5-2024

Process Modeling the Neuroprotective Effects of a Plant-Based Diet on Parkinson's Disease

Julia Mitchell
William & Mary

Process Modeling the Neuroprotective Effects of a Plant-Based Diet on Parkinson's Disease

A thesis presented in candidacy for Departmental Honors in Chemistry from The College of William and Mary

By

Julia C. Mitchell

Accepted for Honors

Randolph Coleman, Ph.D.

Lisa Landino, Ph.D.

Douglas Young, Ph.D.

Denise Damon Wade

Williamsburg, VA

9 May 2024

Table of Contents

Acknowledgements

I would like to express my deepest gratitude to my advisor, Randy Coleman, whose guidance, support, and expertise have been invaluable throughout the entirety of this thesis journey. Your mentorship has not only shaped my academic growth but has also inspired me to strive for excellence in every aspect of my research.

I extend my appreciation to the Charles Center for providing the Honors Fellowship funding that enabled me to pursue this research endeavor. Additionally, I am indebted to the Charles E Flynn Memorial Scholarship for its generous support, which has helped alleviate the financial burdens associated with my academic pursuits. Your contribution has allowed me to focus wholeheartedly on my research, and for that, I am profoundly thankful.

I would like to acknowledge the William and Mary Chemistry Department for providing a nurturing and intellectually stimulating environment in which to conduct my studies. I would like to thank my committee members, Lisa Landino, Doug Young, and Denise Damon-Wade, for their insightful feedback, constructive criticism, and support throughout the development of this thesis. Your expertise and guidance have been invaluable in shaping the direction of my research and refining the quality of my work.

Finally, I extend my heartfelt gratitude to my parents, Chris and Heather Mitchell, for their unconditional love, unwavering encouragement, and unwavering belief in my abilities. To all those mentioned above, and to countless others who have contributed to my academic and personal growth, I extend my sincerest thanks. This thesis would not have been possible without your support, encouragement, and belief in me.

Dedication

This thesis is dedicated to my grandmother, whose unwavering courage in the face of Parkinson's Disease has been a beacon of inspiration throughout my academic journey. Her resilience and strength have fueled my exploration into the potential neuroprotective effects of a plant-based diet against this debilitating condition. With profound gratitude and admiration, I dedicate this work to her, as a testament to her enduring spirit and the profound impact she has had on my life.

Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor symptoms such as tremors, bradykinesia, rigidity, and postural instability. Recent research suggests an avenue for potential neuroprotection through dietary intervention, specifically the adoption of a plant-based diet. A plant-based diet predominantly comprises foods derived from plants, emphasizing fruits, vegetables, grains, legumes, and nuts while minimizing or excluding animal products.This thesis aims to explore the biochemical pathways implicated in PD progression and the potential impact of dietary choices on these pathways. The investigation focuses on several key pathways: alpha-synuclein aggregation, the blood-brain barrier crossing of levodopa, oxidative stress, ferroptosis, and methylmercury-induced dysbiosis. These pathways were modeled via CellDesigner 4.4 and their kinetics were analyzed using COPASI. Analysis indicates that this dietary approach may possess neuroprotective effects, potentially mitigating PD progression. Conversely, findings suggest that the traditional American animal-based diet might heighten the risk of developing PD by exacerbating the aforementioned pathways associated with PD pathogenesis.

Introduction

1. Parkinson's Disease

Parkinson's Disease (PD) is a progressive neurodegenerative disease that is characterized by cognitive decline and various motor symptoms, including tremors, bradykinesia, rigidity, and postural instability (Bloem et al., 2021). This disease is very prevalent, with a reported 6.1 million being affected worldwide in 2016 (Bloem et al., 2021). It is the second most common neurodegenerative disease in the United States, following Alzheimer's Disease, with an estimated 1 million Americans being estimated to have some level of this progressive disorder (NINDS, 2023). It is thought to be caused by a combination of genetic and environmental factors, with more research in recent years looking into the effects of lifestyle choices on progression (Bloem et al., 2021). Only around 10-15% of PD patients report a family history, suggesting that PD is for the most part idiopathic (Rose et al., 2021)

PD has an incredible effect on the people it afflicts. Due to the nature of such a progressive, degenerative disease, it can often progress for decades (Bloem et al., 2021). This results in massive emotional and financial tolls on both the patient and loved ones. On a larger scale, the financial costs of PD are enormous. In the United States, the annual cost of PD treatment is estimated to be approximately $14 billion, not including indirect costs such as loss of productivity (NINDS, 2023). Since PD is an age related disease, most people diagnosed are over the age of 60. Because of the United States' constantly aging population, the number of people diagnosed with PD is expected to double by 2040 (NIH). Given the widespread nature of this disease, it is vital that we find cost-effective ways to treat it.

Biochemically, PD is characterized by low levels of the neurotransmitter dopamine in the basal ganglia caused by the death of dopamine neurons in the substantia nigra (Ramesh, 2023). PD patients lose up to half of their dopamine in this region (Cheng et al., 2010). This lack of dopamine is currently the target for most existing antiparkinsonian therapies. The most commonly prescribed medication for PD is L-DOPA, which targets this dopamine deficiency by supplementing with the amino acid precursor to dopamine (Ramesh et al., 2023). However, there are many other biochemical hallmarks of PD that could be targeted by other treatments, such as dietary treatments. Such hallmarks include but are not limited to oxidative stress, alpha-synuclein aggregation, and gut dysbiosis (Rose et al., 2021). Given the many side effects associated with and unreliability of L-DOPA, a dietary regimen that slowed the progression of PD would be revolutionary to the treatment of this disease.

2. Existing Treatment - L-DOPA

The current standard for PD treatment is focused on restoring dopamine levels via L-DOPA, or *levo*-3,4-dihydroxy-phenylalanine, which is the amino acid precursor to dopamine. Unlike dopamine, L-DOPA is able to cross the blood-brain barrier and be transformed into dopamine in the substantia nigra via DOPA decarboxylase (Ovallath et al., 2017). This is because the transporter used is an amino acid transporter, which needs to recognize the carboxyl and amine groups on levodopa, which can be seen in Figure 1. Orally administered L-DOPA has been shown to increase dopamine levels in the brain and relieve these motor symptoms (Olanow et al., 2017). While it effectively alleviates motor symptoms in the early stages, prolonged use can lead to motor fluctuations and dyskinesias, complicating treatment (Fabbrini et al., 2022). Double blind studies show dyskinesia develops in approximately 16-20% of patients after 9 months of treatment and 50-60% of patients after 3-4 years. In the most extreme cases, patients

will cycle between “on” and “off” periods where the medication will not work. Dopamine agonists have also been used to treat parkinsonian symptoms this way, but these drugs are not as effective as Levodopa (Olanow et al., 2017).

Figure 1. *Shown on the left is dopamine, and shown on the right is levodopa. Levodopa had a carboxyl group that dopamine doesn’t, allowing it to be recognized by the amino acid transporter LAT1.*

Chronic L-DOPA treatment has been known to have many side effects including nausea and vomiting, but these can be somewhat mitigated by coupling treatment with a decarboxylase inhibitor like carbidopa to prevent the peripheral accumulation of dopamine (Olanow et al., 2017). Long-term use may also result in wearing-off phenomena, where the medication's efficacy diminishes over time. Moreover, the financial burden of levodopa and associated medications can be substantial, particularly for individuals without adequate insurance coverage. Given these challenges, emphasizing dietary changes to manage Parkinson's disease becomes crucial to mitigate the reliance on medication. Incorporating a plant-based diet rich in antioxidants and other neuroprotective molecules may offer a complementary approach. This potentially could reduce the need for high doses or prolonged use of levodopa, thus minimizing side effects and alleviating the economic strain associated with medication dependence.

3. Treatment of PD with a Plant-Based Diet

Current research shows a strong association between consuming a plant-based diet and a reduced risk of PD. A plant-based diet focuses on consuming the majority of one’s nutrients from plants, emphasizing fruits, vegetables, whole grains, legumes, nuts, seeds, and oils (Rose et al., 2021). This diet aims to minimize or exclude animal products from the diet, specifically meat,

dairy, and eggs. There are many aspects of a plant-based diet that are thought to contribute to its neuroprotective effects including a lack of animal fat, less protein, more fiber, and more antioxidants/flavonoids. There are several cultures that exist around the world that consume a quasi-vegan diet naturally including sub-saharan black Africans, rural Chinese, and Japanese communities. All of these communities report very low levels of PD compared to the US, adjusted for age (McCarty, 2001).

The plant-based diet has garnered attention for its potential neuroprotective effects, offering multifaceted benefits that may mitigate various neurological risks. One of its key attributes lies in its capacity to counteract oxidative stress, a process implicated in neuronal damage (McCarty, 2001). Oxidative stress occurs when there is an excess of reactive oxygen species (ROS) formation compared to the cells' capacity to use antioxidants to clear them. Multiple studies have shown that vegetarians generally have lower rates of oxidative stress in their cells, demonstrated by lower concentrations of malondialdehyde (MDA, one of the final products of polyunsaturated fatty acids peroxidation) in their cells (Somannovar, 2012). The same study showed that conversely, glutathione peroxidase (an enzymatic antioxidant that removes H2O2) was significantly increased in vegetarians. Rich in antioxidants such as vitamins C and E, carotenoids, and polyphenols, plant-based diets bolster the body's defense against oxidative stress, preventing the harmful effects of free radicals on neuronal cells such as increased apoptosis (Angelova, 2020). This defense mechanism may help reduce the risk of neurodegenerative conditions linked to oxidative stress, such as PD.

Ferroptosis is another mechanism that has been implicated in the progression of PD (Angelova et al., 2020). The same pathways that produce ROS such as hydrogen peroxide and superoxide have been shown to trigger ferroptosis as well. Ferroptosis is a form of regulated cell

death that's characterized by iron-dependent accumulation of lipid peroxides. Plants contain many bioactive phytochemicals that can regulate iron homeostasis and chelate iron, reducing this lipid peroxidation (Zheng et al., 2021). The term ferroptosis is a recently coined term, and the intricacies of the pathways are still being elucidated, but glutathione peroxidase 4 (GPX4) has been identified as a ferroptosis inhibitor (Seok Yang et al., 2014). GPX4 uses glutathione (GSH) as a cofactor to convert potentially toxic lipid peroxidation (LPO) products to non-toxic lipid alcohols, therefore reducing ferroptotic cell death (Zheng et al., 2021). The flavonoids and polyphenols found in plant foods can increase the transcription from Nuclear factor erythroid 2-related factor 2 (Nrf2) to GPX4 and therefore increasing the conversion of LPO products to lipid alcohols and reduce ferroptosis induced cell death (Su et al., 2019).

The misfolding and aggregation of alpha-synuclein is a pathway thought to be involved in the progression of PD. Alpha-synuclein is a small aggregation prone protein that does not have a clear known biological function, but its small oligomers are thought to be important for endogenous functions. When alpha-synuclein aggregates into larger beta sheet conformations, it forms amyloid fibrils that are neurotoxic. The fibrils have the ability to leave a cell, be taken up by another cell, and induce more aggregation (Killinger et al., 2017). Studies have suggested that this mechanism implies that alpha-synuclein acts like a prion. In order for the prion protein to cause disease, it must convert from an alpha-helical structure to a beta sheet conformation. The gut has been hypothesized as an initiating site for alpha-synuclein pathology, defended by a study that showed PD pathology could be induced in rats by injecting aggregated alpha-synuclein into the GI tract (Ulusoy et al., 2013). This suggests that alpha-synuclein prion particles from food could infect a human host.

All alpha-synuclein in dietary meat products contains threonine at the amino acid 53 position, while human alpha-synuclein has alanine at this position. The A53T mutation of human alpha-synuclein was the first identified to be associated with prion alpha-synuclein and PD. This mutation leads to impaired lipid binding and enhanced aggregation properties. This in addition to the oxidation that occurs in meat processing suggests that the alpha-synuclein humans consume from other vertebrate species is more susceptible to fibrillization. While this theory provides evidence that animal products enhance PD pathology, the mechanism is not clear enough to model. Gut microbiome dysbiosis, however, is much clearer. Transplantation of fecal matter from PD patients into the guts of germ-free mice has been linked to alpha-synuclein aggregation and movement dysfunction, demonstrating the importance of a healthy gut for the slowing of PD symptoms (Sampson et al., 2016). An unbalanced or inflamed gut microbiome encourages protein aggregation, which can lead to the aggregation of alpha-synuclein and progression of PD. A plant-based diet holds significant potential in fostering a healthier gut microbiome and mitigating dysbiosis. The diverse array of fibers, prebiotics, and phytonutrients abundant in plant-based foods serves as fuel for beneficial gut bacteria, promoting their growth and diversity. This dietary approach encourages the proliferation of microbes that contribute to gut health, enhancing the production of short-chain fatty acids (SCFAs) crucial for intestinal barrier function and immune modulation. Conversely, the reduced intake of animal products, which can sometimes be associated with a less diverse microbiome and the production of metabolites linked to inflammation, may positively influence the balance of gut bacteria.

Methylmercury, a neurotoxic compound found in certain fish and seafood, poses significant risks to neurological health, especially in vulnerable populations. Upon ingestion, methylmercury readily crosses the blood-brain barrier, where it accumulates in brain tissue, disrupting cellular functions and causing oxidative stress, inflammation, and neuronal damage.

Prolonged exposure to elevated levels of methylmercury has been associated with cognitive deficits, impaired motor function, and general neurotoxicity. Switching to a plant-based diet significantly reduces the intake of methylmercury since plants generally contain much lower levels of this neurotoxin. By opting for plant-based sources of protein and nutrients instead of fish and seafood high in methylmercury, individuals can substantially mitigate their exposure to this harmful compound, thus lowering the associated risks to neurological health.

Protein intake plays a pivotal role in the mitigation of PD due to the competition between dietary amino acids and levodopa for crossing the blood-brain barrier. Most Americans tend to consume protein in excess of their daily needs, inadvertently complicating the efficacy of levodopa . Excessive dietary protein can potentially impede the absorption and transportation of levodopa into the brain via the blood-brain barrier, limiting its availability for converting into dopamine (Boelens et al., 2021). A plant-based diet naturally contains less protein than the traditional western diet, making it optimal for minimizing competition with levodopa. By moderating protein consumption to meet physiological needs rather than overconsumption, there's a potential to mitigate the competition between amino acids and levodopa, allowing more of the medication to cross the blood-brain barrier and exert its therapeutic effects. Additionally, a plant-based diet could decrease the necessary dosage of L-DOPA in PD patients, mitigating the “on-off” fluctuations associated with high L-DOPA dosing (Hawkins et al., 2005). Additionally, the higher fiber content of a plant-based diet has been shown to increase natural bioavailability of levodopa, also reducing the need for high doses (Rose et al., 2021).

Methods

1. Cell Designer

The CellDesigner 4.4 software was utilized to model the pathways associated with oxidative stress, ferroptosis, gut-induced alpha-synuclein aggregation, methylmercury neurotoxicity, and levodopa bioavailability. In biochemical systems modeling, a primary objective is to comprehend the kinetics of biological processes and explore how specific constraints on these processes impact the functionality of the studied system, disease, or organism (Komasilovs et al., 2017). This approach heavily relies on process diagrams that utilize explicit, precise arrows and model symbols to represent individual processes such as catalysis, state transitions, inhibition, and more (Kitano et al., 2005). These diagrams are instrumental in facilitating a clearer understanding of complex biochemical pathways and their implications.

2. Model A: Oxidative Stress

Before describing this first model, it is important to define oxidative stress in more detail. Oxidative stress is a biological phenomenon occurring when there's an imbalance between the production of free radicals, or ROS, and the body's ability to counteract or detoxify their harmful effects through antioxidants. ROS, including superoxide radicals, hydrogen peroxide, and hydroxyl radicals, are natural byproducts of cellular metabolism. Under normal conditions, the body maintains a delicate equilibrium between ROS production and antioxidant defenses. However, various factors like environmental stressors, poor diet, inflammation, and certain medications can disrupt this balance, leading to an excess of ROS. These highly reactive molecules start damaging cellular components such as proteins, lipids, and DNA, triggering a

cascade of oxidative damage and impairing normal cell function. This process, often likened to rusting or decay within the body, is implicated in numerous health conditions, including neurodegenerative diseases, cardiovascular disorders, and aging-related ailments such as PD.

The model starts with a basic pathway for the formation of ROS. In the inner mitochondrial membrane, NADPH oxidase (NOX) catalyzes the reduction of oxygen to superoxide. Superoxide dismutase (SOD) then catalyzes the dismutation of superoxide to hydrogen peroxide. Hydrogen peroxide is then converted into ROS via the Fenton reaction. The Fenton reaction occurs when a ferrous ion is oxidized into a ferric ion via the decomposition of hydrogen peroxide into a hydroxyl radical. The ferric ion then reacts with another hydrogen peroxide molecule to form a hydroperoxyl radical (Trist et al., 2019). The reaction is simplified in the model as the conversion of H_2O_2 to ROS via the oxidation of Fe^{2+}. The formed ROS then go on to trigger multiple apoptotic pathways, several of which are described in this model.

The accumulation of ROS in the mitochondria prompts a structural shift and the relocation of certain pro-apoptotic Bcl-2 family proteins (such as Bax, Bak, Bad, and Bim) to the mitochondria. The accumulation of Bak specifically is modeled. These proteins assemble and form pores in the outer mitochondrial membrane, altering its permeability and enabling the release of pro-apoptotic proteins from the space between the mitochondrial membranes. Among these released proteins are cytochrome c, second mitochondria-derived activator of caspase (Smac), and apoptosis-inducing factor (AIF). Once in the cytosol, cytochrome c binds to Apaf-1 and procaspase-9, collectively activating executioner caspases (like caspase-3), initiating apoptosis by cleaving essential cellular proteins. Meanwhile, Smac enhances caspase activity by obstructing cytoplasmic caspase inhibitor proteins (IAPs). AIF, upon release from the

mitochondria, translocates to the nucleus, inducing chromatin condensation and DNA fragmentation, ultimately leading to cell death (Trist et al., 2019).

These pathways all progress unimpeded when there is a lack of antioxidants to balance formation of free radicals. This can occur when one consumes an animal-based diet deficient in antioxidants. However, the consumption of a plant-based diet rich in fruits, vegetables, and whole grains provides an abundance of bioavailable antioxidants. These antioxidants play a crucial role in impeding and reducing the formation of ROS in the first place. By scavenging free radicals and neutralizing their damaging effects, these antioxidants act as a protective barrier, limiting the initiation and progression of apoptotic pathways triggered by excessive ROS. A plant-based diet not only offers a direct defense against oxidative stress but also indirectly disrupts the cascading effects of ROS on cellular processes, potentially mitigating the activation of apoptotic pathways associated with oxidative damage. Antioxidants are modeled as inhibiting the formation of ROS via the Fenton reaction, as this is likely where the scavenging would occur.

3. Model B: Ferroptosis Model

Ferroptosis, a recently characterized type of regulated cell death (RCD), is dependent on iron and lipotoxicity, following the 2018 recommendation of the Nomenclature Committee on Cell Death (Zheng, 2021). The mevalonate pathway plays a significant role in ferroptosis, contributing to the regulation of lipid metabolism and cellular redox balance. The mevalonate pathway is a series of biochemical reactions responsible for the synthesis of isoprenoids and cholesterol. In the context of ferroptosis, the pathway has implications for lipid metabolism and the maintenance of cellular integrity. One key connection is through the production of coenzyme

Q10 (CoQ10), an essential component of the mitochondrial electron transport chain. CoQ10 acts as an antioxidant, separately from its roll in the electron transport chain, helping to neutralize reactive oxygen species (ROS) and maintain mitochondrial function. In ferroptosis, disruption of the mevalonate pathway can lead to decreased CoQ10 levels, contributing to increased oxidative stress and susceptibility to lipid peroxidation. This pathway was modeled in order to show one of the natural ways that lipid peroxidation is inhibited.

The iron-dependent aspect of ferroptosis is modeled at the top of the model. The ferric ion (Fe3+) binds to transferrin (TF) and enters the cell via the transferrin receptor (TFRC). After endocytosis, Fe3+ is released from TF within endosomes and is subsequently reduced to ferrous iron (Fe2+) by the endosomal metalloreductase STEAP3. The ferrous ion can then be used in the formation of ROS as described in oxidative stress, and these ROS can trigger the formation of lipid peroxidation (LPO) products (Zheng et al., 2021). Dietary antioxidants are modeled as interfering in the formation of ROS similarly to Model A. GPX4, as described previously, utilizes GSH as a co-factor in catalyzing the reduction of lipid hydroperoxides to their corresponding alcohols. GPX4 is regulated by transcription factor Nrf2, shown in the model. The formation of GSH from L-cysteine and L-glutamine is also modeled, dependent on the entrance of L-cysteine into the mitochondria via System X_c-. This is an ATP dependent step. The GPX4/GSH complex is shown as inhibiting the formation of lipid peroxidation products for simplicity.

Polyphenols are a class of naturally occurring compounds abundant in various plant-based foods that have been shown to be ferroptosis inhibitors (Zheng et al., 2021). Flavonoids, a subgroup of polyphenols, exhibit a diverse range of structures and include

subclasses like flavonols, flavones, and anthocyanins. Common sources of flavonoids encompass citrus fruits, berries, tea, and vegetables. Polyphenols, a broader category, encompass compounds with multiple phenolic rings, including flavonoids, phenolic acids, and resveratrol. They are found in fruits, vegetables, whole grains, tea, and red wine. These compounds activate Nrf2/GPX4 signaling, which is critical to the inhibition of ferroptosis. These compounds are modeled as triggering the transcription of GPX4 from Nrf2.

4. **Model C: Gut-Induced Alpha-Synuclein Aggregation**

It is important to elaborate on the gut-brain axis (GBA) before delving into the details of Model C, where the idea of the gut-brain axis is critical to understanding the connection between what we eat and alpha-synuclein aggregation in the brain. The GBA delineates a bidirectional communication network between the central and enteric nervous systems, effectively linking the cognitive and emotional centers of the brain with the gastrointestinal system. This interplay is influenced by the gut microbiota, a diverse community of microorganisms residing in the digestive tract. The GBA orchestrates communication through neural, endocrine, immune, and humoral pathways, enabling the transmission of signals from the gut to the brain and reciprocally (Carabotti et al., 2015). Recent advancements in research, employing methodologies such as germ-free animal models, probiotics, antibiotics, and infection studies, have underscored the pivotal role of the gut-brain axis in shaping both mental and gastrointestinal well-being. This nuanced understanding of the GBA interactions presents promising avenues for the development of targeted therapeutic interventions, including the aggregation of prion-like alpha-synuclein.

The pathway for the aggregation of alpha-synuclein in the gut starts with lipopolysaccharides (LPS) shown binding to toll-like receptor 4 (TLR4) and Nuclear factor

kappa B (NfκB) receptors on immune cells in the gut (Tan, 2021). LPS are large molecules found in the outer membrane of certain bacteria, particularly in the cell wall of Gram-negative bacteria. Structurally, LPS consists of three main components: a lipid portion (lipid A), a core oligosaccharide, and an O-specific polysaccharide or O-antigen. The lipid A region is responsible for the biological activity of LPS and is recognized as an endotoxin (Farhana et al., 2023). When endotoxins like LPS bind to these receptors, they can trigger inflammatory immune responses in the host organism. This is shown by the triggering of proinflammatory cytokine formation in the immune cell. Such cytokines could include TNFα, IL1α, and IL6, The presence of circulating endotoxins and cytokines can trigger systemic inflammation and heighten the permeability of blood vessels in the liver, kidney, and brain, fostering the deposition of misfolded alpha-synuclein in the gut. High consumption of saturated fat, in accordance with the traditional western animal-based diet, increases gut permeability to LPS, therefore triggering these pathways.

Mice studies have shown that a high fiber diet, such as a plant-based diet, attenuates motor deficits and reduces alpha sun aggregation in the substantia nigra of mice (Abdel-Haq et al., 2022). An estimated 70-80% of PD patients experience GI symptoms, mainly constipation, which is why it was postulated nearly 20 years ago that alpha syn aggregation may start at peripheral environmental interfaces such as the GI tract and travel via the vagus nerve to the brain (Braak et al., 2003). The 2022 mice study showed that when alpha-synuclein overexpressing mice were administered with a prebiotic diet (high-fiber), they exhibited enhanced performance in various motor behavior tests and a significant reduction in alpha-synuclein in the substantia nigra (Abdel-Haq et al., 2022). This study was utilized to inform the pathways modeled in Model C. The consumption of dietary fiber is modeled as

entering the gut as butyrate and inhibiting the aggregation of alpha-synuclein in the gut triggered by a high-fat diet. This then prevents the aggregated alpha-synuclein from using the vagus nerve to trigger more alpha-synuclein in the brain, which therefore leads to less dopamine degradation.

5. Model D: Methylmercury

The Mediterranean diet, often recommended as an alternative to more restrictive plant-based diets for slowing neurodegeneration, emphasizes a balanced intake of fruits, vegetables, whole grains, and healthy fats, along with moderate consumption of fish and other lean proteins. This dietary pattern has been associated with various health benefits, including potential neuroprotective effects. However, for individuals already showing symptoms of Parkinson's disease (PD) or those at a higher risk, solely adhering to the Mediterranean diet may not be enough. This is particularly due to concerns related to the intake of methylmercury, a toxic substance found in certain types of fish commonly included in the Mediterranean diet. Excessive exposure to methylmercury has been associated with adverse neurological effects, potentially counteracting the positive aspects of the diet. Mercury concentrations are highest in larger fish such as tuna and swordfish, however methylmercury can be found in nearly all types of fish at some level. Model D attempts to show that limiting methylmercury consumption as much as possible is ideal for limiting the progression of PD.

MeHg disrupts intracellular homeostasis by affecting redox status, glutamine recycling, and calcium homeostasis. Upon ingestion, 95% of methylmercury (MeHg) is absorbed in the gastrointestinal tract (Cariccio et al., 2018). Once absorbed, MeHg is widely distributed and easily enters the CNS, forming a complex with L-cysteine by binding the sulfhydryl group that allows it to cross the blood-brain by using molecular mimicry. Cys-HgMe mimics other large

amino acids to pass through LAT1 to enter the brain and neuronal cells (Cariccio et al., 2018). Once in the neuronal cell, methylmercury slows the normal uptake of cysteine into the cell by triggering System Xc- (xCT). xCT acts as a antiporter that imports one cysteine molecule and exports a glutamate (Koppula et al., 2020). The triggering of xCT therefore downregulates GSH levels in the cell because of the lack of glutamate necessary for the formation of GSH from cysteine via GSH synthetase (Xu et al., 2023). Normally GSH would go on to form a complex as GPX4 and act as an antioxidant against oxidative stress, but the GSH downregulation slows this antioxidant activity, therefore increasing the formation of ROS (Forero-Rodriguez et al., 2021).

Astrocytes, which play a crucial role in controlling extracellular pH, ionic balance, neurotrophic factor secretion, and glutamate uptake, are identified as potential sites for MeHg accumulation. Methylmercury inhibits normal uptake of glutamate via Excitatory Amino Acid Transporter-2 (EAAT2) by astrocytes which leads to an accumulation of glutamate in the synaptic cleft (Bjørklund et al., 2018). The accumulated glutamate then overactivates the N-methyl D-aspartate (NMDA)-type receptor on postsynaptic neurons (Ke et al., 2019). Once this receptor receives glutamate, it opens a calcium channel, allowing calcium ions to flow into the neuron (Ke et al., 2019). Increased intracellular calcium has been shown to increase mitochondrial dysfunction and increase ROS formation, therefore increase oxidative stress in postsynaptic neurons in addition to astrocytes. Calcium does this by stimulating the electron transport chain activity, which is omitted from the model for simplicity (Görlach et al., 2015).

6. Model E: L-DOPA

Model E aims to show how a plant-based diet can increase natural bioavailability of levodopa and increase uptake of levodopa via the blood-brain barrier (BBB). The model begins

with L-dopa on the blood side of the BBB. Here, L-dopa is at risk of being converted into 3-O-methyldopa (3-OMD) by catechol-O-methyltransferase (COMT) or dopamine via DOPA decarboxylase. Once converted into either of these molecules, it can no longer cross the BBB and relieve motor symptoms of PD. This is why it is necessary to take L-dopa with carbidopa, which inhibits the conversion of L-dopa to dopamine before crossing the BBB (Boelens et al., 2021). L-dopa is transported across the BBB via LAT1 (LNAA transporter 1), which is expressed in endothelial cells. Once reaching the brain, L-dopa can be metabolized into dopamine, relieving PD motor symptoms (Lerner et al., 2017).

As discussed, L-dopa treatment raises unpredictable motor fluctuations, specifically "on/off" cycling of effectiveness. This occurs when there are sudden changes in the patient's symptom level that occur without an apparent relationship to L-dopa dosing (Hawkins, 2005). There is often a sort of "honeymoon phase" when patients start taking L-dopa when the medication is very effective, but the effects become more sporadic and unreliable as the patient is on the medication for longer. This is mainly attributed to the competition of L-dopa with other large neutral amino acids (LNAAs) (Boelens et al., 2021). The LNAAs in question are consumed mainly in the form of dietary protein. Because dietary protein is slowing uptake of L-dopa via LAT1, dietary protein is modeled as inhibiting this transport. Various studies in the 1980s and 90s showed there was better motor performance of PD patients on low protein diets because this competition was limited (Lerner et al., 2017). A plant-based diet allows one to still consume enough protein for proper brain and muscle function, without exceeding dietary needs and competing with dosed and natural L-dopa. Additionally, being on a lower protein diet can allow patients to lower their dosage of L-dopa, which can limit the various side effects associated with being on a high dose of L-dopa for an extended period of time, as many PD patients are.

7. Mathematics

Following the creation of Models A-E using CellDesigner 4.4, SBML Squeezer was employed to attribute mathematical equations to each reaction within the model. These equations delineate flux reactions, depicting the generation of species denoted by arrows in CellDesigner. Each reaction embodies a true flux reaction, encompassing protein modifications such as phosphorylation and ubiquitination. To illustrate, if a protein labeled "Protein1" undergoes phosphorylation, CellDesigner recognizes the resultant phosphorylated form as a distinct species, possibly termed "species2," despite retaining the name "Protein1." Consequently, each arrow in the model symbolizes an interaction between two distinct species and is accordingly furnished with a specific flux equation. For non-enzyme catalyzed reactions, the overall reaction rate is governed by the substrate concentration and the rate constant (k_f or k_{cat}) of the reaction. In enzyme-catalyzed reactions, the mathematical framework is encapsulated by Michaelis-Menten equations, in which k_m signifies the enzyme's substrate affinity, and k_{cat} denotes the reaction rate when the enzyme is fully engaged at a saturated substrate concentration (i.e., the maximum reaction rate). This can be observed through the general mass action equation (1) or exemplified in the model for reaction 3 in Model B (equation 2).

$$k_{cat} * [substrate] \quad (1)$$

$$k^1_{ass} * s9 * s53 - k^1_{diss} * s2 * s51 \quad (2)$$

Subsequently, the models were imported into COPASI, a sophisticated simulator for complex biological pathways. COPASI allocates a flux equation to each reaction, representing an A compilation of the model's flux equations is available in Appendix A.

8. Parameter Values

The initial concentrations of species (M) were determined by converting brain tissue species abundances (ppm) sourced from the Pax database and molecular weights (Da) obtained from the RCSB Protein Data Bank and PubChem. These concentrations are detailed in Appendix B.

Results

Results were obtained by running the "Time Course Sensitivities" task in COPASI for 100 seconds with varying x and y axes. The variables chosen for most of the graphs were either transient species concentrations or flux amounts of a particular reaction/transition. The main takeaway from these results is that the data obtained from COPASI supports the claims made in literature about the neuroprotection of a plant-based diet. The accuracy of the models and kinetics based on current literature allow for possible pathway manipulation to gain valuable insight on the effect of dietary changes on these pathways. Unfortunately, there was not sufficient data available to run accurate simulations with Model A, so this oxidative stress/antioxidant consumption focused model is meant to be used primarily as a graphical representation of these pathways without quantitative results.

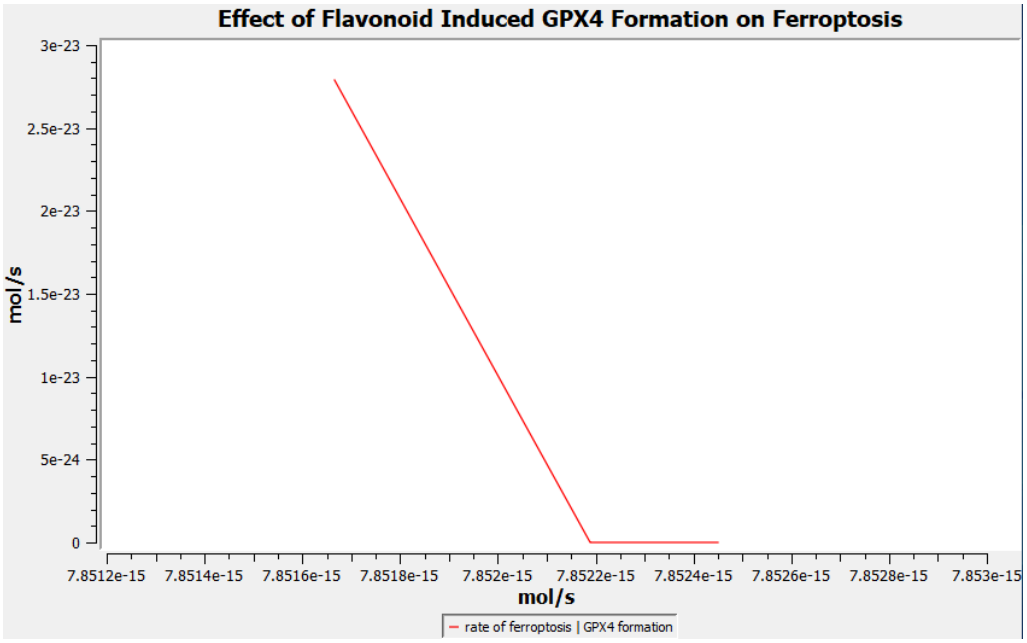


Figure 2. *100 second COPASI time course obtained from Model B. The flux of reaction 39 is graphed versus the flux of reaction 18. Reaction 39 is ferroptosis triggered by lipid peroxidation. Reaction 18 is GPX4 formation stimulated by flavonoid and polyphenol consumption.*

The results obtained from Model B demonstrate the neuroprotective effects of the elevated consumption of flavonoids, polyphenols, and phenylpropanoids associated with a plant-based diet. This is shown in Figure 2 where the rate of lipid peroxidation induced ferroptosis decreases drastically with increased GPX4 transcription via activation of the transcription factor Nrf2. GPX4 demonstrated strong antioxidant properties and has been identified as a critical molecule in limiting ferroptosis rates (Pearson et al., 2021). As described previously, Nrf2/GPX4 signaling is influenced by the consumption of flavonoid molecules such as luteolin, apigenin and tangeretin and polyphenol molecules such as ferulic acid and capsaicinoids (Su, 2019). More specifically, Figure 2 graphs the flux of reaction 39 versus the flux of reaction 18. An increase in Nrf2/GPX4 signaling induced by flavonoids and polyphenols results in more transcription of GPX4, which is then able to form a complex with GSH to inhibit PUFA oxidation. With the subsequent decrease in lipid peroxidation, we also see a decrease in Ferroptosis.

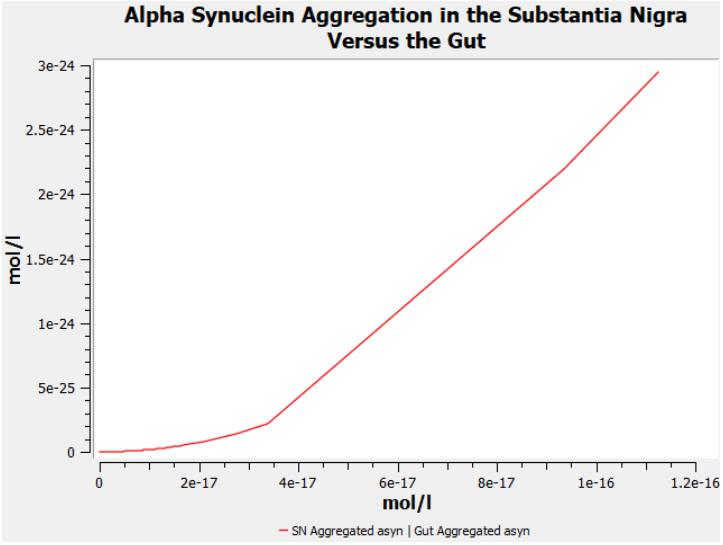


Figure 3. *100 second COPASI time course obtained from Model C. The flux of reaction 17 is graphed versus the flux of reaction 16. Reaction 17 is alpha-synuclein aggregation in the substantia nigra, and reaction 16 is alpha-synuclein aggregation in the gut.*

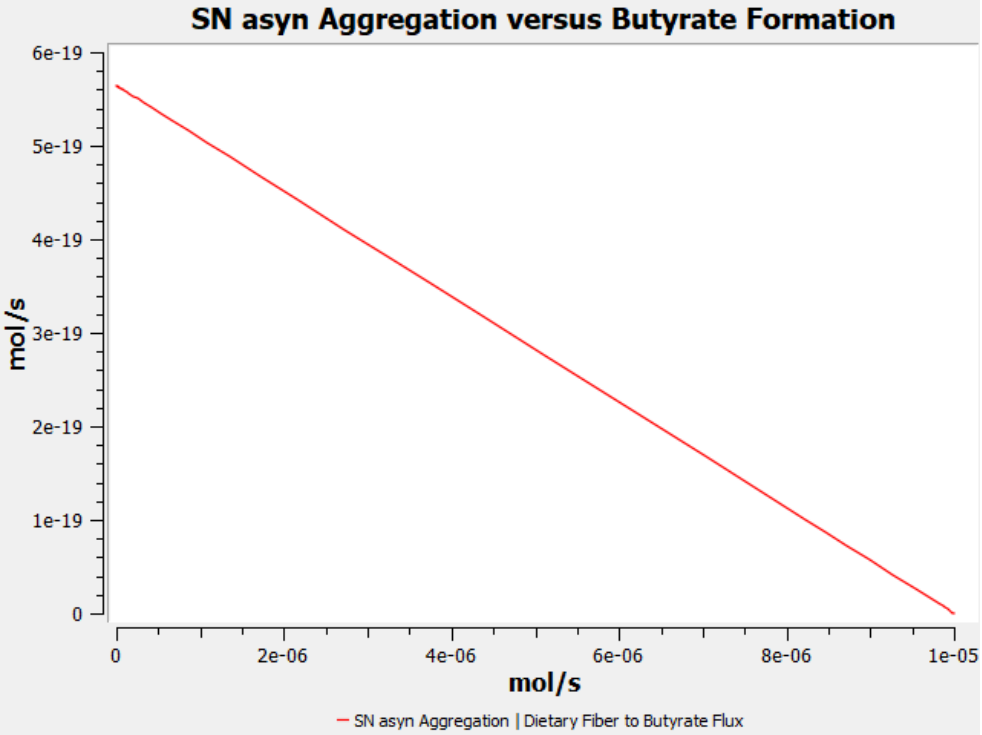


Figure 4. *100 second COPASI time course obtained from Model C. The flux of reaction 17 is graphed versus the flux of reaction 15. Reaction 17 is alpha-synuclein aggregation in the substantia nigra, and reaction 15 is butyrate formation from fiber consumption.*

Figure 3 is taken from the time course from Model C. In this graph we see the flux of alpha-synuclein aggregation in the substantia nigra versus the flux of alpha-synuclein aggregation in the gut. The model's design is derived from the recent rat studies that show alpha-synuclein aggregation can spread from the GI tract to the brain (Santos et al., 2022). When run with protein concentrations found in the Protein Abundance Database, we see that alpha-synuclein aggregation flux in the substantia nigra increases as aggregation flux in the gut increases. The gut aggregation of alpha-synuclein is modeled as being triggered by pro-inflammatory cytokine formation triggered by a high fat diet (Banerjee et al., 2020). This allows us to draw the conclusion that a high fat diet, consistent with the traditional western,

animal-based diet, results in increased alpha-synuclein aggregation in the brain. Figure 4 is also from a time course of Model C. We see, conversely to Figure 3, that alpha-synuclein aggregation flux in the brain decreases as dietary fiber enters the gut as butyrate. We can conclude from this that a diet higher in fiber, such as a plant-based diet, reduces alpha-synuclein aggregation in the brain.

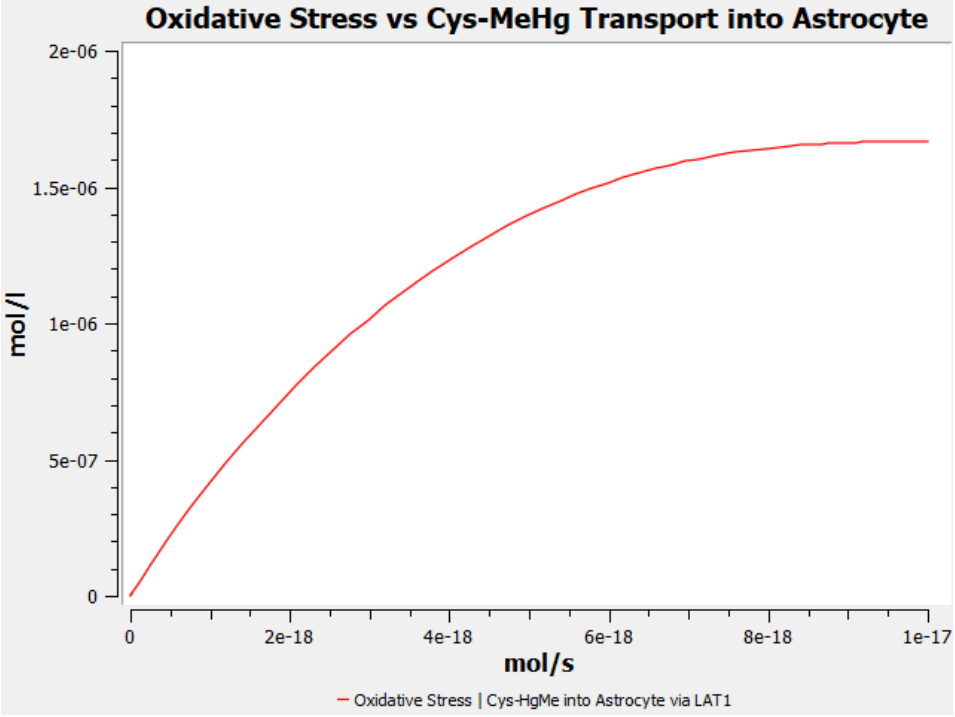


Figure 5. *100 second COPASI time course obtained from Model D. The flux of reaction 14 is graphed versus the flux of reaction 17. Reaction 14 is oxidative stress in astrocytes, and reaction 17 is Cys-MeHg transport into the astrocyte via LAT1.*

Figure 5 shows the results of a time course taken from Model D. A time course run for 100 seconds with starting protein concentrations from the Protein Abundance Database shows that as cysteine bound methylmercury enters the cell via LAT1 transport, oxidative stress increases. Methylmercury forms a complex with cysteine when consumed and enters the brain

(Vellingiri et al., 2021). The complex then enters astrocytes via LAT1 as previously described and stimulates the antiporter System Xc-. This causes glutamate to then leave the cell via System Xc-, meaning it cannot be used to form glutathione and inhibit oxidative stress with GPX4. The glutamate then leaves the astrocyte to trigger influx of Ca^{2+} into the postsynaptic neuron via NMDA, resulting in oxidative stress in the postsynaptic neuron as well. It can be concluded that increased consumption of methylmercury via fish results in increased oxidative stress, a pathway known to increase risk of and progression of PD.

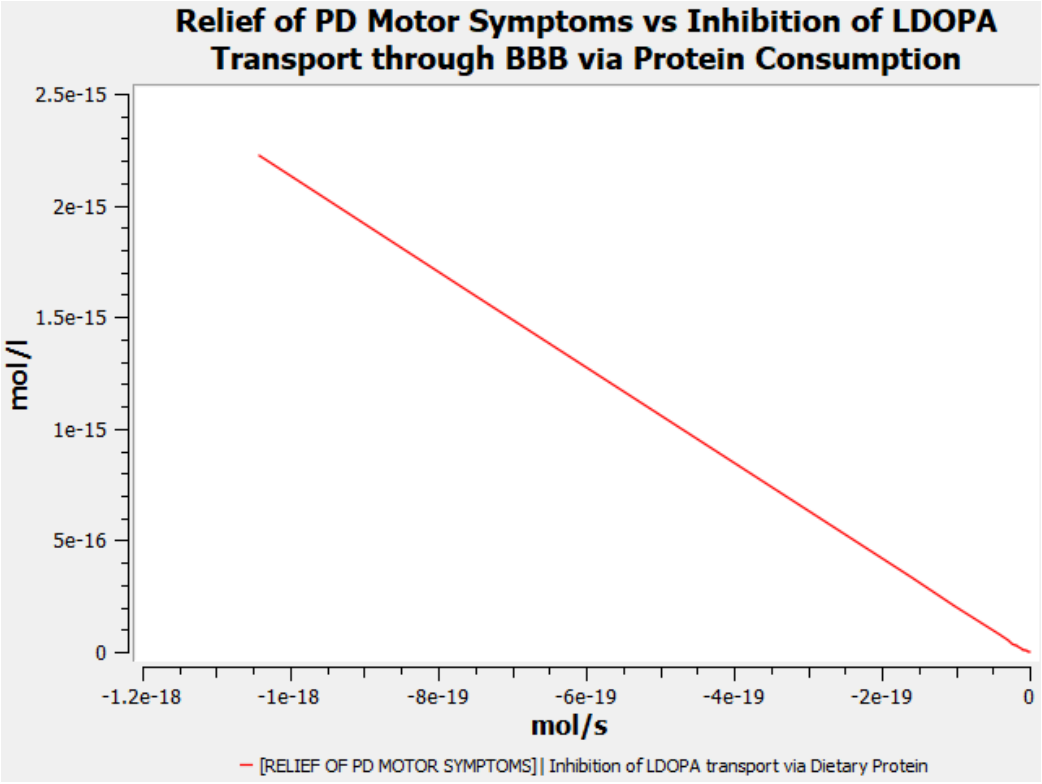


Figure 6. *100 second COPASI time course obtained from Model E. The triggering of [Relief of PD Motor Symptoms] is graphed versus the flux of reaction 7. Reaction 7 is the inhibition of L-dopa crossing the BBB by dietary protein.*

Figure 6 is taken from a 100 second time course of Model E, and shows the relief of PD motor symptoms versus the flux of L-dopa transport inhibition via dietary protein. The motor symptoms meant to be represented by the [RELIEF OF PD MOTOR SYMPTOMS] species are bradykinesia, tremors, rigidity, etc. These symptoms are relieved by the production of more dopamine, which can only happen if L-dopa can cross the blood brain barrier. Based on database concentrations, the relief of motor symptoms via external L-dopa decreases with an increased dietary protein concentration. This happens because the amino acids in dietary protein compete with levodopa for transport across the BBB via LAT1, which is modeled as dietary protein inhibiting L-dopa transport (Fabbrini et al., 2022).

Limitations

The results obtained from COPASI time courses are contingent upon the accuracy of the models created in CellDesigner. However, it is important to acknowledge that these models are based on current understanding and assumptions regarding biochemical pathways. Since the elucidation of these pathways is ongoing, there remains a degree of uncertainty regarding their complete accuracy. Therefore, while the results provide valuable insights, they should be interpreted with caution, recognizing the inherent limitations associated with the assumptions made in the modeling process.

The reliance on the Protein Abundance Database for initial concentrations introduces a limitation in terms of data availability. While efforts were made to utilize available concentrations for each species, not all species had corresponding data. Consequently, some initial concentrations were estimated based on available concentrations of similar species. This estimation introduces a potential source of variability and uncertainty in the modeling results, as the accuracy of these estimates may vary. There was not sufficient data available to use Model A for quantitative analysis, so this model will be used strictly for pathway discussion.

The modeling approach adopted in this study focused on individual pathways, treating them as independent entities. This methodology allows for a detailed examination of each pathway's dynamics; however, it inherently neglects the potential interactions and crosstalk between pathways. As a result, the time course analyses do not capture the complex interplay and synergistic effects that may occur when pathways interact with each other. Future research could explore integrated modeling approaches to address these interactions and provide a more comprehensive understanding of the system dynamics.

Discussion

Literature suggests that a plant-based diet has many different neuroprotective aspects (Rose et al, 2021). There is plentiful anecdotal evidence supporting the neuroprotective nature of a diet where the vast majority of nutrients come from plants. PD is incredibly rare in cultures that are already quasi-vegan such as sub-saharan african and rural chinese cultures, adjusted for age (McCarty et al, 2001). The neurochemical hallmarks of PD that were explored in these model are dopamine deficiency, increased oxidative stress/ mitochondrial distress, ferroptosis, alpha-synuclein aggregation, and methylmercury-induced toxicity. Based on concentration data pulled from the Protein Abundance Database, we see the flux of all of these pathways decreasing with plant-based interventions.

Model A demonstrates how antioxidants can interrupt the formation of ROS which would otherwise go on to trigger several apoptotic pathways associated with neurotoxicity. Although quantitative results were not obtained from this model, its structure and proposal of antioxidant intervention are valuable to the defense of a plant-based diet. Oxidative stress is widely recognized as a significant factor in the development and progression of PD, leading to the degeneration of dopaminergic neurons . This disruption in redox balance within neurons contributes to cell death via various apoptotic pathways. PD, along with other neurodegenerative disorders like Alzheimer’s, Huntington’s, and ALS, is associated with oxidative stress, indicating a common mechanism in neuronal degeneration (Angelova et al., 2020). The brain's high oxygen consumption results in extensive production of ROS, particularly by the electron transport chain in mitochondria, where ROS can damage mitochondrial DNA. Aging also exacerbates ROS production and mitochondrial DNA damage (Rose and Strombom, 2021).

A diet based on plants is effective in reducing oxidative stress due to its abundance of antioxidants. Phytonutrients, natural protective compounds found in plant-based foods, are known for their antioxidant properties (Angelova et al. 2020). Another level of antioxidant protection not modeled is the relationship with Parkin. Parkin, an enzyme responsible for promoting the removal of damaged mitochondria and enhancing mitochondrial growth, plays a crucial role in maintaining mitochondrial efficiency. Increasing Parkin levels in the substantia nigra using viral vectors has been shown to protect against Parkinson's disease in various animal studies (McCarty et al., 2021). Conversely, individuals with inactivating mutations in the Parkin gene tend to develop Parkinson's disease at an early age. Plant-based diets with moderate protein content, low in specific essential amino acids, have the potential to enhance Parkin expression by activating the GCN2 kinase, which subsequently increases ATF4 expression—a protein that stimulates the transcription of the Parkin gene (McCarty et al., 2021).

Antioxidants, vital for scavenging ROS, are primarily sourced from plant-based foods, as they are not naturally present in animal products. Incorporating these foods into our diet becomes essential to combat oxidative stress effectively. Examples of antioxidants include vitamin C found abundantly in citrus fruits like oranges and strawberries, vitamin E abundant in nuts and seeds like almonds and sunflower seeds, and flavonoids present in various colorful fruits and vegetables such as berries and spinach (Gulcin, 2020). These antioxidants play a crucial role in neutralizing free radicals within mitochondria. Antioxidants ameliorate the mitochondrial damage caused by ROS formation by donating electrons to unstable ROS, thereby stabilizing them and preventing further harm to mitochondria and other cellular structures. This process helps maintain mitochondrial function and overall cellular health (Angelova et al., 2020).

Model B explored the basic mechanism of Ferroposis. Ferroptosis, as described, is a type of cell death heavily reliant on iron, characterized by heightened lipid peroxidation and inadequate antioxidant mechanisms such as the GPX4/glutathione complex . Iron plays a pivotal role in inducing ferroptosis, and its absence can impede this cell death pathway, while additional iron supplementation enhances it (Lin et al., 2022). Not addressed in the model is the fact that humans get the bulk of their iron from animal products such as red meat, which would further support the argument against eating animal products to reduce PD risk (Abbaspour et al., 2014). Ferroptosis was initially identified in 2012 as a regulated, iron-dependent cell death process triggered by erastin and RSL-3, leading to lethal lipid peroxide buildup (Dixon et al., 2014). While the exact mechanisms of ferroptosis remain unclear, inhibitors of apoptosis and autophagy have shown little efficacy in preventing it, unlike antioxidants and iron chelators. GPX4, a crucial enzyme, detoxifies lipid hydroperoxides with the assistance of glutathione (GSH), highlighting the significance of cysteine, a precursor of GSH, in cellular defense against oxidative stress (Zheng et al., 2021).

The COPASI plot pulled from a 100 second time course of Model B shows a steep decrease in ferroptosis with an increase in flavonoid and polyphenol stimulated GPX4 formation. This supports claims in literature that flavonoids and polyphenols inhibit ferroptosis. Some such flavonoids include quercetin, kaempferol, and daidzein, the structures of which are shown in Figure 7 (Zheng et al., 2021). Quercetin is found in onions, scallions, kale, broccoli, apples, berries, and teas (Janabi et al., 2020). It acts as an antioxidant with radical-scavenging, iron-chelating, and reducing abilities. Quercetin activates NRF2 as shown in the model and modulates ferroptosis-related signals, indicating its potential involvement in quercetin's biological effects (Zheng et al., 2021). Kaempferol is naturally abundant in fruits, vegetables,

and herbs like tea and broccoli (Janabi et al., 2020). Kaempferol and its derivative kaempferide protect neuronal cells from ferroptosis induced by erastin by reducing mitochondrial superoxide production and activating NRF2/HO-1 signaling to counteract oxidative stress (Zheng et al., 2021). Daidzein, a naturally occurring isoflavone, is primarily obtained from soybeans and soy products like tofu and soy milk, forming a significant component of traditional Asian diets (Ubaid et al., 2023). This explains the very low rates of PD in asian countries. Additionally, it can be found in other legumes such as chickpeas and lentils (Janabi, 2020). Its mechanism of action involves antioxidant properties, such as scavenging free radicals and chelating iron ions, thereby reducing oxidative stress and preventing the accumulation of lipid peroxides that drive ferroptosis (Ubaid et al., 2023). All of these molecules that have the ability to inhibit ferroptosis are only available through the consumption of plants, emphasizing the importance of consuming the majority of one's nutrients through plants in order to optimize neuroprotection against PD.

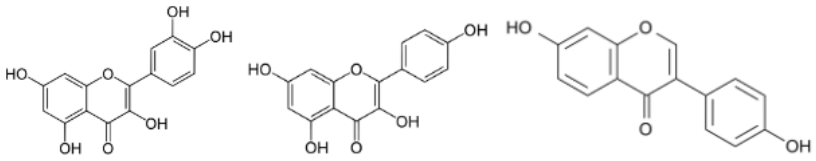


Figure 7. *Left to right, the structures of quercetin, kaempferol, and daidzein are shown. All have antioxidant abilities and have been shown to increase transcription of GPX4.*

The results from the time courses from Model C defend the benefits of a plant-based diet in two ways. First, they show that the increased fiber content of a plant-based diet can prevent neurotoxic alpha-synuclein aggregation in the brain. When consumed, dietary fiber goes through microbial fermentation to form butyrate, which inhibits the misfolding of alpha-synuclein in the gut by fostering a healthy gut microbiome (Tan et al., 2021). Butyrate increases colonic glucagon-like peptide-1 to elevate anaerobic bacterial levels, while decreased butyrate

concentration is associated with increased oxidative bacterial species and therefore increased oxidative stress (Tan et al., 2021). Studies show the importance of a healthy gut to reduce PD risk via fecal transplants in mice. Transplantation of fecal matter from PD patients into the guts of germ-free mice has been linked to SCFA alteration, alpha-synuclein aggregation, and movement dysfunction (Sampson et al., 2017). The gut microbiome in general has been shifting towards a pro-inflammatory state, contributing to the aggregation of alpha-synuclein. Specific bacterial strains associated with PD have been identified, with some exhibiting increased prevalence in PD patients. These bacteria, including members of Enterobacteriaceae, Akkermansia, Catabacter, Oscillospira, Lactobacillus, and Bifidobacterium species, are known to secrete endotoxins that induce inflammation and may contribute to aggregation. The previously discussed Abdel-Haq et al mice studies showed that the gut microbiome of alpha-synuclein overexpressing mice adopted a healthier profile upon prebiotic (fiber) treatment, and they concluded that prebiotic feeding reverses pathogenic microglial states in those mice. This is supported by the COPASI time course pulled from Model C demonstrating that dietary fiber reduces alpha-synuclein aggregation in the brain.

Secondly, these results show that a diet high in animal fat increases proinflammatory cytokine formation, resulting in more alpha-synuclein aggregation. An increase in saturated fat consumption, specifically from animal fats, has been shown to increase levels of lipopolysaccharides, which bind to TLR4 and NFkB receptors to induce proinflammatory cytokine formation (Basak et al., 2022). The increase in these endotoxins and cytokines creates a hostile and inflammatory environment in the gut that encourages misfolding of proteins like alpha synuclein. This is demonstrated in Model C and the subsequent COPASI time course plots that show increased LPS binding increases alpha-synuclein aggregation. Because if the mice

studies connect gut health to alpha-synuclein aggregation in the brain, it is safe to conclude that an increase in alpha-synuclein aggregation in the gut would be reflected in the substantia nigra of a patient as well.

Additionally, there is an entire level of complexity not modeled for this thesis which is the way in which these pathways interact with each other. For the sake of this study, each pathway was analyzed independently in Cell Designer, but in reality they all exacerbate each other. Alpha-synuclein aggregation and oxidative stress are particularly linked. The same proinflammatory cytokines that cause more alpha-synuclein misfolding and aggregation also promote mitochondrial defects, reactive oxygen species formation, and activation of apoptotic pathways (Tan et al., 2021). Some studies have even suggested that alpha-synuclein aggregation is often responsible for an increase in oxidative stress and subsequent lipid peroxidation. Angelova et al. demonstrated that mixed cultures of neurons produced significantly more reactive oxygen species when treated with aggregated versus non-aggregated alpha-synuclein (2015). This leads us to conclude that the reduction of alpha-synuclein aggregation pathway flux as a result of fiber consumption could also reduce the oxidative stress pathways in Model A. Additionally, the increase in alpha-synuclein aggregation flux as a result of a high fat diet could exacerbate the oxidative stress pathways in Model A.

The time course pulled from Model D with starting protein concentrations from the Protein Abundance Database shows that oxidative stress increases Cys-MeHg flux into the cell increases. Based on current literature, mercury, commonly encountered through fish consumption, is considered harmful to human health, being labeled as “the most toxic nonradioactive element” (Cariccio et al., 2018). The brain is particularly vulnerable to mercury's effects, with it possibly persisting there for over 16 years (Torrey et al., 2023). Exposure to

mercury, whether during fetal development or in adulthood, can lead to lasting neuropsychological impairments. Mercury exposure is linked to Parkinson's disease symptoms like tremors and facial stiffness, as it can damage dopamine neurons and contribute to the formation of Lewy bodies, characteristic of the disease (Bjorklund et al., 2018). Autopsy findings further support the association between mercury accumulation in brain regions relevant to Parkinson's disease and the presence of Lewy bodies (Pamphlett et al., 2022).

The reason for including this model in a defense for a plant-based diet is that it differentiates plant-based eating from the often recommended Mediterranean diet. The main difference between the Mediterranean diet and a plant-based one is the consumption of fish. A mediterranean diet is for all intents and purposes a plant-based diet, but intentionally includes a low/moderate consumption of poultry and seafood. Despite the findings that methylmercury can stimulate the progression of neurotoxic pathways, fish are consistently listed in literature as having many neuroprotective effects. This is mainly attributed to the richness of omega-3 in fish (Lister, 2020). Because fish themselves are known to be brain-healthy and it is only the methyl-mercury thought to be neurotoxic, it can be concluded that it is not necessary to completely eliminate fish from the diet to optimize PD risk reduction. Rather it would be optimal to limit consumption of fish with the highest concentrations of methyl-mercury, e.g. tuna and swordfish (USFDA, 2024).

Finally, a time course from Model E with original protein concentrations form the Protein Abundance Database shows that an increase in dietary protein consumption results in a a decrease in PD motor symptom relief that would normally result from levodopa crossing the BBB. Several studies investigated the impact of dietary protein on levodopa therapy, with high-protein diets leading to increased plasma levels of certain amino acids, diminishing the

effectiveness of levodopa and worsening motor performance. Conversely, reducing daytime protein intake through protein-redistribution diets (PRDs) improved and prolonged motor function in patients with fluctuating responses to levodopa (Knight et al., 2022). The interference of protein with levodopa therapy is attributed to competitive absorption between large neutral amino acids (LNAAs) and levodopa, both of which utilize similar transport systems at the intestinal wall and BBB. Excessive protein consumption exacerbates this competition, particularly at the BBB, resulting in more significant motor fluctuations. While high LNAA plasma concentrations do not impede levodopa's systemic circulation, they do hinder its anti-Parkinsonian effect, possibly by impeding its absorption into the brain (Olanow, 2017).

The high cost and side effects associated with levodopa as a medication underscore the importance of optimizing its efficacy to ensure maximum therapeutic benefit (Ovallath et al., 2017). Given that levodopa's ability to cross the BBB is crucial for its effectiveness, minimizing factors that impede this process becomes paramount. Therefore, adopting a diet low in protein, especially during the daytime when levodopa is typically administered, may help mitigate this interference, allowing for enhanced levodopa delivery to the brain and thus improving symptom management. This could potentially mitigate the need for excessively high dosages and minimize the financial burden and side effects associated with the drug. This strategy not only emphasizes the importance of dietary management in optimizing Parkinson's disease treatment but also highlights the potential for personalized approaches to medication administration in order to achieve better therapeutic outcomes.

Conclusion

Based on the extensive exploration of neuroprotective mechanisms and pathways implicated in PD, particularly focusing on dietary interventions and the neurochemical hallmarks of the condition, several key conclusions can be drawn. Firstly, literature strongly suggests that a plant-based diet offers significant neuroprotective benefits, as evidenced by the rarity of PD in cultures where plant-based diets predominate. Moreover, various pathways implicated in PD, including dopamine deficiency, oxidative stress, ferroptosis, alpha-synuclein aggregation, and methylmercury-induced toxicity, show decreased activity with plant-based interventions. This aligns with findings demonstrating the ability of flavonoids and polyphenols found in plants to inhibit ferroptosis, a crucial pathway in PD pathogenesis. Additionally, dietary fiber from plant-based diets appears to prevent alpha-synuclein aggregation in the brain by fostering a healthy gut microbiome, while high animal fat consumption exacerbates inflammation and alpha-synuclein aggregation. The complex interplay between these pathways underscores the importance of considering holistic dietary approaches in PD management.

Furthermore, the inclusion of mercury metabolism in the discussion highlights the necessity of distinguishing between plant-based diets and those like the Mediterranean diet, which includes fish consumption. While fish may contain neuroprotective omega-3 fatty acids, methylmercury poses risks, suggesting a need for moderation in fish consumption to optimize PD risk reduction. Lastly, the impact of dietary protein on levodopa therapy suggests that reducing protein intake, especially during levodopa administration, may enhance its efficacy, potentially reducing the need for high dosages and minimizing associated costs and side effects. These findings collectively emphasize the significance of dietary modifications in mitigating PD

risk and optimizing therapeutic outcomes, paving the way for personalized dietary strategies in PD management.

It is important to emphasize that this study is not meant to convey that consuming animal products will always result in the development and progression of Parkinson's Disease, or even that everybody should be consuming a plant-based diet. There are many reasons why people are unable to adopt a plant-based diet. For example, someone with many nutritional deficiencies may not find a plant-based diet is suitable for them. Someone may also have different goals in their nutrition, such as weight gain or an increase in muscle mass. This thesis is simply meant to show that an adult who is at risk of or already experiencing symptoms of PD may want to adopt a plant-based diet in order to limit their risk and prevent the exacerbation of PD pathways caused by animal-based foods and increase the efficacies of medications they would likely be prescribed. Additionally, an increase in fiber and antioxidant consumption associated with a plant-based diet could slow the progression of neurodegeneration and motor symptoms associated with PD.

In addition to the insights gained from the current study, several areas warrant further investigation to deepen our understanding of the relationship between diet and PD management. Firstly, while the literature strongly supports the neuroprotective benefits of a plant-based diet, more rigorous clinical trials are needed to confirm these findings and elucidate the specific dietary components that confer these benefits. Controlled intervention studies comparing different plant-based diets and their impact on PD progression, as well as long-term observational studies to assess their effects on disease outcomes, would provide valuable insights. Secondly, the mechanisms underlying the neuroprotective effects of specific dietary components, such as flavonoids, polyphenols, and dietary fiber, require further elucidation.

Future research could focus on identifying the precise pathways involved in mediating these effects and exploring potential synergies between different dietary constituents. Additionally, understanding how individual genetic variations influence dietary responses in PD patients could facilitate personalized dietary recommendations tailored to individual needs. Furthermore, while the current study highlights the potential benefits of reducing protein intake during levodopa therapy, more research is needed to optimize dietary strategies for enhancing levodopa efficacy while minimizing adverse effects. This could involve investigating the optimal timing and composition of meals in relation to levodopa administration and exploring the role of other dietary factors, such as micronutrients and gut microbiota composition, in modulating levodopa response.

In conclusion, the exploration of dietary interventions for PD management represents a promising avenue for improving patient outcomes and enhancing quality of life. Future research endeavors aimed at elucidating the intricate mechanisms underlying the influence of diet on PD pathogenesis and treatment response hold tremendous potential in informing evidence-based dietary strategies. By gaining a deeper understanding of how dietary factors modulate PD progression, we can tailor interventions to optimize neuroprotection, alleviate symptoms, and enhance treatment efficacy. The integration of dietary considerations into PD management protocols has the capacity to revolutionize current treatment paradigms, offering a holistic approach that addresses both symptom management and disease progression. Ultimately, the pursuit of further research in these areas not only contributes to advancing our scientific understanding but also holds the promise of tangible benefits for individuals living with PD and their caregivers.

References

1. Abbaspour, N.; Hurrell, R.; Kelishadi, R. Review on iron and its importance for human health. *J. Res. Med. Sci.* **2014***, 19*, 164-174.

2. Abdel-Haq, R.; Schlachetzki, J. C.; Boktor, J. C.; Cantu-Jungles, T. M.; Thron, T.; Zhang, M.; Bostick, J. W.; Khazaei, T.; Chilakala, S.; Morais, L. H.; Humphrey, G.; Keshavarzian, A.; Katz, J. E.; Thomson, M.; Knight, R.; Gradinaru, V.; Hamaker, B. R.; Glass, C. K.; Mazmanian, S. K. A prebiotic diet modulates microglial states and motor deficits in α-synuclein overexpressing mice. **2022***, 11*.

3. Aho, V. T. E.; Houser, M. C.; Pereira, P. A. B.; Chang, J.; Rudi, K.; Paulin, L.; Hertzberg, V.; Auvinen, P.; Tansey, M. G.; Scheperjans, F. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. *Mol Neurodegeneration* **2021***, 16*.

4. Angelova, P. R.; Horrocks, M. H.; Klenerman, D.; Gandhi, S.; Abramov, A. Y.; Shchepinov, M. S. Lipid peroxidation is essential for α-synuclein-induced cell death. *J. Neurochem.* **2015***, 133*, 582-589 DOI:10.1111/jnc.13024.

5. Angelova, P. R.; Esteras, N.; Abramov, A. Y. Mitochondria and lipid peroxidation in the mechanism of neurodegeneration: Finding ways for prevention. *Medicinal Research Reviews* **2020***, 41*, 770.

6. Banerjee, A.; Das, D.; Paul, R.; Roy, S.; Bhattacharjee, A.; Prasad, S. K.; Banerjee, O.; Mukherjee, S.; Maji, B. K. Altered composition of high-lipid diet may generate reactive oxygen species by disturbing the balance of antioxidant and free radicals. **2020***, 31*.

7. Basak, S.; Banerjee, A.; Pathak, S.; Duttaroy, A. K. Dietary Fats and the Gut Microbiota: Their impacts on lipid-induced metabolic syndrome. *Journal of Functional Foods* **2022***, 91*, 105026 DOI:10.1016/j.jff.2022.105026.

8. Bjorklund, G.; Stejskal, V.; Urbina, M. A.; Dadar, M.; Chirumbolo, S.; Mutter, J. Metals and Parkinson's Disease: Mechanisms and Biochemical Processes. *Curr. Med. Chem.* **2018***, 25*, 2198-2214 DOI:10.2174/0929867325666171129124616.

9. Bjørklund, G.; Tinkov, A. A.; Dadar, M.; Rahman, M. M.; Chirumbolo, S.; Skalny, A. V.; Skalnaya, M. G.; Haley, B. E.; Ajsuvakova, O. P.; Aaseth, J. Insights into the Potential Role of Mercury in Alzheimer's Disease. *J Mol Neurosci* **2019**.

10. Bloem, B. R.; Okun, M. S.; Klein, C.; Bastiaan, P.; Bloem, R. Parkinson's disease. **2021**.

11. Boelens keun, J. T.; Arnoldussen, I. A.; Vriend, C.; Van de rest, O. Dietary Approaches to Improve Efficacy and Control Side Effects of Levodopa Therapy in Parkinson's Disease: A Systematic Review. *Advances in Nutrition* **2021***, 12*, 2265.

12. Braak, H.; Tredici, K. D.; Rüb, U.; de Vos, R. A. I.; Jansen Steur, E. N. H.; Braak, E. Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol. Aging* **2003***, 24*, 197-211 DOI:10.1016/S0197-4580(02)00065-9.

13. Carabotti, M.; Scirocco, A.; Maselli, M. A.; Severi, C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems.

14. Cariccio, V. L.; Samà, A.; Bramanti, P.; Mazzon, E. Mercury Involvement in Neuronal Damage and in Neurodegenerative Diseases. *Biol Trace Elem Res* **2018***, 187*, 341.

15. Cheng, H.; Ulane, C. M.; Burke, R. E. Clinical progression in Parkinson disease and the neurobiology of axons. *Annals of Neurology* **2011***, 67*, 715.

16. Colón-Rodríguez, A.; Colón-Carrión, N. M.; Atchison, W. D. AMPA receptor contribution to methylmercury-mediated alteration of intracellular Ca2+ concentration in human induced pluripotent stem cell motor neurons. *NeuroToxicology* **2020***, 81*, 116.

17. Cuervo-Zanatta, D.; Syeda, T.; Sánchez-Valle, V.; Irene-Fierro, M.; Torres-Aguilar, P.; Torres-Ramos, M. A.; Shibayama-Salas, M.; Silva-Olivares, A.; Noriega, L. G.; Torres, N.; Tovar, A. R.; Ruminot, I.; Barros, L. F.; García-Mena, J.; Perez-Cruz, C. Dietary Fiber Modulates the Release of Gut Bacterial Products Preventing Cognitive Decline in an Alzheimer's Mouse Model. *Cell. Mol. Neurobiol.* **2023***, 43*, 1595-1618 DOI:10.1007/s10571-022-01268-7.

18. Dixon, S. J.; Stockwell, B. R. The role of iron and reactive oxygen species in cell death. *Nature Chemical Biology* **2014***, 10*, 9-17 DOI:10.1038/nchembio.1416.

19. Fabbrini, A.; Guerra, A. Pathophysiological Mechanisms and Experimental Pharmacotherapy for L-Dopa-Induced Dyskinesia. *JEP* **2022***, Volume13*, 469.

20. Forero-Rodríguez, L. J.; Josephs-Spaulding, J.; Flor, S.; Pinzón, A.; Kaleta, C. Parkinson’s Disease and the Metal–Microbiome–Gut–Brain Axis: A Systems Toxicology Approach. *Antioxidants* **2021***, 11*.

21. Gago-Dominguez, M.; Jiang, X.; Castelao, J. E. Lipid peroxidation, oxidative stress genes and dietary factors in breast cancer protection: a hypothesis. **2007**.

22. Gulcin, İ Antioxidants and antioxidant methods: an updated overview. *Arch Toxicol* **2020a***, 94*, 651.

23. Gulcin, İ Antioxidants and antioxidant methods: an updated overview. *Arch. Toxicol.* **2020b***, 94*, 651-715 DOI:10.1007/s00204-020-02689-3.

24. Görlach, A.; Bertram, K.; Hudecova, S.; Krizanova, O. Calcium and ROS: A mutual interplay. *Redox Biology* **2015***, 6*, 260.

25. Hawkins, R. A.; Mokashi, A.; Simpson, I. A. An active transport system in the blood–brain barrier may reduce levodopa availability. *Exp. Neurol.* **2005***, 195*, 267-271 DOI:10.1016/j.expneurol.2005.04.008.

26. Ke, T.; Gonçalves, F. M.; Gonçalves, C. L.; Dos Santos, A. A.; Rocha, J. B. T.; Farina, M.; Skalny, A.; Tsatsakis, A.; Bowman, A. B.; Aschner, M. Post-translational modifications in MeHg-induced neurotoxicity. *Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease* **2018***, 1865*, 2068.

27. Killinger, B. A.; Labrie, V. Vertebrate food products as a potential source of prion-like α-synuclein. *npj Parkinson's Disease* **2017***, 3*.

28. Kitano, H.; Funahashi, A.; Matsuoka, Y.; Oda, K. Using process diagrams for the graphical representation of biological networks. *Nat Biotechnol* **2005***, 23*, 961.

29. Knight, E.; Geetha, T.; Burnett, D.; Babu, J. R. The Role of Diet and Dietary Patterns in Parkinson's Disease. *Nutrients* **2022a***, 14*, 4472. doi: 10.3390/nu14214472 DOI:10.3390/nu14214472.

30. Knight, E.; Geetha, T.; Burnett, D.; Babu, J. R. The Role of Diet and Dietary Patterns in Parkinson's Disease. *Nutrients* **2022b**, *14*.

31. Koppula, P.; Zhuang, L.; Gan, B. Cystine transporter SLC7A11/xCT in cancer: ferroptosis, nutrient dependency, and cancer therapy. *protein. cell.* **2020**, *12*, 599-620 DOI:10.1007/s13238-020-00789-5.

32. Lerner, R. P.; Francardo, V.; Fujita, K.; Bimpisidis, Z.; Jourdain, V. A.; Tang, C. C.; Dewey, S. L.; Chaly, T.; Cenci, M. A.; Eidelberg, D. Levodopa-induced abnormal involuntary movements correlate with altered permeability of the blood-brain-barrier in the basal ganglia. *Sci Rep* **2017**, *7*.

33. Lin, K.; Chen, S.; Lin, K.; Liou, C.; Lan, M.; Chuang, Y.; Wang, P.; Lee, J.; Wang, F.; Lin, H.; Lin, T. Iron Brain Menace: The Involvement of Ferroptosis in Parkinson Disease. *Cells* **2022**, *11*, 3829. doi: 10.3390/cells11233829 DOI:10.3390/cells11233829.

34. Lister, T. Nutrition and Lifestyle Interventions for Managing Parkinson's Disease: A Narrative Review. *J. Mov. Disord.* **2020**, *13*, 97-104 DOI:10.14802/jmd.20006.

35. Ludtmann, M. H. R.; Angelova, P. R.; Horrocks, M. H.; Choi, M. L.; Rodrigues, M.; Baev, A. Y.; Berezhnov, A. V.; Yao, Z.; Little, D.; Banushi, B.; Al-Menhali, A. S.; Ranasinghe, R. T.; Whiten, D. R.; Yapom, R.; Dolt, K. S.; Devine, M. J.; Gissen, P.; Kunath, T.; Jaganjac, M.; Pavlov, E. V.; Klenerman, D.; Abramov, A. Y.; Gandhi, S. α-synuclein oligomers interact with ATP synthase and open the permeability transition pore in Parkinson's disease. *Nat Commun* **2018**, *9*.

36. Mccarty, M. F. Does a vegan diet reduce risk for Parkinson's disease? **2001**.

37. McCarty, M. F.; Lerner, A. Perspective: Low Risk of Parkinson's Disease in Quasi-Vegan Cultures May Reflect GCN2-Mediated Upregulation of Parkin. *Adv. Nutr.* **2021**, *12*, 355-362 DOI:10.1093/advances/nmaa112.

38. NIH National Institute of Neurological Disorders and Stroke Parkinson's Disease: Challenges, Progress, and Promise . *https://www.ninds.nih.gov/current-research/focus-disorders/parkinsons-disease-research/parkinsons-disease-challenges-progress-and-promise#:~:text=Following%20Alzheimer's%20disease%2C%20Parkinson's%20disease,before%20the%20age%20of%2050.*

39. Olanow, C. W.; Stocchi, F. Levodopa: A new look at an old friend. *Movement Disorders* **2017**, *33*, 859.

40. Ovallath, S.; Sulthana, B. Levodopa: History and therapeutic applications. *Ann Indian Acad Neurol* **2024**, *20*.

41. Pamphlett, R.; Bishop, D. P. Mercury is present in neurons and oligodendrocytes in regions of the brain affected by Parkinson's disease and co-localises with Lewy bodies. *PLoS One* **2022**, *17*, e0262464 DOI:10.1371/journal.pone.0262464.

42. Pearson, A. N.; Carmicheal, J.; Jiang, L.; Lei, Y. L.; Green, M. D. Contribution of Lipid Oxidation and Ferroptosis to Radiotherapy Efficacy. *IJMS* **2021**, *22*.

43. Picca, A.; Calvani, R.; Coelho-Junior, H. J.; Landi, F.; Bernabei, R.; Marzetti, E. Mitochondrial Dysfunction, Oxidative Stress, and Neuroinflammation: Intertwined Roads to Neurodegeneration. *Antioxidants* **2020**, *9*.

44. Pistollato, F.; Battino, M. Role of plant-based diets in the prevention and regression of metabolic syndrome and neurodegenerative diseases. *Trends in Food Science & Technology* **2014***, 40*, 62.

45. Ramesh, S.; Arachchige, A. S. P. M. Depletion of dopamine in Parkinson's disease and relevant therapeutic options: A review of the literature. *AIMSN* **2023***, 10*, 200.

46. Rose, S.; Strombom, A. Preventing and Treating of Parkinson's Disease with a Plant-Based Diet. *OAJNN* **2021***, 15*.

47. Sahoo, K.; Sharma, A. Understanding the mechanistic roles of environmental heavy metal stressors in regulating ferroptosis: adding new paradigms to the links with diseases. *Apoptosis* **2023***, 28*, 277.

48. Sampson, T. R.; Debelius, J. W.; Thron, T.; Janssen, S.; Shastri, G. G.; Ilhan, Z. E.; Challis, C.; Schretter, C. E.; Rocha, S.; Gradinaru, V.; Chesselet, M.; Keshavarzian, A.; Shannon, K. M.; Krajmalnik-Brown, R.; Wittung-Stafshede, P.; Knight, R.; Mazmanian, S. K. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. *Cell* **2017***, 167*, 1469.

49. Santos, L. S.; Cordeiro, G. S.; Matos, R. J. B.; Perez, G. S.; Silva, R. T.; Boaventura, G. T.; Barreto-Medeiros, J. M. High-fat diet promotes hypothalamic inflammation in animal models: a systematic review. *Nutr. Rev.* **2022***, 80*, 392-399 DOI:10.1093/nutrit/nuab033.

50. Sarchione, A.; Marchand, A.; Taymans, J.; Chartier-Harlin, M. Alpha-Synuclein and Lipids: The Elephant in the Room? *Cells* **2021***, 10*, 2452. doi: 10.3390/cells10092452 DOI:10.3390/cells10092452.

51. Somannavar, M. Correlation between oxidative stress and antioxidant defence in South Indian urban vegetarians and non-vegetarians Article in European Review for Medical and Pharmacological Sciences • March 2012. **2014**.

52. Stefanis, L. -Synuclein in Parkinson's Disease. *Cold Spring Harbor Perspectives in Medicine* **2011***, 2*, a009399.

53. Su, L.; Zhang, J.; Gomez, H.; Murugan, R.; Hong, X.; Xu, D.; Jiang, F.; Peng, Z. Reactive Oxygen Species-Induced Lipid Peroxidation in Apoptosis, Autophagy, and Ferroptosis. *Oxidative Medicine and Cellular Longevity* **2019***, 2019*, 1.

54. Tan, L. Y.; Yeo, X. Y.; Bae, H.; Lee, D. P. S.; Ho, R. C.; Kim, J. E.; Jo, D.; Jung, S. Association of Gut Microbiome Dysbiosis with Neurodegeneration: Can Gut Microbe-Modifying Diet Prevent or Alleviate the Symptoms of Neurodegenerative Diseases? *Life* **2021***, 11*.

55. Torrey, E. F.; Simmons, W. Mercury and Parkinson's Disease: Promising Leads, but Research Is Needed. *Parkinsons Dis.* **2023***, 2023*, 4709322 DOI:10.1155/2023/4709322.

56. Trist, B. G.; Hare, D. J.; Double, K. L. Oxidative stress in the aging substantia nigra and the etiology of Parkinson's disease. *Aging Cell* **2019***, 18*.

57. Ubaid, M.; Salauddin; Shadani, M. A.; Kawish, S. M.; Albratty, M.; Makeen, H. A.; Alhazmi, H. A.; Najmi, A.; Zoghebi, K.; Halawi, M. A.; Ali, A.; Alam, M. S.; Iqbal, Z.; Mirza, M. A. Daidzein from Dietary Supplement to a Drug Candidate: An Evaluation of Potential. *ACS Omega* **2023***, 8*, 32271-32293 DOI:10.1021/acsomega.3c03741.

58. Ulusoy, A.; Rusconi, R.; Pérez-revuelta, B. I.; Musgrove, R. E.; Helwig, M.; Winzen-reichert, B.; Monte, D. A. D. Caudo-rostral brain spreading of α-synuclein through vagal connections. *EMBO Mol Med* **2013***, 5*, 1119.

59. Vellingiri, B.; Suriyanarayanan, A.; Abraham, K. S.; Venkatesan, D.; Iyer, M.; Raj, N.; Gopalakrishnan, A. V. Influence of heavy metals in Parkinson's disease: an overview. *J Neurol* **2022***, 269*, 5798.

60. Vidović, M.; Rikalovic, M. G. Alpha-Synuclein Aggregation Pathway in Parkinson's Disease: Current Status and Novel Therapeutic Approaches. *Cells* **2022***, 11*.

61. Virmani, T.; Tazan, S.; Mazzoni, P.; Ford, B.; Greene, P. E. Motor fluctuations due to interaction between dietary protein and levodopa in Parkinson's disease. *J Clin Mov Disord* **2016***, 3*.

62. Waheed Janabi, A. H.; Kamboh, A. A.; Saeed, M.; Xiaoyu, L.; BiBi, J.; Majeed, F.; Naveed, M.; Mughal, M. J.; Korejo, N. A.; Kamboh, R.; Alagawany, M.; Lv, H. Flavonoid-rich foods (FRF): A promising nutraceutical approach against lifespan-shortening diseases. *Iran. J. Basic Med. Sci.* **2020***, 23*, 140-153 DOI:10.22038/IJBMS.2019.35125.8353.

63. Winterbourn, C. C. Toxicity of iron and hydrogen peroxide: the Fenton reaction. *Toxicol. Lett.* **1995***, 82-83*, 969-974 DOI:10.1016/0378-4274(95)03532-X.

64. Xu, X.; Wang, S.; Zhang, L.; Lu, A.; Lin, Y.; Liu, J.; Yan, C. Methylmercury induced ferroptosis by interference of iron homeostasis and glutathione metabolism in CTX cells. *Environmental Pollution* **2023***, 335*.

65. Yang, D.; Zhao, D.; Ali Shah, S. Z.; Wu, W.; Lai, M.; Zhang, X.; Li, J.; Guan, Z.; Zhao, H.; Li, W.; Gao, H.; Zhou, X.; Yang, L. The Role of the Gut Microbiota in the Pathogenesis of Parkinson's Disease. *Front. Neurol.* **2019***, 10*.

66. Yang, W. S.; Sriramaratnam, R.; Welsch, M. E.; Shimada, K.; Skouta, R.; Viswanathan, V. S.; Cheah, J. H.; Clemons, P. A.; Shamji, A. F.; Clish, C. B.; Brown, L. M.; Girotti, A. W.; Cornish, V. W.; Schreiber, S. L.; Stockwell, B. R. Regulation of Ferroptotic Cancer Cell Death by GPX4. *Cell* **2014***, 156*, 317.

67. Yang, Y.; Stewart, T.; Zhang, C.; Wang, P.; Xu, Z.; Jin, J.; Huang, Y.; Liu, Z.; Lan, G.; Liang, X.; Sheng, L.; Shi, M.; Cai, Z.; Zhang, J. Erythrocytic α-Synuclein and the Gut Microbiome: Kindling of the Gut-Brain Axis in Parkinson's Disease. *Movement Disorders* **2023***, 39*, 40.

68. Zheng, K.; Dong, Y.; Yang, R.; Liang, Y.; Wu, H.; He, Z. Regulation of ferroptosis by bioactive phytochemicals: Implications for medical nutritional therapy. *Pharmacological Research* **2021***, 168*.

Appendix A: Model Equations

Model A Equations

$$\frac{d([O2]\cdot V_{OMM})}{dt} = -\left(\frac{[NOX]\cdot\left(\frac{kcatp\_1}{kM\_1\_s2}\cdot[O2]-\frac{kcatn\_1}{kM\_1\_s3}\cdot["O2-"]\right)}{1+\frac{[O2]}{kM\_1\_s2}+\frac{["O2-"]}{kM\_1\_s3}}\right)$$

$$\frac{d(["O2-"]\cdot V_{OMM})}{dt} = +\left(\frac{[NOX]\cdot\left(\frac{kcatp\_1}{kM\_1\_s2}\cdot[O2]-\frac{kcatn\_1}{kM\_1\_s3}\cdot["O2-"]\right)}{1+\frac{[O2]}{kM\_1\_s2}+\frac{["O2-"]}{kM\_1\_s3}}\right)$$

$$-V_{OMM}\cdot\left(\frac{\frac{[SOD]\cdot\left(\frac{kcatp\_2}{kM\_2\_s3}\cdot["O2-"]-\frac{kcatn\_2}{kM\_2\_s4}\cdot[H2O2]\right)}{1+\frac{["O2-"]}{kM\_2\_s3}+\frac{[H2O2]}{kM\_2\_s4}}}{V_{OMM}}\right)$$

$$\frac{d([H2O2]\cdot V_{OMM})}{dt} = +V_{OMM}\cdot\left(\frac{\frac{[SOD]\cdot\left(\frac{kcatp\_2}{kM\_2\_s3}\cdot["O2-"]-\frac{kcatn\_2}{kM\_2\_s4}\cdot[H2O2]\right)}{1+\frac{["O2-"]}{kM\_2\_s3}+\frac{[H2O2]}{kM\_2\_s4}}}{V_{OMM}}\right)$$

$$-((kass\_3\cdot[H2O2]\cdot["Fe2+"]-kdiss\_3\cdot[ROS]\cdot["Fe3+"]))$$

$$\frac{d(["Fe2+"]\cdot V_{OMM})}{dt} = -((kass\_3\cdot[H2O2]\cdot["Fe2+"]-kdiss\_3\cdot[ROS]\cdot["Fe3+"]))$$

$$\frac{d(["Fe3+"]\cdot V_{OMM})}{dt} = +((kass\_3\cdot[H2O2]\cdot["Fe2+"]-kdiss\_3\cdot[ROS]\cdot["Fe3+"]))$$

$$\frac{d([ROS]\cdot V_{OMM})}{dt} = +((kass\_3\cdot[H2O2]\cdot["Fe2+"]-kdiss\_3\cdot[ROS]\cdot["Fe3+"]))$$

$$\frac{d(["CYT\ C"]\cdot V_{OMM})}{dt} = -\left(\frac{[BAK\_2]}{kA\_13\_s20+[BAK\_2]}\cdot\frac{kI\_13\_s20}{kI\_13\_s20+[BAK\_2]}\cdot(kass\_13\cdot["CYT\ C"]-kdiss\_13\cdot["-"])\right)$$

$$\frac{d([BAK]\cdot V_{OMM})}{dt} = -2\cdot V_{OMM}\cdot\left(\frac{\frac{[ROS]}{kA\_4\_s7+[ROS]}\cdot\frac{kI\_4\_s7}{kI\_4\_s7+[ROS]}\cdot\left(kass\_4\cdot[BAK]^2-kdiss\_4\cdot[BAK\_2]\right)}{V_{OMM}}\right)$$

$$\frac{d([BAK\_2]\cdot V_{OMM})}{dt} = +V_{OMM}\cdot\left(\frac{\frac{[ROS]}{kA\_4\_s7+[ROS]}\cdot\frac{kI\_4\_s7}{kI\_4\_s7+[ROS]}\cdot\left(kass\_4\cdot[BAK]^2-kdiss\_4\cdot[BAK\_2]\right)}{V_{OMM}}\right)$$

$$\frac{d(["-"]\cdot V_{CELL})}{dt} = +\left(\frac{\frac{[BAK\_2]}{kA\_13\_s20+[BAK\_2]}\cdot kI\_13\_s20}{kI\_13\_s20+[BAK\_2]}\cdot(kass\_13\cdot["CYT\ C"]-kdiss\_13\cdot["-"])\right)$$

$$\frac{d([APOPTOSIS]\cdot V_{CELL})}{dt} = +V_{CELL}\cdot\left(\frac{kass\_6\cdot["CASPASE\text{-}3"]-kdiss\_6\cdot[APOPTOSIS]}{V_{CELL}}\right)$$
$$+(kass\_10\cdot["DNA\ FRAGMENTATION"]-kdiss\_10\cdot[APOPTOSIS])$$

$$\frac{d([SMAC\{OMM\}]\cdot V_{OMM})}{dt} = -\left(\frac{\frac{[BAK\_2]}{kA\_12\_s20+[BAK\_2]}\cdot kI\_12\_s20}{kI\_12\_s20+[BAK\_2]}\cdot(kass\_12\cdot[SMAC\{OMM\}]-kdiss\_12\cdot[SMAC\{CELL\}])\right)$$

$$\frac{d([SMAC\{CELL\}]\cdot V_{CELL})}{dt} = +\left(\frac{\frac{[BAK\_2]}{kA\_12\_s20+[BAK\_2]}\cdot kI\_12\_s20}{kI\_12\_s20+[BAK\_2]}\cdot(kass\_12\cdot[SMAC\{OMM\}]-kdiss\_12\cdot[SMAC\{CELL\}])\right)$$

$$\frac{d([AIF\{OMM\}]\cdot V_{OMM})}{dt} = -\left(\frac{\frac{[BAK\_2]}{kA\_11\_s20+[BAK\_2]}\cdot kI\_11\_s20}{kI\_11\_s20+[BAK\_2]}\cdot(kass\_11\cdot[AIF\{OMM\}]-kdiss\_11\cdot[AIF\{CELL\}])\right)$$

$$\frac{d([AIF\{CELL\}]\cdot V_{CELL})}{dt} = -((kass\_8\cdot[AIF\{CELL\}]-kdiss\_8\cdot[AIF\{NUCLEUS\}]))$$
$$+\left(\frac{\frac{[BAK\_2]}{kA\_11\_s20+[BAK\_2]}\cdot kI\_11\_s20}{kI\_11\_s20+[BAK\_2]}\cdot(kass\_11\cdot[AIF\{OMM\}]-kdiss\_11\cdot[AIF\{CELL\}])\right)$$

$$\frac{d([AIF\{NUCLEUS\}]\cdot V_{NUCLEUS})}{dt} = +((kass\_8\cdot[AIF\{CELL\}]-kdiss\_8\cdot[AIF\{NUCLEUS\}]))$$
$$-V_{NUCLEUS}\cdot\left(\frac{kass\_9\cdot[AIF\{NUCLEUS\}]-kdiss\_9\cdot["DNA\ FRAGMENTATION"]}{V_{NUCLEUS}}\right)$$

$$\frac{d(["DNA\ FRAGMENTATION"]\cdot V_{NUCLEUS})}{dt} = +V_{NUCLEUS}\cdot\left(\frac{kass\_9\cdot[AIF\{NUCLEUS\}]-kdiss\_9\cdot["DNA\ FRAGMENTATION"]}{V_{NUCLEUS}}\right)$$
$$-(kass\_10\cdot["DNA\ FRAGMENTATION"]-kdiss\_10\cdot[APOPTOSIS])$$

$$\frac{d(["CASPASE\text{-}3"]\cdot V_{CELL})}{dt} = -V_{CELL}\cdot\left(\frac{kass\_6\cdot["CASPASE\text{-}3"]-kdiss\_6\cdot[APOPTOSIS]}{V_{CELL}}\right)$$

Model B Equations

$$\frac{d([ROOH]\cdot V_{Mitochondria})}{dt} = +V_{Mitochondria}\cdot\left(\frac{kass\_1\cdot[R]\cdot["Fe2+"]-kdiss\_1\cdot[ROOH]\cdot["Fe3+\{Mitochondria\}"]}{V_{Mitochondria}}\right) -((kass\_2\cdot[ROOH]-kdiss\_2\cdot[ROS]))$$

$$\frac{d([R]\cdot V_{Mitochondria})}{dt} = -V_{Mitochondria}\cdot\left(\frac{kass\_1\cdot[R]\cdot["Fe2+"]-kdiss\_1\cdot[ROOH]\cdot["Fe3+\{Mitochondria\}"]}{V_{Mitochondria}}\right)$$

$$\frac{d([ROS]\cdot V_{Mitochondria})}{dt} = +((kass\_2\cdot[ROOH]-kdiss\_2\cdot[ROS]))$$

$$\frac{d([Ferroptosis]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{kass\_18\cdot["Lipid\ Peroxidation"]-kdiss\_18\cdot[Ferroptosis]}{V_{default}}\right)$$

$$\frac{d([PUFA]\cdot V_{Mitochondria})}{dt} = -\left(\frac{\frac{[ROS]}{kA\_3\_s10+[ROS]}\cdot kI\_3\_s10}{kI\_3\_s10+[ROS]}\cdot(kass\_3\cdot[PUFA]-kdiss\_3\cdot["PUFA\text{-}OOH"])\right)$$

$$\frac{d(["PUFA\text{-}OOH"]\cdot V_{Mitochondria})}{dt} = +\left(\frac{\frac{[ROS]}{kA\_3\_s10+[ROS]}\cdot kI\_3\_s10}{kI\_3\_s10+[ROS]}\cdot(kass\_3\cdot[PUFA]-kdiss\_3\cdot["PUFA\text{-}OOH"])\right) -((kass\_4\cdot["PUFA\text{-}OOH"]-kdiss\_4\cdot["Lipid\ Peroxidation"]))$$

$$\frac{d([GSH]\cdot V_{Mitochondria})}{dt} = +V_{Mitochondria}\cdot\left(\frac{kass\_6\cdot[glutamate]\cdot[cysteine\{Mitochondria\}]-kdiss\_6\cdot[GSH]}{V_{Mitochondria}}\right) -V_{Mitochondria}\cdot\left(\frac{kass\_19\cdot[GPX4]\cdot[GSH]-kdiss\_19\cdot[s87]}{V_{Mitochondria}}\right)$$

$$\frac{d([glutamate]\cdot V_{Mitochondria})}{dt} = -V_{Mitochondria}\cdot\left(\frac{kass\_6\cdot[glutamate]\cdot[cysteine\{Mitochondria\}]-kdiss\_6\cdot[GSH]}{V_{Mitochondria}}\right)$$

$$\frac{d([cysteine\{default\}]\cdot V_{default})}{dt} = -(kass\_15\cdot[cysteine\{default\}]\cdot["System\ Xc\text{-}"]-kdiss\_15\cdot[cysteine\{Mitochondria\}]\cdot["System\ Xc\text{-}"])$$

$$\frac{d([cysteine\{Mitochondria\}]\cdot V_{Mitochondria})}{dt} = -V_{Mitochondria}\cdot\left(\frac{kass\_6\cdot[glutamate]\cdot[cysteine\{Mitochondria\}]-kdiss\_6\cdot[GSH]}{V_{Mitochondria}}\right) +(kass\_15\cdot[cysteine\{default\}]\cdot["System\ Xc\text{-}"]-kdiss\_15\cdot[cysteine\{Mitochondria\}]\cdot["System\ Xc\text{-}"])$$

$$\frac{d(["Fe3+\{default\}"]\cdot V_{default})}{dt} = -(kass\_8\cdot["Fe3+\{default\}"]\cdot[TFR4C]-kdiss\_8\cdot["Fe3+\{Mitochondria\}"]\cdot[TFR4C])$$

$$\frac{d(["Fe3+\{Mitochondria\}"]\cdot V_{Mitochondria})}{dt} = +(kass\_8\cdot["Fe3+\{default\}"]\cdot[TFR4C]-kdiss\_8\cdot["Fe3+\{Mitochondria\}"]\cdot[TFR4C]) +V_{Mitochondria}\cdot\left(\frac{kass\_1\cdot[R]\cdot["Fe2+"]-kdiss\_1\cdot[ROOH]\cdot["Fe3+\{Mitochondria\}"]}{V_{Mitochondria}}\right) -V_{Mitochondria}\cdot\left(\frac{[STEAP3]\cdot\left(\frac{kcatp\_9}{kM\_9\_s51}\cdot["Fe3+\{Mitochondria\}"]-\frac{kcatn\_9}{kM\_9\_s53}\cdot["Fe2+"]\right)}{1+\frac{["Fe3+\{Mitochondria\}"]}{kM\_9\_s51}+\frac{["Fe2+"]}{kM\_9\_s53}}\right)$$

$$\frac{d(["Fe2+"]\cdot V_{Mitochondria})}{dt} = -V_{Mitochondria}\cdot\left(\frac{kass\_1\cdot[R]\cdot["Fe2+"]-kdiss\_1\cdot[ROOH]\cdot["Fe3+\{Mitochondria\}"]}{V_{Mitochondria}}\right) +V_{Mitochondria}\cdot\left(\frac{[STEAP3]\cdot\left(\frac{kcatp\_9}{kM\_9\_s51}\cdot["Fe3+\{Mitochondria\}"]-\frac{kcatn\_9}{kM\_9\_s53}\cdot["Fe2+"]\right)}{1+\frac{["Fe3+\{Mitochondria\}"]}{kM\_9\_s51}+\frac{["Fe2+"]}{kM\_9\_s53}}\right)$$

$$\frac{d([\text{"HMG-CoA"}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\left[\text{"HMG-CoA Reductase"}\right]\cdot\left(\frac{kcatp\_11}{kM\_11\_s54}\cdot[\text{"HMG-CoA"}]-\frac{kcatn\_11}{kM\_11\_s55}\cdot[\text{Mevalonate}]\right)}{1+\frac{[\text{"HMG-CoA"}]}{kM\_11\_s54}+\frac{[\text{Mevalonate}]}{kM\_11\_s55}}\right)\Big/V_{default}$$

$$\frac{d([\text{Mevalonate}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{kcatp\_12\cdot[\text{"Mevalonate kinase"}]\cdot[\text{Mevalonate}]\cdot[\text{ATP}]}{ki\_12\_s75\cdot kM\_12\_s75}-\frac{kcatn\_12\cdot[\text{"Mevalonate kinase"}]\cdot[\text{"Mevalonate-5-P"}]\cdot[\text{ADP}]}{ki\_12\_s76\cdot kM\_12\_s69}}{1+\frac{[\text{Mevalonate}]}{ki\_12\_s75}+\frac{[\text{ATP}]}{ki\_12\_s75}+\frac{[\text{"Mevalonate-5-P"}]}{ki\_12\_s69}+\frac{[\text{ADP}]}{ki\_12\_s76}+\frac{[\text{"Mevalonate-5-P"}]\cdot[\text{ADP}]}{ki\_12\_s76\cdot kM\_12\_s69}+\frac{[\text{Mevalonate}]\cdot[\text{ATP}]}{ki\_12\_s75\cdot kM\_12\_s75}}\right)\Big/V_{default}$$

$$+V_{default}\cdot\left(\frac{\left[\text{"HMG-CoA Reductase"}\right]\cdot\left(\frac{kcatp\_11}{kM\_11\_s54}\cdot[\text{"HMG-CoA"}]-\frac{kcatn\_11}{kM\_11\_s55}\cdot[\text{Mevalonate}]\right)}{1+\frac{[\text{"HMG-CoA"}]}{kM\_11\_s54}+\frac{[\text{Mevalonate}]}{kM\_11\_s55}}\right)\Big/V_{default}$$

$$\frac{d([\text{"Mevalonate-5-P"}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{kcatp\_13\cdot[\text{"Phosphomevalonate kinase"}]\cdot[\text{"Mevalonate-5-P"}]\cdot[\text{ATP}]}{ki\_13\_s75\cdot kM\_13\_s75}-\frac{kcatn\_13\cdot[\text{"Phosphomevalonate kinase"}]\cdot[\text{"Mevalonate-5-PP"}]\cdot[\text{ADP}]}{ki\_13\_s76\cdot kM\_13\_s70}}{1+\frac{[\text{"Mevalonate-5-P"}]}{ki\_13\_s75}+\frac{[\text{ATP}]}{ki\_13\_s75}+\frac{[\text{"Mevalonate-5-PP"}]}{ki\_13\_s70}+\frac{[\text{ADP}]}{ki\_13\_s76}+\frac{[\text{"Mevalonate-5-PP"}]\cdot[\text{ADP}]}{ki\_13\_s76\cdot kM\_13\_s70}+\frac{[\text{"Mevalonate-5-P"}]\cdot[\text{ATP}]}{ki\_13\_s75\cdot kM\_13\_s75}}\right)\Big/V_{default}$$

$$+V_{default}\cdot\left(\frac{\frac{kcatp\_12\cdot[\text{"Mevalonate kinase"}]\cdot[\text{Mevalonate}]\cdot[\text{ATP}]}{ki\_12\_s75\cdot kM\_12\_s75}-\frac{kcatn\_12\cdot[\text{"Mevalonate kinase"}]\cdot[\text{"Mevalonate-5-P"}]\cdot[\text{ADP}]}{ki\_12\_s76\cdot kM\_12\_s69}}{1+\frac{[\text{Mevalonate}]}{ki\_12\_s75}+\frac{[\text{ATP}]}{ki\_12\_s75}+\frac{[\text{"Mevalonate-5-P"}]}{ki\_12\_s69}+\frac{[\text{ADP}]}{ki\_12\_s76}+\frac{[\text{"Mevalonate-5-P"}]\cdot[\text{ADP}]}{ki\_12\_s76\cdot kM\_12\_s69}+\frac{[\text{Mevalonate}]\cdot[\text{ATP}]}{ki\_12\_s75\cdot kM\_12\_s75}}\right)\Big/V_{default}$$

$$\frac{d([\text{"Mevalonate-5-PP"}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{-\frac{}{ki\_13\_s75\cdot kM\_13\_s75}-\frac{}{ki\_13\_s76\cdot kM\_13\_s70}}{1+\frac{[\text{"Mevalonate-5-P"}]}{ki\_13\_s75}+\frac{[\text{ATP}]}{ki\_13\_s75}+\frac{[\text{"Mevalonate-5-PP"}]}{ki\_13\_s70}+\frac{[\text{ADP}]}{ki\_13\_s76}+\frac{[\text{"Mevalonate-5-PP"}]\cdot[\text{ADP}]}{ki\_13\_s76\cdot kM\_13\_s70}+\frac{[\text{"Mevalonate-5-P"}]\cdot[\text{ATP}]}{ki\_13\_s75\cdot kM\_13\_s75}}\right)\Big/V_{default}$$

$$-V_{default}\cdot\left(\frac{\left[\text{"Mevalonate-5-PP decarboxylase"}\right]\cdot\left(\frac{kcatp\_14}{kM\_14\_s70}\cdot[\text{"Mevalonate-5-PP"}]-\frac{kcatn\_14}{kM\_14\_s71}\cdot[\text{IPP}]\right)}{1+\frac{[\text{"Mevalonate-5-PP"}]}{kM\_14\_s70}+\frac{[\text{IPP}]}{kM\_14\_s71}}\right)\Big/V_{default}$$

$$\frac{d([\text{IPP}]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\left[\text{"Mevalonate-5-PP decarboxylase"}\right]\cdot\left(\frac{kcatp\_14}{kM\_14\_s70}\cdot[\text{"Mevalonate-5-PP"}]-\frac{kcatn\_14}{kM\_14\_s71}\cdot[\text{IPP}]\right)}{1+\frac{[\text{"Mevalonate-5-PP"}]}{kM\_14\_s70}+\frac{[\text{IPP}]}{kM\_14\_s71}}\right)\Big/V_{default}$$

$$\frac{d([\text{ATP}]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{kcatp\_13\cdot[\text{"Phosphomevalonate kinase"}]\cdot[\text{"Mevalonate-5-P"}]\cdot[\text{ATP}]}{ki\_13\_s75\cdot kM\_13\_s75}-\frac{kcatn\_13\cdot[\text{"Phosphomevalonate kinase"}]\cdot[\text{"Mevalonate-5-PP"}]\cdot[\text{ADP}]}{ki\_13\_s76\cdot kM\_13\_s70}}{1+\frac{[\text{"Mevalonate-5-P"}]}{ki\_13\_s75}+\frac{[\text{ATP}]}{ki\_13\_s75}+\frac{[\text{"Mevalonate-5-PP"}]}{ki\_13\_s70}+\frac{[\text{ADP}]}{ki\_13\_s76}+\frac{[\text{"Mevalonate-5-PP"}]\cdot[\text{ADP}]}{ki\_13\_s76\cdot kM\_13\_s70}+\frac{[\text{"Mevalonate-5-P"}]\cdot[\text{ATP}]}{ki\_13\_s75\cdot kM\_13\_s75}}\right)\Big/V_{default}$$

$$-V_{default}\cdot\left(\frac{\frac{kcatp\_12\cdot[\text{"Mevalonate kinase"}]\cdot[\text{Mevalonate}]\cdot[\text{ATP}]}{ki\_12\_s75\cdot kM\_12\_s75}-\frac{kcatn\_12\cdot[\text{"Mevalonate kinase"}]\cdot[\text{"Mevalonate-5-P"}]\cdot[\text{ADP}]}{ki\_12\_s76\cdot kM\_12\_s69}}{1+\frac{[\text{Mevalonate}]}{ki\_12\_s75}+\frac{[\text{ATP}]}{ki\_12\_s75}+\frac{[\text{"Mevalonate-5-P"}]}{ki\_12\_s69}+\frac{[\text{ADP}]}{ki\_12\_s76}+\frac{[\text{"Mevalonate-5-P"}]\cdot[\text{ADP}]}{ki\_12\_s76\cdot kM\_12\_s69}+\frac{[\text{Mevalonate}]\cdot[\text{ATP}]}{ki\_12\_s75\cdot kM\_12\_s75}}\right)\Big/V_{default}$$

$$\frac{d([ADP]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{ki\_13\_s75\cdot kM\_13\_s75}{1+\frac{["Mevalonate\text{-}5\text{-}P"]}{ki\_13\_s75}+\frac{[ATP]}{ki\_13\_s75}+\frac{["Mevalonate\text{-}5\text{-}PP"]}{ki\_13\_s70}+\frac{[ADP]}{ki\_13\_s76}+\frac{["Mevalonate\text{-}5\text{-}PP"]\cdot[ADP]}{ki\_13\_s76\cdot kM\_13\_s70}+\frac{["Mevalonate\text{-}5\text{-}P"]\cdot[ATP]}{ki\_13\_s75\cdot kM\_13\_s75}}\cdot\frac{kcatp\_12\cdot["Mevalonate\ kinase"]\cdot[Mevalonate]\cdot[ATP]}{ki\_12\_s75\cdot kM\_12\_s75}-\frac{ki\_13\_s76\cdot kM\_13\_s70}{1+\frac{[Mevalonate]}{ki\_12\_s75}+\frac{[ATP]}{ki\_12\_s75}+\frac{["Mevalonate\text{-}5\text{-}P"]}{ki\_12\_s69}+\frac{[ADP]}{ki\_12\_s76}+\frac{["Mevalonate\text{-}5\text{-}P"]\cdot[ADP]}{ki\_12\_s76\cdot kM\_12\_s69}+\frac{[Mevalonate]\cdot[ATP]}{ki\_12\_s75\cdot kM\_12\_s75}}\cdot\frac{kcatn\_12\cdot["Mevalonate\ kinase"]\cdot["Mevalonate\text{-}5\text{-}P"]\cdot[ADP]}{ki\_12\_s76\cdot kM\_12\_s69}}{V_{default}}\right)$$

$$+V_{default}\cdot\left(\frac{\frac{kcatp\_12\cdot["Mevalonate\ kinase"]\cdot[Mevalonate]\cdot[ATP]}{ki\_12\_s75\cdot kM\_12\_s75}-\frac{kcatn\_12\cdot["Mevalonate\ kinase"]\cdot["Mevalonate\text{-}5\text{-}P"]\cdot[ADP]}{ki\_12\_s76\cdot kM\_12\_s69}}{1+\frac{[Mevalonate]}{ki\_12\_s75}+\frac{[ATP]}{ki\_12\_s75}+\frac{["Mevalonate\text{-}5\text{-}P"]}{ki\_12\_s69}+\frac{[ADP]}{ki\_12\_s76}+\frac{["Mevalonate\text{-}5\text{-}P"]\cdot[ADP]}{ki\_12\_s76\cdot kM\_12\_s69}+\frac{[Mevalonate]\cdot[ATP]}{ki\_12\_s75\cdot kM\_12\_s75}}\cdot\frac{1}{V_{default}}\right)$$

$$\frac{d([GPX4]\cdot V_{Mitochondria})}{dt} = +\left(\frac{["flavenoids,\ polyphenols,\ phenylpropanoids"]}{kA\_5\_s17+["flavenoids,\ polyphenols,\ phenylpropanoids"]}\cdot kI\_5\_s17}{kI\_5\_s17+["flavenoids,\ polyphenols,\ phenylpropanoids"]}\cdot(kass\_5\cdot[NRF2]-kdiss\_5\cdot[GPX4])\right)$$

$$-V_{Mitochondria}\cdot\left(\frac{kass\_19\cdot[GPX4]\cdot[GSH]-kdiss\_19\cdot[s87]}{V_{Mitochondria}}\right)$$

$$\frac{d([CoQ10]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{\frac{[IPP]}{kA\_16\_s71+[IPP]}\cdot kI\_16\_s71}{kI\_16\_s71+[IPP]}\cdot(kass\_16\cdot[CoQ10]-kdiss\_16\cdot["CoQ10\text{-}H2"])}{V_{default}}\right)$$

$$\frac{d(["CoQ10\text{-}H2"]\cdot V_{default})}{dt} = +V_{default}\cdot\left(\frac{\frac{[IPP]}{kA\_16\_s71+[IPP]}\cdot kI\_16\_s71}{kI\_16\_s71+[IPP]}\cdot(kass\_16\cdot[CoQ10]-kdiss\_16\cdot["CoQ10\text{-}H2"])}{V_{default}}\right)$$

$$\frac{d(["Lipid\ Peroxidation"]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{kass\_18\cdot["Lipid\ Peroxidation"]-kdiss\_18\cdot[Ferroptosis]}{V_{default}}\right)$$

$$+((kass\_4\cdot["PUFA\text{-}OOH"]-kdiss\_4\cdot["Lipid\ Peroxidation"]))$$

$$\frac{d([s87]\cdot V_{Mitochondria})}{dt} = +V_{Mitochondria}\cdot\left(\frac{kass\_19\cdot[GPX4]\cdot[GSH]-kdiss\_19\cdot[s87]}{V_{Mitochondria}}\right)$$

$$\frac{d([NRF2]\cdot V_{Mitochondria})}{dt} = -\left(\frac{["flavenoids,\ polyphenols,\ phenylpropanoids"]}{kA\_5\_s17+["flavenoids,\ polyphenols,\ phenylpropanoids"]}\cdot kI\_5\_s17}{kI\_5\_s17+["flavenoids,\ polyphenols,\ phenylpropanoids"]}\cdot(kass\_5\cdot[NRF2]-kdiss\_5\cdot[GPX4])\right)$$

Model C Equations

$$\frac{d([\text{"ASYN\{"SUBSTANTIA NIGRA"\}"}]\cdot V_{\text{"SUBSTANTIA NIGRA"}})}{dt} = -2\cdot\left(\frac{[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}]}{kA\_7\_s31+[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}]}\cdot kI\_7\_s31}{kI\_7\_s31+[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}]}\cdot(kass\_7\cdot[\text{"ASYN\{"SUBSTANTIA NIGRA"\}"}]^2-kdiss\_7\cdot[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}])\right)$$

$$\frac{d([BUTYRATE]\cdot V_{\text{"GI TRACT/ GUT"}})}{dt} = +((kass\_5\cdot[\text{"DIETARY FIBER"}]-kdiss\_5\cdot[BUTYRATE]))$$

$$\frac{d([\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]\cdot V_{\text{"IMMUNE CELL"}})}{dt} = +V_{\text{"IMMUNE CELL"}}\cdot\left(\frac{kass\_4\cdot[NFKB]-kdiss\_4\cdot[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}{V_{\text{"IMMUNE CELL"}}}\right)$$
$$+V_{\text{"IMMUNE CELL"}}\cdot\left(\frac{kass\_3\cdot[TLR4]-kdiss\_3\cdot[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}{V_{\text{"IMMUNE CELL"}}}\right)$$

$$\frac{d([NFKB]\cdot V_{\text{"IMMUNE CELL"}})}{dt} = -V_{\text{"IMMUNE CELL"}}\cdot\left(\frac{kass\_4\cdot[NFKB]-kdiss\_4\cdot[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}{V_{\text{"IMMUNE CELL"}}}\right)$$

$$\frac{d([LPS]\cdot V_{\text{"GI TRACT/ GUT"}})}{dt} = -\left(\frac{[\text{"HIGH FAT DIET"}]}{kA\_2\_s34+[\text{"HIGH FAT DIET"}]}\cdot kI\_2\_s34}{kI\_2\_s34+[\text{"HIGH FAT DIET"}]}\cdot(kass\_2\cdot[LPS]\cdot[TLR4]-kdiss\_2\cdot[TLR4])\right)$$
$$-\left(\frac{[\text{"HIGH FAT DIET"}]}{kA\_1\_s34+[\text{"HIGH FAT DIET"}]}\cdot kI\_1\_s34}{kI\_1\_s34+[\text{"HIGH FAT DIET"}]}\cdot(kass\_1\cdot[LPS]\cdot[NFKB]-kdiss\_1\cdot[NFKB])\right)$$

$$\frac{d([TLR4]\cdot V_{\text{"IMMUNE CELL"}})}{dt} = -V_{\text{"IMMUNE CELL"}}\cdot\left(\frac{kass\_3\cdot[TLR4]-kdiss\_3\cdot[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}{V_{\text{"IMMUNE CELL"}}}\right)$$

$$\frac{d([\text{"DIETARY FIBER"}]\cdot V_{default})}{dt} = -((kass\_5\cdot[\text{"DIETARY FIBER"}]-kdiss\_5\cdot[BUTYRATE]))$$

$$\frac{d([\text{"ASYN\{"GI TRACT/ GUT"\}"}]\cdot V_{\text{"GI TRACT/ GUT"}})}{dt} = -2\cdot\left(\frac{[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}{kA\_6\_s10+[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}\cdot kI\_6\_s10}{kI\_6\_s10+[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}\cdot(kass\_6\cdot[\text{"ASYN\{"GI TRACT/ GUT"\}"}]^2-kdiss\_6\cdot[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}])\right)$$

$$\frac{d([\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}]\cdot V_{\text{"SUBSTANTIA NIGRA"}})}{dt} = +\left(\frac{[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}]}{kA\_7\_s31+[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}]}\cdot kI\_7\_s31}{kI\_7\_s31+[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}]}\cdot(kass\_7\cdot[\text{"ASYN\{"SUBSTANTIA NIGRA"\}"}]^2-kdiss\_7\cdot[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}])\right)$$

$$\frac{d([dopamine]\cdot V_{\text{"SUBSTANTIA NIGRA"}})}{dt} = -V_{\text{"SUBSTANTIA NIGRA"}}\cdot\left(\frac{\frac{[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}]}{kA\_8\_s33+[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}]}\cdot kI\_8\_s33}{kI\_8\_s33+[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}]}\cdot(kass\_8\cdot[dopamine]-kdiss\_8\cdot[sa31\_degraded])}{V_{\text{"SUBSTANTIA NIGRA"}}}\right)$$

$$\frac{d([sa31\_degraded]\cdot V_{\text{"SUBSTANTIA NIGRA"}})}{dt} = +V_{\text{"SUBSTANTIA NIGRA"}}\cdot\left(\frac{\frac{[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}]}{kA\_8\_s33+[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}]}\cdot kI\_8\_s33}{kI\_8\_s33+[\text{"ASYN\_2\{"SUBSTANTIA NIGRA"\}"}]}\cdot(kass\_8\cdot[dopamine]-kdiss\_8\cdot[sa31\_degraded])}{V_{\text{"SUBSTANTIA NIGRA"}}}\right)$$

$$\frac{d([\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}]\cdot V_{\text{"GI TRACT/ GUT"}})}{dt} = +\left(\frac{[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}{kA\_6\_s10+[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}\cdot kI\_6\_s10}{kI\_6\_s10+[\text{"PROINFLAMMATORY CYTOKINE FORMATION"}]}\cdot(kass\_6\cdot[\text{"ASYN\{"GI TRACT/ GUT"\}"}]^2-kdiss\_6\cdot[\text{"ASYN\_2\{"GI TRACT/ GUT"\}"}])\right)$$

Model D Equations

$$\frac{d([PUFA]\cdot V_{ASTROCYTE})}{dt} = -V_{ASTROCYTE}\cdot\left(\frac{kass\_2\cdot[PUFA]-kdiss\_2\cdot[\text{"PUFA-OOH"}]}{V_{ASTROCYTE}}\right)$$

$$\frac{d([MeHg]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{kass\_1\cdot[MeHg]\cdot[cysteine(default)]-kdiss\_1\cdot[\text{"Cys-HgMe(default)"}]\cdot V_{default}}{V_{default}}\right)$$

$$\frac{d([\text{"Cys-HgMe(default)"}]\cdot V_{default})}{dt} = -(kass\_14\cdot[\text{"Cys-HgMe(default)"}]\cdot V_{default}-kdiss\_14\cdot[\text{"Cys-HgMe(BRAIN)"}])$$
$$+V_{default}\cdot\left(\frac{kass\_1\cdot[MeHg]\cdot[cysteine(default)]-kdiss\_1\cdot[\text{"Cys-HgMe(default)"}]\cdot V_{default}}{V_{default}}\right)$$

$$\frac{d([\text{"OXIDATIVE STRESS(ASTROCYTE)"}]\cdot V_{ASTROCYTE})}{dt} = +V_{ASTROCYTE}\cdot\left(\frac{kass\_6\cdot[\text{"PUFA-OOH"}]-kdiss\_6\cdot[\text{"OXIDATIVE STRESS(ASTROCYTE)"}]}{V_{ASTROCYTE}}\right)$$

$$\frac{d([GSH]\cdot V_{ASTROCYTE})}{dt} = +V_{ASTROCYTE}\cdot\left(\frac{[\text{"GSH Synthetase"}]\cdot\left(\frac{kcatp\_13}{kM\_13\_s44}\cdot[cysteine(ASTROCYTE)]\cdot\frac{kcatn\_13}{kM\_13\_s33}\cdot[GSH]\right)}{1+\frac{[cysteine(ASTROCYTE)]}{kM\_13\_s44}+\frac{[GSH]}{kM\_13\_s33}}}{V_{ASTROCYTE}}\right)$$
$$-V_{ASTROCYTE}\cdot\left(\frac{kass\_5\cdot[GPX4]\cdot[GSH]-kdiss\_5\cdot[s87]}{V_{ASTROCYTE}}\right)$$

$$\frac{d([\text{"PUFA-OOH"}]\cdot V_{ASTROCYTE})}{dt} = -V_{ASTROCYTE}\cdot\left(\frac{kass\_6\cdot[\text{"PUFA-OOH"}]-kdiss\_6\cdot[\text{"OXIDATIVE STRESS(ASTROCYTE)"}]}{V_{ASTROCYTE}}\right)$$
$$+V_{ASTROCYTE}\cdot\left(\frac{kass\_2\cdot[PUFA]-kdiss\_2\cdot[\text{"PUFA-OOH"}]}{V_{ASTROCYTE}}\right)$$

$$\frac{d([cysteine(BRAIN)]\cdot V_{BRAIN})}{dt} = -(kass\_14\cdot[cysteine(BRAIN)]\cdot[\text{"System Xc-"}]-kdiss\_14\cdot[cysteine(ASTROCYTE)]\cdot[\text{"System Xc-"}])$$

$$\frac{d([s87]\cdot V_{ASTROCYTE})}{dt} = +V_{ASTROCYTE}\cdot\left(\frac{kass\_5\cdot[GPX4]\cdot[GSH]-kdiss\_5\cdot[s87]}{V_{ASTROCYTE}}\right)$$

$$\frac{d([GPX4]\cdot V_{ASTROCYTE})}{dt} = -V_{ASTROCYTE}\cdot\left(\frac{kass\_5\cdot[GPX4]\cdot[GSH]-kdiss\_5\cdot[s87]}{V_{ASTROCYTE}}\right)$$

$$\frac{d([\text{"Cys-HgMe(ASTROCYTE)"}]\cdot V_{ASTROCYTE})}{dt} = +(kass\_7\cdot[\text{"Cys-HgMe(BRAIN)"}]\cdot[LAT1]-kdiss\_7\cdot[\text{"Cys-HgMe(ASTROCYTE)"}]\cdot[LAT1])$$

$$\frac{d([cysteine(ASTROCYTE)]\cdot V_{ASTROCYTE})}{dt} = -V_{ASTROCYTE}\cdot\left(\frac{[\text{"GSH Synthetase"}]\cdot\left(\frac{kcatp\_13}{kM\_13\_s44}\cdot[cysteine(ASTROCYTE)]\cdot\frac{kcatn\_13}{kM\_13\_s33}\cdot[GSH]\right)}{1+\frac{[cysteine(ASTROCYTE)]}{kM\_13\_s44}+\frac{[GSH]}{kM\_13\_s33}}}{V_{ASTROCYTE}}\right)$$
$$+(kass\_14\cdot[cysteine(BRAIN)]\cdot[\text{"System Xc-"}]-kdiss\_14\cdot[cysteine(ASTROCYTE)]\cdot[\text{"System Xc-"}])$$

$$\frac{d([\text{"Ca2+(BRAIN)"}]\cdot V_{BRAIN})}{dt} = -(kass\_12\cdot[\text{"Ca2+(BRAIN)"}]\cdot V_{BRAIN}\cdot[NMDA]-kdiss\_12\cdot[\text{"Ca2+(\"POSTSYNAPTIC NERUON\")"}]\cdot[NMDA])$$

$$\frac{d([\text{"Ca2+(\"POSTSYNAPTIC NERUON\")"}]\cdot V_{\text{"POSTSYNAPTIC NERUON"}})}{dt} = +(kass\_12\cdot[\text{"Ca2+(BRAIN)"}]\cdot V_{BRAIN}\cdot[NMDA]-kdiss\_12\cdot[\text{"Ca2+(\"POSTSYNAPTIC NERUON\")"}]\cdot[NMDA])$$
$$-V_{\text{"POSTSYNAPTIC NERUON"}}\cdot\left(\frac{kass\_13\cdot[\text{"Ca2+(\"POSTSYNAPTIC NERUON\")"}]-kdiss\_13\cdot[\text{"OXIDATIVE STRESS(\"POSTSYNAPTIC NERUON\")"}]}{V_{\text{"POSTSYNAPTIC NERUON"}}}\right)$$

$$\frac{d([\text{"OXIDATIVE STRESS(\"POSTSYNAPTIC NERUON\")"}]\cdot V_{\text{"POSTSYNAPTIC NERUON"}})}{dt} = +V_{\text{"POSTSYNAPTIC NERUON"}}\cdot\left(\frac{kass\_13\cdot[\text{"Ca2+(\"POSTSYNAPTIC NERUON\")"}]-kdiss\_13\cdot[\text{"OXIDATIVE STRESS(\"POSTSYNAPTIC NERUON\")"}]}{V_{\text{"POSTSYNAPTIC NERUON"}}}\right)$$

$$\frac{d([\text{"Cys-HgMe(BRAIN)"}]\cdot V_{BRAIN})}{dt} = +(kass\_14\cdot[\text{"Cys-HgMe(default)"}]\cdot V_{default}-kdiss\_14\cdot[\text{"Cys-HgMe(BRAIN)"}])$$
$$-(kass\_7\cdot[\text{"Cys-HgMe(BRAIN)"}]\cdot[LAT1]-kdiss\_7\cdot[\text{"Cys-HgMe(ASTROCYTE)"}]\cdot[LAT1])$$

$$\frac{d([glutamate(ASTROCYTE)]\cdot V_{ASTROCYTE})}{dt} = -(kass\_14\cdot[glutamate(ASTROCYTE)]\cdot[\text{"System Xc-"}]-kdiss\_14\cdot[glutamate(BRAIN)]\cdot[\text{"System Xc-"}])$$

$$\frac{d([glutamate(BRAIN)]\cdot V_{BRAIN})}{dt} = +(kass\_14\cdot[glutamate(ASTROCYTE)]\cdot[\text{"System Xc-"}]-kdiss\_14\cdot[glutamate(BRAIN)]\cdot[\text{"System Xc-"}])$$

$$\frac{d([cysteine(default)]\cdot V_{default})}{dt} = -V_{default}\cdot\left(\frac{kass\_1\cdot[MeHg]\cdot[cysteine(default)]-kdiss\_1\cdot[\text{"Cys-HgMe(default)"}]\cdot V_{default}}{V_{default}}\right)$$

Model E Equations

$$\frac{d([LDOPA\{default\}]\cdot V_{default})}{dt} = +(kass\_3\cdot[LDOPA\{PERIPHERY\}]\cdot[LAT1\{PERIPHERY\}]-kdiss\_3\cdot[LDOPA\{default\}]\cdot V_{default}\cdot[LAT1\{PERIPHERY\}])$$
$$-(kass\_2\cdot[LDOPA\{default\}]\cdot V_{default}\cdot[LAT1\{BRAIN\}]-kdiss\_2\cdot[LDOPA\{BRAIN\}]\cdot[LAT1\{BRAIN\}])$$

$$\frac{d([LDOPA\{BRAIN\}]\cdot V_{BRAIN})}{dt} = -V_{BRAIN}\cdot\left(\frac{["DOPA\ DECARBOXYLASE\{BRAIN\}"]\cdot\left(\frac{kcatp\_7}{kM\_7\_s11}\cdot[LDOPA\{BRAIN\}]-\frac{kcatn\_7}{kM\_7\_s29}\cdot[DOPAMINE\{BRAIN\}]\right)}{1+\frac{[LDOPA\{BRAIN\}]}{kM\_7\_s11}+\frac{[DOPAMINE\{BRAIN\}]}{kM\_7\_s29}}\right)$$
$$+(kass\_2\cdot[LDOPA\{default\}]\cdot V_{default}\cdot[LAT1\{BRAIN\}]-kdiss\_2\cdot[LDOPA\{BRAIN\}]\cdot[LAT1\{BRAIN\}])$$

$$\frac{d([LDOPA\{PERIPHERY\}]\cdot V_{PERIPHERY})}{dt} = -V_{PERIPHERY}\cdot\left(\frac{["CATECHOL\text{-}O\text{-}METHYLTRANSFERASE"]\cdot\left(\frac{kcatp\_6}{kM\_6\_s12}\cdot[LDOPA\{PERIPHERY\}]-\frac{kcatn\_6}{kM\_6\_s24}\cdot["3\text{-}O\text{-}METHYLDOPA"]\right)}{1+\frac{[LDOPA\{PERIPHERY\}]}{kM\_6\_s12}+\frac{["3\text{-}O\text{-}METHYLDOPA"]}{kM\_6\_s24}}\right)$$
$$-V_{PERIPHERY}\cdot\left(\frac{["DOPA\ DECARBOXYLASE\{PERIPHERY\}"]\cdot\left(\frac{kcatp\_5}{kM\_5\_s12}\cdot[LDOPA\{PERIPHERY\}]-\frac{kcatn\_5}{kM\_5\_s23}\cdot[DOPAMINE\{PERIPHERY\}]\right)}{1+\frac{[CARBIDOPA]}{KIa\_5}+\left(\frac{[LDOPA\{PERIPHERY\}]}{kM\_5\_s12}+\frac{[DOPAMINE\{PERIPHERY\}]}{kM\_5\_s23}\right)\cdot\left(1+\frac{[CARBIDOPA]}{KIb\_5}\right)}\right)$$
$$-(kass\_3\cdot[LDOPA\{PERIPHERY\}]\cdot[LAT1\{PERIPHERY\}]-kdiss\_3\cdot[LDOPA\{default\}]\cdot V_{default}\cdot[LAT1\{PERIPHERY\}])$$

$$\frac{d([DOPAMINE\{PERIPHERY\}]\cdot V_{PERIPHERY})}{dt} = +V_{PERIPHERY}\cdot\left(\frac{["DOPA\ DECARBOXYLASE\{PERIPHERY\}"]\cdot\left(\frac{kcatp\_5}{kM\_5\_s12}\cdot[LDOPA\{PERIPHERY\}]-\frac{kcatn\_5}{kM\_5\_s23}\cdot[DOPAMINE\{PERIPHERY\}]\right)}{1+\frac{[CARBIDOPA]}{KIa\_5}+\left(\frac{[LDOPA\{PERIPHERY\}]}{kM\_5\_s12}+\frac{[DOPAMINE\{PERIPHERY\}]}{kM\_5\_s23}\right)\cdot\left(1+\frac{[CARBIDOPA]}{KIb\_5}\right)}\right)$$

$$\frac{d(["3\text{-}O\text{-}METHYLDOPA"]\cdot V_{PERIPHERY})}{dt} = +V_{PERIPHERY}\cdot\left(\frac{["CATECHOL\text{-}O\text{-}METHYLTRANSFERASE"]\cdot\left(\frac{kcatp\_6}{kM\_6\_s12}\cdot[LDOPA\{PERIPHERY\}]-\frac{kcatn\_6}{kM\_6\_s24}\cdot["3\text{-}O\text{-}METHYLDOPA"]\right)}{1+\frac{[LDOPA\{PERIPHERY\}]}{kM\_6\_s12}+\frac{["3\text{-}O\text{-}METHYLDOPA"]}{kM\_6\_s24}}\right)$$

$$\frac{d([DOPAMINE\{BRAIN\}]\cdot V_{BRAIN})}{dt} = -V_{BRAIN}\cdot\left(\frac{kass\_8\cdot[DOPAMINE\{BRAIN\}]-kdiss\_8\cdot["RELIEF\ OF\ PD\ MOTOR\ SYMPTOMS"]}{V_{BRAIN}}\right)$$
$$+V_{BRAIN}\cdot\left(\frac{["DOPA\ DECARBOXYLASE\{BRAIN\}"]\cdot\left(\frac{kcatp\_7}{kM\_7\_s11}\cdot[LDOPA\{BRAIN\}]-\frac{kcatn\_7}{kM\_7\_s29}\cdot[DOPAMINE\{BRAIN\}]\right)}{1+\frac{[LDOPA\{BRAIN\}]}{kM\_7\_s11}+\frac{[DOPAMINE\{BRAIN\}]}{kM\_7\_s29}}\right)$$

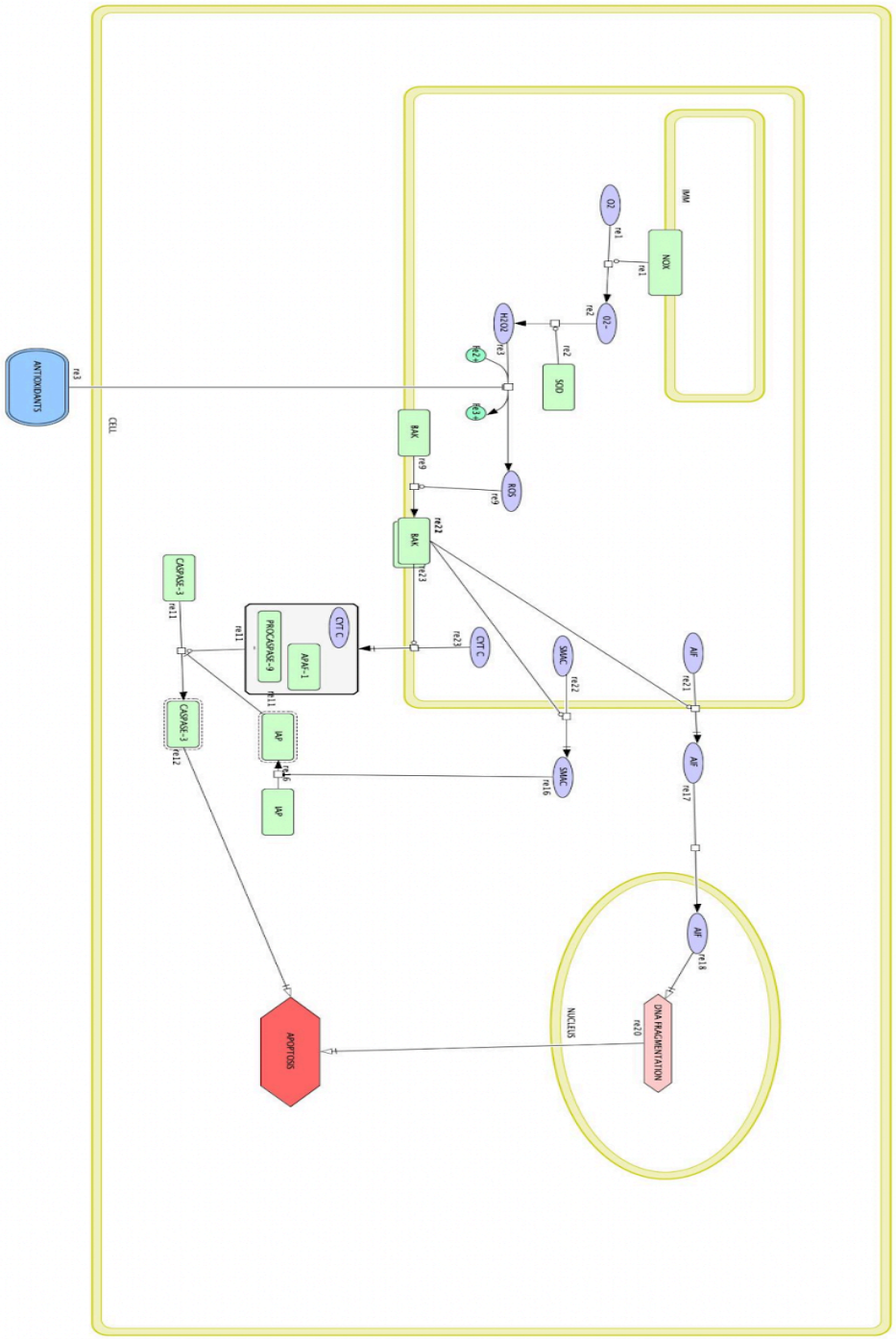
$$\frac{d(["RELIEF\ OF\ PD\ MOTOR\ SYMPTOMS"]\cdot V_{BRAIN})}{dt} = +V_{BRAIN}\cdot\left(\frac{kass\_8\cdot[DOPAMINE\{BRAIN\}]-kdiss\_8\cdot["RELIEF\ OF\ PD\ MOTOR\ SYMPTOMS"]}{V_{BRAIN}}\right)$$

Appendix B: Table of Initial Concentrations

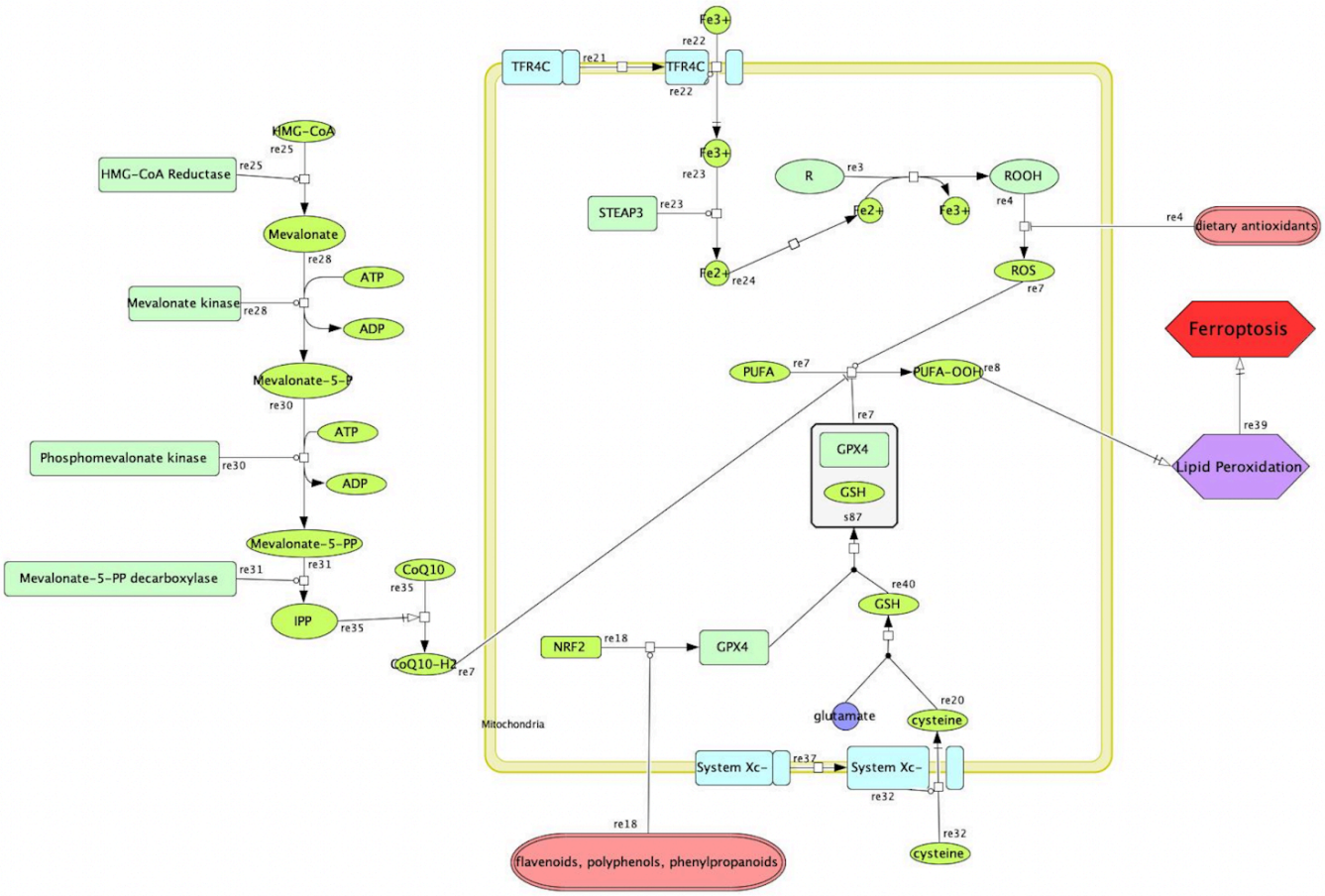
Species	Concentration (M)
NOX5	1.89E-10
SOD2	3.20E-05
BAK	3.01E-08
AIF	9.40E-07
SMAC	3.50E-06
APAF1	2.99E-09
PROCASPASE 9	2.74E-09
CASPASE 3	1.05E-06
Mevalonate Kinase	1.36E-07
Phosphomevalonate kinase	3.51E-06
Mevalonate-5-PP Decarboxylase	4.17E-07
CoQ10	1.09E-06
NRF2	1.57E-08
STEAP3	8.54E-10
TLR4	1.31E-09
NFKB	6.43E-09
ASYN GUT	1.48E-05
CATECHOL-O-METHYLTRANSFERASE	2.60E-06
DOPA DECARBOXYLASE	4.47E-09
GPX4	2.16E-05
KEAP1	1.89E-09
ASYN BRAIN	2.33E-04
NMDA	2.24E-07
GSH Synthetase	1.17E-06
LAT1	4.00E-07
TFR4C	2.39E-07

Appendix C: Model Images

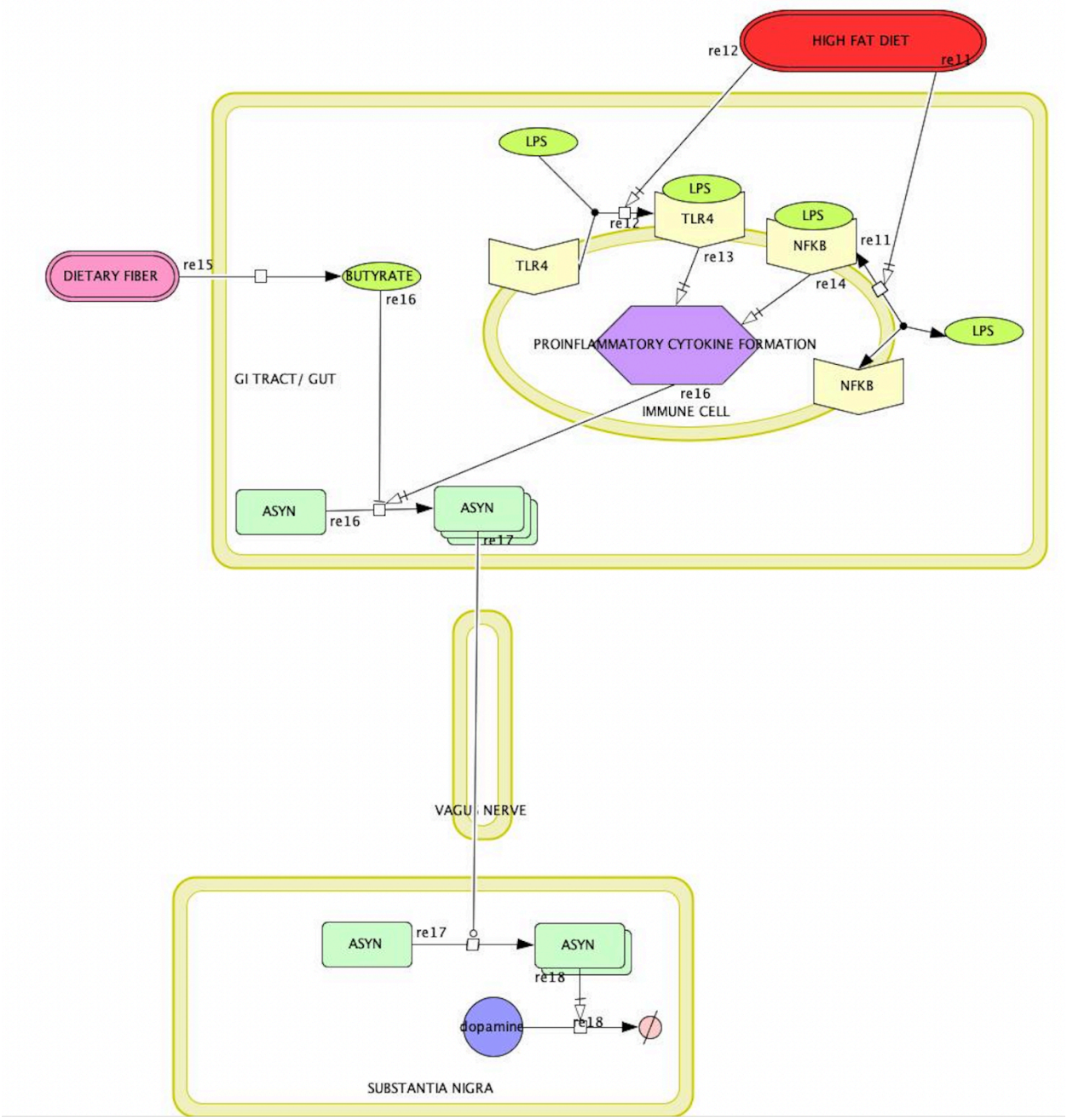
Model A



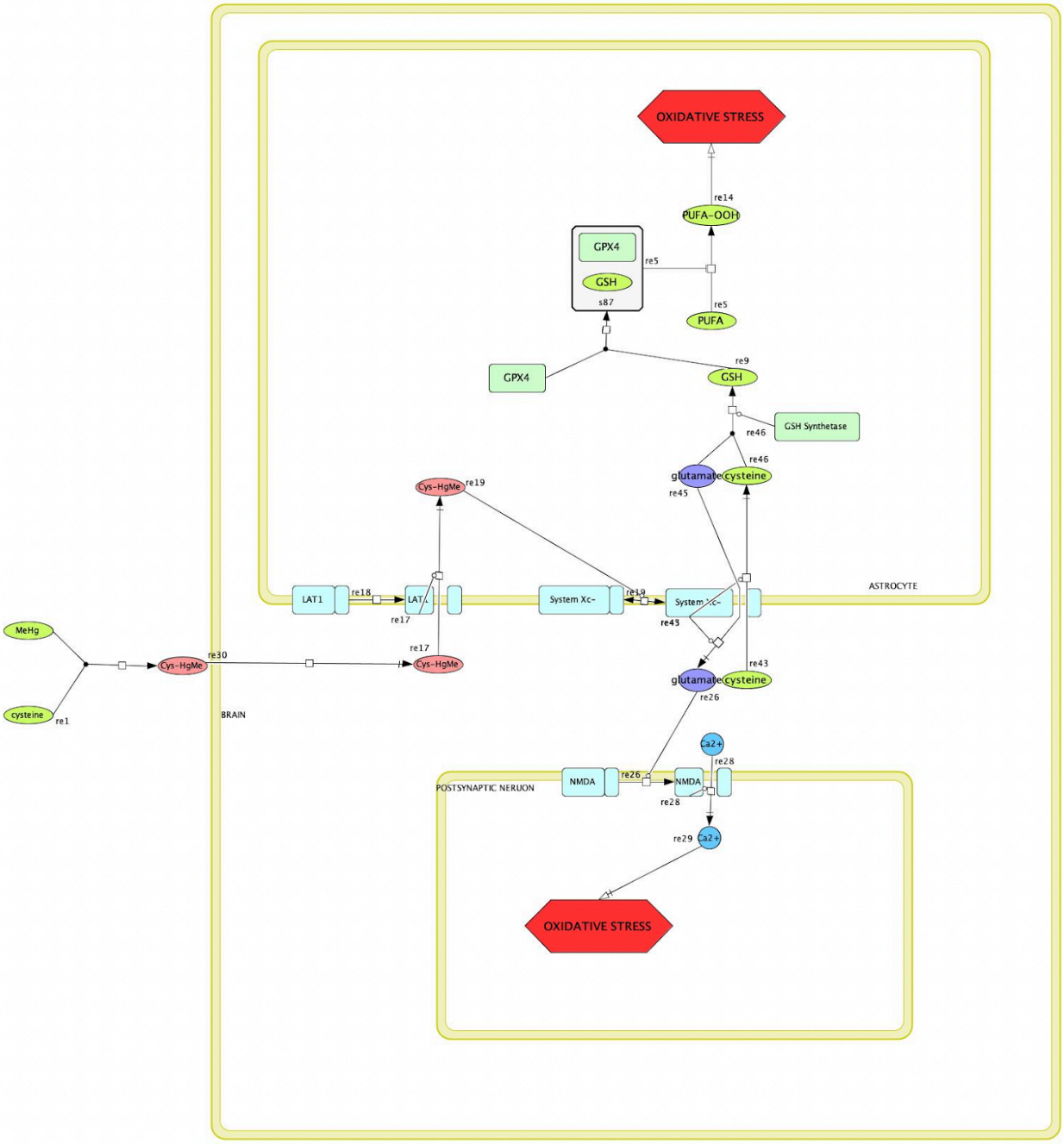
Model B


Fe3+
re22
TFR4C
re21
TFR4C
re22
HMG-CoA
re25
HMG-CoA Reductase
re25
Mevalonate
re28
ATP
Mevalonate kinase
re28
ADP
Mevalonate-5-P
re30
ATP
Phosphomevalonate kinase
re30
ADP
Mevalonate-5-PP
re31
Mevalonate-5-PP decarboxylase
re31
IPP
re35
CoQ10
re35
CoQ10-H2
re7
Fe3+
re23
STEAP3
re23
Fe2+
re24
R
re3
Fe2+
Fe3+
ROOH
re4
re4
dietary antioxidants
ROS
re7
Ferroptosis
PUFA
re7
PUFA-OOH
re8
re7
GPX4
GSH
s87
re39
Lipid Peroxidation
re40
GSH
NRF2
re18
GPX4
glutamate
re20
cysteine
Mitochondria
System Xc-
re37
System Xc-
re32
re18
re32
cysteine
flavenoids, polyphenols, phenylpropanoids

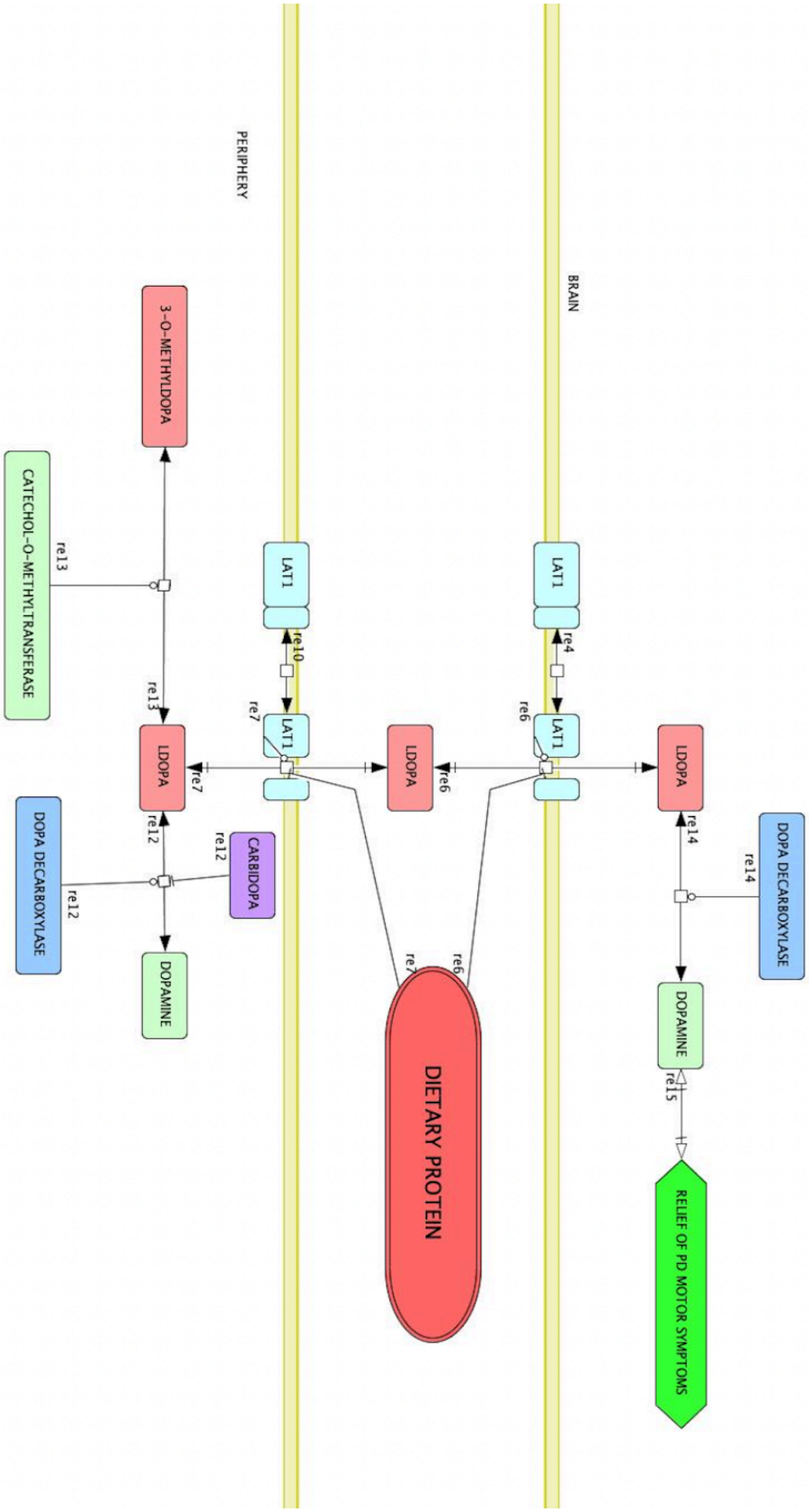
Model C


HIGH FAT DIET
re12
re11
LPS
LPS
TLR4
re12
LPS
NFKB
re11
TLR4
re13
re14
DIETARY FIBER
re15
BUTYRATE
re16
PROINFLAMMATORY CYTOKINE FORMATION
LPS
GI TRACT/ GUT
NFKB
re16
IMMUNE CELL
ASYN
re16
ASYN
re17
VAGUS NERVE
ASYN
re17
ASYN
re18
dopamine
re18
SUBSTANTIA NIGRA

Model D


OXIDATIVE STRESS
re14
PUFA-OOH
GPX4
GSH
s87
re5
re5
PUFA
GPX4
re9
GSH
GSH Synthetase
re46
re46
glutamate
Cysteine
re45
Cys-HgMe
re19
LAT1
re18
LAT1
re17
System Xc-
re19
System Xc-
re43
ASTROCYTE
MeHg
Cys-HgMe
re30
Cys-HgMe
re17
cysteine
re1
BRAIN
re43
glutamate
Cysteine
re26
Ca2+
re28
NMDA
re26
NMDA
re28
POSTSYNAPTIC NERUON
re29
Ca2+
OXIDATIVE STRESS

Model E


PERIPHERY
BRAIN
3-O-METHYLDOPA
CATECHOL-O-METHYLTRANSFERASE
re13
re13
LAT1
re10
re7
LAT1
LDOPA
re7
LDOPA
re12
re12
CARBIDOPA
re12
DOPA DECARBOXYLASE
DOPAMINE
LAT1
re4
re6
LAT1
LDOPA
re6
LDOPA
re14
re14
DOPA DECARBOXYLASE
DOPAMINE
re15
RELIEF OF PD MOTOR SYMPTOMS
re7
re6
DIETARY PROTEIN