Modeling long-term dynamic effects of brain injury on biological mechanisms of potential Parkinson's disease

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Abstract

Parkinson's disease (PD), the second most common neurodegenerative disorder affecting over ten million individuals worldwide, is a multifactorial disease influenced by several biological mechanisms and environmental risk factors. Complex interactions controlled by feedback relationships between neuroinflammation, oxidative damage, mitochondria, protein accumulation, and neuron sub-systems are at the center of the brain. While some lifestyle elements reduce vulnerability, head trauma greatly raises the risk for PD. Trauma-induced neuroinflammation is the most prominent short-term consequence, and due to the intricate structure of brain, multiple variables are affected in long-term. To study those impacts on potential PD progression, we constructed an individual-level system dynamics model of a specific brain region where dopamine-producing neurons reside. After obtaining the normal aging dynamics, various brain injury scenarios are investigated to see whether healthy individuals would exhibit PD-like behaviors. Then, possible genetic variation and/or lifestyle factors such as healthy diet and exercise are tested on both healthy and PD-prone people. Using available qualitative and quantitative data, the model is structurally and behaviorally validated and scenario experiments are carried out.

(7500 words excluding references)

1. INTRODUCTION

The human body in general, and brain in particular, are extremely dynamic closed systems driven by numerous feedback loops. Brain governs several essential mechanisms and serves as the control center of the nervous system. To protect brain, blood-brain barrier separates serum factors and neurotoxins (Abbott et al., 2006). Destroyed neurons cannot be renewed, and the average number of neurons inevitably decreases during aging (Mrak et al., 1997), which results in chemical and functional abnormalities (Peters, 2006). Consequently, the burden of neurodegenerative diseases and the challenges in maintaining brain health rise as the population ages.

Disorders of the nervous system that are characterized by the death of neurons over time are referred to as neurodegenerative diseases (NDs). Parkinson's disease (PD), an idiopathic condition with both motor and non-motor symptoms, is the second most common ND (Sherer et al., 2012). According to Parkinson's Foundation, the total number of people affected by PD is more than 10 million (Parkinson's Disease Foundation, 2022). Based on PD-related mortality from 114 different nations from 1994 to 2019, an estimated 1,064,753 people died (Lampropoulos et al., 2022). In addition to health risks, PD poses a great economic threat since it cost the United States economy $51.9 billion in 2017, and it is expected to rise to $79.1 billion in 2037 (Yang et al., 2020). Available medications only relieve symptoms and cannot prevent or cure the disorder.

Loss of dopaminergic (dopamine-producing) neurons in the substantia nigra of brain and the emergence of abnormal aggregates composed of insoluble alpha-synuclein proteins are the pathological hallmarks of PD (Beitz, 2014). It is a multifaceted disorder influenced by several interacting mechanisms. The accumulation of alpha-synuclein proteins, disruption of protein clearance pathways, mitochondrial dysfunction, oxidative damage, and neuroinflammation are the most prominent and interacting factors (Dauer & Przedborski, 2003; Fujita et al., 2014). Vicious cycles result from the positive feedback among these mechanisms, and PD eventually permanently impairs an individual's brain functions.

While some lifestyle elements such as a healthy diet and regular exercise reduce vulnerability, head trauma greatly increases the risk (Simon et al., 2020). Several NDs have been linked to brain injury, but the greatest evidence points to the development of PD (Delic et al., 2020). Trauma-induced neuroinflammation is the most reasonable explanation for the connection between brain injury and PD (Qian et al., 2010). Following the initial injury, neuroinflammation might last for years in the damaged regions (Schimmel et al., 2017).

A disruption in brain function driven by external factors, such as falls, accidents, or sports-related injuries, is known as traumatic brain injury (TBI). Concussion is the most widespread TBI and its symptoms range from mild to severe. The majority of brain injuries are repetitive and mild, thus, neuroimaging cannot detect them (Briggs et al., 2016). The risk of having PD in later life is 56% greater for veterans with a history of TBI (Delic et al., 2020). The high proportion of TBIs in the United States occurs in men, who are also two times more likely to have PD diagnosed than women (Miller & Cronin-Golomb, 2010; Taylor et al., 2017). Athletes participating in contact sports are frequently at risk of brain injuries and suffering cognitive impairment (Jordan et al., 1997). The link between TBI and PD gained more attention when the world-famous boxer Muhammed Ali was diagnosed with this condition.

The mathematical biology of PD models is classified into three groups: (1) alpha-synuclein aggregation, (2) pathogenesis, and (3) pathology propagation (Bakshi et al., 2019). Alpha-synuclein models try to derive parameters involved in the aggregation, whereas pathogenesis models focus on some or all interactions between alpha-synuclein, dopamine metabolism, and reactive species. Pathology propagation models received less attention due to the complexity of brain anatomy. Existing models typically include one feedback loop in short-term within a limited scope. They tend to have a partial understanding of the system by only focusing on one-way cause-and-effect relationship between variables rather than circular causalities. Depending on the modeling purpose, TBI-related system dynamics models are classified into three categories: (1) acute injury, (2) complex recovery, and (3) care delivery (Kenzie et al., 2022). TBI-related system dynamics models do not consider the potential connection between PD and TBI-induced neuroinflammation.

We aim to construct an individual (patient)-level model of substantia nigra, a region in the brain where dopaminergic neurons reside, to capture the long-term effects of brain injury on potential pathways leading to PD progression. After obtaining the dynamics of a normal aging brain, different brain injury scenarios are examined to see whether healthy individuals develop PD-like behavior. Finally, possible lifestyle factors such as a healthy diet and regular exercise, and potential protective strategies are evaluated on both healthy and PD-prone individuals. Future research on successful therapies and preventative measures is likely to benefit from an understanding of the potential link between PD and TBI, thanks to dynamic simulation models with a systemic approach.

2. MODEL OVERVIEW

Considering the long-term dynamic effects of brain injury on potential PD progression, we determined the key variables and relations of brain that have been consistently at the center of PD pathogenesis research. Thus, model sectors are defined as: (1) neuroinflammation, (2) protein aggregation, (3) dopaminergic neuron, (4) oxidative damage, and (5) mitochondria.

Neuroinflammation represents the inflammatory response within brain. This mechanism is regulated by the generation of inflammatory mediators by microglia cells (DiSabato et al., 2016). Protein aggregation sector depicts the accumulation of toxic forms of alpha-synuclein which is linked to neurodegeneration (Beyer, 2006). Neuron sector stands for the population of dopaminergic neurons in human SN. Oxidative damage sector describes the oxidative stress-induced damage in brain over time and the anti-oxidant mechanism efforts to mitigate this damage. The free radical theory of aging (also known as the oxidative stress theory of aging) is predicated on the notion that age-related functional

declines are caused by oxidative damage (Beckman & Ames, 1998). In contrast to many studies regarding aging as an external factor, we use oxidative damage to endogenously integrate the impact of aging into our research. The last sector, mitochondria, portrays the main source of energy in brain.

Several balancing (B) and reinforcing (R) feedback loops regulate the system. Microglia sense molecules released by dying neurons and become activated (Picca et al., 2021). **Neuronal phagocytosis loop (B1)** enables activated microglia to remove cellular debris of dead neurons (Yin et al., 2017).
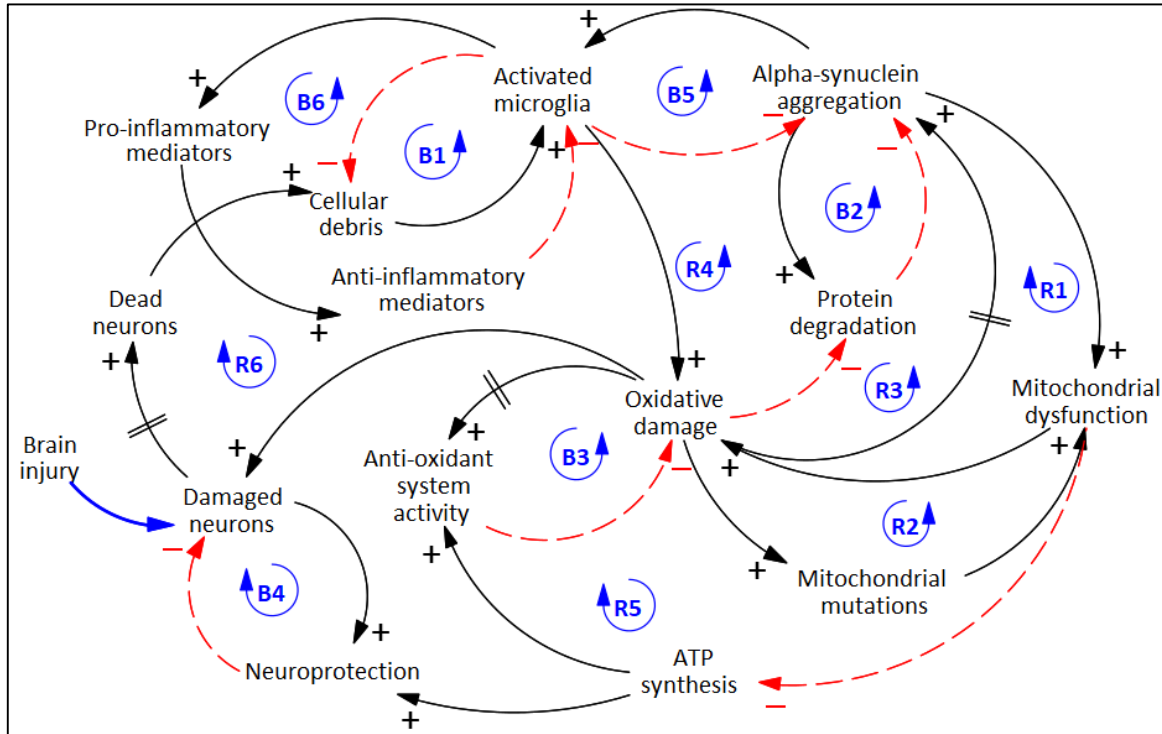
Figure 1 Causal loop diagram

There are two balancing loops controlling the amounts of toxic protein aggregation: **protein degradation loop (B2)**, and **protein phagocytosis loop (B5).** The soluble forms of alpha-synuclein are degraded by protein degradation mechanism (Goldberg, 2003). When aggregated soluble protein levels exceed the cell's elimination ability, they transform into insoluble forms. These substances induce microglial activation and further clearance by phagocytosis (Picca et al., 2021).

In response to oxidative damage, brain has antioxidant defense system (Lee et al., 2010). Glutathione (GSH) is one of the most abundant antioxidants in the brain (Bharath et al., 2002) which is utilized in our model for antioxidant regulation. It reduces reactive species by binding to those metabolites and provides protection (Riederer et al., 1989). Oxidative damage lowers the amount of GSH through this chemical reaction, but in response, antioxidant activity increases to restore GSH to the proper amount. This is the mechanism of **antioxidant regulation loop (B3).**

Neurons cannot be renewed since they are post-mitotic cells. Consequently, neuroprotection is essential for maintaining neuronal health. Brain-derived neurotrophic factor (BDNF) is a key molecule involved in the survival of dopaminergic neurons (Hyman et al., 1991). This molecule is captured in **neuroprotection loop (B4)**.

By producing pro-inflammatory mediators, activated microglia promote an inflammatory response. To limit the adverse effects of excessive inflammation, neuroinflammation is kept under control by anti-inflammatory mediators (Sugimoto et al., 2016). The interaction between microglia and inflammatory mediators is thus described through **neuroinflammation loop (B6).**

Misfolded alpha-synuclein inhibits mitochondrial function and plays a pivotal role in mitochondrial dysfunction (Du et al., 2020). Impaired mitochondria produce increased levels of oxidative stress. The alpha-synuclein proteins are then subjected to oxidation, which amplifies their tendency to form insoluble conformations (Paxinou et al., 2001). This vicious cycle is represented by **mitochondrial oxidative damage loop (R1)**. In addition to oxidizing proteins, oxidative damage also disrupts the protein degradation mechanism (Pajares et al., 2015), which in turn promotes a further positive feedback loop. This secondary loop is presented by **reduced protein degradation loop (R3).**

Another positive loop that adversely impacts mitochondrial function is deletion mutations in mitochondrial DNA (mtDNA) driven by oxidative damage. This is represented in **oxidative damage on mitochondria loop (R2)**. Because mitochondria are very sensitive to oxidative damage, mtDNA deletions accumulate over time. Resulted mitochondrial dysfunction leads to enhanced production of oxidative damage, which in turn increases the generation of mtDNA mutations (Druzhyna et al., 2008).

Considering our research question, neuroinflammation plays an essential role. To defend brain health, acute neuroinflammation clears toxic materials by phagocytosis. However, enzymes necessary for phagocytosis produce reactive species and result in oxidative damage (Dupré-Crochet et al., 2013). If acute neuroinflammation evolves into chronic neuroinflammation, it indicates a self-perpetuating detrimental response (Frank-Cannon et al., 2009). **Neuroinflammatory oxidative damage loop (R4)** depicts this vicious cycle.

Dysfunctional mitochondria are unable to synthesize sufficient Adenosine triphosphate (ATP), the source of energy for use and storage at cellular level. ATP deficiency adversely affects neuroprotection and antioxidant regulation (Sian et al., 1994). Two reinforcing loops resulting from ATP shortage are: **ATP impact on antioxidant capacity loop (R5)**, and **ATP impact on neuroprotection loop (R6).**

3. MODEL DESCRIPTION

The substantia nigra (SN) region in the brain of a healthy 30-year-old individual is simulated up to 80 years of age using a time horizon of 50 years. The simplified stock-flow diagram of the model is given in **Figure 2**. Some real-life variables and relations change rapidly and their dynamics lose their meaning at a month level. To have a model structure that serves our purpose, average levels of most variables are used, instead of instantaneous production or degradation values. The detailed model formulation and stock-flow diagrams are presented in Appendix.

Using values of brain-related variables with autopsy reports poses a great challenge for this study. Post-mortem analyses of normal individuals of various ages are investigated to depict real-life behaviors since instant measurement of changes in the brain is not possible. When those analyses are inadequate, fold changes specified during aging in rodent experimental studies or expert reviews are utilized. By putting together all available knowledge, approximate real reference behaviors for the key variables are established (See model behavior and validation). Comparisons between normal aging and PD are employed to calculate the maximum value parameters and effect function saturation points. Experts believe that if people live long enough, they will all develop Parkinsonian symptoms, thus, it is assumed that PD is an advanced (hence pathological) condition of aging.

3.1. Neuroinflammation Sector

Neuroinflammation sector consists of four stocks: (1) resting microglia, (2) activated microglia, (3) pro-inflammatory mediators, and (4) anti-inflammatory mediators. Microglia can have resting or activated phenotypes depending on the microenvironment in the brain.
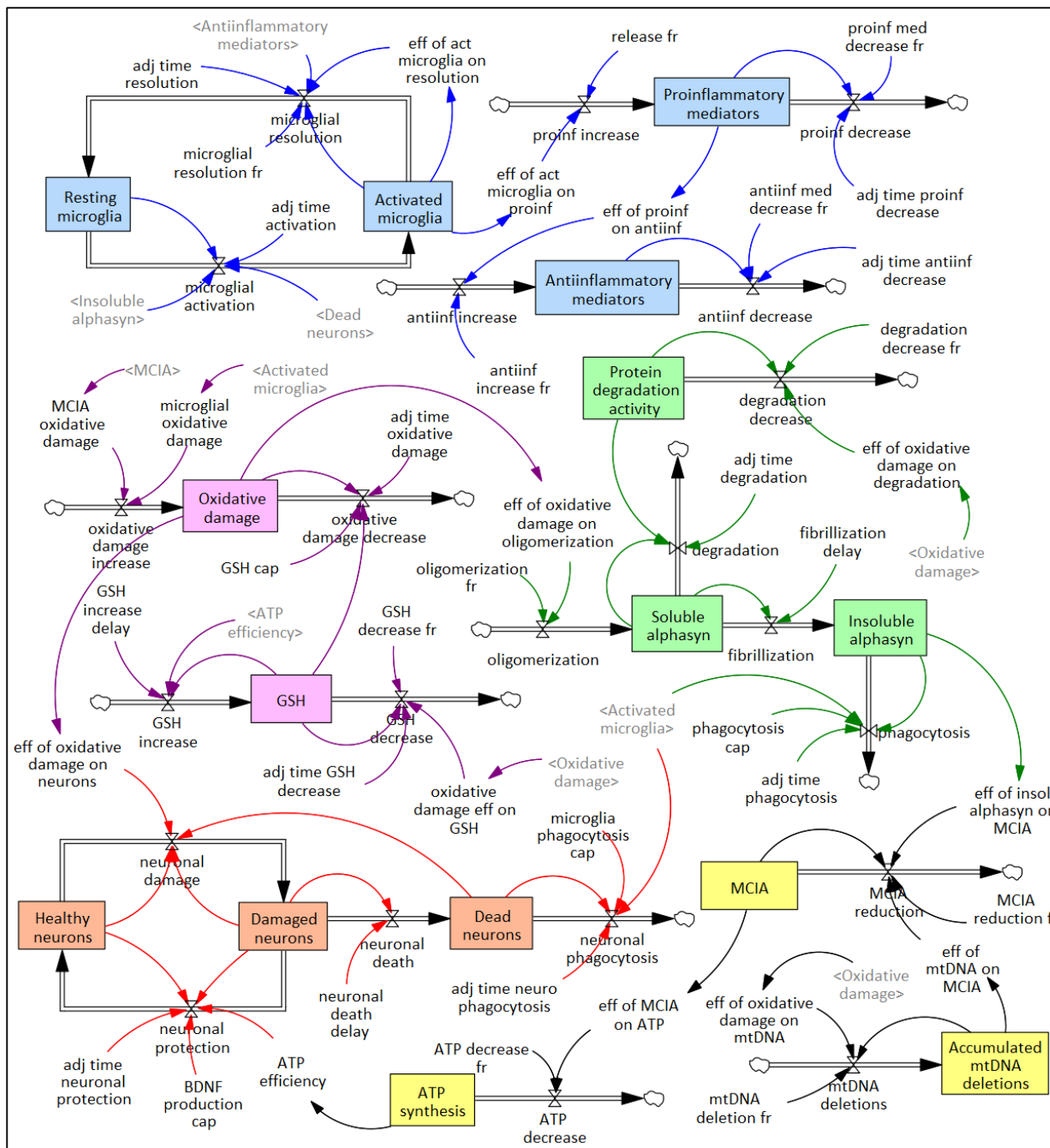
**Figure 2** Simplified stock-flow diagram of the model

There are two flows *microglial activation* and *microglial resolution* regulating the values of microglia stocks. By using several studies including neuronal and microglial densities with microglia phenotypes ratio in mice, we estimated the initial microglia values for human SN (Henry et al., 2009; Lawson et al., 1990; Pakkenberg et al., 1991; Timmer et al., 2007).

Table 1 Neuroinflammation sector stocks

| Stock Name	Initial Value	Unit
Activated microglia	3,319	microglia
Resting microglia	162,664	microglia
Pro-inflammatory mediators	11	pg/mg
Anti-inflammatory mediators	11	pg/mg

Microglial activation can be triggered by either insoluble alpha-synuclein aggregates or dead neurons if there are enough microglia in *resting microglia* stock. *Microglial discrepancy,* the difference between the actual and desired activated microglia levels, influences *microglial resolution* flow. Under normal circumstances, some activated microglia are assumed to be present for brain health. *Resolution fraction* is sensitive to microglial density which is incorporated into the model by *effect of activated microglia on resolution*. Responsible materials for an effective resolution, *anti-inflammatory mediators*, are further multiplied by this fraction.

microglial resolution= MIN((microglial discrepancy/adj time), antiinf mediators*microglial resolution fraction*eff of activated microglia on resolution)
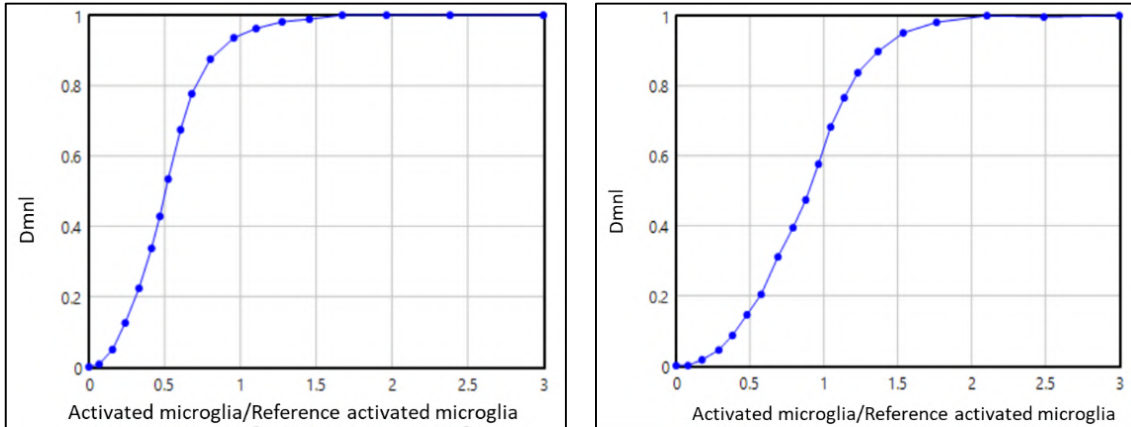
(a)Microglia effect on resolution

(b)Microglia effect on pro-inflammation
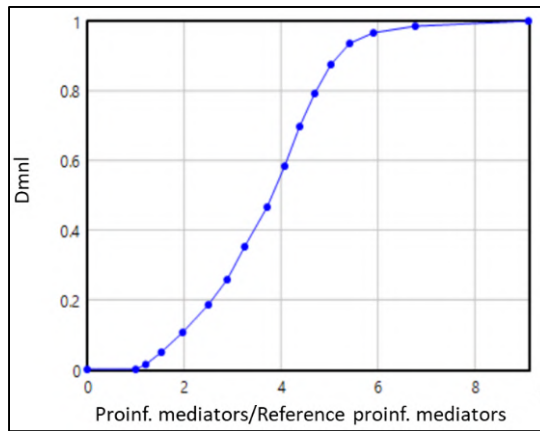
(c)Pro-inflammation effect on anti-inflammation

Figure 3 Graphical functions of effects in neuroinflammation sector

Pro-inflammatory mediators stand for TNF-α cytokines. The initial value is obtained from a study comparing the TNF-α contents of control and PD patient brains (Mogi et al., 1994). *Pro-inflammatory increase* is regulated by *pro-inflammatory release fraction* multiplied by *effect of activated microglia on pro-inflammation*. Higher densities of microglia result in a more inflammatory response due to the self-perpetuating nature of neuroinflammation. *Proinflammatory decrease* then comes into play in response to an increase in the pro-inflammatory level.

proinflammatory increase=proinf release fraction*eff of activated microglia on proinflam

IL-10 cytokine represents *anti-inflammatory mediators*. Its concentration in the brain is not available in the literature, thus, IL-10 initial value is determined based on a study indicating the TNF-α/IL-10 ratio for healthy adults (Porcher et al., 2021). *Anti-inflammatory increase* depends on the amount of pro-

inflammatory mediators since IL-10 generation is triggered by TNF-α. *Anti-inflammatory decrease* follows a similar procedure to the previously explained pro-inflammatory decrease.

antiinflammatory increase= increase fraction*eff of proinflam mediators on antiinflam increase

The graphical functions in neuroinflammation sector are displayed in **Figure 3**. *Reference activated microglia* corresponds to the amount of activated microglia an elderly individual at the age of 80 has. In advanced PD cases, this number can rise up to threefold. Effects of activated microglia on both *microglial resolution* and *pro-inflammatory increase* saturate around 1 because they are calibrated according to maximum value parameters. Those effects are 0 until the desired level of activated microglia (x=0.08) is reached. *Reference pro-inflammatory mediators* is equal to initial value of the stock. For lower levels than the desired (until x=1), proinflammation does not affect anti-inflammation. Depending on the activated microglia level, pro-inflammatory mediators level can rise up to 10-fold.

3.2. Protein Aggregation Sector

There are three stocks in this sector: (1) soluble alpha-synuclein, (2) insoluble alpha-synuclein, and (3) protein degradation activity. The *protein degradation activity* implied in the model is the ubiquitin–proteasome system (UPS) which is considered to degrade short-lived and soluble proteins (Goldberg, 2003). This stock is presented by peptidyl glutamyl-peptide hydrolytic (PGPH), the most impacted activity of UPS (Chondrogianni & Gonos, 2005). The stock unit is chosen to be fluorescence units (FU)/min/microgram protein, in line with the measurements in the literature (McNaught et al., 2003). UPS clears *soluble alpha-synuclein* proteins, whereas activated microglia phagocytize *insoluble alpha-synuclein* (Chu & Kordower, 2007).

Table 2 Protein aggregation sector stocks

Stock Name	Initial Value	Unit
Soluble alpha-synuclein	0	microgram/mg protein
Insoluble alpha-synuclein	0	microgram/mg protein
Protein degradation activity	39	Fu/(min*microgram protein)

Alpha-synuclein aggregation is regulated by *oligomerization*, *degradation*, *fibrillization*, and *phagocytosis*. The degree of oxidative damage affects *oligomerization.* Protein degradation efficiency, actual protein degradation divided by the desired level, regulates the *degradation.* Under normal conditions, protein degradation is capable of degrading soluble forms of alpha-synuclein protein, thus, preventing fibrillization. However, oxidative damage reduces degradation activity. The accumulated alpha-synuclein eventually forms fibrils. *Fibrillization delay* is obtained from an in vitro experiment (Conway et al., 2000). *Fibrillization,* the outflow of *soluble alpha-synuclein*, creates the inflow of *insoluble alpha-synuclein*, and, activated microglia-mediated *phagocytosis* forms the outflow.

oligomerization= oligomerization fraction*eff of oxidative damage on oligomerization

phagocytosis= MIN(insoluble alpha syn/adj time, activated microglia*phagocytosis capacity* microglial activation by protein)

Given that there are two sources of microglial activation, the assigned microglia numbers for phagocytosis of both alpha-synuclein and dead neurons must be determined. To address this, we used an auxiliary called *microglial activation by protein*.

microglial activation by protein=ZIDZ(activation by alphasyn, total activation)

Since there is no substantial inflow within the scope of our research, *protein degradation activity* is solely controlled by an outflow that is governed by oxidative damage. *Degradation activity decrease* is formulated by considering *effect of oxidative damage on degradation* by *degradation decrease fraction.*

$$\textit{degradation activity decrease=eff of oxidative damage on degradation*degradation}$$
$$\textit{compensation*degradation decrease fraction}$$

The graphical functions in protein degradation sector are presented in **Figure 4**. *Reference oxidative damage* refers to the amount of oxidative damage an elderly individual at the age of 80 has. For PD patients, this value can be up to 4 times the normal value. *Oligomerization fraction* is equal to the elderly individual at the age of 80. For PD cases, this can show 50% increase and saturates around y=1.5. The oxidative damage effect on protein degradation is S-shaped. At the beginning, there is not much sensitivity to the increasing damage, then nonlinear graph saturates.
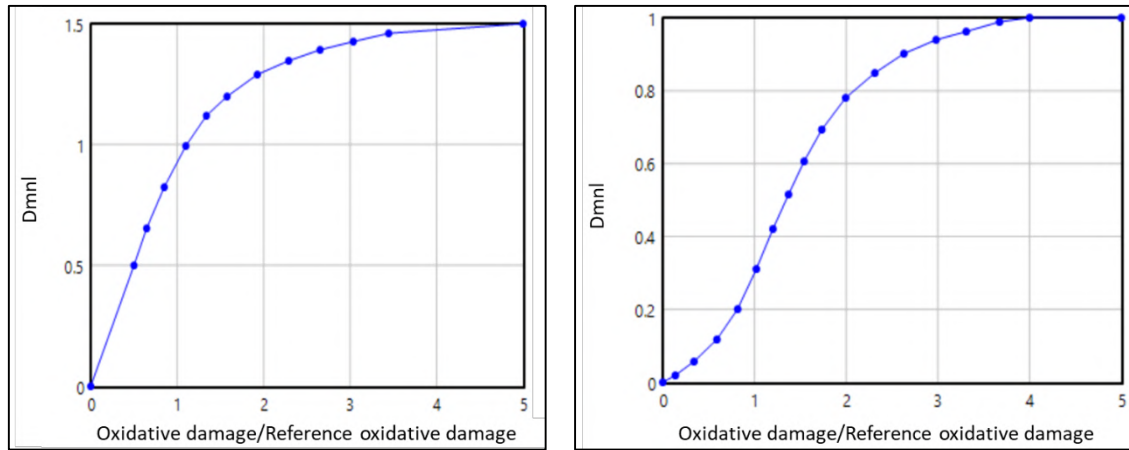
(a)Oxidative damage effect on oligomerization   (b)Oxidative damage effect on degradation

Figure 4 Graphical functions for protein aggregation sector effects

3.3. Dopaminergic Neuron Sector

This sector represents the population of dopaminergic neurons in human SN with three stocks: (1) healthy neurons, (2) damaged neurons, and (3) dead neurons.

Table 3 Dopaminergic neuron sector stocks

Stock Name	Initial Value	Unit
Healthy neurons	450,000	neuron
Damaged neurons	170	neuron
Dead neurons	28	neuron

Healthy neurons stock represents the neurons that effectively perform their functions. When cells are exposed to elevated levels of oxidative damage, DNA oxidation occurs, resulting in *damaged neurons*. Depending on the neuroprotection capacity, some of the damaged neurons are repaired and rejoin the healthy neurons. Insufficient neuroprotection, however, creates a flow to *dead neurons*.

According to a post-mortem analysis, the pigmented dopaminergic neuron in human SN for young adults is around 450,000 (Rudow et al., 2008). At the beginning of the simulation, some amount of damaged and dead neurons are also expected. We determined the initial values for those stocks as a result of trial runs. *Neuronal protection*, *neuronal damage, neuronal death* and *neuronal phagocytosis* regulate the levels of the sector stocks.

Neuronal damage is affected by oxidative damage intensity. In addition, the availability of healthy neurons is a determinant factor for this flow. The probability of neuronal damage increases with healthy neuron abundance. As it is not significant to the model, damage that occurs to cells that are already damaged or dead is not of concern.

Neuronal damage=(min neuronal damage*eff of oxidative damage on neurons*neuronal damage availability)+brain injury

*neuronal damage availability=healthy neurons/total neurons*

BDNF, one of the prominent neuroprotective factors expressed by dopaminergic neurons, represents the neuroprotection capacity in our model. In contrast to their healthy counterparts, damaged neurons produce approximately 20% reduced BDNF (Howells et al., 2000). In addition, neuroprotection is highly dependent on *ATP efficiency*.

BDNF neuroprotection capacity=BDNF production capacity*(healthy neurons+damaged neurons*(1-BDNF production reduction))*ATP efficiency

Damaged neurons, die after some time. Lewy body-containing neurons have a six-month lifespan (Greffard et al., 2010). We thus assumed a 6-month delay. The last flow, *neuronal phagocytosis*, is controlled by the amount of activated microglia. As previously mentioned, to determine the amount of activated microglia responsible for neuronal phagocytosis, we multiplied the microglia level by *(1-microglial activation by protein)*.

neuronal phagocytosis=MIN(dead neurons/adj time, activated microglia*microglia phagocytosis capacity*(1-microglial activation by protein))

Under normal circumstances, there is no oxidative damage in neurons. Therefore, initiation of oxidative damage results in some minimum amount of neuronal damage. Later, the graph saturates around y=4, meaning maximum neuronal damage depending on oxidative damage is approximately four times the minimum value.
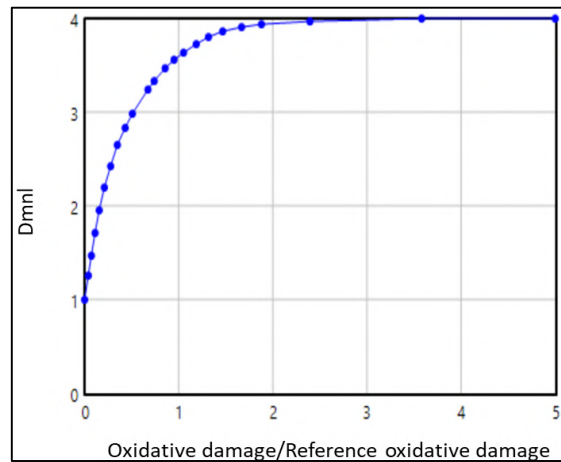
Figure 5 Oxidative damage effect on neuronal damage

3.4. Oxidative Damage Sector

There are two stocks in this sector: (1) oxidative damage, and (2) GSH. A biomarker is used to quantify the proportion of positively stained neurons that are oxidatively damaged. The stock's unit is thus determined to be dimensionless. Healthy people had oxidative damage ranging from 0% to 15%, increasing with age. However, in those with PD, it could go up to 50% (Yoritaka et al., 1996). It is essential to underline that oxidative damage of 0 does not imply the individual is not experiencing oxidative stress. All people are subjected to oxidative stress occasionally, which is mitigated by antioxidant mechanism. On the other hand, oxidative damage in this study refers to the harm resulting from oxidative stress over time on cells and their functions.

Table 4 Oxidative damage sector stocks

| Stock Name	Initial Value	Unit
Oxidative damage	0	dmnl
GSH	56.8	microgram/gram

Oxidative damage increase is caused by dysfunctional mitochondria and activated microglia. *MCIA* is the abbreviation for Mitochondrial Complex I Activity, which is chosen as the mitochondrial function representation in our model. *Mitochondrial oxidative damage (OD)* formulates oxidative generation via mitochondria-related pathways. In case of mitochondrial dysfunction, electrons are leaked to the neurons, exacerbating oxidative damage.

oxidative damage increase= mitochondrial OD + microglial OD

*mitochondrial OD=MIN(1, (1-MCIA efficiency))*mitochondrial OD production*

Activated microglia are the other source of oxidative damage. As the amount of activated microglia grows, cells that stimulate each other produce more enzymes, leading to an uncontrolled increase in oxidative damage. To obtain *actual microglial oxidative damage production,* we include the *effect of activated microglia on oxidative damage*.
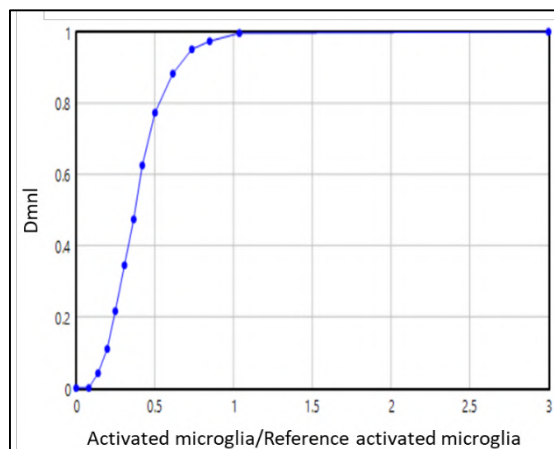
oxidative damage decrease=MIN(oxidative damage/adj time, GSH *GSH capacity*eff of oxidative damage on GSH capacity)
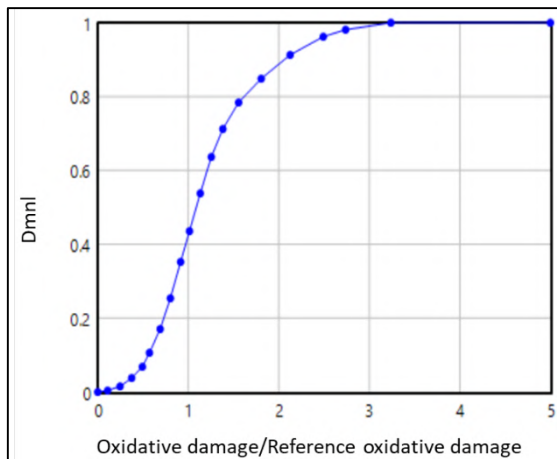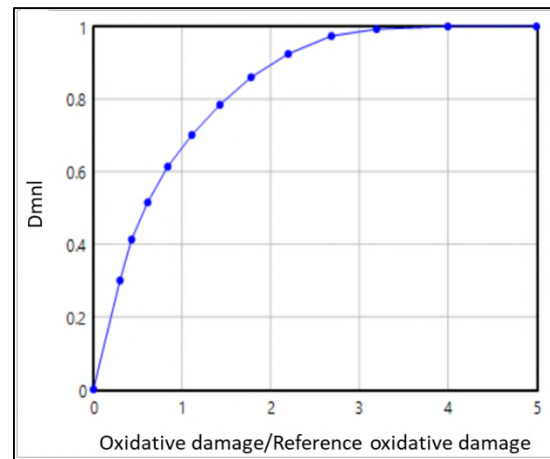
(a)Oxidative damage effect on GSH capacity   (b)Oxidative damage effect on GSH decrease

(c) Activated microglia effect on oxidative increase

Figure 6 Graphical effect functions in oxidative damage sector

GSH depicts the antioxidant capacity in our model. Thus, *oxidative damage decrease* is regulated via GSH level. The multiplication of *GSH* and *GSH capacity* gives the possible decrease. Existing oxidative damage also reduces capacity negatively. To this end, we employed *effect of oxidative damage on GSH capacity* to determine the actual capacity.

GSH decrease=MIN(GSH /adj time, eff of oxidative damage on GSH* GSH decrease fraction

GSH increase=GSH discrepancy*ATP efficiency/GSH increase delay

The presence of oxidative damage causes a decrease in GSH due to the reaction between oxidant and anti-oxidant materials. Thus, *GSH decrease* is formulated including the *effect of oxidative damage on GSH*. We then proposed that cells should try to bring their GSH amount to desired levels. Thus, *GSH discrepancy* between the desired and the actual values triggers *GSH increase*. In a follow-up study, scientists find out that GSH supplementation increases GSH level after 3 months (Mischley et al., 2017).

The graphical functions are illustrated in **Figure 6**. Oxidative damage effect on GSH capacity is S-shaped. A rapid rise starts around x=0.5, and then, graphs saturates at x=3 with an output value of around 1. Since it is calibrated according to the maximum value of GSH capacity. On the other hand, oxidative damage effect for GSH decrease shows a sharp and linear increase at first, and then saturates at oxidative densities of PD patients. For lower microglia levels than the desired (until x=0.08), microglia do not affect oxidative damage.

3.5. Mitochondria Sector

There are three stocks in mitochondria sector: (1) accumulated mtDNA deletions, (2) mitochondrial complex I activity, and (3) ATP synthesis.

Table 5 Mitochondria sector stocks

Stock Name	Initial Value	Unit
Accumulated mtDNA deletions	20	dmnl
Mitochondrial Complex I Activity	24.7	nmol/(min*mg)
ATP synthesis	100	dmnl

Accumulated mtDNA deletions, which are regulated by a net flow called *mtDNA deletions,* stand for the DNA deletion mutations during aging. Studies investigating this variable measure the amount of deletion in terms of percentage. Thus, it is formulated such that it cannot surpass 100. When oxidative damage increases, more mtDNA deletions accumulate. Higher densities of oxidative damage result in more devastating impacts, thus, we include the *effect of oxidative damage on mtDNA* in our formula. According to a study, 20% of mtDNA deletions were observed even in individuals aged 20 years (Dölle et al., 2016). An inflow other than oxidative damage-related causes should increase mtDNA deletions.

mtDNA deletions=(other sources of deletions+mtDNA deletion fraction*eff of oxidative damage on mtDNA)*mtDNA deletion possibility
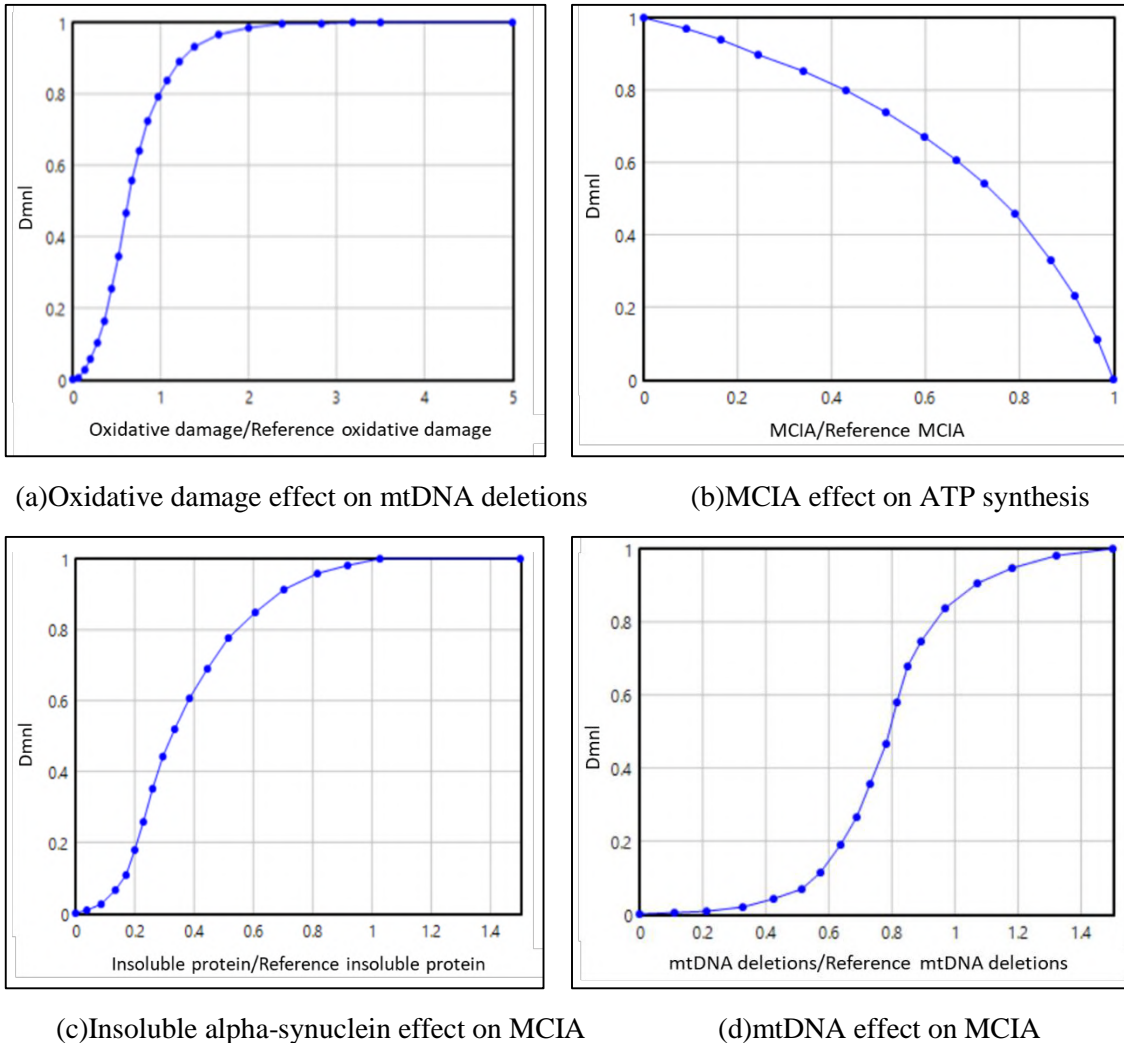
Mitochondrial complex I activity (MCIA), is the largest enzyme complex of the mitochondrial functions, therefore it is implemented into our model for mitochondrial function (Mimaki et al., 2012). The mtDNA deletions and insoluble alpha-synuclein protein both contribute to *MCIA reduction*.

MCIA reduction=MCIA reduction fraction*(eff of mtDNA on MCIA+eff of insoluble alphasyn on MCIA)*MCIA compensation

The last stock in our model is the *ATP synthesis*. This stock is approximately 100% while a person is young, but it gradually declines during aging due to MCIA decline.

ATP decrease=eff of MCIA on ATP*ATP decrease fraction

The graphical functions of mitochondria sector are displayed in **Figure 7**. Oxidative damage effect on mtDNA deletions graph shows a rapid rise around x=0.5 and saturates around y=1 because of the calibration according to the maximum value of *mtDNA deletion fraction*. The desired MCIA level corresponds to *reference MCIA*. For young healthy individuals, the input for the graphical function is around 1, which gives an output of 0. Thus, there will be no MCIA-induced ATP synthesis decrease. If the input ratio gets closer to 0, the *ATP decrease fraction* reaches its maximum value. The *reference insoluble protein* corresponds to the amount of insoluble alpha-synuclein an advanced PD has. In a similar manner, *reference mtDNA deletions* are also set to the level of PD patients.

(a)Oxidative damage effect on mtDNA deletions

(b)MCIA effect on ATP synthesis

(c)Insoluble alpha-synuclein effect on MCIA

(d)mtDNA effect on MCIA

Figure 7 Graphical effect functions in mitochondria sector

## 4. MODEL BEHAVIOR AND VALIDATION

The model is simulated by Vensim DSS software, version 9.3.0. The simulation time unit and time step are chosen as one month, and 0.0625 months, respectively. The time horizon is 600 months, which stands for 50 years for a 30-year-old healthy individual up to the age of 80. The direct structure tests are simultaneously accomplished through the model construction phase. The measurement of brain activities and materials by post-mortem analysis makes instant detection of abnormalities practically impossible. Thus, lacking information and predicted real reference behaviors for a healthy aging brain have been derived from insights based on rodent experimental studies. A direct extreme condition test for each equation is performed in isolation, and dimensional consistency is satisfied. All model variables have real-life meanings and units.

4.1. Equilibrium Run

The system examined has no natural equilibrium, since the brain and related subsystems change by aging, resulting in disequilibrium (dynamics). However, just to test the structure of the model, it can be simulated under some hypothetical (extreme) equilibrium conditions. Some examples of such conditions in our model are having no initial activated microglia, no external increase in oxidative damage and mitochondrial DNA deletions, and no initial damaged neurons. In selected hypothetical conditions, it is expected that brain variables would remain at equilibrium. As a result, we observe constant equilibrium values for the key variables. Obtained equilibrium dynamics are provided in Appendix.

4.2. Base Run

Comparing graphical or visual measurements of the most common behavior patterns with simulation output is the key approach in testing validity of the model behavior. **Figure 9** demonstrates the reference behavior for pigmented dopaminergic neurons in SN of both healthy controls and PD patients.
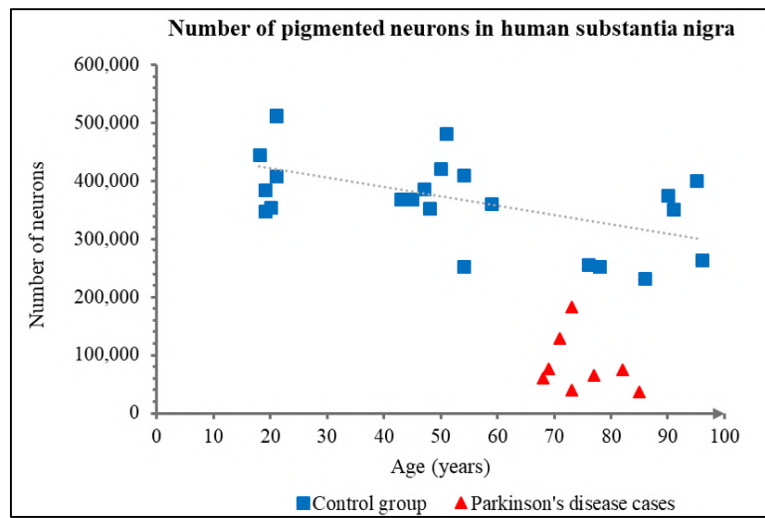
Figure 8 Reference behavior for neurons (data from (Rudow et al., 2008))

No graph or measurement exists in the literature that can be utilized to assess directly the model behavior for several stocks. Thus, qualitative approximate reference behaviors are predicted from partial data in the literature (post-mortem analyses, rodent experimental studies, expected behaviors by experts) to employ in the model calibration for the base run (normal aging). They are included in Vensim via *GRAPH* functions to compare with the model outputs in the base run. The model behavior reflects the expected approximate real reference behaviors.
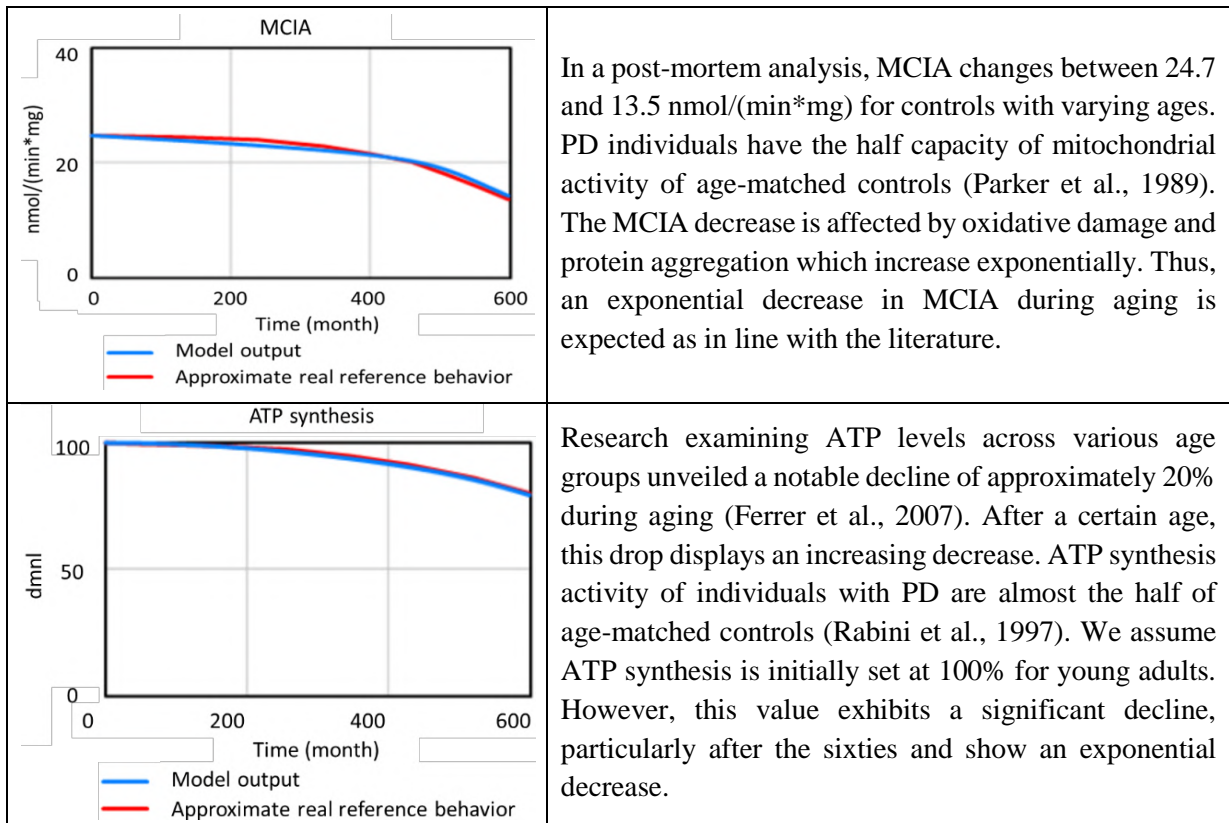
Table 6 Comparison of model behavior and approximate real reference behavior

Key variables	Explanation
	The number of pigmented dopaminergic neurons in human SN for healthy adults is almost 450,000. There is a linear decrease during aging which amplifies later. The remaining dopaminergic neurons are roughly 300,000 for elderly controls which means a 33% neuronal loss during aging (**Figure 8**) (Rudow et al., 2008). PD patients are believed to lose 50% of neurons before the diagnosis (Chaudhuri & Titova, 2019), and the pigmented ones are typically lost (Zecca et al., 2001).

Insoluble alpha-synuclein

(y-axis: microgram/milligram protein; x-axis: Time (month))

Model output
Approximate real reference behavior

Insoluble alpha-synuclein is equal to 0 under normal conditions since it is a toxic protein form which is harmful to neurons. The soluble alpha-synuclein quantity (Quinn et al., 2012), the ratio between the toxic and healthy forms (Sharon et al., 2003), and the insoluble/soluble alpha-synuclein ratio (Wills et al., 2010) are used to determine the values in the SN at elderly ages for PD and control. The alpha-synuclein number in human SN shows an exponential increase during aging (Chu & Kordower, 2007).

Protein degradation activity

(y-axis: FU/(min*microgram protein); x-axis: Time (month))

Model output
Approximate real reference behavior

Aged cells experience a 1.5–2 fold decline in proteasomal activities (Chondrogianni & Gonos, 2005). The post-mortem analysis of brain SN revealed the protein degradation value for an elderly control. The levels of protein degradation for PD is 45% reduced compared to healthy controls (McNaught et al., 2003). In a study showing protein degradation activity for different ages, there was not much change until 60s, however after that point a nonlinear decrease occurs (Jung et al., 2007).

Activated microglia

(y-axis: microglia; x-axis: Time (month))

Model output
Approximate real reference behavior

The total microglial number does not change with age (VanGuilder et al., 2011). However, microglia undergo increasing activation as individuals advance in age (Eyolfson et al., 2020). Activated microglia amount in aged mice is 12.5 times the number in adult mice. The fold change between healthy and PD mice is 2.5 (Henry et al., 2009). According to neuroimaging, age-related dystrophy in microglia cells rises linearly in adults while exponentially in elderly (Koellhoffer et al., 2017).

Pro-inflammatory mediators

(y-axis: picogram/milligram; x-axis: Time (month))

Model output
Approximate real reference behavior

Pro-inflammatory mediators are secreted by activated microglia, therefore, their dynamics are highly dependent on microglia level. While a linear increase with a lower slope is expected in adulthood, this becomes self-perpetuating in older ages. TNF-α level triples during aging (Porcher et al., 2021). PD patients have roughly three times higher TNF-α levels than controls in post-mortem analyses (Mogi et al., 1994). Pro-inflammatory mediators can grow much more than anti-inflammatory mediators.

Anti-inflammatory mediators are released in an autocrine way, with or after pro-inflammatory mediators (Brodacki et al., 2008). Therefore, their dynamics are dependent on pro-inflammatory mediators. IL-10 level doubles as individuals age (Porcher et al., 2021). In an experimental study conducted for mice, the fold change between elderly PD and control is 1.2 (Akundi et al., 2011). This demonstrates that pro-inflammatory mediators can grow much more.

There is no assessment of reactive species in brain. Instead, oxidative stress-induced damage by immunostaining is determined. We obtain the positively stained nigral neurons for oxidative damage for healthy control and PD (Yoritaka et al., 1996). The oxidative damage (%) was ranging between 0 and 15 for controls, whereas for PD cases this may reach up to 55. The behavior of oxidative damage during aging is believed to be exponential (Druzhyna et al., 2008).

Riederer and coworkers analysed the GSH amounts in the brains of controls and PD patients (Riederer et al., 1989). According to varying age groups the initial and final values are defined. The human brain tries to raise the GSH level to the desired level as it declines after its reaction with ROS. However, it is assumed that GSH production, which is basically dependent on mitochondrial energy (Sian et al., 1994), exhibits similar behavior to ATP level.

Mitochondrial DNA deletions accumulate during life (Druzhyna et al., 2008). The percentage of mtDNA deletions demonstrates a statistically significant positive correlation with age. The SN neurons of individuals with PD have higher levels of mtDNA deletions, compared with age-matched controls (Dölle et al., 2016). Starting from young adulthood ages, it is assumed from the same paper that there is a linear increase for mtDNA deletions which amplifies after.

	In a post-mortem analysis, MCIA changes between 24.7 and 13.5 nmol/(min*mg) for controls with varying ages. PD individuals have the half capacity of mitochondrial activity of age-matched controls (Parker et al., 1989). The MCIA decrease is affected by oxidative damage and protein aggregation which increase exponentially. Thus, an exponential decrease in MCIA during aging is expected as in line with the literature.
	Research examining ATP levels across various age groups unveiled a notable decline of approximately 20% during aging (Ferrer et al., 2007). After a certain age, this drop displays an increasing decrease. ATP synthesis activity of individuals with PD are almost the half of age-matched controls (Rabini et al., 1997). We assume ATP synthesis is initially set at 100% for young adults. However, this value exhibits a significant decline, particularly after the sixties and show an exponential decrease.

5. SCENARIO ANALYSIS

The aim of scenario analysis is to explore whether external administration of traumatic brain injuries would create PD-like outcomes in aging human brains with different injury characteristics. A total of 1152 simulation runs are observed. After determining some important variables by sensitivity analysis, we investigate the impacts of some daily life activities and potential treatment strategies for both PD-prone and healthy individuals. The appendix contains an explanation of the sensitivity analysis in detail.

5.1. Brain injury scenarios
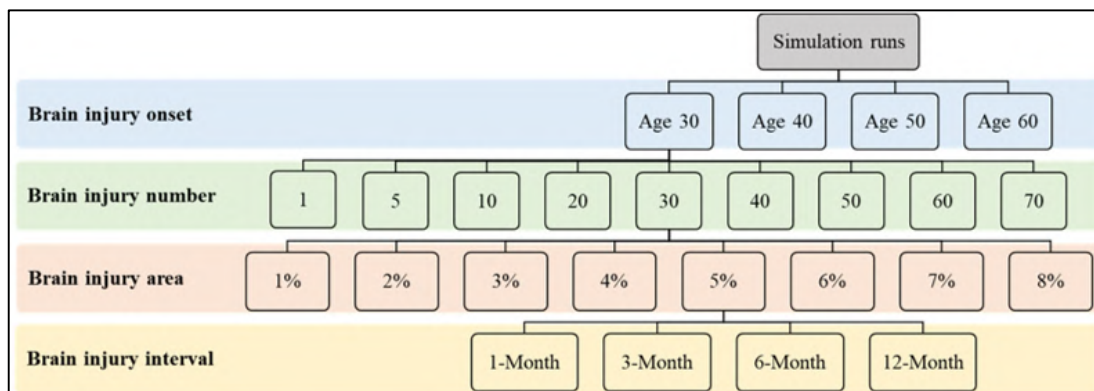
**Figure 9** Scenario runs with varying injury properties

PD is characterized by both alpha-synuclein accumulation and dopaminergic neuronal loss, therefore, we need to examine these two variables together. The most frequently cited study for dopaminergic neuronal loss shows that approximately 31% is lost at initial symptom onset (Cheng et al., 2010). Given the absence of a clinical diagnosis, 50% of neurons are already lost before diagnosis (Chaudhuri & Titova, 2019). Thus, we defined the neuronal loss thresholds as 30% for symptom onset and 50% for diagnosis. During aging, alpha-synuclein accumulation grows to about 1 microgram/mg protein, but in PD patients,

it rises to two to three times that amount. We assumed those with an alpha-synuclein accumulation level of more than 2 microgram/mg protein are in poor health. Individuals who have both protein and neuronal unhealthy conditions are believed to have PD.

In our study, the affected area in substantia nigra by an injury is employed to express the severity of the trauma. The model is given pulses with a binary variable called *brain injury pulse* to indicate when there are injuries. The duration element of *PULSE TRAIN* function is set to 0, since injuries are immediate.

brain injury=brain injury pulse*healthy neurons*affected area
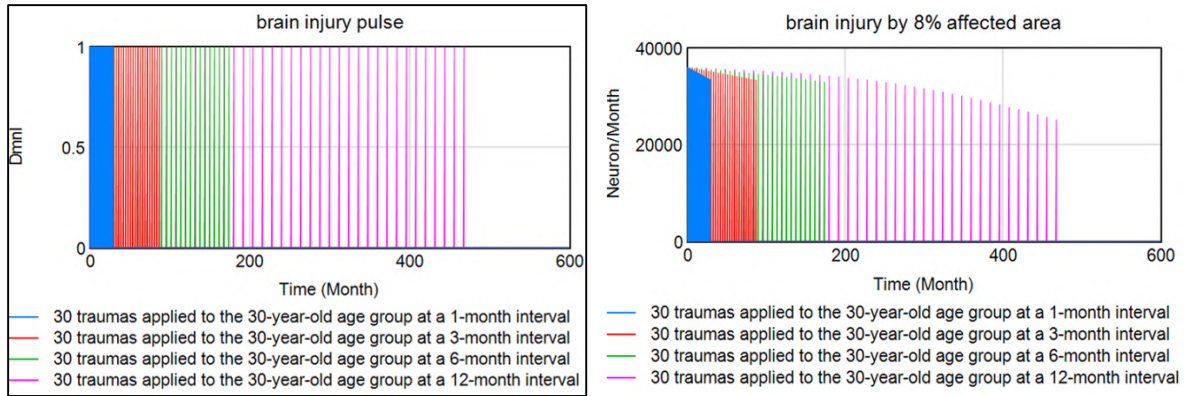
Figure 10 Brain injury scenarios

Younger people have more neurons damaged as a consequence of trauma to the same affected area than elderly people. Because they have higher neuronal density. They also have higher neuroprotection capacity since protective materials are mainly produced by healthy neurons. Trauma-induced neuronal death, as expected, increases microglial activation. This further affects the oxidative damage and mitochondria sectors which in turn limit the protective mechanisms and exacerbate the neuronal damage and protein aggregation.
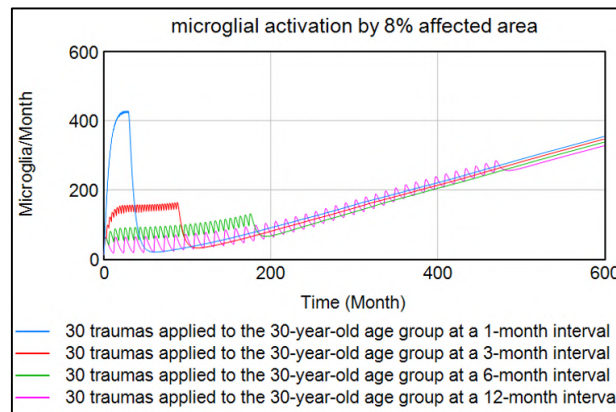
Figure 11 Microglial activation by brain injuries for different intervals

5.1.1. Scenario 1: severity of repetitive brain injuries

A total amount of 30 traumas in different severities are applied monthly to a healthy 30-year-old individual to examine if those scenarios would result in PD. Trauma induces neuronal loss at all levels compared to normal aging. Disease characteristics are possible in affected areas of 4% and more. Depending on the impact area, a healthy 30-year-old individual may show PD-like output in long-term as a result of repetitive TBIs. Scientists focus on the remaining neurons expressed as a percentage, rather than the absolute number, thus, we provide the percentage calculation for the model.
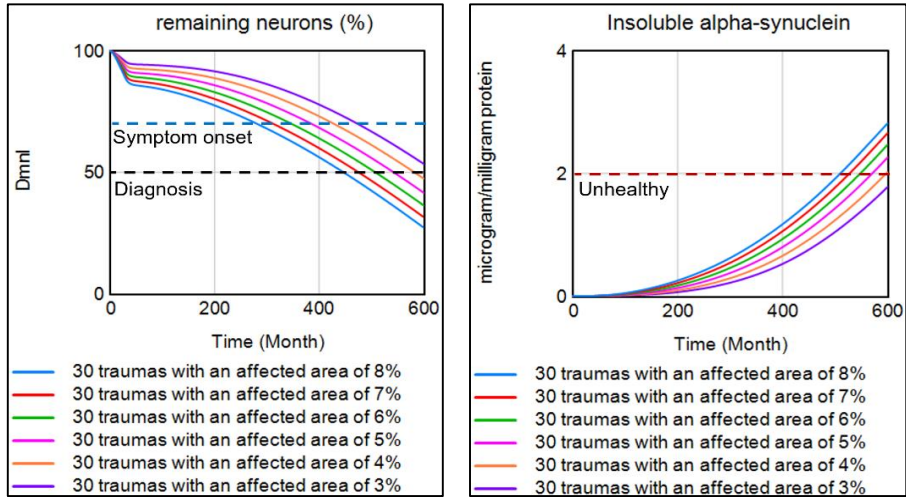
Figure 13 Comparative plots of scenario 1

5.1.2. Scenario 2: number of repetitive brain injuries

This scenario is aimed to investigate the impact of the number of TBIs. First, we reduce the number of monthly injuries for 8% affected area which resulted in PD-like behavior previously. Later, we increase the number of injuries for 3% injury area.
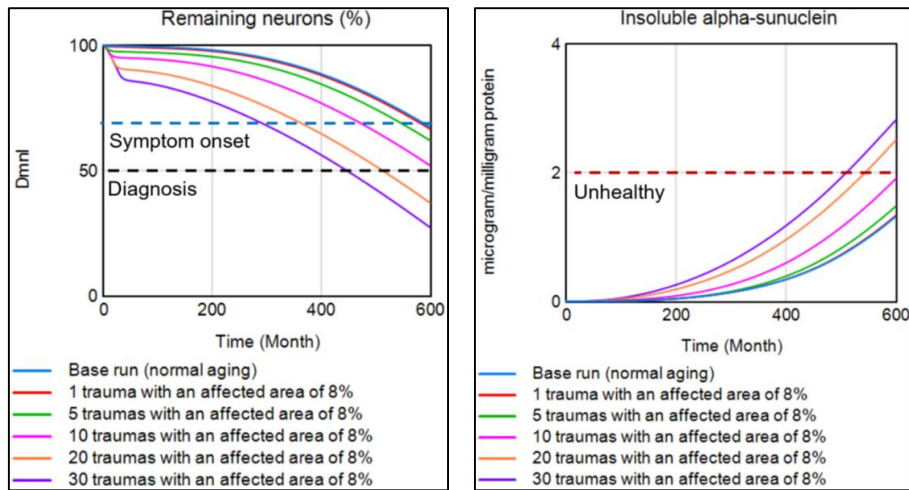

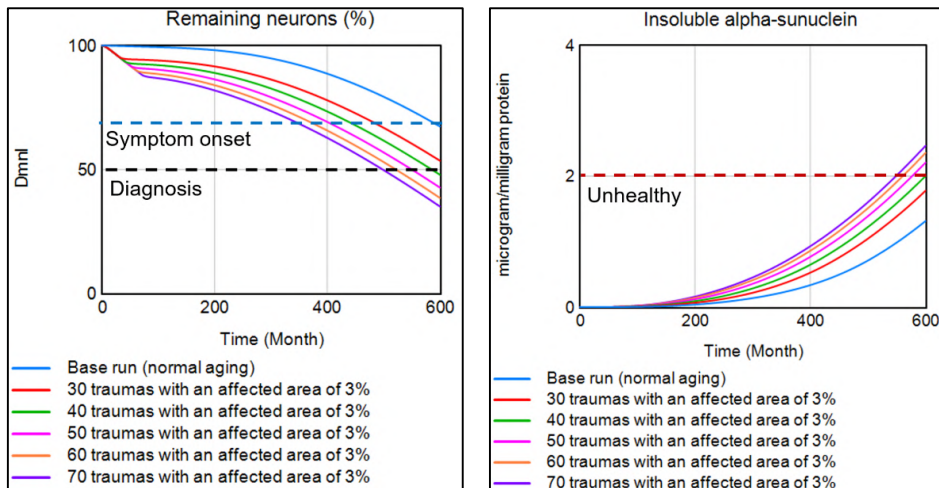**Figure 14** Comparative plots of scenario 2-1

Figure 15 Comparative plots of scenario 2-2

The quantity of traumas is significant for both higher and lower severities. While we observe 20 TBIs at 8% severity (affected area) produce PD-like output, similar results could not be obtained for 10 or fewer traumas. Contrarily, while we could not observe PD-like output for 30 traumas at 3% severity, for greater sets of traumas PD-like outputs are possible.

5.1.3. Scenario 3: interval of repetitive brain injuries

The purpose of this scenario is to examine the frequency of traumas. We change the interval of brain injuries for 30-year-old group. There is reduced alpha-synuclein accumulation in response to larger time intervals between injuries. More protein aggregation as a result of frequent injuries can be explained by the overwhelmed balancing mechanisms. Although protective mechanisms' ability becomes lower during aging, still earlier and more frequent traumas have longer-term impact on PD vulnerability.
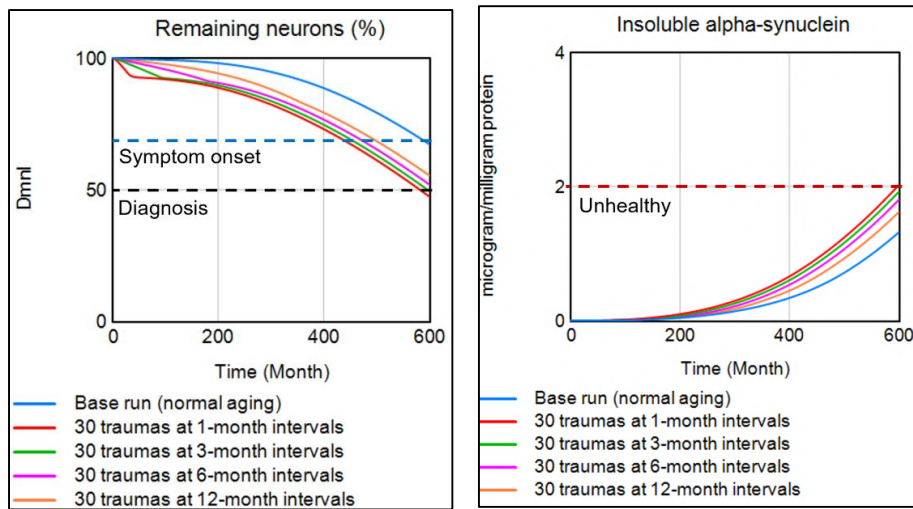

Figure 16 Comparative plots of scenario 3

5.1.4. Scenario 4: onset of repetitive brain injuries

To investigate whether an age group is more vulnerable in terms of trauma-induced potential PD progression, a total 30 traumas with an affected area of 5% are administered monthly to different age groups. Elderly people who experience neuronal loss following brain injury may experience neurological issues, however, protein accumulation is not seen in those individuals. The earlier the trauma begins, the greater the impact in terms of PD vulnerability. A certain period time is required for PD to develop. According to simulation runs, it is not possible to observe the immediate vulnerability after TBIs.
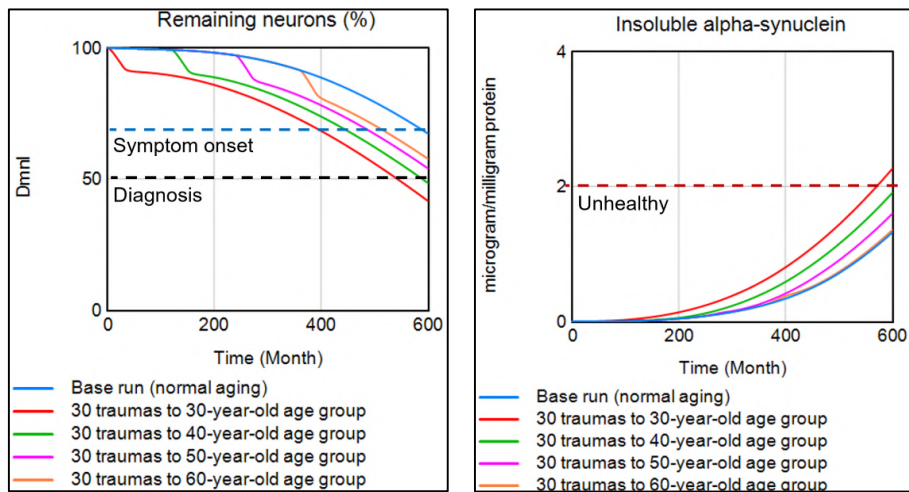

Figure 17 Comparative plots of scenario 4

5.1.5. Scenario 5: late-onset of repetitive brain injury

The previous scenario demonstrates a higher PD vulnerability for early age onset. In this scenario, we focus on the administration of traumas to elderly people, thus, a 60-year-old individual has experienced repetitive TBIs with different severities and numbers. Scenario runs reveal that protein aggregation is less than normal aging. The underlying reason may be that a part of the activated microglia also degrades the toxic alpha-synuclein forms. This supports the outputs of the previous scenario. Repeated TBIs must start early in life, be more severe than a certain threshold, and occur with a specific consistency to generate potential PD patients.
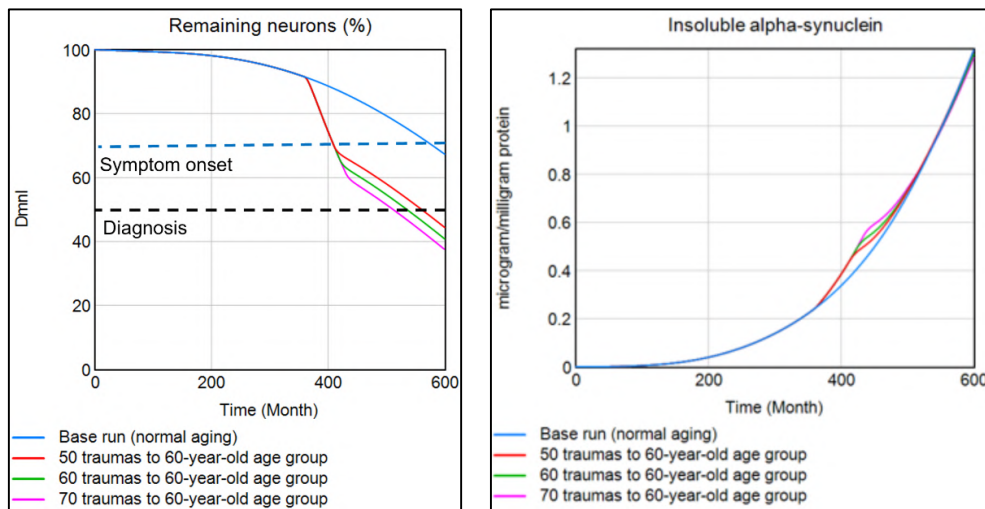

Figure 18 Comparative plots of scenario 5

5.2. Protective scenarios

People's susceptibility to certain diseases may be determined by genetic factors. Varying degrees of interplay between genetic predisposition and environmental factors impose a risk for PD (Shulman et al., 2011). We try to explore the protective impacts of genetic variance/treatment potentials and daily activities on TBI-induced PD-like outputs by implementing some improvements to the most essential variables. Previously, we observed that young individuals (30-year-old group) who experienced 30 brain injuries in total at 1-month intervals with an affected area of 8% showed PD-like behavior. Thus, throughout this section, we refer to these individuals as PD-prone.

5.2.1. Healthy diet and regular exercise

Clinical studies indicate that dietary intake of natural antioxidants mitigates neurodegeneration by destroying oxidative compounds (Zandi et al., 2004) and physical activity positively affects the expression of BDNF (Tuon et al., 2014). We hypothetically increase the initial value of GSH and parameter value of BDNF production capacity by 15% to monitor the potential protective impact of a healthy diet and regular exercise.

5.2.2. Genetic variance

We increase the initial values of mitochondrial complex 1 activity and protein degradation by 15% to investigate the impact of possible genetic variance for potential treatment opportunities. Since healthy nutrition and exercise may be insufficient in terms of protein accumulation, such a complementary strategy is expected to offer longer-term benefits.
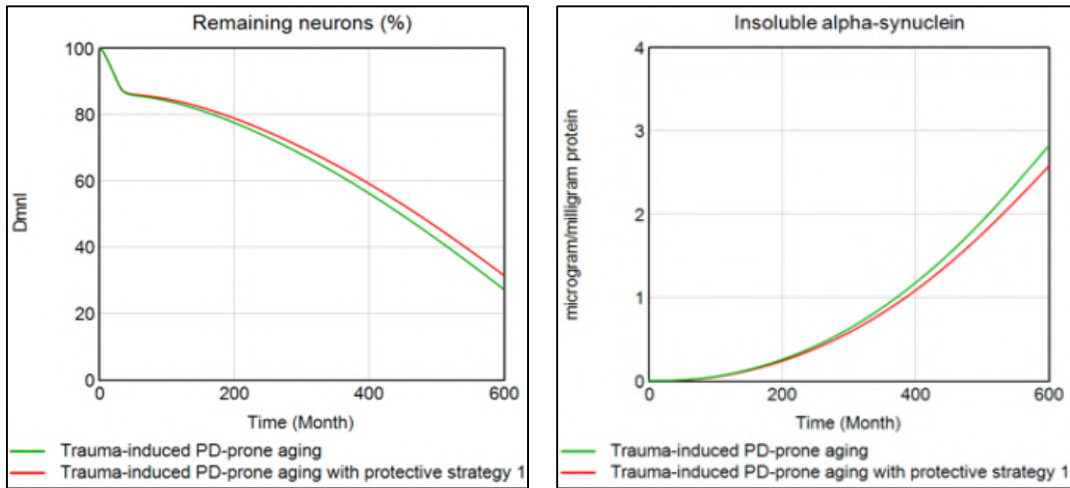
Figure 19 Comparative plots of protective strategy 1
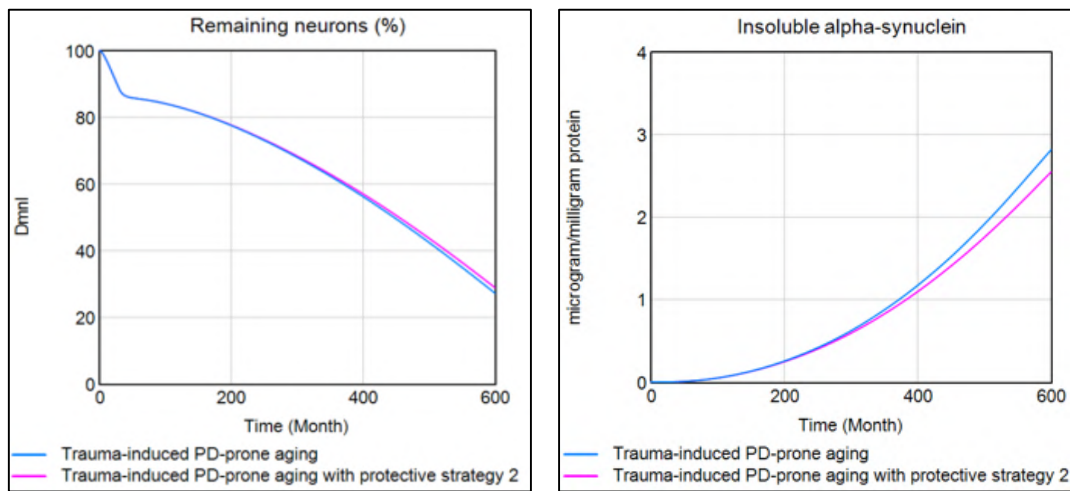
Figure 20 Comparative plots of protective strategy 2

5.2.3. Combined protective strategy

This strategy aims to combine the benefits of two previous approaches by integrating a diet rich in antioxidant nutrients and regular exercise with possible treatments and/or genetic variance that enhance protein degradation and mitochondrial activity to create a synergistic effect.
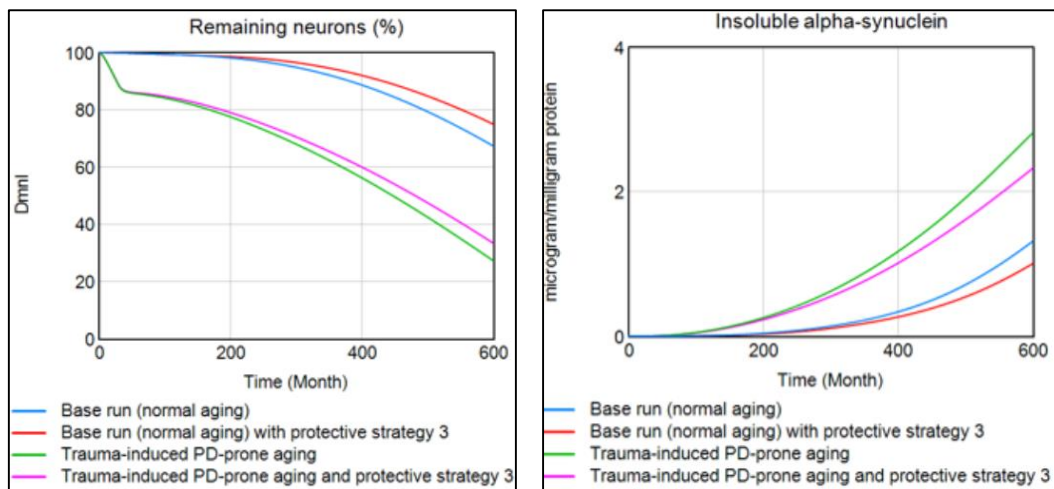
Figure 21 Comparative plots of protective strategy 3 (combined)

The combined strategy demonstrates a restorative effect on both trauma-induced PD-prone individuals and individuals experiencing the natural aging process. It is also important to identify potential therapeutic strategies that can alleviate or mitigate age-related non-motor and/or motor issues.
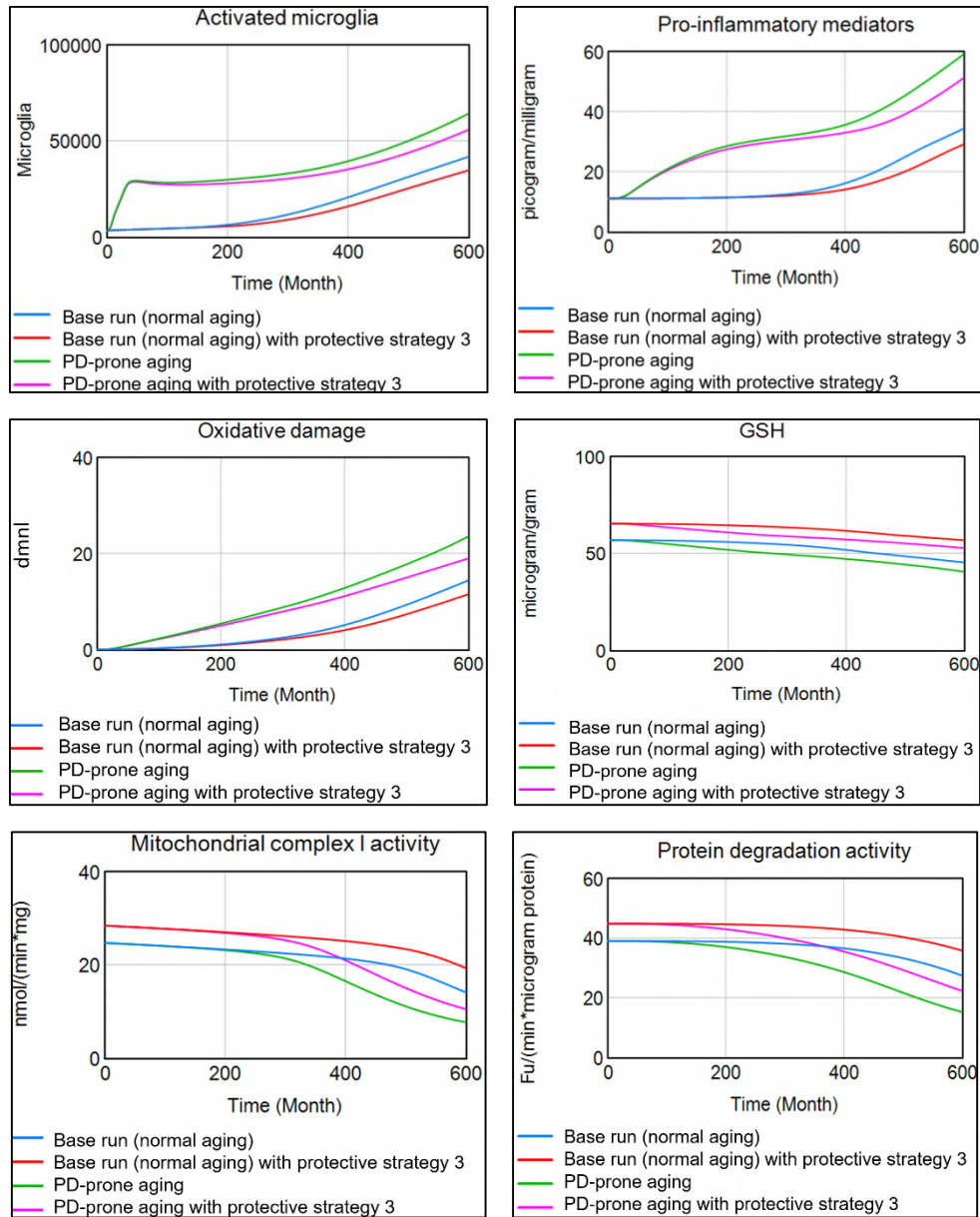

Figure 22 Final values of key stocks for combined protective strategy

We further monitor the effect of combined protective strategy on other important variables in the system. Individuals who have higher levels of protein degradation capacity genetically or due to possible treatments are less likely to have high levels of protein aggregation. GSH enhancement is a promising strategy for lowering oxidative damage. Better mitochondrial activity reduces oxidative damage, and, has an impact on both antioxidant function and neuroprotection by ATP-related pathways. BDNF is critical for neuronal survival but its impact on protein removal is not straightforward.

In Table 7, the percentage changes at the end of simulation for remaining neurons and insoluble alpha-synuclein aggregates are summarized. The desired outcome is to reduce the levels of insoluble alpha-synuclein while simultaneously increasing the number of remaining neurons.

Table 7 Protective strategy comparisons for PD-prone and normal aging

	PD-prone aging		Normal aging	
	Insoluble alpha-synuclein	Remaining neurons (%)	Insoluble alpha-synuclein	Remaining neurons (%)
Healthy diet and regular exercise	-8.60%	15.50%	-8.10%	5.50%
Genetic variance	-9.60%	6.10%	-16.10%	5.60%
Combined strategy	-17.40%	22.50%	-23.60%	11.30%

The time course of PD is postponed by 4 years with this strategy. The median time taken between stages of Hoehn and Yahr (H&Y), the most common and widely used scale to estimate disease severity, is approximately 2 years (Zhao et al., 2010). A 4-year interval is particularly significant for improving the quality of life for patients by reducing the disease symptoms and slowing down the transition between disease stages. Since people who are not exposed to TBIs also experience non-motor and motor problems during aging, it is also important to identify the effective possible therapeutic approaches for a healthier aging process.
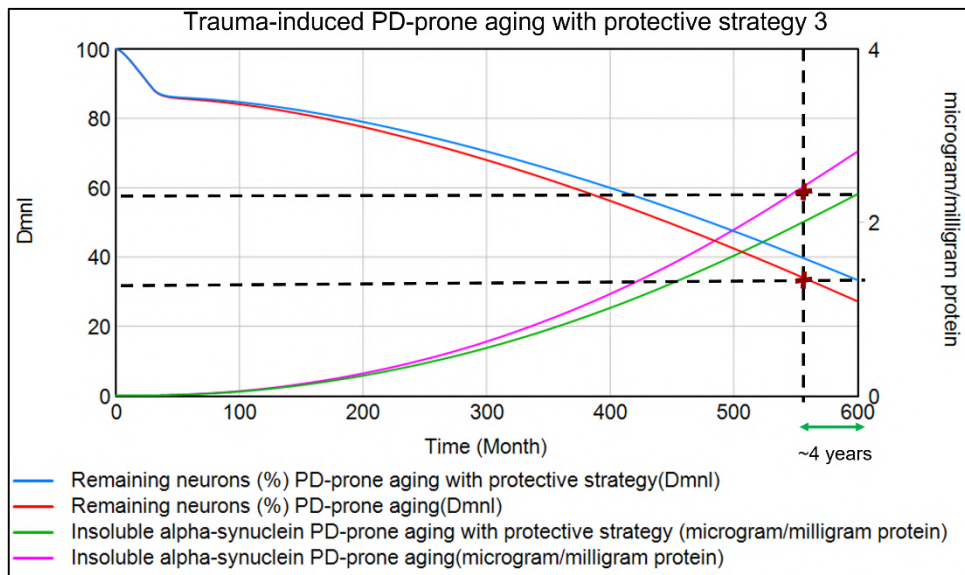
Figure 23 Potential disease symptom delay by protective strategy 3 (combined)

The findings of a study revealed that medical improvements that postpone the onset of Alzheimer's disease by 5 years result in 41% lower prevalence and 40% lower cost. This 5-year-delay leads to 2.7 additional life years which is approximately 5 disease-free years (Zissimopoulos et al., 2015). Treatment and prevention strategies delaying the onset of PD are also expected to generate significant economic and longevity benefits.

CONCLUSION

There is an ongoing interest in fully understanding the underlying complex pathways leading to PD. There is an important link between brain traumas and PD, mainly resulting from neuroinflammation-induced mechanisms. Due to the dynamic nature of the brain, many other sectors are affected in the long-term. In this study, we built a system dynamics model of a brain region where dopamine-producing neurons reside, to monitor the long-term dynamic effects of brain injury on potential mechanisms leading to PD development. After exploring the normal aging dynamics, it is investigated whether individuals exhibit Parkinsonian-like output after having experienced repetitive brain injuries. Finally, potential positive impacts of genetic variance and/or healthy lifestyle factors are tested.

The difficulties in monitoring, data collection, and quantifying brain-related variables are the primary challenges for this research because only post-mortem analysis allows for neuropathological diagnosis. Thus, in the validation phase, qualitative and quantitative knowledge gained from autopsy reports and animal experimental studies are employed. Our model is validated by structure and behavior tests.

We next analyzed different scenarios to investigate the association between PD and brain injury. To investigate the significance of age during the first trauma, four age groups are studied. Each age group is then exposed to repetitive brain injuries with varying numbers, intervals, and severities. Our findings suggest that healthy individuals who are subjected to brain trauma at an early age may produce PD-like outcomes later in life. Those over the age of 40 experience some neuronal loss, however, there is no substantial protein aggregation, the other pathological definition for PD. The earlier the trauma begins, the greater the impact in terms of PD susceptibility, indicating that PD takes some time to form after repetitive injuries. Repeated TBIs must start early in life, be more severe than a threshold, and occur with a particular consistency with short intervals to produce PD-like behaviors in long-term. Otherwise, balancing mechanisms are able to compensate for the TBI-induced harm.

A diet rich in antioxidants and regular exercise are demonstrated to be a promising anti-PD strategy. Treatment methods or genetic variance that promote mitochondrial activity and protein degradation are also confirmed to be favorable for both PD and normal aging brains. Our combined strategy reduces alpha-synuclein aggregation by 17.4% and increases remaining neurons by 22.5% in PD-prone people. Thus, the time course of PD is approximately postponed by 4 years. The quality-adjusted life year of potential PD patients can be extended by delaying symptoms and/or avoiding disease pathogenesis.

The model serves well our purposes in this study: it provides us with a quantitative tool to experiment with different brain injury scenarios to observe long-term impacts and potential protective strategies. The ultimate aim of the research is to provide a comprehensive understanding of PD-related brain dynamics in interaction with external factors and to identify the most effective mechanisms for the treatment and prevention strategies. The work presented is naturally open to development by including discoveries from new field data and empirical studies.

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