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A mathematical model of insulin resistance in Parkinson's disease

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ABSTRACT

This paper introduces a mathematical model representing the biochemical interactions between insulin signaling and Parkinson's disease. The model can be used to examine the changes that occur over the course of the disease as well as identify which processes would be the most effective targets for treatment. The model is mathematized using biochemical systems theory (BST). It incorporates a treatment strategy that includes several experimental drugs along with current treatments. In the past, BST models of neurodegeneration have used power law analysis and simulation (PLAS) to model the system. This paper recommends the use of MATLAB instead. MATLAB allows for more flexibility in both the model itself and in data analysis. Previous BST analyses of neurodegeneration began treatment at disease onset. As shown in this model, the outcomes of delayed, realistic treatment and full treatment at disease onset are significantly different. The delayed treatment strategy is an important development in BST modeling of neurodegeneration. It emphasizes the importance of early diagnosis, and allows for a more accurate representation of disease and treatment interactions.

1. Introduction

PD is a neurodegenerative disorder characterized by dopaminergic neuron death in the substantia nigra pars compacta and results in physical symptoms such as tremors, rigidity, and bradykinesia as well as psychological symptoms such as an increased risk of dementia, depression, and anxiety. Insulin resistance, a precursor of T2DM, is a result of a diet high in fats and sugars. Insulin signaling pathways and PD pathogenesis have been experimentally proven to converge (Morris et al., 2008, 2011), yet clinical data is inconsistent (Bosco et al., 2012). The model includes production of ROS and RNS, p38 phosphorylation, tau protein hyperphosphorylation, inflammation, and dopamine synthesis, degradation, and transport. This paper presents a mathematical model that details the interactions between these processes and how they can combine to influence neuronal death.

This disease simulation makes use of a modeling strategy know as BST, which was established by Savageu in 1969 and developed further by Voit in 2000. BST uses ODEs to model changes in reaction rates and species concentrations throughout the progression of the disease. This model includes a baseline state, which depicts a healthy cell, a disease state, modeling a cell with PD and insulin resistance, and a treatment state, which is a disease state cell including several treatment options. The disease state was created by activating trigger points within the baseline model that initiated disease development, and the treatment state was created by introducing a mixture of drugs at two times: the onset of the disease, and halfway through the disease progression. These treatments target reactions the models shows are important in PD pathogenesis where it converges with insulin signaling pathways.

2. Methods

2.1. Modeled pathways

This section explains several key pathways in the model, demonstrating the extent to which insulin signaling influences the biochemistry of PD. The system was modeled using the

Abbreviations: BST, biochemical systems theory; PLAS, power law analysis and simulation; PD, Parkinson's disease; T2DM, type-II diabetes mellitus; ROS, reactive oxygen species; RNS, reactive nitrogen species; ODE, ordinary differential equation; PPARG, peroxisome-proliferator-activated receptor γ; IL-6, interleukin-6; IL-1β, interleukin-1β; TNFα, tumor necrosis factor α; MCSF, macrophage colony-stimulating factor; COX2, cyclooxygenase 2; NO, nitric oxide; H_2O_2, hydrogen peroxide; O_2-, superoxide radical; OH-, hydroxyl radical; ONOO-, peroxynitrite; HNO_2, nitrous acid; NF-κB, nuclear factor κB; VMAT, vesicular monoamine transporter proteins; SOD2, superoxide dismutase 2; PI3K, phosphatidylinositol 3 kinase; PIP2, phosphatidylinositol bisphosphate; PIP3, phosphatidylinositol trisphosphate; GSK-3β, glycogen synthase kinase 3β; MKP-1, mitogen-activated protein kinase phosphatase 1; DUPS1, dual specificity protein phosphatase 1; PTP, permeability transition pore; AIF, apoptosis-inducing factor; SMAC/DIABLO, second mitochondria-derived activator of caspases/direct iap binding protein with low pI; IAP, inhibitor of apoptosis; NAC, *N*-acetylcysteine; NOS, nitric oxide synthase; NSAID, non-steroidal anti-inflammatory drug; ALS, amyotrophic lateral sclerosis.

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biochemical pathway visualization program CellDesigner. For a full model of the system, please refer to Fig. A.1 in Appendix A.

2.1.1. Insulin signaling and inflammation

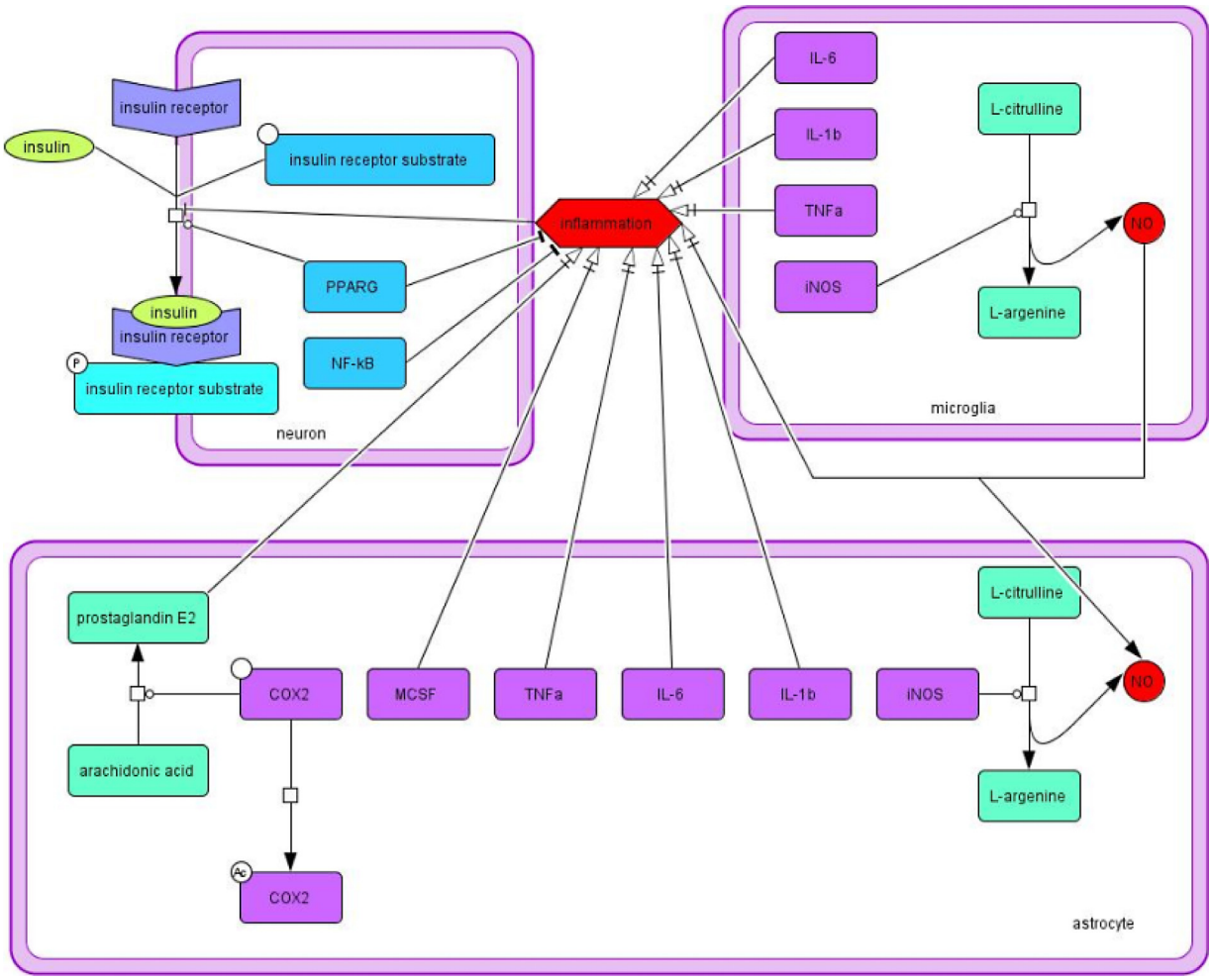
Insulin signaling begins with insulin binding to the insulin receptor on the cellular membrane, which causes phosphorylation of the insulin receptor substrate (Takahashi et al., 1996). Insulin signaling is promoted by PPARG, which is also a transcription factor for proteins important in antioxidant scavenging and mitochondrial repair (Miranda et al., 1999; Mudo et al., 2012; Xing et al., 2007). Insulin signaling is inhibited by the chronic inflammation present in PD. The inflammation is a result of cytokine production in astrocytes and microglia, specifically cytokines IL-1β, IL-6, TNFα, and MCSF (Ghosh et al., 2007; Glass et al., 2010). Overproduction of NO promoted by nitric oxide synthase (Hunot et al., 1996), prostaglandin synthesis promoted by COX2 (Xing et al., 2007), and NF-κB in the neuron and glia are also contributing factors. Inflammation is deceased by the presence of PPARG (Ricote et al., 1998). This process is outlined in Model 1 .

2.1.2. Dopamine

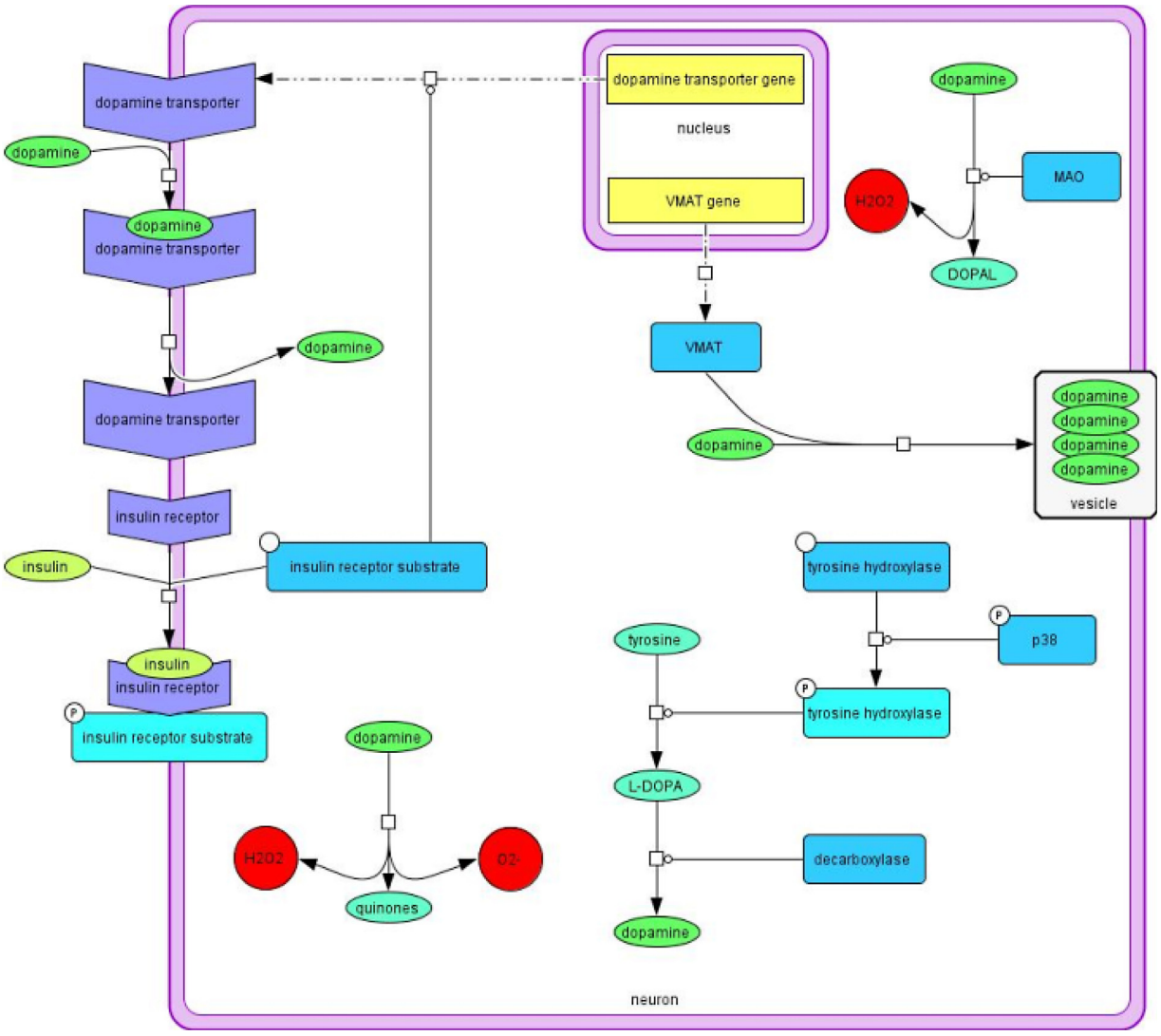
Dopamine is produced in the neuron through the conversion of tyrosine to L-DOPA, and L-DOPA to dopamine (Model 2). Tyrosine hydroxylase, which is activated via phosphorylation by phosphorylated p38, promotes L-DOPA synthesis, and decarboxylase promotes the final step in the process to produce dopamine (Yu et al., 2005). Dopamine can also enter the cell through the dopamine transporter, which is upregulated by insulin signaling (Patterson et al., 1998). Free dopamine in the cell can be degraded into quinones, H_2O_2, and O_2- (Yu et al., 2005), or use a monoamine oxidase promoter, producing H_2O_2 and DOPAL (Marchitti et al., 2007). Alternatively, dopamine is collected into vesicles to be released at synapses. Vesicular dopamine is protected from degradation and the resulting production of ROS. VMAT are important in sequestering the dopamine into vesicles. VMAT is downregulated in PD (Xiong et al., 2011).

2.1.3. Reactive oxygen and nitrogen species

ROS are the result of dopamine degradation and mitochondrial dysfunction in PD. Mitochondrial dysfunction creates an excess of O_2-, which can be converted to H_2O_2 by SOD2. The H_2O_2 can then be converted to water by glutathione or catalase (Evans et al., 2002), or OH- by Fe through the Fenton reaction. Dopamine degradation also produces H_2O_2 and O_2- in the cell. NO, a RNS, is produced in both the neuron and the glia from L-citrulline, and is membrane-permeable (Hunot et al., 1996). The NO can react with O_2- to create ONOO-, which is extremely dangerous to the neuron (Beckman and Crow, 1993). Excessive ROS and RNS can react easily with vital cellular species causing lipid peroxidation, misfolded proteins, DNA damage, and endoplasmic reticulum and mitochondrial stress, all of which decrease cellular function and increase the risk of cell death. ROS and RNS can also trigger the caspase cascade, initiating apoptosis (Choi et al., 2004; Ko et al., 2005) Model 3 .



Model 1. Mechanisms of inflammation and factors influencing insulin signaling.



Model 2. Reactions and cellular processes involving dopamine.

2.1.4. Tau phosphorylation, neurofibrillary tangles, and Lewy bodies

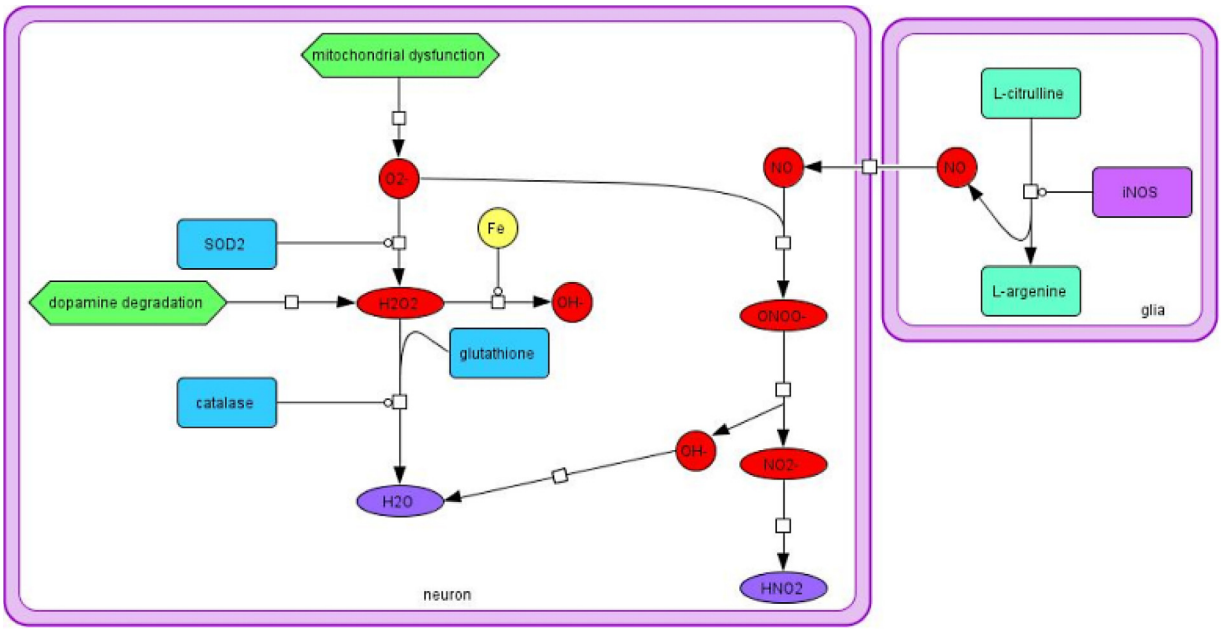
Insulin signaling phosphorylates PI3K (Piao et al., 2012), which in turn phosphorylates PIP2, creating PIP3. PIP3 deactivates GSK-3β through phosphorylation, which prevents it from promoting tau hyperphosphorylation (Lucas et al., 2001). Tau hyperphosphorylation is also promoted by phosphorylated p38 (Zarubin and Han, 2005). The tau protein is important in microtubule stabilization, so the loss of function caused by the hyperphosphorylation results in impeded axonal transport. Hyperphosphorylated tau is a component of aggregates such as neurofibrillary tangles and Lewy bodies, which are characteristic of PD (Arima et al., 1999; Bancher et al., 1993). Lewy bodies also contain proteins such as parkin and α-synuclein, which aggregate as a result of ROS interactions that cause them to misfold (Winklhofer et al., 2003; Zheng et al., 2010) Model 4 .

2.1.5. p38 Phosphorylation

The p38 mitogen-activated protein kinase is involved in several different pathways in this model. p38 is activated by phosphorylation, which is promoted by prostaglandins, tumor necrosis factor α receptor 1 signaling, and ROS (Choi et al., 2004). Inhibition of p38 phosphorylation is caused by insulin signaling (Heidenreich and Kummer, 1996) and the MKP-1 expressed by the DUSP1 gene (Taylor et al., 2013). p38 promotes caspase 9 maturation leading to apoptosis, tau phosphorylation, tyrosine hydroxylase activation, Bax/tBID complex formation resulting in mitochondrial membrane depolarization and related dysfunction, and finally Hsp27 activation (Snyder et al., 2009; Yu et al., 2005; Zarubin and Han, 2005). Hsp27 can inhibit tau phosphorylation, increase glutathione expression, inhibit Fas ligand binding, and decrease Lewy body formation by preventing α-synuclein aggregates from accumulating in the Lewy bodies (Choi et al., 2012; Mehlen et al., 1996a,b; Shimura et al., 2004; Zourlidou et al., 2004). p38 can also be ubiquitinated by the E3 ubiquitin ligase parkin and degraded (Ko et al., 2005). Parkin is downregulated in PD which causes an increase in p38 Model 5 .

2.1.6. Cell death

Cytosolic ROS can directly cause apoptosis by activating the caspase cascade (Choi et al., 2004; Ko et al., 2005), and mitochondrial ROS can indirectly activate the caspase cascade by opening the PTP of the mitochondria and releasing cytochrome c (Moon et al., 2005), SMAC/DIABLO, and AIF. SMAC/DIABLO increases caspase activity by binding to IAP proteins, which prevent the IAP from binding to and inhibiting caspases 3 and 9. Cell death can also be triggered in a caspase-independent manner by DNA fragmentation and chromosome condensation initiated by the migration of the AIF from the mitochondria to the nucleus



Model 3. Synthesis and degradation of reactive oxygen and nitrogen species.

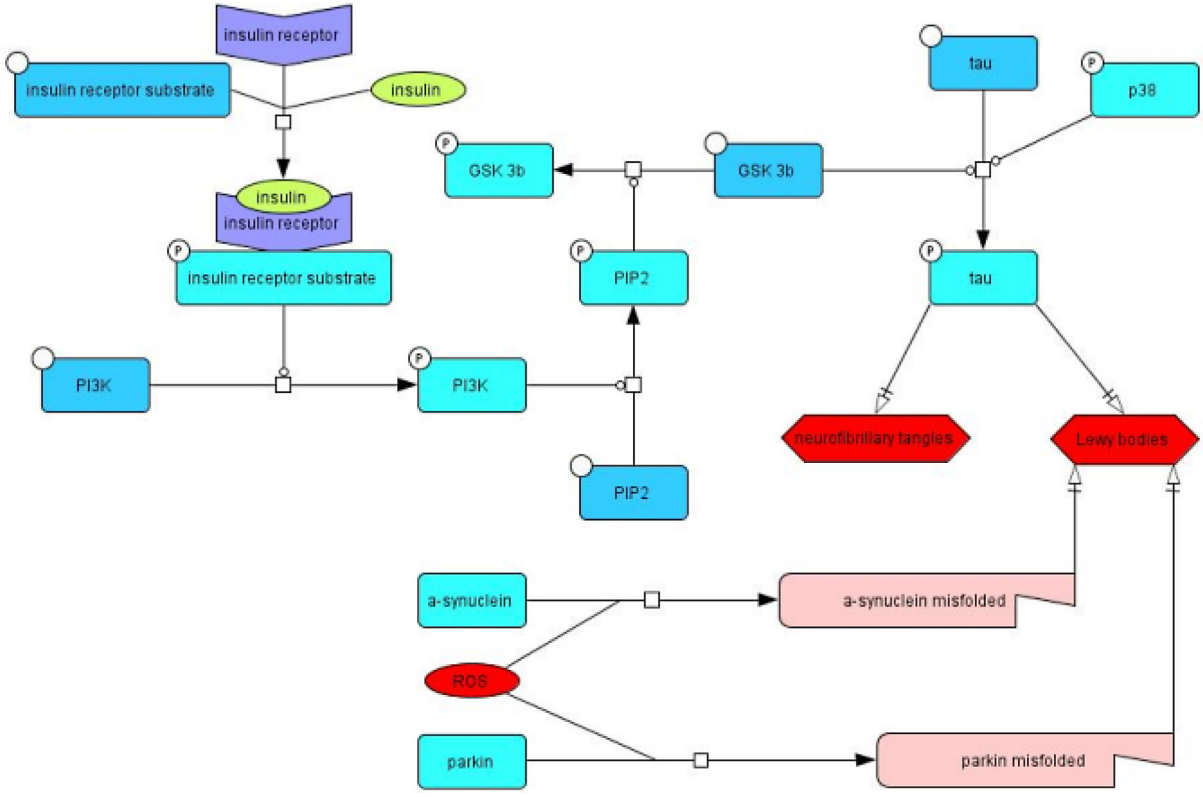
(Susin et al., 1999). Furthermore, hyperphosphorylated tau can create neurofibrillary tangles and Lewy bodies, inducing cell death Model 6 .

2.2. Biochemical systems theory

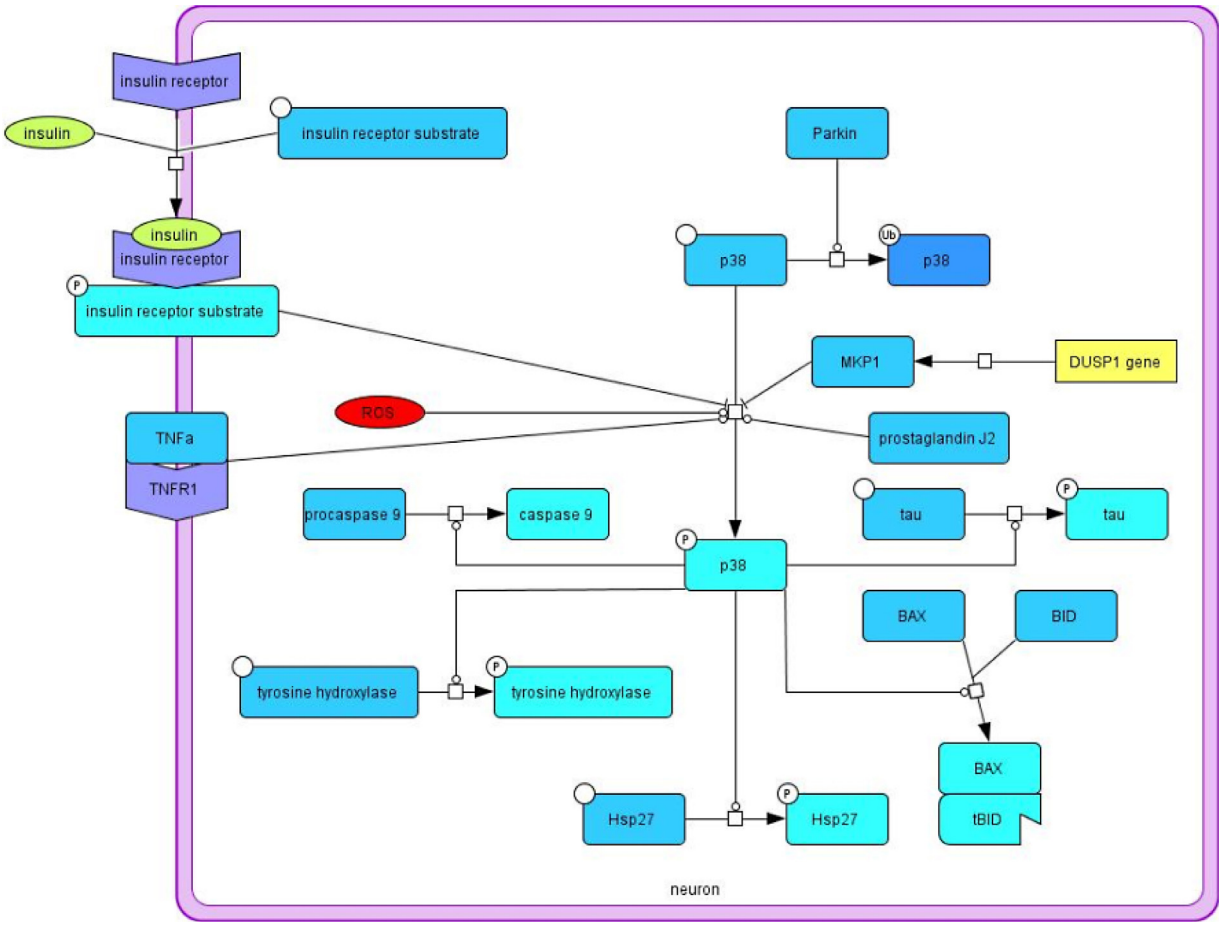
The system was mathematized using BST to create a dynamic model in MATLAB of the species concentrations and reaction rates as they change over the course of the disease. For further information on the use of BST to model neurodegenerative disease systems using PLAS, see this lab's previous work (Broome and Coleman, 2011; Sass et al., 2009; Yeager and Coleman, 2010). See Appendix A for a sample of the code used to model the system.

2.2.1. Initial values

Initial values are assigned to both independent and dependent variables. Independent variables are species that are not the products of any process or reaction in the system, whereas



Model 4. The effects of insulin resistance on tau hyperphosphorylation, neurofibrillary tangle accumulation, and Lewy body production.

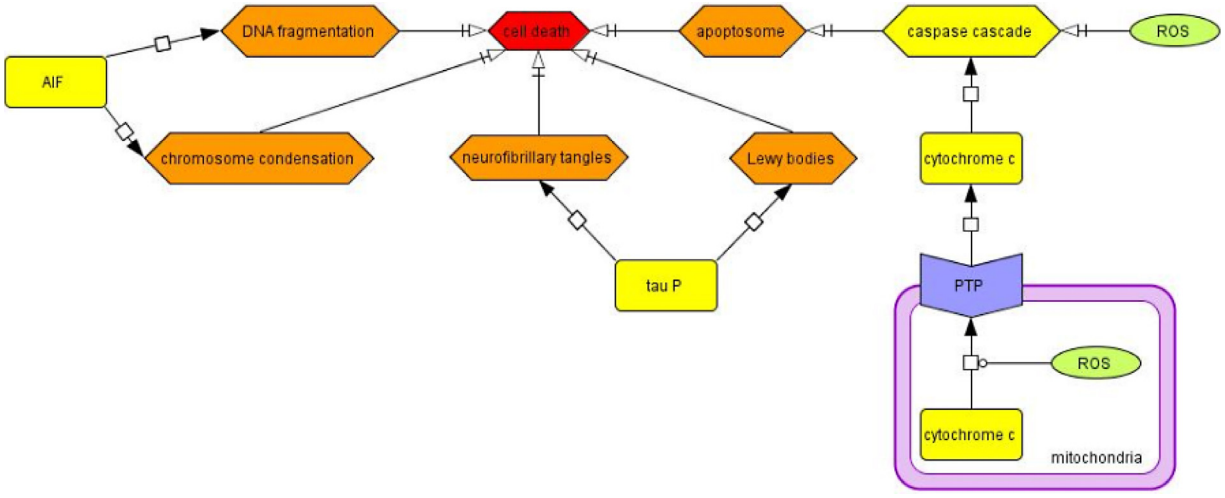


Model 5. Mechanisms influencing p38 phosphorylation and its effects on the cell.

dependent variables are the product of at least one process or reaction. The values are assigned on a relative rather than absolute basis which allows for the estimation of unknown values. When available, values from the literature are taken into consideration and adapted to the relative scale.

2.2.2. Flux equations

Flux equations, each of which is assigned a location in the matrix J, describe the relative reaction rates. Each flux equation takes into account the concentrations of the reactant species and a rate constant or rate equation. Every reaction or process in the model is assigned a flux equation. Flux equations take the following form: $J(88) = X(258) \times Xind(75)$. In this case, J(88) represents L-DOPA synthesis, the 88th value in J. Xind(75) represents the independent variable tyrosine, and X(258) represents the rate ODE. Rate equations consist of a constant multiplied by the sum of all promoters and inhibitors, where promoters have positive concentration values and inhibitors have negative



Model 6. Cellular processes contributing to the death of SNPc neurons.

concentration values. In this case, X(258) = 0.0001 × X(92), where X(92) represents the promoter phosphorylated tyrosine hydroxylase. In the event that a reaction or process does not include any promoters or inhibitors, a rate constant, specified as a value in the array k, is included instead. An example of an unmodified reaction is the equation for the formation of the IAP inhibition complex: J(96) = k(54) × Xind(82) × X(102), where k(54) is the rate constant, X(102) is cytosolic SMAC/DIABLO, and Xind(82) is IAP.

2.2.3. Systems equations

Each dependent variable is assigned a systems equation, which describes the relative concentration of the species. Systems equations consist of the sum of all the flux equations in which the dependent variable is a reactant subtracted from the sum of all flux equations in which the dependent variable is a product. For example, X(93) = X(258) × Xind(75) − X(259) × X(93), where X(93) represents L-DOPA, X(258) × Xind(75) represents L-DOPA synthesis from tyrosine, and X(259) × X(93) represents dopamine synthesis from L-DOPA.

2.2.4. Data analysis

This system exists in three states: a baseline state, a disease state, and a treatment state. The baseline state is created to mimic a healthy system. Once an accurate baseline state is reached, the disease state is triggered by revising specific initial concentrations and rate constants that are abnormal in PD. In order to analyze the effects of PD on the system the baseline state is subtracted from the disease state so that any species with a positive value is elevated during the disease and any species with a negative value means the species is less present in PD. The treatment state, which is prepared by adding treatment options to the disease state, is compared to the baseline state in the same manner. This comparative method works to reduce inaccuracies inherent in the relative values methodology. The model is intended to provide information on relative trends only, not absolute values. Two treatment states, one in which the treatment is introduced at disease onset, and one in which treatment is introduced halfway through disease progression ($t = 75$), are created. This delay is a novel technique in the evaluation of treatments in neurodegeneration using BST, and provides significant insight into the efficacy of the treatment states. The delay is a more realistic simulation of the effects the treatments will have on the patient, as diagnosis and subsequent treatment at disease onset is unlikely to occur. The comparative disease state and two comparative treatment states are then graphed together in order to assess the impact of the treatment strategy on the disease both in the best-case scenario and the more realistic scenario.

3. Results

3.1. Insulin signaling and inflammation

3.1.1. Disease state

Insulin signaling is impaired by decreasing the rate at which it binds to the insulin receptor. The relative concentration of the insulin receptor complex continues to decrease as the disease progresses. Normal insulin signaling also decreases compared to the baseline in response to the effects of PD (Fig. 1). Inflammation increases in the PD state compared to the baseline state as a result of an increase in ROS, NF- κB signaling in the astrocytes and microglia, and cytokine expression (Fig. 2).

3.1.2. Treatment state

The lack of insulin signaling is partially corrected for by the inclusion of pioglitazone and sodium butyrate, which act as insulin sensitizers (Gao et al., 2009; Hu et al., 2013). Insulin signaling is fully recovered in the model when it is initially at normal levels, and is significantly recovered in the insulin resistant model as well during full treatment (Fig. 1). With a delayed initiation of treatment, insulin signaling in both the initially insulin resistant

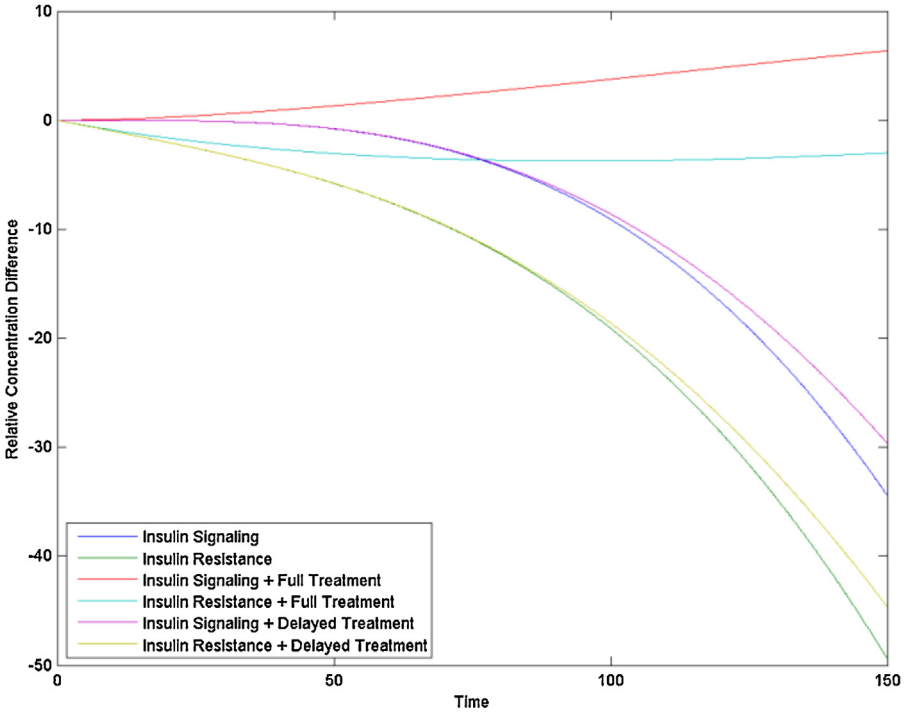


Fig. 1. Insulin signaling: a comparison between a Parkinson disease model that initially includes insulin resistance and one that begins with normal insulin signaling.

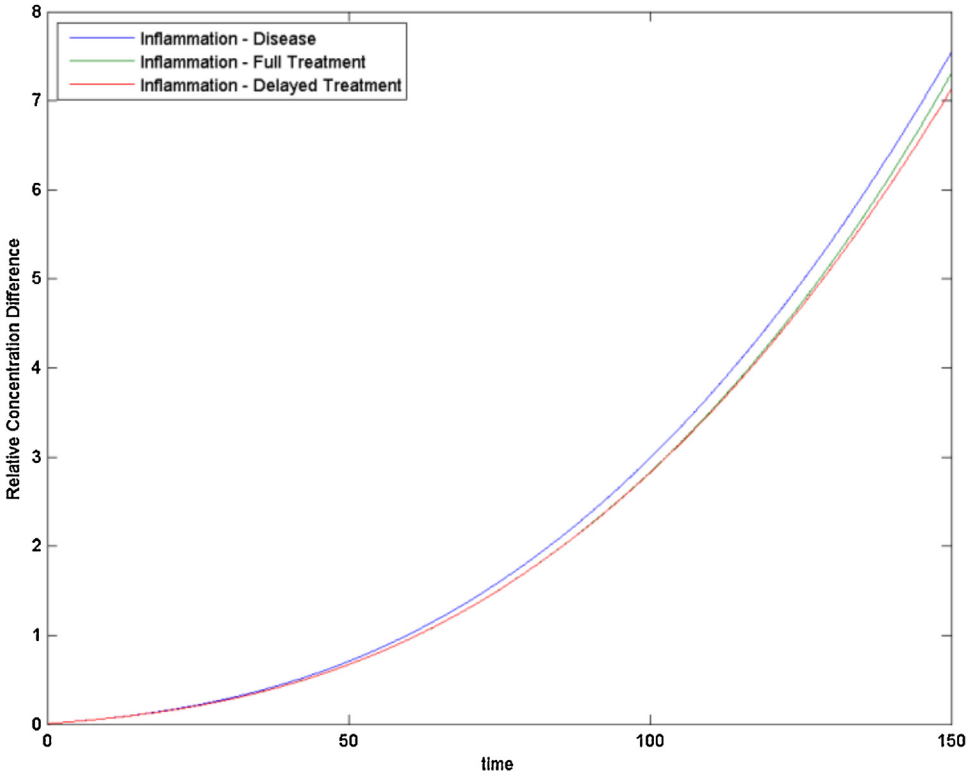


Fig. 2. Inflammation: an increase in inflammation which is to some extent corrected by the treatment state.

and initially insulin sensitive models are partially corrected but continue on a downward trend. Inflammation is corrected by treatments of vitamin D (Chang et al., 2004), NAC, and aspirin (Ambhore et al., 2014). Vitamin D inhibits NOS from producing pro-inflammatory NO in the glia. NAC inhibits NF- κB from entering the nucleus (Oka et al., 2000), thereby reducing expression of inflammatory cytokines. NAC also acts as a COX2 inhibitor, reducing the production of prostaglandins. Aspirin

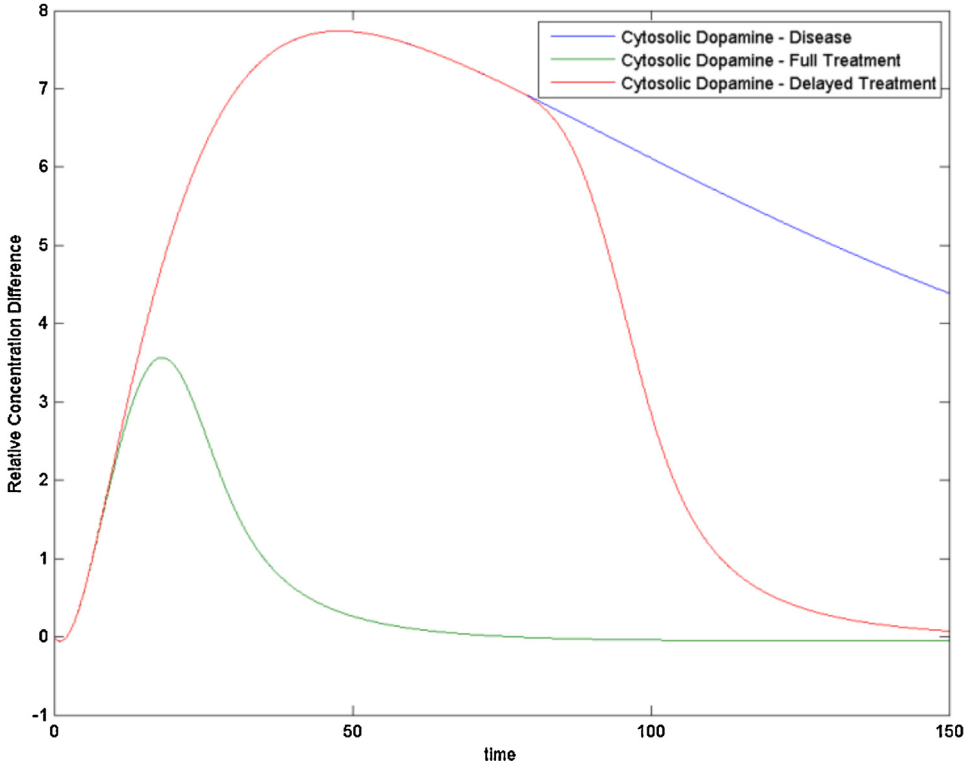


Fig. 3. Cytosolic dopamine: increased levels of cytosolic dopamine levels which are eventually fully rectified in the treatment state.

acetylates COX2, inhibiting its function as a promoter of prostaglandin synthesis. The decrease in cytokine, NO, and prostaglandin concentrations accordingly decrease inflammation, although inflammation is still largely present (Fig. 2). The full treatment state was similar to the delayed state in the prevention of inflammation.

3.2. Dopamine

3.2.1. Disease state

Dopamine levels are manipulated in the disease state by decreasing the concentration of VMAT transporters that allow the dopamine to be sequestered into vesicles. Extracellular dopamine concentrations are reduced to account for the degeneration of nearby dopaminergic neurons from PD, thereby reducing intercellular dopamine signaling. Dopamine degradation rates are increased in the disease state. Cytosolic dopamine levels actually increase in the PD model (Fig. 3); however, vesicle dopamine is decreased (Fig. 4). Cytosolic dopamine is undesirable in the cell because it is vulnerable to degradation into ROS. Vesicle dopamine is the preferred form because it is protected from degradation and is available for signaling at the synapse.

3.2.2. Treatment state

Treatments for dopamine imbalances in the PD neuron include vitamin D (Puchacz et al., 1996) and edaravone (Xiong et al., 2011). These two treatments complement each other because vitamin D increases cytosolic dopamine levels by increasing expression of tyrosine hydroxylase, which is important in dopamine synthesis, while edaravone promotes VMAT expression, increasing the ability of dopamine to be transported to the vesicles. The treatment state initially follows the disease state progression with a sharp increase in cytosolic dopamine levels and corresponding decrease in dopamine vesicle concentration, but then corrects to normal cytosolic dopamine levels (Fig. 3). Full treatment returns to normal levels much more quickly than delayed treatment does, and delayed treatment reaches the same maximum concentration difference as the disease state before declining. Only a slight decrease from baseline in vesicle dopamine concentration is observed with full treatment (Fig. 4). Delayed treatment allows for a much larger gap from the baseline that is never recovered within the scope of the model.

3.3. Reactive oxygen and nitrogen species

3.3.1. Disease state

Mitochondrial dysfunction, dopamine metabolism rate, ROS production rates, and RNS production rates are increased in the disease state while antioxidant concentrations are decreased to trigger ROS and RNS accumulation. The ROS and RNS portrayed in Fig. 5 consist of the sums of the levels of cytosolic O_2-, H_2O_2, OH-, ONOO-, NO, and mitochondrial O_2- in the neuron, as well as extracellular NO.

3.3.2. Treatment state

Antioxidant treatments included in the model are vitamin D, edaravone, and NAC (Samuni et al., 2013). Vitamin D can help to decrease cytosolic O_2- concentrations, and prevent Ca^{2+} influx into the cell. Ca^{2+} buildup in the mitochondria can cause excess O_2- production (Gandhi et al., 2009). Edaravone prevents mitochondrial DNA damage, reducing mitochondrial dysfunction (Xiong et al., 2011). NAC acts as an antioxidant in several ways. It is a precursor to glutathione, which is important in neutralizing H_2O_2. It can also react with ONOO- to degrade it into NO_2- and OH-,

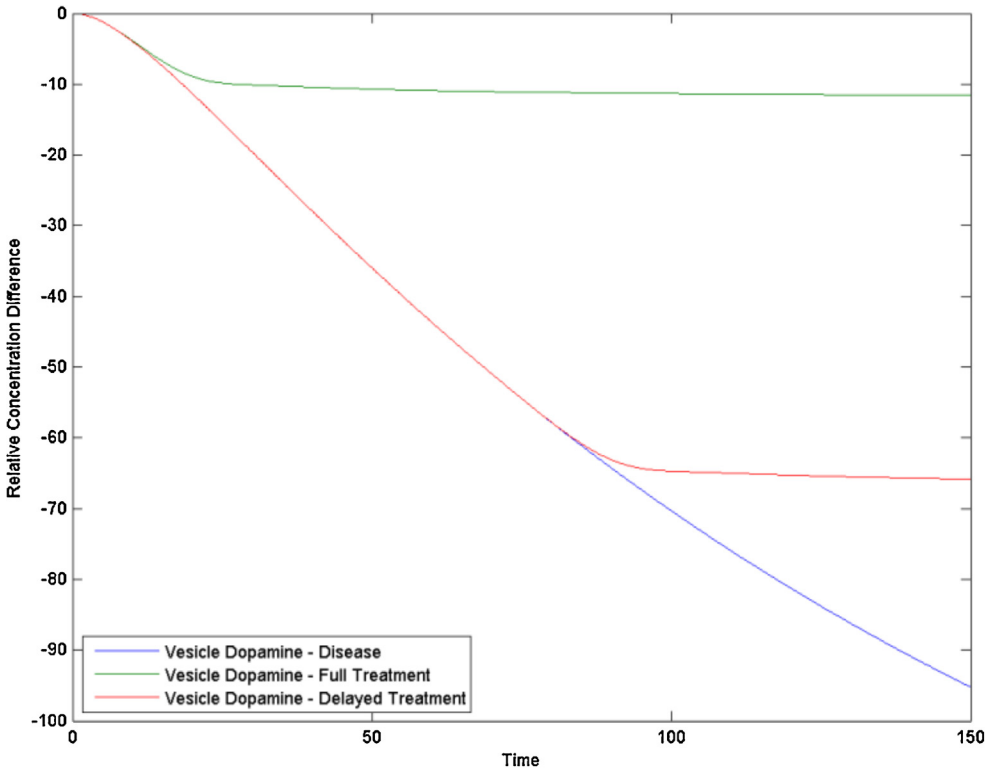


Fig. 4. Vesicle dopamine: the decrease in cytosolic dopamine levels in the disease state is prevented in the treatment state, and the vesicle concentration becomes more constant.

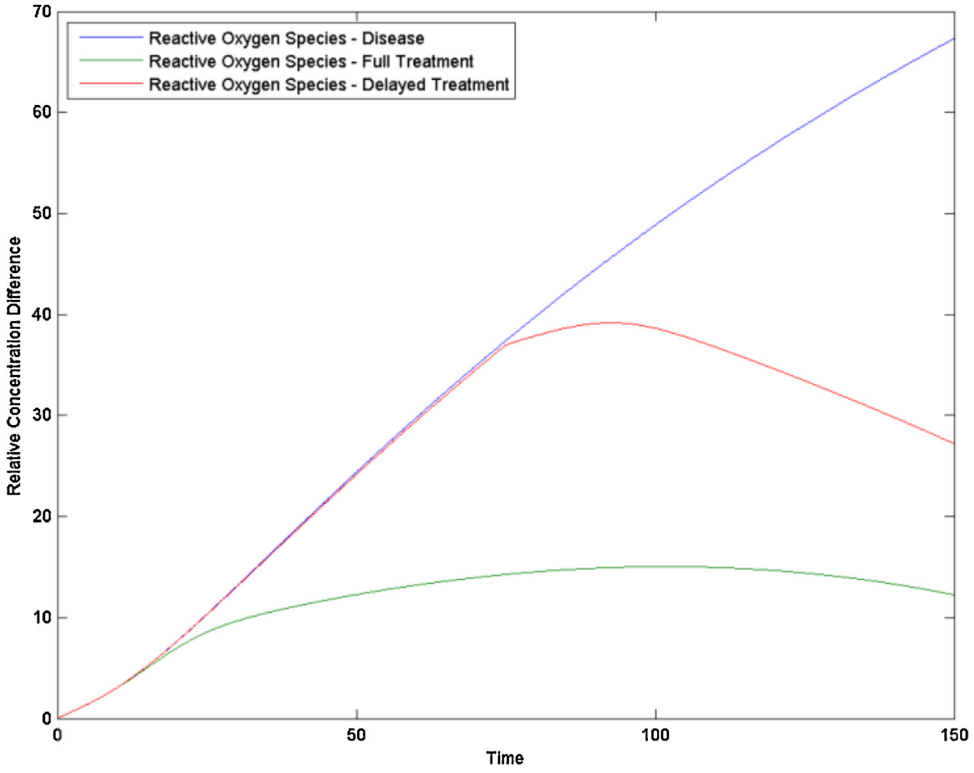


Fig. 5. Reactive oxygen species: the level of reactive oxygen species is much lower in the treatment state than the disease state.

and then react with those two species to form HNO_2 and water. Full treatment greatly reduced ROS and RNS presence in the neuron (Fig. 5). Delayed treatment originally follows the course of the disease state, but then begins to approach the full treatment state.

3.4. Tau phosphorylation, neurofibrillary tangles, and Lewy bodies

3.4.1. Disease state

Tau phosphorylation is triggered by increasing activated GSK-3β concentrations by decreasing insulin signaling, indirectly triggering p38 phosphorylation, and increasing α-synuclein aggregations, which interact with tau and create toxic accumulations of the two proteins (Lei et al., 2010). Hyperphosphorylated tau in the disease state increases sharply compared to the baseline state (Fig. 6). Neurofibrillary tangles are a consequence of tau hyperphosphorylation and increase accordingly (Fig. 7). Lewy bodies are the result of aggregated α-synuclein, hyperphosphorylated tau, and other misfolded proteins, and increase in concentration as these species become more numerous (Fig. 8).

3.4.2. Treatment state

Treatments included in the model that affect tau phosphorylation, neurofibrillary tangles, and Lewy bodies are lithium (Petit-Paitel et al., 2009), edaravone (Zhou et al., 2013), and sodium butyrate (Taylor et al., 2013). Lithium promotes GSK-3β phosphorylation, which prevents it from phosphorylating tau. Edaravone also inhibits tau phosphorylation. Sodium butyrate triggers the expression of MKP-1, which prevents tau phosphorylation by inhibiting p38 activation. Phosphorylated tau is considerably diminished in the treatment state, but is still present (Fig. 6). Neurofibrillary tangles (Fig. 7) and Lewy bodies (Fig. 8) decline at a greater rate. In these three cases, a delayed treatment does cause a decrease in species concentration, but still continues the upward trend characteristic of the disease state. Delayed treatment slows the accumulation of these species but does not prevent it.

3.5. p38 Phosphorylation

3.5.1. Disease state

Decreasing the rate of insulin signaling, increasing the concentrations of ROS, and increasing the presence of prostaglandin J2 from the baseline state increases the activation of p38 in the disease state (Fig. 9). A decrease in the availability of parkin as an E3 ubiquitin ligase in the p38 degradation pathway is also a contributing factor to the excess p38 phosphorylation. As a result of p38 phosphorylation, mitochondrial dysfunction, apoptosis, tau phosphorylation, dopamine synthesis, and Hsp27 activation also increase.

3.5.2. Treatment state

The full treatment state reduces p38 concentrations past the baseline state (Fig. 9). Activation by MKP-1 through sodium butyrate treatment inhibits p38 phosphorylation (Taylor et al., 2013). Sodium butyrate increases expression of the DUSP1 gene, increasing the expression of MKP-1. This phosphatase is responsible for dephosphorylating p38, rendering it inactive. The reduction in ROS levels also contributed to the decline of the p38 concentration, as they are less available to promote the phosphorylation. Delayed treatment failed to produce similar results, instead predicting an increase in phosphorylated p38 compared to the baseline state, but still producing a positive impact by remaining at a lower concentration than in the disease state.

3.6. Cell death

3.6.1. Disease state

Cell death can be triggered by apoptosome formation following activation of the caspase cascade by ROS in the cytosol, or by mitochondrial dysfunction and release of cytochrome c.

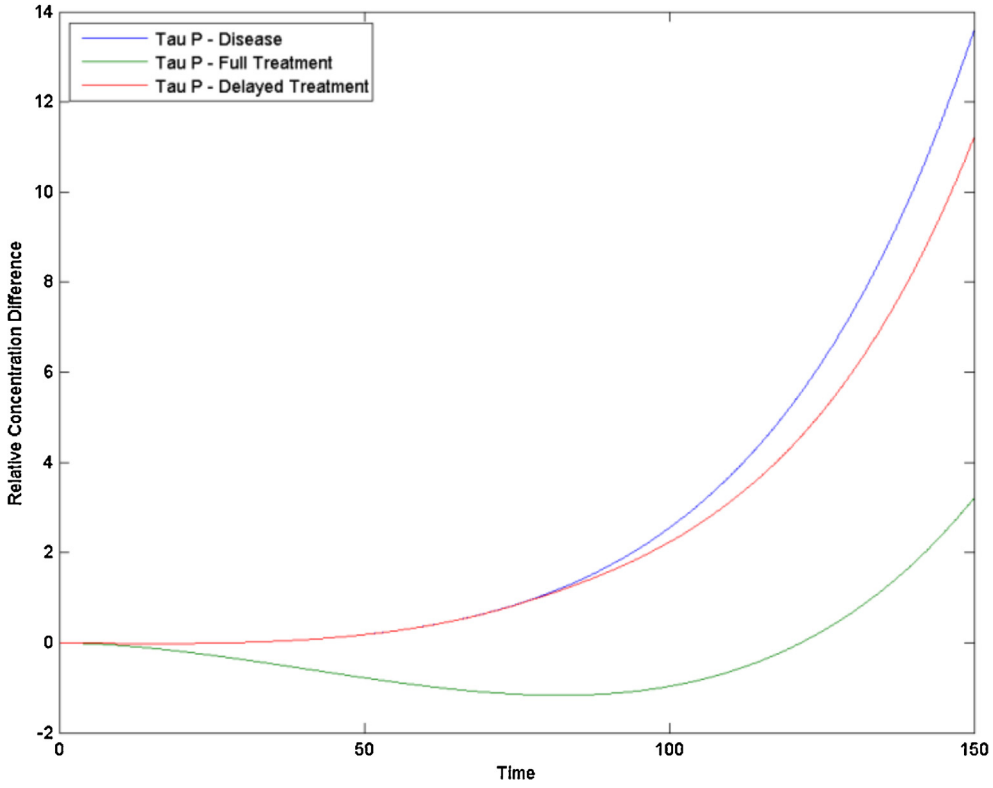


Fig. 6. Phosphorylated tau: tau phosphorylation is elevated in Parkinson's disease, but is slowed in the treatment state.

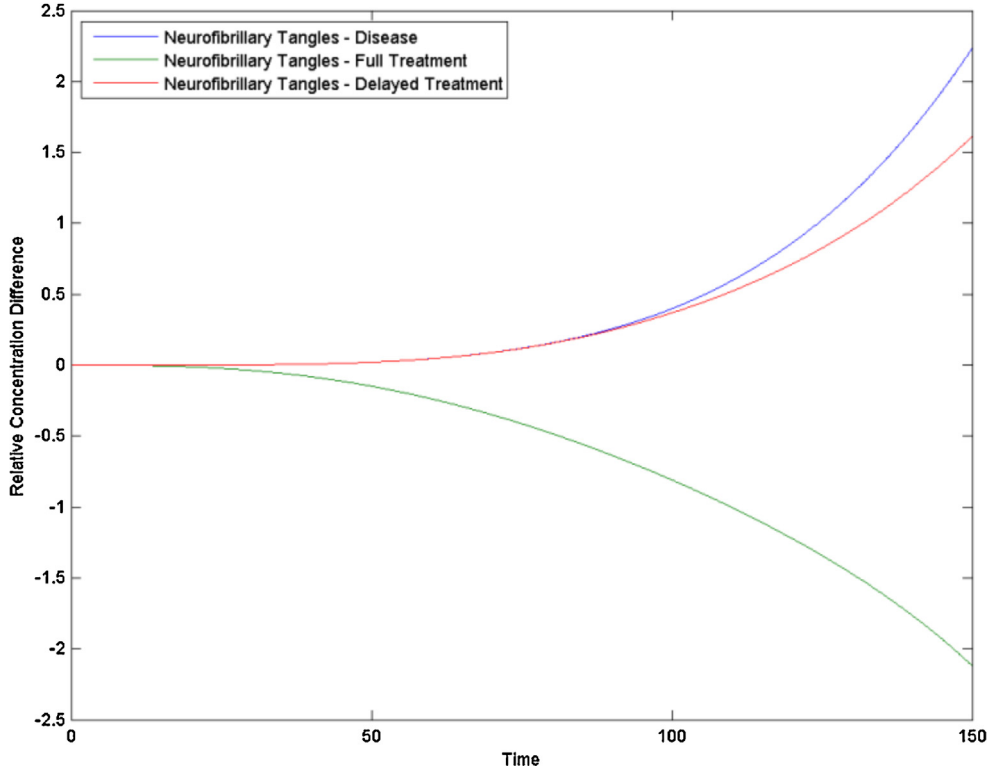


Fig. 7. Neurofibrillary tangles: neurofibrillary tangles are increasingly present in the disease state, but are present at a lower level in the treatment state.

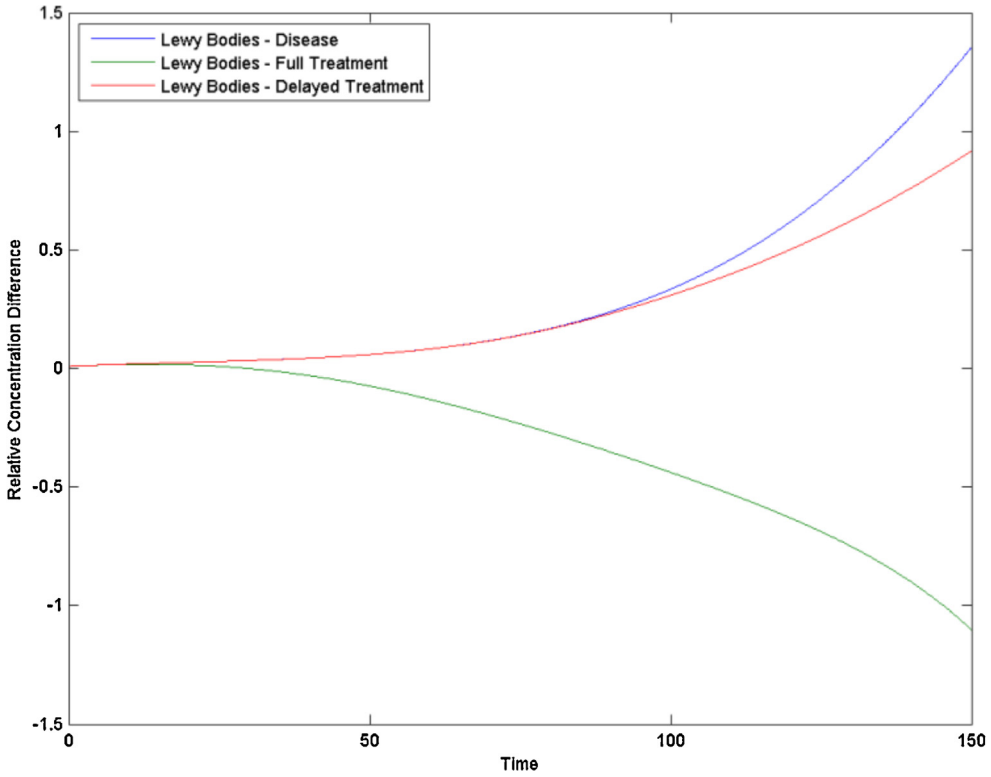


Fig. 8. Lewy bodies: Lewy body increase in Parkinson's disease is lessened in the treatment state.

Both cytosolic and mitochondrial ROS are elevated in the disease state. Lewy bodies and neurofibrillary tangles can also cause cell death. Finally, DNA fragmentation and chromosome condensation caused by AIF presence in the nucleus can lead to apoptosis. AIF is released along with cytochrome c as the PTP opens on the mitochondrial membrane. These factors all contribute to the increased probability of apoptosis seen as the model progresses (Fig. 10).

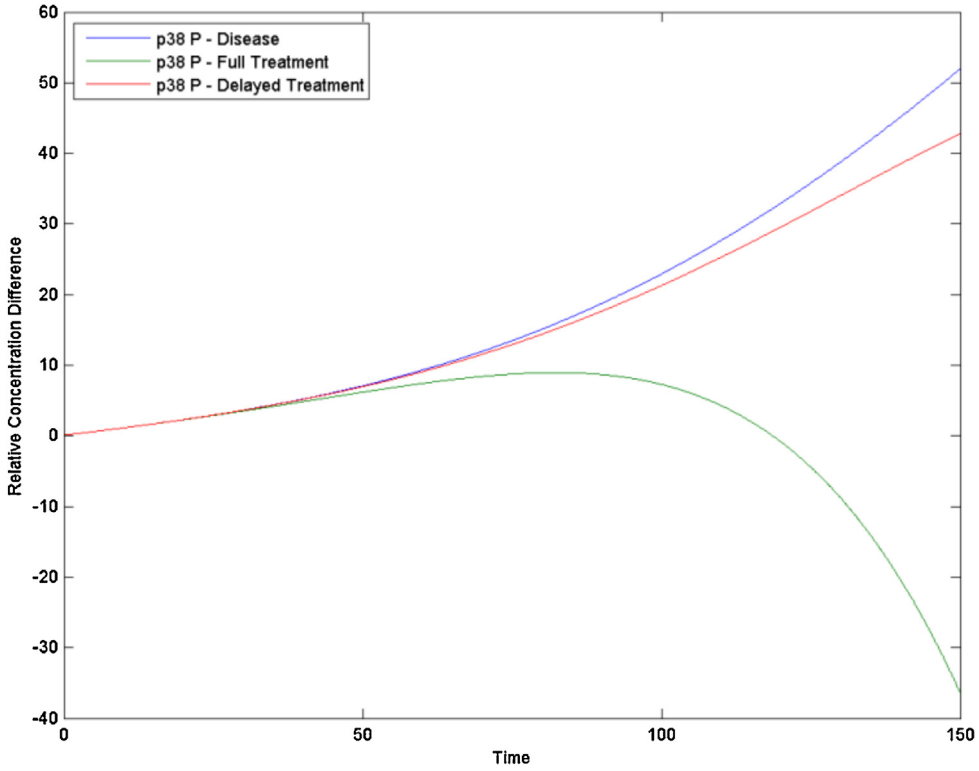


Fig. 9. Phosphorylated p38: the disease state includes increased phosphorylation of p38, which is attenuated in the treatment state.

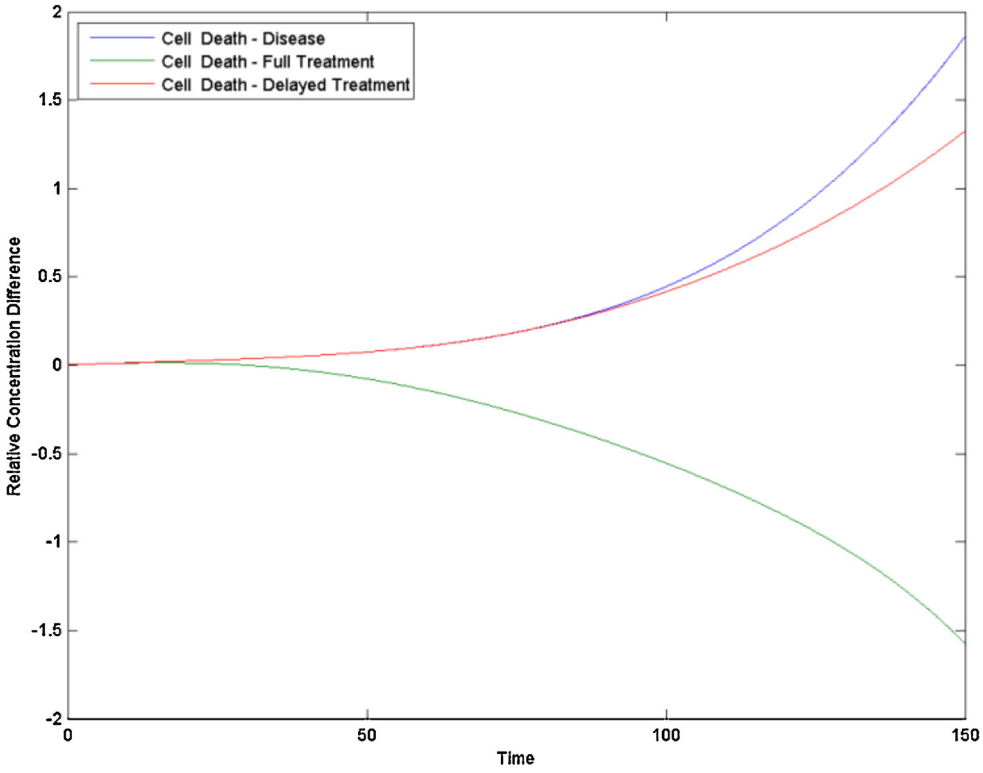


Fig. 10. Cell death: the treatment state corrects for some of the cell death caused by pathways influenced by insulin signaling in Parkinson's disease.

3.6.2. Treatment state

Apoptosis is prevented by several drugs including edaravone (Cheng et al., 2014; Xiong et al., 2011), Sodium butyrate (Taylor et al., 2013), cyclosporin A, and nortriptyline (Lamarche et al., 2013). Edaravone prevents apoptosis by inhibiting tau phosphorylation, promoting the expression of the mitochondrial protein Bcl-XL, and inhibiting the expression of the related Bax protein. The Bax protein binds to the truncated version of Bid and increases opening of the PTP. Bcl-XL can bind to the Bax/Bid complex to prevent this process. Sodium butyrate inhibits the apoptotic proteins Jun and p38 from being activated through its promotion of MKP-1 expression. Cyclosporin A and nortriptyline prevent the PTP from opening and releasing apoptotic factors such as cytochrome c, SMAC/DIABLO, and AIF. Cell death is successfully prevented if the treatment is presented at disease onset, but is still present, albeit in a diminished state, when the treatment is delayed.

4. Discussion

4.1. Disease state

The disease state model mimics the current understanding of PD in that it shows increases in inflammation, apoptotic factors, ROS and RNS, abnormal dopamine concentrations, and elevated levels of phosphorylated tau, neurofibrillary tangles, and Lewy bodies, which are characteristic of PD. These factors are only a fraction of the numerous of processes that typify PD, which also include but are not limited to the misfolding of α-synuclein, gene mutations, endoplasmic reticulum stress, and ubiquitin proteasome system malfunction, which are not fully explored in this model. The disease state modeled here is exacerbated by a loss of insulin signaling, usually caused by an excess of fats and sugars in the diet and a major factor in the development of T2DM. The model also suggests that dopaminergic neuronal insulin signaling is highly impaired in PD. This is likely caused by PD effects such as chronic inflammation and oxidative stress, which are common causes of insulin resistance in T2DM patients (Evans et al., 2002).

4.2. Treatment state

The model suggests a variety of treatment options to ameliorate both causes and symptoms of PD. Vitamin D, lithium, aspirin, NAC, edaravone, pioglitazone, Sodium butyrate, cyclosporin A, and nortriptyline are the treatments included in the version of the model presented in this paper. Vitamin D acts as a ROS scavenger as well as decreasing inflammation. Lithium is a GSK 3β inhibitor. It is currently used as a treatment for bipolar disorder, but is being researched as a treatment for PD. Aspirin, a common, over-the-counter pain medication, is a NSAID and inhibits the inflammatory cytokine COX2. NAC acts as both an anti-inflammatory and antioxidant compound by inhibiting NF-κB, increasing glutathione concentrations, and reacting to neutralize ROS and RNS. NAC is currently used as a treatment for a variety of psychiatric conditions including schizophrenia, obsessive-compulsive disorder, and addiction (Dean et al., 2011). Edaravone protects against mitochondrial damage and tau phosphorylation, while promoting dopamine entry into vesicles. It is currently being investigated as a PD medication, as well as being involved in ongoing clinical trials to evaluate its potential as a treatment for ALS, another neurodegenerative disease. Pioglitazone is a known insulin sensitizer and is used in the treatment of T2DM. Sodium butyrate prevents apoptosis by inhibiting the activation of pro-apoptotic proteins p38 and Jun. It also acts as an insulin sensitizer, and is currently being studied as a treatment for T2DM and the neurodegenerative condition Huntington's disease. Cyclosporin A, an immunosuppressant, and nortriptyline, an antidepressant, both block apoptosis by preventing the PTP from opening.

PD symptoms occur only after the disease progression is well under way. Treatment, therefore, is often delayed. This model

includes one condition in which treatment is introduced at the onset of the disease, and one in which treatment is introduced halfway through the modeled disease progression. As the model is concerned with data compared to a standard rather than absolute values, a definite time scale is not necessary to view trends in the treatment state relative to the disease state. The differences between the scenarios highlight the importance of early detection of PD and, for the familial version of the disease, the introduction of possible preventative measures. The delayed treatment states for insulin resistance (Fig. 1), cell death (Fig. 10), p38 phosphorylation (Fig. 9), Lewy bodies (Fig. 8), neurofibrillary tangles (Fig. 7), and tau phosphorylation (Fig. 6) each resemble their disease state simulations more than their full treatment states. ROS (Fig. 5) and inflammation (Fig. 2) levels are partially corrected, but still high. Cytosolic dopamine (Fig. 3) levels eventually return to normal, and while vesicle dopamine (Fig. 4) levels are stabilized with treatment, the original concentration was not restored.

4.3. MATLAB

This paper introduces a new protocol for coding neurodegenerative systems using MATLAB instead of PLAS. Unlike PLAS, MATLAB is capable of analyzing all aspects of the quantitative model, from solving the ODEs to preparing graphs. PLAS requires the use of separate programs such as Microsoft Excel for any data analysis and visualization required after the ODEs are solved. MATLAB is also able to take into account multiple qualitative outcome possibilities for a single species. In other words, MATLAB is able to recognize a condition, such as a species reaching a threshold concentration, and substitute the original equation with an alternate one leading to a qualitatively different outcome once the species reaches the threshold. Another advantage of MATLAB is the ability to order the solutions to the equations so that the species most sensitive to the change are immediately apparent. Finally, MATLAB can introduce new events, such as introducing or altering treatment dosages, at any time during the simulation. PLAS is only able to use the initial values given at the onset of the simulation. Overall, MATLAB is the more flexible and efficient analytical tool.

5. Conclusion

This model explores the reciprocal intensification of PD and insulin resistance through a mathematical lens. It provides a quick, cost-effective means of evaluating possible PD treatment options for patients who also exhibit insulin resistance, and suggests mechanisms for the interactions between the two conditions. The model emphasizes dopaminergic neuron deterioration through ROS production via dysfunctional mitochondria and dopamine metabolism as well as Lewy body and neurofibrillary tangle production through hyperphosphorylated tau accumulation. The model also simulates the reduction in insulin signaling that occurs as a result of the chronic inflammation and ROS production that can accompany PD. Insulin signaling is partially lost even when it is not initially impaired. Finally, the model evaluates the neuroprotective ability of a variety of treatments, both experimental and currently available to treat PD or T2DM. The model predicts that a combined approach, initiated as early as possible and targeting a wide range of pathways, is the most effective.

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The qualitative model was developed using the program CellDesigner version 4.3, and can be found at http://www.celldesigner.org/.

The mathematical model was developed using MATLAB R2014a, which could be found at the following website upon beginning this work: http://www.mathworks.com/products/matlab/.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.compbiolchem.2015.04.003.

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