$

$$\frac{d([\text{DOPAC}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[\text{"Aldehyde- dehydrogenase"}]\cdot\left(\frac{kcatp\_6}{kM\_6\_s42}\cdot[\text{DOPAL}]-\frac{kcatn\_6}{kM\_6\_s2}\cdot[\text{DOPAC}]\right)}{1+\frac{[\text{DOPAL}]}{kM\_6\_s42}+\frac{[\text{DOPAC}]}{kM\_6\_s2}}}{V_{default}}\right)$$

$$-V_{default}\cdot\left(\frac{\frac{[\text{COMT}]\cdot\left(\frac{kcatp\_8}{kM\_8\_s2}\cdot[\text{DOPAC}]-\frac{kcatn\_8}{kM\_8\_s3}\cdot[\text{HVA}]\right)}{1+\frac{[\text{DOPAC}]}{kM\_8\_s2}+\frac{[\text{HVA}]}{kM\_8\_s3}}}{V_{default}}\right)$$

$$\frac{d([\text{HVA}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[\text{"Aldehyde- dehydrogenase"}]\cdot\left(\frac{kcatp\_7}{kM\_7\_s4}\cdot[\text{Homovanillin}]-\frac{kcatn\_7}{kM\_7\_s3}\cdot[\text{HVA}]\right)}{1+\frac{[\text{Homovanillin}]}{kM\_7\_s4}+\frac{[\text{HVA}]}{kM\_7\_s3}}}{V_{default}}\right)$$

$$+V_{default}\cdot\left(\frac{\frac{[\text{COMT}]\cdot\left(\frac{kcatp\_8}{kM\_8\_s2}\cdot[\text{DOPAC}]-\frac{kcatn\_8}{kM\_8\_s3}\cdot[\text{HVA}]\right)}{1+\frac{[\text{DOPAC}]}{kM\_8\_s2}+\frac{[\text{HVA}]}{kM\_8\_s3}}}{V_{default}}\right)$$

$$\frac{d([\text{"3,4 DOPAL"}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[\text{"High Iron"}]}{kA\_9\_s40+[\text{"High Iron"}]}\cdot kI\_9\_s40}{kI\_9\_s40+[\text{"High Iron"}]}\cdot(kass\_9\cdot[\text{Dopamine}]\cdot[O2]-kdiss\_9\cdot[\text{"3,4 DOPAL"}]\cdot[H2O2])}{V_{default}}\right)$$

$$\frac{d([O2]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{[\text{"High Iron"}]}{kA\_9\_s40+[\text{"High Iron"}]}\cdot kI\_9\_s40}{kI\_9\_s40+[\text{"High Iron"}]}\cdot(kass\_9\cdot[\text{Dopamine}]\cdot[O2]-kdiss\_9\cdot[\text{"3,4 DOPAL"}]\cdot[H2O2])}{V_{default}}\right)$$

$$\frac{d([H2O2]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{[\text{"High Iron"}]}{kA\_10\_s40+[\text{"High Iron"}]}\cdot kI\_10\_s40}{kI\_10\_s40+[\text{"High Iron"}]}\cdot(kass\_10\cdot[H2O2]-kdiss\_10\cdot[\bullet OH])}{V_{default}}\right)$$

$$+V_{default}\cdot\left(\frac{\frac{[\text{"High Iron"}]}{kA\_9\_s40+[\text{"High Iron"}]}\cdot kI\_9\_s40}{kI\_9\_s40+[\text{"High Iron"}]}\cdot(kass\_9\cdot[\text{Dopamine}]\cdot[O2]-kdiss\_9\cdot[\text{"3,4 DOPAL"}]\cdot[H2O2])}{V_{default}}\right)$$

$$\frac{d([\bullet OH]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{kass\_11\cdot[\bullet OH]-kdiss\_11\cdot[\text{"Oxidative Stress"}]}{V_{default}}\right)$$

$$+V_{default}\cdot\left(\frac{\frac{[\text{"High Iron"}]}{kA\_10\_s40+[\text{"High Iron"}]}\cdot kI\_10\_s40}{kI\_10\_s40+[\text{"High Iron"}]}\cdot(kass\_10\cdot[H2O2]-kdiss\_10\cdot[\bullet OH])}{V_{default}}\right)$$

$$\frac{d([\text{"Oxidative Stress"}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{kass\_11\cdot[\bullet OH]-kdiss\_11\cdot[\text{"Oxidative Stress"}]}{V_{default}}\right)$$

## Appendix C

Table of Initial Concentrations

| Species | Concentration (M) |
|---|---|
| Levodopa | 1.25E-26 **(a)** |
| AAAD | 1.52E-07 |
| Aldehyde-dehydrogenase | 6.95E-07 |
| COMT | 5.99E-06 |
| MAO | 1.15E-06 |
| O2 | 1.00E-06 **(b)** |
| High Iron | 8.30E-19 **(c)** |
| Ketamine | 1.25E-25 **(d)** |
| Glutamate | 1.00E-06 **(e)** |
| AMPAR | 6.33E-08 |
| VDCC | 1.02E-08 |
| Ca2+ | 1.00E-06 **(f)** |
| TrkB | 2.89E-08 |
| eEF2K | 1.42E-07 |
| NMDAR | 6.05E-11 |

Values are sourced from Uniprot and Pax databases unless otherwise specified.

(a) Approximating from typical dose of 100mg converted to Dalton (Da) and used inferred ppm value of 0.75.

(b) Hypothetical concentration based on general ion concentrations found in literature.

(c) Approximate number calculated from: Reinert, et al., 2022 and inferred ppm value of 10.

(d) Approximating from typical dose of 10mg converted to Dalton (Da) and used inferred ppm value of 0.75.

(e) Hypothetical concentration based on general neurotransmitter concentrations found in literature.

(f) Hypothetical concentration based on general ion concentrations found in literature.