



University of Camerino

SCHOOL OF SCIENCE AND TECHNOLOGY

MSc in Computer Science
Multiagent System

**Parkinson's disease:
Exploring α -Synuclein and the Gut-Brain Axis**

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1. Abstract

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the degeneration of dopaminergic neurons in the substantia nigra. A compelling new hypothesis suggests that α -synuclein pathology may originate within the microbiota, particularly in the intestinal lumen (IL), and then propagate to the enteric nervous system (ENS) before advancing to the central nervous system (CNS) via the vagus nerve. This study aims to investigate and model this hypothesized pathway of the microbiota-intestine-brain axis using computational simulation.

Using Repast4Py, an agent-based modeling platform, our goal is to simulate the dynamics of α -synuclein aggregation and transmission within the intestinal lumen, and to observe its impact on the CNS. Through this simulation, we aim to gain insights into the potential role of intestinal α -synuclein in PD pathogenesis and to explore novel therapeutic strategies targeting the microbiota-intestine-brain axis.

2. Introduction

Parkinson's disease (PD) is a prevalent and debilitating neurodegenerative disorder characterized by the progressive degeneration of dopaminergic neurons in the substantia nigra region of the brain. This neuronal loss gives rise to the hallmark motor symptoms of PD, including tremors, rigidity, and bradykinesia, alongside various non-motor symptoms such as cognitive impairment and intestinal dysfunction.

The etiology of PD is multifactorial and not fully elucidated, although accumulating evidence implicates α -synuclein aggregation as a pathological hallmark of the disease. α -Synuclein, primarily located in presynaptic terminals of neurons, is involved in the formation of Lewy bodies, distinctive protein aggregates observed in PD brains.

Recent studies have postulated a potential role of the intestinal microbiota in PD pathogenesis. This hypothesis suggests that α -synuclein pathology may initiate in the intestinal lumen, potentially due to environmental triggers or genetic predisposition, resulting in the accumulation of α -synuclein aggregates. Subsequently, these aggregates could propagate to the enteric nervous system (ENS), a complex network of neurons within the intestinal wall, and then ascend via the vagus nerve to reach the central nervous system (CNS), including the brainstem regions affected in PD.

Understanding the dynamics of α -synuclein transmission along this gut-brain axis is critical for elucidating the mechanisms underlying PD progression. Computational modeling approaches provide a valuable tool to simulate and analyze such complex biological systems. Repast4Py, a Python-based agent-based modeling platform, enables researchers to construct detailed simulations of interactions between agents (representing cells, molecules, or organisms) within a spatially explicit environment. By leveraging Repast4Py, researchers can simulate the spatiotemporal dynamics of α -synuclein aggregation and transmission in the intestinal lumen, ENS, and CNS, thereby elucidating how these processes contribute to PD pathophysiology.

In this study, our objective is to explore and simulate the hypothesized gut-brain axis pathway of α -synuclein propagation using Repast4Py. By modeling this intricate biological system, we aim to gain insights into the mechanisms driving PD and identify potential targets for therapeutic intervention. Furthermore, this research may pave the way for the development of computational tools to aid in early diagnosis and personalized treatment strategies for PD and related neurodegenerative disorders.

3. Investigation

Literary Study

Gut Microbiota: A Novel Therapeutic Target for Parkinson's Disease

This scientific review, published in the journal *Frontiers in Immunology*, is curated by Zhihong Sun and peer-reviewed by experts from China and the United States. The article, authored by Manlian Zhu, Feng Chen, Zongxin Ling, and colleagues, focuses on the role of gut microbiota in Parkinson's Disease (PD). PD is the second most common neurodegenerative disorder, primarily characterized by motor dysfunction. Recent studies have shown that gut dysbiosis is involved in the onset, development, and progression of PD. Gut microbiota may influence PD through various mechanisms, including increased intestinal permeability, neuroinflammation, abnormal aggregation of α -synuclein, oxidative stress, and reduced neurotransmitter production. Gut microbiota is considered a potential diagnostic and therapeutic target for PD. It can be modulated through various interventions such as probiotics, prebiotics, synbiotics, postbiotics, microbiota transplantation, dietary modification, and traditional Chinese medicine. This review synthesizes recent research on the profiles and functions of PD-associated gut microbiota, the potential roles and mechanisms of gut microbiota in PD, and microbiota-targeted intervention strategies for PD. Understanding the roles and underlying mechanisms of PD-associated gut microbiota can provide new insights into the pathogenesis of PD and lead to novel therapeutic strategies for the disease. The findings indicate that gut microbiota could be a key factor in the progression of PD and a promising target for future treatments [2].

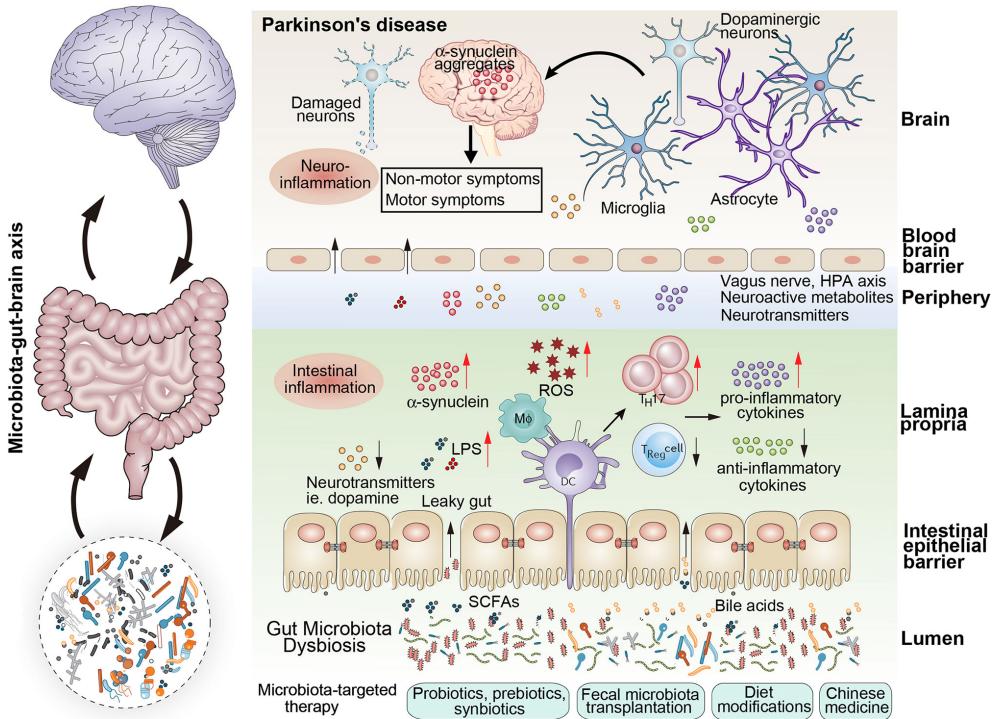


Figure 3.1: The schematic representation of the gut microbiota dysbiosis associated with parkinson's disease.

Parkinson's Disease: A Multisystem Disorder

Parkinson's disease has traditionally been considered a brain disorder characterized by motor disturbances, but in recent decades, the perception of Parkinson's disease (PD) has changed dramatically. It has been recognized that PD is a multi-organ and multisystem pathology involving the central nervous system, enteric nervous system, autonomic nervous system, adaptive immune system, and gastrointestinal tract (GI). In addition to motor symptoms, non-motor symptoms (NMS) have been acknowledged, such as hyposmia/anosmia, REM sleep behavior disorder, depression, anxiety, cardiac sympathetic denervation, and constipation, which may precede dopaminergic neuronal loss and motor symptoms of PD by several years. Risk factors for PD include advanced age, male sex, age of disease onset, genetic factors, and environmental influences. Environmental exposures such as smoking, pesticide and heavy metal exposure, as well as coffee consumption and medication use, can influence the risk of developing PD. The gut microbiome plays a key role in PD pathophysiology, with evidence supporting the association between intestinal dysbiosis and PD development. Furthermore, the "double-hit" hypothesis has been proposed, suggesting that the olfactory bulb and vagus nerve are key points that allow an unknown infectious agent in the gut to trigger PD. Dysfunction of the blood-brain barrier (BBB) has been linked to PD progression, with evidence of increased BBB permeability that may allow transport of α -synuclein and systemic inflammation into the brain. In conclusion, PD is a complex disease involving a range of genetic, environmental, and pathophysiological factors. Involvement of the gut microbiome, vagus nerve, and BBB provides new perspectives for understanding and treating PD [3].

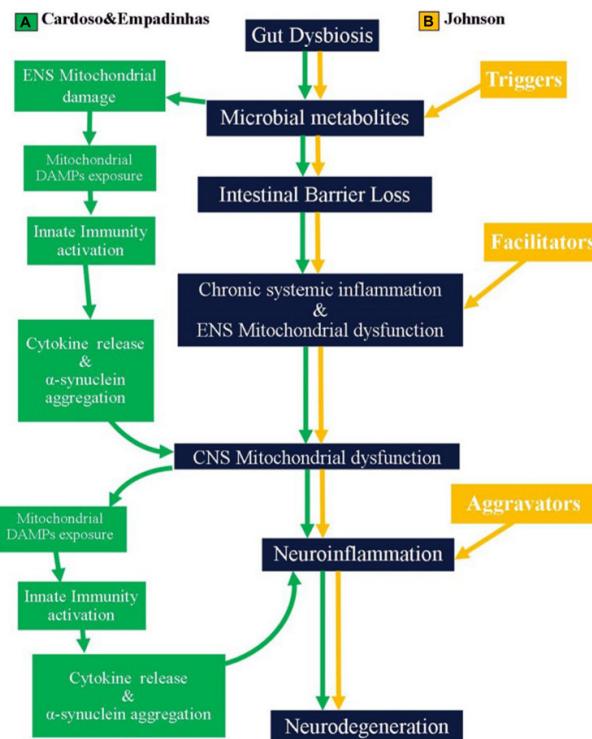


Figure 3.2: Schematic of the Cardoso & Empadinhas and Johnson et al. hypotheses proposing gut dysbiosis as a trigger of PD

Gastrointestinal disorders in Parkinson's disease and other Lewy body diseases

The document examines gastrointestinal disorders in PD and other Lewy body diseases, focusing on the role of the gut microbiota in intestinal and brain-related pathologies associated with PD. It highlights how constipation is commonly present in PD patients and may precede motor symptoms. Additionally, it discusses the role of the gut microbiota in promoting inflammation and oxidative stress at the intestinal level, with potential implications for the progression of Parkinson's disease. The document underscores the importance of the gut microbiota in the pathogenesis of Parkinson's disease, emphasizing the involvement of bacteria such as *Akkermansia*, which degrades the intestinal mucosal layer, and *Faecalibacterium* and *Roseburia*, which produce short-chain fatty acids (SCFAs) with anti-inflammatory properties. Furthermore, it highlights the association between gut microbiota, inflammation, and α -synuclein accumulation in the enteric nervous system and the brain. Moreover, the document reports that gut dysbiosis is associated with reduced SCFAs, vitamins, polyamines, and secondary bile acids, with potential effects on intestinal permeability and inflammation. It emphasizes how gut dysbiosis and alterations in SCFA production are common in Parkinson's disease and Lewy body diseases, with potential implications for disease progression. Finally, it highlights how early interventions targeting the gut microbiota and its metabolites may potentially delay or mitigate the development and progression of Parkinson's disease and Lewy body pathologies [4].

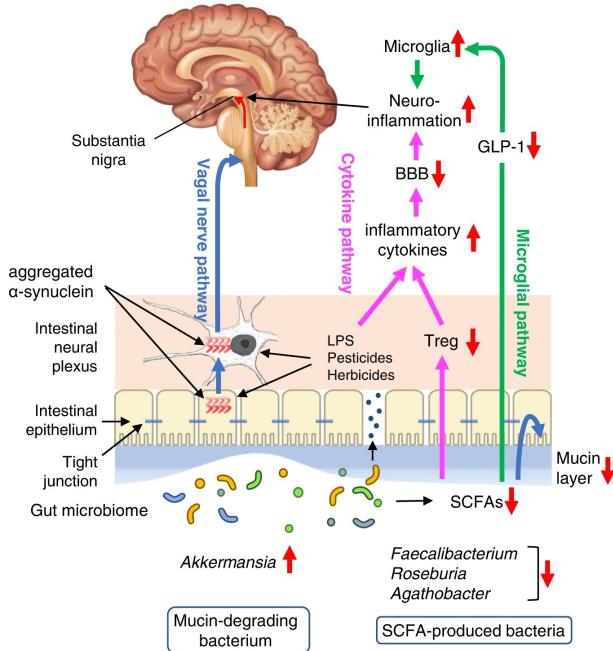


Figure 3.3: Triple-hit hypothesis of gut microbiota in Parkinson’s disease.

The Gut–Brain Axis and Its Relation to Parkinson’s Disease: A Review

The document titled "The Gut–Brain Axis and Its Relation to Parkinson’s Disease: A Review" explores the relationship between the gut microbiota and Parkinson’s Disease. PD is a neurodegenerative disorder characterized by the accumulation of α -synuclein proteins within the brain. Despite advancements in the field, the underlying mechanisms of the disease remain elusive. However, research suggests a potential link between intestinal commensal bacteria and the brain, known as the microbiota-gut-brain axis. Accumulating evidence suggests that gastrointestinal symptoms often precede motor symptoms of PD, supporting the hypothesis of involvement of the intestinal microbiota in the pathological mechanisms of the disease. The presence of healthy gut microbiota appears to promote blood-brain barrier integrity, while dysbiosis is associated with increased harmful substances, intestinal damage, and neuroinflammation. Additionally, the document explores the proposal by Braak and colleagues suggesting involvement of the gastrointestinal tract in the development and progression of PD. The dynamics of gut microbiota have been observed in individuals with PD, with an increase in certain bacterial species and a decrease in others, correlated with symptom severity. The composition of the microbiota also appears to influence the effectiveness of PD medications, such as levodopa, and may represent a potential target for enhancing treatment efficacy. Furthermore, microbiota-targeted interventions, such as probiotic use, could offer benefits in improving gastrointestinal symptoms and reducing systemic inflammation levels through modulation of inflammatory pathways. Other potential interventions include the use of antibiotics or fecal transplants to alter microbiota composition and improve PD-related symptoms. The outcomes of such interventions and their effectiveness are currently under investigation [5].

Parkinson's Disease from the Gut

The document explores the relationship between Parkinson's Disease and the gastrointestinal tract, highlighting the possibility that PD may originate in the intestine. PD is a debilitating neurodegenerative condition associated with both motor and non-motor symptoms, including constipation and other gastrointestinal disturbances. The primary protein involved in the formation of characteristic pathological lesions of PD is α -synuclein. It is believed that the misfolding of this protein has the ability to spread from cell to cell akin to prions, leading to the formation of protein aggregates. Numerous pieces of evidence suggest that PD might originate in the intestine, as gastrointestinal symptoms often manifest before neurological signs, and aggregations of α -synuclein have been found in the enteric nerves of PD patients. Additionally, patients undergoing vagotomy have a reduced risk of developing PD. Further evidence indicates that gut microbiota and their secretions may influence PD pathogenesis. Studies in mice have demonstrated that transplantation of gut microbiota from PD patients induces motor dysfunctions similar to PD, suggesting a potential role of gut microbiota in regulating PD pathology. Moreover, enteroendocrine cells (EECs) exhibit numerous neuron-like characteristics, including α -synuclein expression, and form neuronal connections with enteric nerves, providing a potential mechanism for the transmission of pathology from the intestinal mucosa to the nervous system. The document concludes by emphasizing the possibility of using intestinal samples as an early diagnostic tool for PD, as typical PD pathological lesions have been detected in intestinal tissues of patients. Additionally, it underscores the importance of considering the gastrointestinal tract as a potential therapeutic target for managing PD, suggesting that dietary modifications or interventions targeting gut microbiota could positively influence disease pathogenesis and progression. Thus, the document provides an in-depth insight into the possible intestinal origin of PD, highlighting the diagnostic and therapeutic implications of this theory[6].

The gut-brain axis in Parkinson's disease: Possibilities for food-based therapies

The document explores the role of the ENS in Parkinson's disease and potential dietary-based therapies. PD, characterized by both motor and non-motor symptoms, may have an intestinal origin, involving the accumulation of α -synuclein and mucosal inflammation within the enteric nervous system. The ENS may be implicated in the pathological progression of PD to the central nervous system, suggesting a significant gut-brain interaction. Furthermore, the document examines the effect of dietary therapies involving dietary components such as phospholipid precursors, cofactors, probiotics, prebiotics, and synbiotics, in improving motor and non-motor symptoms in PD patients. These therapies could impact the composition of the gut microbiota, improve intestinal mucosal integrity, and reduce pro-inflammatory responses, potentially influencing PD pathogenesis. Moreover, they could enhance the absorption of levodopa, the commonly used drug in PD treatment, thereby reducing side effects and improving overall treatment efficacy. These findings provide a robust foundation for future clinical studies assessing the effectiveness of these dietary therapies in treating PD [7].

Fighting Parkinson's disease: The return of the mitochondria

Parkinson's disease is a neurodegenerative disorder that affects the motor system, leading to the progressive loss of dopaminergic neurons in the substantia nigra. This con-

dition is associated with mitochondrial dysfunction, increased production of reactive oxygen species, and the accumulation of alfa-synuclein in nerve cells. Mitochondrial dysfunction has long been studied in relation to Parkinson's disease, and emerging evidence suggests that artificial mitochondrial transfer/transplantation could represent a promising therapeutic strategy. The aim of this study is to shed light on the role of mitochondria, both inside and outside cells, in Parkinson's disease and to explore how artificial mitochondrial transfer could be used as an innovative therapy for this condition. Furthermore, it is suggested that mitochondrial therapy could serve as a preventive measure, pushing research efforts in this direction. Mitochondrial dysfunctions are closely related to the pathogenesis of neurodegenerative diseases, including Parkinson's disease. Mitochondrial loss of function, impairment of degradation through mitophagy, and interactions with other proteins and organelles have been linked to Parkinson's disease. Additionally, mitochondrial transfer and artificial transplantation represent a promising research area for developing new therapies for this disease. Evidence suggests that mitochondria can also exist outside cells, and their status and function may influence the pathogenesis of central nervous system diseases. The release of circulating mitochondrial DNA may be correlated with various central nervous system pathologies, including Parkinson's disease. Moreover, mitochondrial transfer and artificial transplantation represent a promising research area for developing new therapies for Parkinson's disease. Preliminary studies have shown that mitochondrial transfer and transplantation can improve cellular function and replace damaged mitochondrial DNA [8].

Nicotinamide adenine dinucleotide (NADH): a new therapeutic approach to Parkinson's disease

The document "Nicotinamide adenine dinucleotide (NADH): a new therapeutic approach to Parkinson's disease", explores dopamine deficiency as a biochemical cause of Parkinson's disease and proposes a novel therapeutic approach using the coenzyme NADH to stimulate the biosynthesis of L-DOPA. This approach is based on the idea of enhancing the activity of the key enzyme, tyrosine hydroxylase (TH), involved in dopamine biosynthesis. The study involved 885 Parkinson's patients in a trial where NADH was administered both intravenously and orally. The results showed a positive clinical effect in approximately 80% of the patients, with an improvement in disability correlated to age and disease duration. Furthermore, NADH intake demonstrated an increase in dopamine production in neuroblastoma cells, indicating a potential stimulation of endogenous L-DOPA biosynthesis. The oral formulation of NADH exhibited a clinical effect similar to the intravenous one, suggesting the potential efficacy of this therapeutic approach. However, further research is needed to confirm the clinical effectiveness of NADH as a new therapeutic approach for Parkinson's disease [9].

α -Synuclein binds TOM20 and inhibits mitochondrial protein import in Parkinson's disease

The document explores the link between α -synuclein accumulation and mitochondrial dysfunction in Parkinson's disease. The authors report that certain forms of modified α -synuclein bind with high affinity to the TOM20 presequence receptor of the mitochondrial protein import machinery, inhibiting its interaction with the co-receptor TOM22 and compromising mitochondrial protein import. This leads to defective mitochondrial respiration, increased production of reactive oxygen species, and loss of

mitochondrial membrane potential. Post-mortem examination of Parkinson's disease tissue reveals aberrant α -synuclein interactions in nigrostriatal neurons associated with the loss of imported mitochondrial proteins, thus confirming this pathogenic process in human disease. Modest reduction in endogenous α -synuclein is sufficient to maintain mitochondrial protein import in an *in vivo* model of Parkinson's disease. Additionally, *in vitro* systems show that overexpression of TOM20 or a mitochondrial targeting signal peptide has beneficial effects and preserves protein import. The authors conclude that this study defines a novel pathogenic mechanism in Parkinson's disease, identifies toxic species of wild-type α -synuclein, and unveils new therapeutic strategies for neuroprotection. The document provides insights into defects in mitochondrial electron transport chain, production of reactive oxygen species, and loss of mitochondrial membrane potential resulting from the interaction between α -synuclein and the TOM20 presequence receptor. Furthermore, the relevance of these findings to human disease is discussed, with evidence of aberrant α -synuclein-TOM20 interaction in nigrostriatal neurons in Parkinson's disease. Finally, new therapeutic approaches are proposed, such as reducing α -synuclein levels and overexpressing TOM20, to counteract detrimental effects on mitochondrial protein import. The document offers a detailed overview of interactions between α -synuclein and the mitochondrial protein import machinery, describing their pathophysiological implications and suggesting potential therapeutic strategies for Parkinson's disease. The authors provide a robust scientific foundation for further research and the development of new therapies [10].

Mitochondrial dysfunction in Parkinson's disease – a key disease hallmark with therapeutic potential

The document discusses the significance of mitochondrial dysfunction in Parkinson's disease, emphasizing the current inability to slow disease progression. The review highlights failures in attempts to target mitochondrial dysfunction and synthesizes the cellular determinants of mitochondrial dysfunction, including impairment of electron transport chain complex I, oxidative stress, disrupted mitochondrial quality control mechanisms, and cellular bioenergetic deficiency. Additionally, mitochondrial pathways to neurodegeneration are examined within the current context of PD pathogenesis, along with past and current therapeutic strategies. The document underscores that PARK gene mutations (PARK6, PARK2, PARK7, PARK17, PARK23) are closely linked to mitochondrial dysfunction and integrity. It also highlights the causal relationship between α -synuclein pathology and mitochondrial dysfunction, emphasizing that excess α -synuclein can lead to reduced mitochondrial complex I activity, alterations in mitochondrial membrane potential, and increased oxidative stress. Finally, it discusses therapeutic approaches targeting mitochondrial dysfunction, such as the use of antioxidants, antidiabetic drugs, glucagon-like peptide 1 (GLP-1) receptor agonists, PPAR γ receptor agonists, and gene therapy strategies for PINK1 and Parkin. The article highlights the limitations of existing therapies and suggests that a promising future approach might involve limiting harmful mitochondrial stimuli as an alternative therapeutic strategy. The document provides a detailed overview of mitochondrial dysfunction in the context of Parkinson's disease and current and future therapeutic strategies [11].

4. Formal MAS Model

Idea

In this formal analysis of a Multi-Agent System, we have identified four interconnected environments: the Microbiota, the Intestinal Lumen, the Enteric Nervous System (ENS), and the Central Nervous System (CNS) [2]. These environments are crucial in the context of Parkinson's disease (PD), particularly emphasizing the role of the intestinal lumen in disease progression, alongside the Enteric Nervous System (ENS). The transmission of α -synuclein from the microbiota to the intestinal lumen and its subsequent propagation to the CNS are pivotal events contributing to mitochondrial dysfunction.

Parkinson's disease is increasingly acknowledged as a multisystem disorder involving pathophysiological processes extending beyond the brain, implicating both the microbiota and the intestinal lumen in disease onset and advancement. The concept of α -synuclein transfer from the gastrointestinal tract to the brain via the vagus nerve is instrumental in comprehending the systemic manifestations of PD. Upon reaching the CNS, α -synuclein aggregates can disrupt mitochondrial activity, precipitating neuronal degeneration and the characteristic motor and non-motor symptoms observed in PD. In our Multi-Agent System, each environment demonstrates autonomous behavior.

Building upon this model, we can integrate agent-based dynamics to simulate the propagation of α -synuclein across these environments. Each environment-agent can possess distinct properties such as cellular uptake mechanisms, protein aggregation kinetics, or neuroinflammatory responses, which collectively influence the disease trajectory. By incorporating these factors into our Multi-Agent System, we aim to illuminate the intricate biological interactions driving PD progression, thereby offering insights into potential therapeutic strategies targeting various stages of the disease pathway.

Furthermore, this model can be enriched by including additional factors contributing to PD pathogenesis, such as genetic predispositions, environmental exposures, and immune system dysregulation.

Microbiota Environment

We have identified the set of agents that constitute the microbiota, denoted as Ag_m , along with the set of their corresponding actions.

$$Ag_m = \{SCFA, Epithelialcells, LPS\}$$

The set of states identified within the microbiota are represented below:

$$M = \{m_0, m_1, m_2\}$$

where,

- m_0 state indicates an healthy microbiota
- m_1 state, microbiota with a reduction of SCFA agents and subsequently, an increase of intestinal permeability.
- m_2 state stands for an environment without LPS bacteria, a lower number of SCFA and a higher level of permeability.

Thus, the environment Env_m is a triple:

$$Env_m = \{M, m_0, \tau\}$$

where M is the set of our environment states, m_0 is the initial state and τ is a transformation function that map the run to a subset of M .

The system has one run contained in R^{Ac_m} :

$$r_1 : m_0 \xrightarrow{\text{microbiotaDysbiosis}} m_1 \xrightarrow{\text{LPStransport}} m_2$$

As written before, the Microbiota system includes three agents: SCFA, Epithelial cells and LPS bacteria. Each agent is a reactive agent and they can be described using this strategy:

- *SCFA*

see: $m_0 \rightarrow SCFAdecrease$
action: $SCFAdecrease \rightarrow MicrobiotaDysbiosis$
do: $MicrobiotaDysbiosis \times SCFAdecrease \rightarrow m_1$

- *Epithelial cell*

see: $m_0 \rightarrow IncreasePermeability$
action: $IncreasePermeability \rightarrow MicrobiotaDysbiosis$
do: $MicrobiotaDysbiosis \times IncreasePermeability \rightarrow m_1$

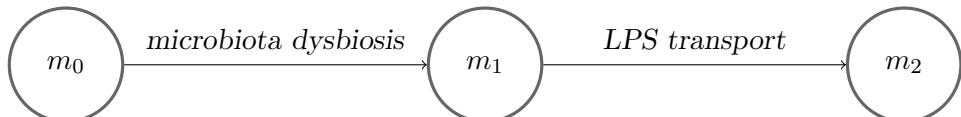
- *LPS*

see: $m_1 \rightarrow UnstableMicrobiota$
action: $UnstableMicrobiota \rightarrow LPStransport$
do: $LPStransport \times UnstableMicrobiota \rightarrow m_2$

The set of action is:

$$Ac_m = \{MicrobiotaDysbiosis, LPStransport\}$$

The evolution of microbiota is represented using this model:



Intestinal Lumen Environment

We have identified the set of agents that constitute the Lumen, denoted as Ag_l , along with the set of their corresponding actions.

$$Ag_l = \{TNF - \alpha, LPS, \alpha - sin\}$$

The set of states identified within the lumen are represented below:

$$L = \{l_0, l_1, l_2, l_3\}$$

where,

- l_0 state, lumen where LPS are already arrived.
- l_1 state, the system is inflamed. TNF- α were activated due to the presence of LPS.
- l_2 state stands for the production of α -synuclein.
- l_3 state, α -synuclein are transported in the ENS and subsequently in CNS via vagus nerve.

Thus, the environment Env_l is a triple:

$$Env_l = \{L, l_0, \tau\}$$

where L is the set of our environment states, l_0 is the initial state and τ is a transformation function that map the run to a subset of L . The system has one run contained in R^{Ag_l} :

$$r_1 : l_0 \xrightarrow{\text{inflammation}} l_1 \xrightarrow{\alpha\text{-sin production}} l_2 \xrightarrow{\alpha\text{-sin transport}} l_3$$

Intestinal Lumen includes three agents. LPS and α -synuclein are reactive agents, while TNF- α is an adaptive agent. They can be described with:

- $TNF - \alpha$ has:

see: $l_0 \rightarrow LPSpresence$
action: $LPSpresence \rightarrow Inflammation$
do: $Inflammation \times LPSpresence \rightarrow l_1$

- LPS

see: $l_1 \rightarrow systemInflamed$
action: $systemInflamed \rightarrow \alpha\text{-sinProduction}$
do: $\alpha\text{-sinProduction} \times systemInflamed \rightarrow l_2$

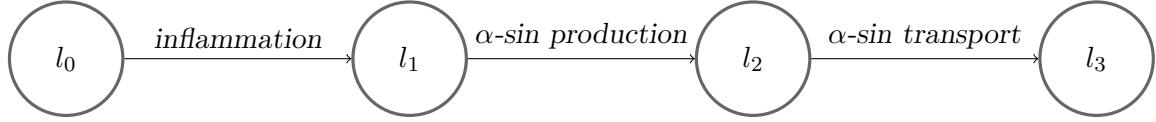
- α -sinucleina

see: $l_2 \rightarrow \alpha\text{-sinPresence}$
action: $\alpha\text{-sinPresence} \rightarrow \alpha\text{-sinTransport}$
do: $\alpha\text{-sinTransport} \times \alpha\text{-sinPresence} \rightarrow l_3$

The set of action is:

$$Ac_l = \{Inflammation, \alpha - sinProduction, \alpha - sinTransport\}$$

The evolution of Intestinal Lumen is represented using this model:



ENS Environment

In line with our earlier discussion, the Enteric Nervous System (ENS) is conceptualized here as an Interface Environment representing a critical communication channel between the Intestinal Lumen Environment and the Central Nervous System (CNS) Environment, facilitated notably by the vagus nerve. This nerve serves as a key conduit for communication between these two distinct physiological environments. The ENS acts as a sophisticated interface within the gastrointestinal tract, playing a pivotal role in transmitting signals and information from the intestinal lumen to the CNS. This neural interface is essential for conveying sensory and regulatory inputs from the gut to higher brain centers, influencing various physiological processes and responses.

CNS Environment

For this last environment, we have identified the set of agents that constitute the CNS, denoted as Ag_c , along with the set of their corresponding actions.

$$Ag_c = \{\alpha - sinucleina, NADH, ROS, Electron, Oxygen\}$$

The set of states identified within the CNS are represented below:

$$C = \{c_0, c_1, c_2, c_3, c_4\}$$

where,

- c_0 state indicates the arrival of alpha-synuclein in the CNS from vagus nerve.
- c_1 state indicates the aggregation of alpha-synuclein into the CNS.
- c_2 state represents Electron Transport Chain (ETC) Damage. This state signifies the occurrence of damage to the Electron Transport Chain and subsequently the Electrons' release.
- c_3 state is a direct consequence of ETC damage and indicates the generation of Reactive Oxygen Species (ROS). When the ETC is damaged, the normal flow of electrons through the respiratory chain is disrupted, leading to leakage of electrons that react with molecular oxygen to form ROS.
- c_4 state represents oxidative stress that occurs when there is an imbalance between the production of ROS and the ability of the cell to detoxify these reactive molecules.

Thus, the environment Env_c is a triple:

$$Env_c = \{C, c_0, \tau\}$$

where C is the set of our environment states, c_0 is the initial state and τ is a transformation function that map the run to a subset of C .

The system has one run contained in $R^{A_{c_c}}$:

$$r_1 : c_0 \xrightarrow{\alpha\text{-sin aggregation}} c_1 \xrightarrow{\text{ElectronRelease}} c_2 \xrightarrow{\text{ROSgeneration}} c_3 \xrightarrow{\text{OxidativeStress}} c_4$$

The CNS environment includes five agents that are α -synuclein, NADH, Electron, Oxygen and ROS. They are reactive agents and they can be described with:

- α -sinucleina

see: $c_0 \rightarrow \text{clearMitochondria}$
action: $\text{clearMitochondria} \rightarrow \alpha\text{-sinAggregation}$
do: $\alpha\text{-sinAggregation} \times \text{clearMitochondria} \rightarrow c_1$

- NADH

see: $c_1 \rightarrow \text{alphaAggregated}$
action: $\text{alphaAggregated} \rightarrow \text{ElectronRelease}$
do: $\text{ElectronRelease} \times \text{alphaAggregated} \rightarrow c_2$

- Electron

see: $c_2 \rightarrow \text{ETCdamage}$
action: $\text{ETCdamage} \rightarrow \text{ROSgeneration}$
do: $\text{ROSgeneration} \times \text{ETCdamage} \rightarrow c_3$

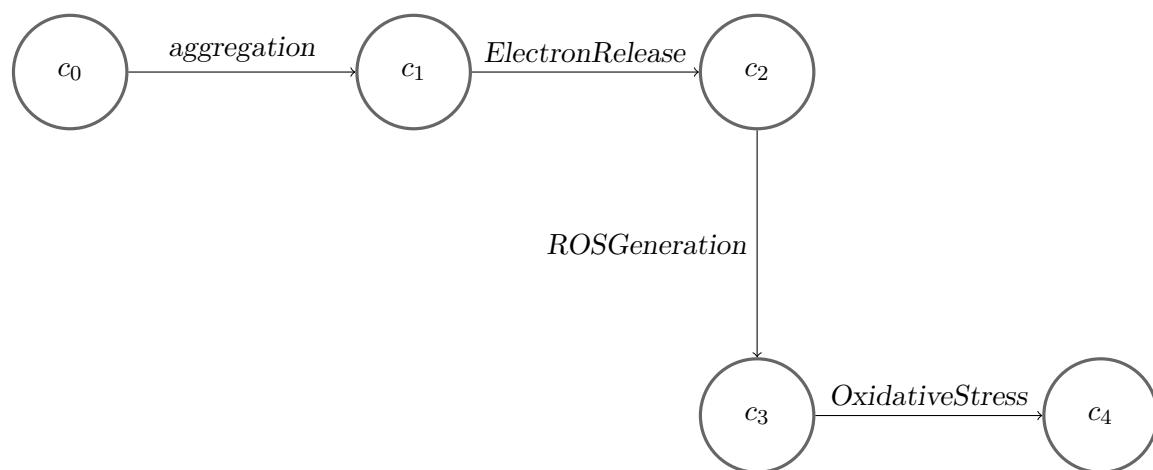
- Oxygen

see: $c_2 \rightarrow \text{ETCdamage}$
action: $\text{ETCdamage} \rightarrow \text{ROSgeneration}$
do: $\text{ROSgeneration} \times \text{ETCdamage} \rightarrow c_3$

- ROS

see: $c_3 \rightarrow \text{ROSincrement}$
action: $\text{ROSincrement} \rightarrow \text{OxidativeStress}$
do: $\text{OxidativeStress} \times \text{ROSincrement} \rightarrow c_4$

The evolution of CNS is represented using this model:



5. Implementation

In this chapter, we detail the implementation specifics of the code for our multi-agent system developed using Repast4py [12]. We have written code for each environment (Microbiota, Intestinal Lume, CNS), excluding the vagus nerve and Enteric Nervous System (ENS) and vagus nerve due to theirs non-relevance for implementation purposes and theirs computational overhead.

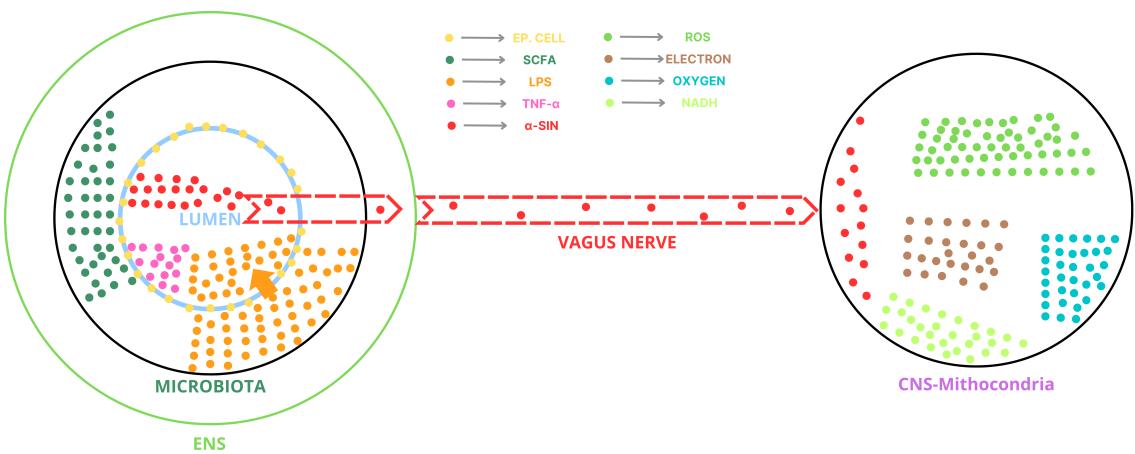


Figure 5.1: Our idea of system's implementation.

Introduction to Repast4py

Repast for Python (Repast4Py) is the latest addition to the Repast Suite, a collection of free and open-source software for agent-based modeling and simulation. It extends the capabilities of Repast HPC by enabling the creation of large, distributed agent-based models (ABMs) that can utilize multiple processing cores. Distributed ABMs allow for the development of intricate systems models that address complex societal problems. While Repast HPC is developed in C++ and caters to high-performance computing (HPC) experts, Repast4Py is a Python package designed to facilitate easier adoption by researchers from various scientific disciplines seeking to employ large-scale distributed ABM methods. Repast4Py is released under the BSD-3 open-source license and incorporates Numba, NumPy, PyTorch packages, and the Python C API to build a scalable modeling system capable of harnessing significant HPC resources and modern computing architectures.

Repast4py - Main features

Below are the key features of Repast4Py:

- Distributed Simulation Framework: Repast4Py is designed for distributed simulations where the simulation workload is divided among multiple computer processes, communicating via message passing using MPI (Message Passing Interface).
- Contexts and Projections: Repast4Py organizes a model using concepts of contexts and projections. A context acts as a container with set semantics, allowing any type of object to be stored within it. From a modeling perspective, a context represents a population of agents within the model. Projections impose structure onto the population defined within a context. Projections can take various forms, such as a network structure enabling agents to form links with each other, a grid where agents are situated in a matrix-like space, or a continuous space where an agent's location is represented by non-discrete coordinates. Projections are associated with contexts in a many-to-one relationship, meaning each context can be associated with multiple projections.
- Scheduling Events: In Repast simulations, the progression of time is managed through a discrete-event scheduler where the simulation moves forward by identifying and executing scheduled events. These events are scheduled to occur at specific ticks, which serve as indicators of event priority rather than representing real clock-time. Ticks determine the sequence in which events occur relative to each other.

Microbiota Implementation

As we written in the last chapter, in this environment there are three agents (SCFA, LPS, Epithelial Cell). We are going to describe their behavior and their implementation in Repast4py.

SCFA

SCFA stands for Short-Chain Fatty Acids. They have been linked to numerous health benefits, including the maintenance of gut barrier integrity, which means that they produce mucin, which is a gel-like substance that forms a protective barrier over the epithelial cells lining the gut. This behavior leads to have a permeability of gut barrier low. Thus, an healthy gut barrier doesn't allow the passage of molecules, toxins, and pathogens from the gut lumen into the bloodstream or surrounding tissues.

```
1 class SCFA(core.Agent):  
2     TYPE = 0  
3  
4     def __init__(self, a_id, rank):  
5         super().__init__(id=a_id, type=SCFA.TYPE, rank=rank)  
6  
7     def save(self) -> Tuple:  
8         return (self.uid,)
```

Listing 5.1: SCFA class

We observe that SCFA agent has a TYPE variable that defines the agent type id for the SCFA agents and a method called save that is used in Repast4py for saving

agent state when it moves from a process to another.

```

1 def step(self):
2     grid = model.microbiotaGrid
3     pt = grid.get_location(self)
4     nghs = model.ngh_finderMicrobiota.find(pt.x, pt.y)
5
6     at = dpt(0, 0)
7     maximum = [[], -(sys.maxsize - 1)]
8     for ngh in nghs:
9         at._reset_from_array(ngh)
10        count = 0
11        for obj in grid.get_agents(at):
12            if obj.uid[1] == CellulaEpiteliale.TYPE:
13                count += 1
14        if count > maximum[1]:
15            maximum[0] = [ngh]
16            maximum[1] = count
17        elif count == maximum[1]:
18            maximum[0].append(ngh)
19
20    max_ngh = maximum[0][random.default_rng.integers(0, len(maximum[0]))]
21
22    if not np.all(max_ngh == pt.coordinates):
23        space_pt = model.microbiotaSpace.get_location(self)
24        direction = (max_ngh - pt.coordinates[0:3]) * 0.5
25        model.move(self, space_pt.x + direction[0], space_pt.y + direction
[1])

```

Listing 5.2: SCFA step method

Finally, the SCFA class imports the step method, which describes the behavior of SCFA agents. In particular, the step method retrieves the position of the current agent and moves it to the location where the maximum number of epithelial cells has been found..

LPS

LPS stands for Lipopolysaccharide. It's a molecule found in the outer membrane of Gram-negative bacteria. In the human body, exposure to LPS can occur through the gut when the intestinal barrier is compromised (such as in cases of dysbiosis or leaky gut). LPS can then enter intestinal Lume and trigger an immune response, leading to inflammation. In our case LPS are generated in Microbiota environment and they will move into Lume during the dysbiosis phase. In the Lume context, LPS will be able to generate alpha-synuclein.

```

1 class LPS(core.Agent):
2     TYPE = 1
3
4     def __init__(self, a_id, rank):
5         super().__init__(id = a_id, type = LPS.TYPE, rank=rank)
6
7     def save(self) -> Tuple:
8         return (self.uid,)

```

Listing 5.3: LPS Class

The structure of LPS class is the same of SCFA. It has a TYPE variable that defines the agent type id for LPS agents and a save method used for memorizing the agent state.

```

1 def stepMicrobiota(self):
2     grid = model.microbiotaGrid
3     pt = grid.get_location(self)
4
5     space_pt = model.microbiotaSpace.get_location(self)
6     direction = pt.coordinates * 0.4
7     model.move(self, space_pt.x + direction[0], space_pt.y + direction[1])

```

Listing 5.4: LPS step method

The LPS class has two step methods: one defines the behavior in the Microbiota environment, while the other describes the behavior in the Lume context. The first step method indicates that agents can move into Microbiota randomly by getting the current position of the agent and choosing a direction.

Epithelial cell

Epithelial cells play a crucial role in forming the intestinal barrier, which is essential for maintaining the integrity and function of the gastrointestinal tract. One of the function of Intestinal Barrier is to allow the absorption of nutrients, water and electrolytes from the gut lumen into the bloodstream while preventing the passage of larger molecules, pathogens, and toxins. The permeability of the barrier specifies how many substances can pass from one system to another.

```

1 class CellulaEpiteliale(core.Agent):
2
3     TYPE = 2
4
5     def __init__(self, a_id, rank):
6         super().__init__(id = a_id, type = CellulaEpiteliale.TYPE, rank=rank)
7         self.permeability = 10
8
9     def save(self) -> Tuple:
10        return (self.uid, self.permeability)

```

Listing 5.5: Epithelial Cell Class

The Epithelial cell are two variables: the basic TYPE variable and permeability that has an initial value equals to 10. This parameter specifies the state of Intestinal Barrier that is compromised by the SCFA's decrease.

```

1 def step(self):
2     if self.permeability <= 80:
3         self.permeability += (self.permeability * 5) / 100

```

Listing 5.6: Epithelial Cell step method

We can observe that Epithelial cell agents don't have any movement. The step method increases the permeability when SCFA begins to decrease.

Intestinal Lumen Implementation

TNF- α

Tumor necrosis factor alpha (TNF-alpha) is a pro-inflammatory cytokine produced by various immune cells, in response to infection or inflammation. It plays a central role in the immune response and in the regulation of inflammation.

In our implementation they are generated within Intestinal Lumen and they are able to activate the immune response when LPS agents enter into Lumen.

```

1 class TNFalpha(core.Agent):
2     TYPE = 3
3
4     def __init__(self, a_id, rank):
5         super().__init__(id = a_id, type = TNFalpha.TYPE, rank=rank)
6
7     def save(self) -> Tuple:
8         return (self.uid)

```

Listing 5.7: TNF-alpha class

The TNF- α class has the TYPE variable that specifies the type of agents.

```

1 def step(self):
2     grid = model.lumeGrid
3     pt = grid.get_location(self)
4     nghs = model.ngh_finderLume.find(pt.x, pt.y)
5
6     at = dpt(0, 0)
7     maximum = [[], -(sys.maxsize - 1)]
8     for ngh in nghs:
9         at._reset_from_array(ngh)
10        count = 0
11        for obj in grid.get_agents(at):
12            if obj.uid[1] == LPS.TYPE:
13                count += 1
14            if count > maximum[1]:
15                maximum[0] = [ngh]
16                maximum[1] = count
17            elif count == maximum[1]:
18                maximum[0].append(ngh)
19
20    max_ngh = maximum[0][random.default_rng.integers(0, len(maximum[0]))]
21
22    if not np.all(max_ngh == pt.coordinates):
23        space_pt = model.lumeSpace.get_location(self)
24        direction = (max_ngh - pt.coordinates[0:3]) * 0.5
25        model.moveLume(self, space_pt.x + direction[0], space_pt.y +
26        direction[1])
27
28        pt = grid.get_location(self)
29        for obj in grid.get_agents(pt):
30            if obj.uid[1] == LPS.TYPE:
31                model.generate_alfasin(pt)
32                break

```

Listing 5.8: TNF-alpha step method

TNF- α agents activate the immune response when the number of LPS agents into lumen exceeds a threshold, resulting in an inflammatory state indicated by setting the inflammation variable to True. When immune response occurs, TNF- α starting to produce alpha-synuclein within the environment.

LPS

The structure of LPS class is just represented in the Microbiota environment.

```

1 def stepLume(self):
2     grid = model.lumeGrid
3     pt = grid.get_location(self)
4
5     space_pt = model.lumeSpace.get_location(self)
6     direction = pt.coordinates * 0.4
7     model.moveLume(self, space_pt.x + direction[0], space_pt.y +
    direction[1])

```

Listing 5.9: LPS step methods

```

1 if self.LumeContext.contains_type(LPS.TYPE):
2     for l2 in self.LumeContext.agents(LPS.TYPE):
3         l2.stepLume()
4         if self.getNumberLPS() > 180:
5             self.inflammation = True
6             probability_of_release = 0.3
7             if rd.random() <= probability_of_release:
8                 if model.getNumberTnf() < 400:
9                     model.generate_TNFalpha()

```

Listing 5.10: generation of TNF-alpha in Model step method

We can see that when the number of LPS agents exceeds a threshold, set to 180, the inflammation attribute is activated, leading to a production of TNF- α .

To manage computational resources more efficiently, we introduce a probability-based mechanism for releasing TNF- α agents and a maximum number of agents that can be generated. This approach helps prevent excessive proliferation of TNF- α agents during simulation, which would otherwise impose a significant computational burden.

α -synuclein

Alpha-synuclein is a protein that plays a role in regulating neurotransmitter release and synaptic function. However, in Parkinson's disease, alpha-synuclein misfolds and aggregates, forming insoluble fibrils that accumulate inside neurons. These aggregated alpha-synuclein fibrils are believed to contribute to neuronal dysfunction and death. Nevertheless, many scientists have discovered that these proteins could be generated during inflammatory process within the Intestinal Lumen and subsequently move to Enteric Nervous System [13].

```

1 class AlfaSinucleina(core.Agent):
2     TYPE = 4
3
4     def __init__(self, a_id, rank):
5         super().__init__(id = a_id, type = AlfaSinucleina.TYPE, rank=rank)
6

```

```

7  def save(self) -> Tuple:
8      return (self.uid,)
9
10 def stepLume(self):
11     grid = model.lumeGrid
12     pt = grid.get_location(self)
13
14     space_pt = model.lumeSpace.get_location(self)
15     direction = pt.coordinates * 0.4
16     model.moveLume(self, space_pt.x + direction[0], space_pt.y +
direction[1])

```

Listing 5.11: alpha-synuclein class

CNS Implementation

In CNS implementation we have studied the behavior of α -synucleins within the mitochondria. In particular, when alpha-synucleins arrive from the gut, they can be aggregate to mitochondrias and damage their structure causing the mitochondria dysfunction.

The mitochondria environment contains five agents: alpha-synuclein, NADH, ROS, electron and oxygen.

NADH

Nicotinamide adenine dinucleotide (NADH) is a coenzyme found in all living cells. It is involved in several important metabolic reactions, particularly those related to energy production (ATP).

In summary, NADH plays a crucial role in the electron transport chain (ETC) by donating electrons to the chain, which ultimately leads to the production of ATP.

```

1 class Nadh(core.Agent):
2     TYPE = 5
3
4     def __init__(self, a_id, rank):
5         super().__init__(id=a_id, type=Nadh.TYPE, rank=rank)
6
7     def save(self) -> Tuple:
8         return (self.uid,)
9
10    def generate_electron(self, pt):
11        e = Electron(model.electron_id, model.rank)
12        model.electron_id += 1
13        model.NervousContext.add(e)
14        model.moveNervous(e, pt.x, pt.y)

```

Listing 5.12: NADH class

As for the Microbiota agents, NADH class has a TYPE variable that defines the agent type id for NADH agents and a save method used for memorizing the agent state, while the last method is used to generate an electron agents when there is an interaction between alpha-synuclein and NADH.

```

1     def step(self):
2         grid = model.nervousGrid

```

```

3     pt = grid.get_location(self)
4     nghs = model.ngh_finderNervous.find(pt.x, pt.y)
5
6     minimum = [[], sys.maxsize]
7     at = dpt(0, 0)
8     for ngh in nghs:
9         at._reset_from_array(ngh)
10    count = 0
11    for obj in grid.get_agents(at):
12        if obj.uid[1] == AlfaSinucleina.TYPE:
13            count += 1
14    if count < minimum[1]:
15        minimum[0] = [ngh]
16        minimum[1] = count
17    elif count == minimum[1]:
18        minimum[0].append(ngh)
19
20    min_ngh = minimum[0][random.default_rng.integers(0, len(minimum[0]))]
21
22    if not np.all(min_ngh == pt.coordinates):
23        space_pt = model.nervousSpace.get_location(self)
24        direction = (min_ngh - pt.coordinates) * 0.8
25        model.moveNervous(self, space_pt.x + direction[0], space_pt.y +
direction[1])
26
27    pt = grid.get_location(self)
28    for obj in grid.get_agents(pt):
29        if obj.uid[1] == AlfaSinucleina.TYPE:
30            # release of electron with a 0.8 index of probability
31            probability_of_release = 0.3
32            if rd.random() <= probability_of_release:
33                self.generate_electron(pt)
34                break

```

Listing 5.13: NADH step method

The step method defines the behavior of NADH agents. These agents are capable of moving in mitochondria space, and if they collide an alpha-synuclein, they may release an electron agent. It has been decided to set the probability percentage for releasing an electron to 30%.

α -synuclein

Alpha-synuclein is the same agent described in Microbiota section. However, It assumes a different behavior.

```

1 def stepNervous(self):
2     grid = model.nervousGrid
3     pt = grid.get_location(self)
4     nghs = model.ngh_finderNervous.find(pt.x, pt.y)
5
6     at = dpt(0, 0)
7     maximum = [[], -(sys.maxsize - 1)]
8     for ngh in nghs:
9         at._reset_from_array(ngh)
10    count = 0
11    for obj in grid.get_agents(at):
12        if obj.uid[1] == Nadh.TYPE:

```

```

13         count += 1
14     if count > maximum[1]:
15         maximum[0] = [ngh]
16         maximum[1] = count
17     elif count == maximum[1]:
18         maximum[0].append(ngh)
19
20     max_ngh = maximum[0][random.default_rng.integers(0, len(maximum[0]))]
21
22     if not np.all(max_ngh == pt.coordinates):
23         space_pt = model.nervousSpace.get_location(self)
24         direction = (max_ngh - pt.coordinates[0:3]) * 0.5
25         model.moveNervous(self, space_pt.x + direction[0], space_pt.y +
direction[1])

```

Listing 5.14: alpha-synuclein step method

As we observe, the alpha-synuclein agents are able to move within the mitochondrial environment to search for NADH agents.

Electron

Electrons within mitochondria play a crucial role in cellular respiration, which is the process by which cells generate energy in the form of ATP. During cellular respiration, electrons are transferred along a series of protein complexes in the inner mitochondrial membrane, known as the electron transport chain (ETC).

Nevertheless, the alpha-synuclein aggregation can impair mitochondrial function and disrupt the electron transport chain. This disruption can lead to inefficient energy production by releasing electrons from ETC.

```

1 class Electron(core.Agent):
2
3     TYPE = 6
4
5     def __init__(self, a_id, rank):
6         super().__init__(id=a_id, type=Electron.TYPE, rank=rank)
7
8     def save(self) -> Tuple:
9         return (self.uid,)

```

Listing 5.15: Electron class

```

1     def step(self):
2         grid = model.nervousGrid
3         pt = grid.get_location(self)
4         nghs = model.ngh_finderNervous.find(pt.x, pt.y)
5
6         maximum = [[], -(sys.maxsize - 1)]
7         for ngh in nghs:
8             at = dpt(*ngh)
9             count = 0
10            for obj in grid.get_agents(at):
11                if obj.uid[1] == Oxygen.TYPE:
12                    count += 1
13            if count > maximum[1]:
14                maximum[0] = [ngh]
15                maximum[1] = count

```

```

16         elif count == maximum[1]:
17             maximum[0].append(ngh)
18
19     max_ngh = maximum[0][random.default_rng.integers(0, len(maximum[0]))]
20
21     if not np.all(max_ngh == pt.coordinates):
22         space_pt = model.nervousSpace.get_location(self)
23         direction = (max_ngh - pt.coordinates[0:3]) * 0.7
24         model.moveNervous(self, space_pt.x + direction[0], space_pt.y +
25         direction[1])
26
27     electron_fusion = []
28     pt = grid.get_location(self)
29     for obj in grid.get_agents(pt):
30         if obj.uid[1] == Oxygen.TYPE:
31             obj.fusion()
32             electron_fusion.append(self)
33             break
34
35
36     return electron_fusion

```

Listing 5.16: Electron step method

The step method returns the list of electrons that have had an interaction with Oxygen for generating ROS agents.

Oxygen

Oxygen plays a critical role in mitochondria as the final electron acceptor in the electron transport chain (ETC), which is part of cellular respiration.

In Parkinson disease, they can interact with electrons to form reactive oxygen species (ROS) and this process can lead to oxidative stress.

```

1 class Oxygen(core.Agent):
2
3     TYPE = 7
4
5     def __init__(self, a_id, rank):
6         super().__init__(id=a_id, type=Oxygen.TYPE, rank=rank)
7         self.ElectronFusion = False
8
9     def save(self) -> Tuple:
10        return (self.uid, self.ElectronFusion)
11
12     def fusion(self):
13        self.ElectronFusion = True

```

Listing 5.17: Oxygen class

The Oxygen class has a boolean variable that defines whether the current oxygen agent has joined with an electron. Initially, it is set to False, and if the union occurs, it becomes True. Additionally, there is a method for generating ROS agents, which allows ROS agents to be added to the Nervous Context and positioned at a specified location.

```

1     def step(self):
2         grid = model.nervousGrid
3         pt = grid.get_location(self)

```

```

4     nghs = model.ngh_finderNervous.find(pt.x, pt.y)
5
6     maximum = [[], -(sys.maxsize - 1)]
7     for ngh in nghs:
8         at = dpt(*ngh)
9         count = 0
10        for obj in grid.get_agents(at):
11            if obj.uid[1] == Electron.TYPE:
12                count += 1
13            if count > maximum[1]:
14                maximum[0] = [ngh]
15                maximum[1] = count
16            elif count == maximum[1]:
17                maximum[0].append(ngh)
18
19        max_ngh = maximum[0][random.default_rng.integers(0, len(maximum[0]))]
20
21    if not np.all(max_ngh == pt.coordinates):
22        space_pt = model.nervousSpace.get_location(self)
23        direction = (max_ngh - pt.coordinates[0:3]) * 0.7
24        model.moveNervous(self, space_pt.x + direction[0], space_pt.y +
25        direction[1])
26
27    return(self.ElectronFusion, pt)

```

Listing 5.18: Oxygen step method

As we said before, when an oxygen agent catch an electron, the boolean variable is setted to True and a new ROS agent is generated. Obviously, both the oxygen and electron are removed from the context.

```

1     electron_fusion = []
2     if self.NervousContext.contains_type(Electron.TYPE):
3         for e in self.NervousContext.agents(Electron.TYPE):
4             electron_fusion = e.step()
5
6
7     for j in electron_fusion:
8         self.NervousContext.remove(j)
9
10    oxigen_fusion = []
11    if self.NervousContext.contains_type(Oxygen.TYPE):
12        for o in self.NervousContext.agents(Oxygen.TYPE):
13            fusion, pt = o.step()
14            if fusion == True:
15                oxigen_fusion.append(o)
16                self.generate_ros(pt)
17
18    for i in oxigen_fusion:
19        self.NervousContext.remove(i)

```

Listing 5.19: Fusion process defined in Model's step method

ROS

Reactive oxygen species (ROS) within mitochondria can arise as byproducts of cellular respiration, particularly during the electron transport chain (ETC) process.

Excessive production of ROS within mitochondria can lead to oxidative stress, a condition characterized by an imbalance between ROS production and the cell's antioxidant defenses. Oxidative stress can damage cellular components, including lipids, proteins, and DNA, and contribute to the development of various diseases, including neurodegenerative disorders like Parkinson's disease.

```
1 class ROS(core.Agent):
2
3     TYPE = 8
4
5     def __init__(self, a_id, rank):
6         super().__init__(id=a_id, type=ROS.TYPE, rank=rank)
7
8     def save(self) -> Tuple:
9         return (self.uid,)
10
11    def step(self):
12        grid = model.nervousGrid
13        pt = grid.get_location(self)
14
15        space_pt = model.nervousSpace.get_location(self)
16        direction = pt.coordinates * 0.3
17        model.moveNervous(self, space_pt.x + direction[0], space_pt.y +
direction[1])
```

Listing 5.20: ROS class

ENS and Vagus Nerve

From a theoretical perspective, α -synucleins are produced within the intestinal lumen by activating inflammatory responses. As mentioned earlier, when microbiota dysbiosis occurs, the permeability of the intestinal barrier increases, allowing certain organisms (e.g., lipopolysaccharides, LPS) to move into the lumen. This inflammatory response triggers the production of α -synuclein, which then migrate through the enteric nervous system (ENS) and subsequently to the CNS via the vagus nerve.

The ENS is a complex network of neurons located within the gastrointestinal tract wall. It regulates various gastrointestinal functions and communicates with the CNS through the vagus nerve. After microbiota dysbiosis (leaky gut), α -synucleins are produced within the lumen and subsequently pass into the enteric nervous system. Given the interconnectedness between the ENS and CNS through various nerves, including the vagus nerve, α -synucleins can traverse to the CNS at a speed estimated to be between 5–10 mm/day [1].

In our implementation, we considered the microbiota and intestinal lumen as two communicating environments with permeable epithelial cells. Thus, when α -synucleins are produced, they are directly transported from the lumen to the central nervous system.

Regarding the implementation of the ENS and vagus nerve, we viewed these systems as communication channels facilitating the movement of agents (such as α -synucleins) between the gut and CNS. However, we chose to exclude explicit modeling of the ENS and vagus nerve due to computational considerations. From a computational standpoint, including additional environments without significant agent interaction or internal state evolution would be overly complex.

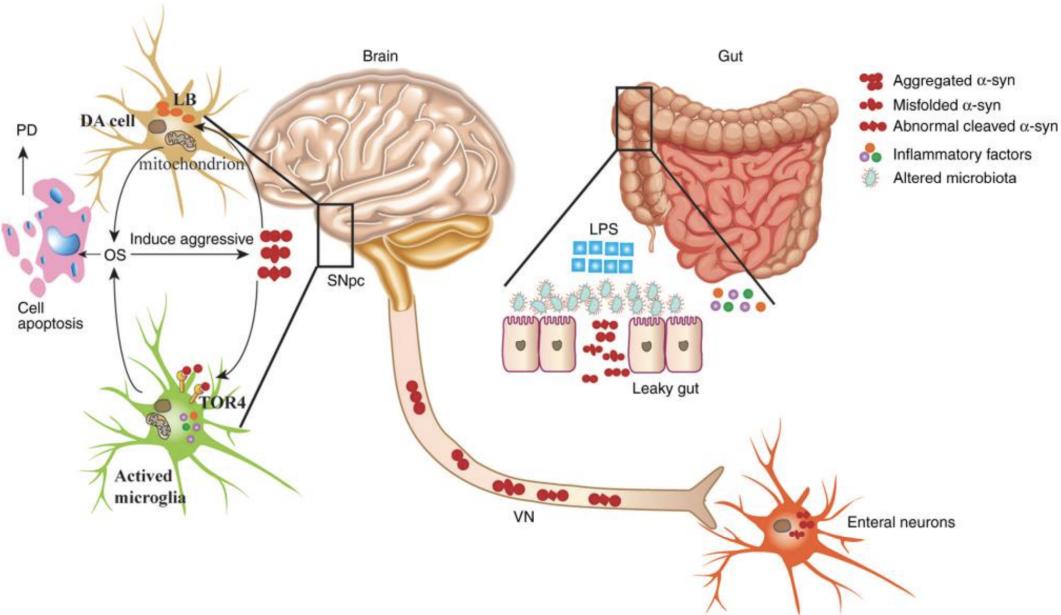


Figure 5.2: System description with ENS and Vagus Nerve. [1]

In the case of the ENS and VN, there is no internal state, and the agents passing through them do not exhibit significant interactions or behaviors. One way to represent the ENS could be to treat it as a small set of agents within the lumen environment. If an α -synuclein agent reaches these ENS agents, they could automatically be transported to the CNS. This concept is illustrated in the graph below.

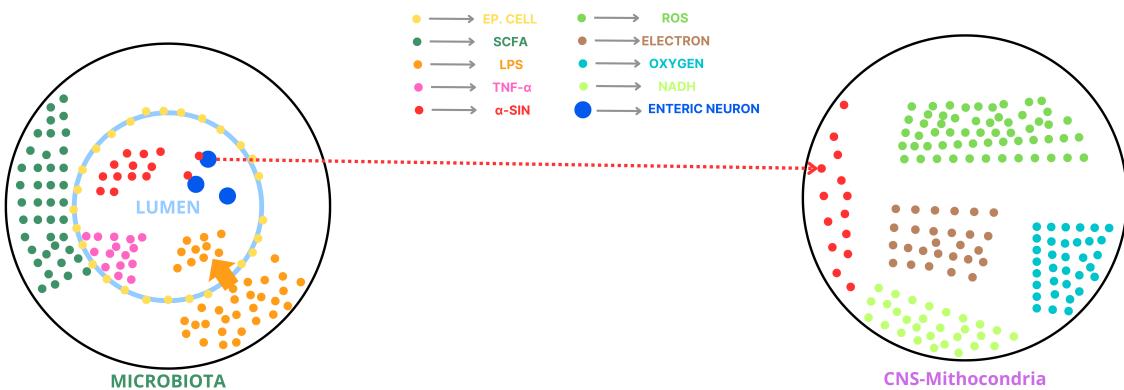


Figure 5.3: Idea of Enteric Nervous System implementation.

6. Scalability

Scalability in a multi-agent application model refers to the system's ability to handle an increase in the model's size, the number of agents, and the complexity of interactions among them without compromising performance or efficiency. There are several key considerations for evaluating the scalability of a multi-agent application:

- Model Size: Scalability refers to the ability to handle an increase in the model's size, such as the number of agents or the extension of the space in which they operate. A scalable model should be able to manage a growing number of agents without experiencing a significant degradation in performance.
- Distribution and Parallelism: A scalable multi-agent application should be designed to fully leverage distributed and parallel resources. This may involve distributing agents across multiple computing nodes or using parallelism techniques to perform computationally intensive operations simultaneously.

In this project, we distributed the agents within the simulation space according to the number of ranks set. This approach ensures a balanced distribution, preventing any single process from being overloaded with too many agents compared to others.

During the model testing phase, we varied both the number of agents and the size of the space in which they were placed. These variations led to differences in execution times, resulting in either shorter or longer durations for the model to run.

In summary, scalability in a multi-agent application model focuses on the system's ability to efficiently and reliably handle an increase in the size and complexity of the model, optimally utilizing available resources, and dynamically adapting to variations in execution conditions.

7. Future works - Treatment Strategy

For this chapter, we have evaluated various treatment strategies based on the findings outlined in document 3:

- Levodopa
- Probiotics

Levodopa is a naturally occurring amino acid in the human body that is primarily utilized for the treatment of Parkinson's disease to augment dopamine levels in the brain and mitigate associated symptoms. Studies suggest that Levodopa can indeed have an impact on the gastrointestinal (GI) system. Although its primary role is to manage Parkinson's symptoms by boosting dopamine levels in the brain, its administration can lead to various effects within the GI tract. One significant consideration involves the metabolism and absorption of levodopa. While levodopa is primarily converted into dopamine in the brain, a portion of it can be metabolized in the GI tract before reaching the brain. This metabolic process may be influenced by specific foods or interactions with other medications, potentially affecting the effectiveness of levodopa therapy. Furthermore, levodopa can cause GI-related side effects. Common GI side effects associated with levodopa include nausea, vomiting, constipation, and decreased appetite. The severity of these effects can vary and may impact the overall tolerability of the medication.

Probiotics refer to specific microorganisms administered in adequate quantities to confer health benefits by restoring microbiota balance and supporting immune function. Common probiotic strains include Lactobacilli, Enterococci, Bifidobacteria, *Bacillus subtilis* and yeasts, among others. Researches as 3 indicate that probiotics can enhance **intestinal epithelial integrity**, fortify barrier function, foster a balanced mucosal immune response, and inhibit the growth of pathogenic bacteria. Several studies have underscored the favorable impacts of probiotics on gastrointestinal health, immune modulation, and overall well-being.

Our choice

Following this initial introduction, we decided to incorporate **probiotic treatment**, specifically *Bacillus subtilis*, into our project due to our focus on *intestinal barrier permeability*. Levodopa was not considered as it lacked a clear relevance to the project and there is uncertainty about its role in impacting the gastrointestinal system.

New Model

The model changes minimally, specifically focusing on the microbiota environment. The role of the artificial agent is indeed to enhance the intestinal barrier, **delaying** the cascade of dysfunction that leads to Parkinson's disease.

Microbiota Environment

So, we changed the Ag_m .

$$Ag_m = \{SCFA, Epithelialcells, LPS, Probiotic\}$$

The set of states identified within the microbiota are represented below:

$$M = \{m_0, m_1, m_2, m_3\}$$

where,

- m_0 state indicates an healthy microbiota
- m_1 state, microbiota with a reduction of SCFA agents and subsequently, an increase of intestinal permeability.
- m_2 state, indicate the enhancement of the intestinal barrier following probiotic administration. This state represent an environment with an intestinal barrier more solid, reducing the LPS transport.
- m_3 state stands for an environment without LPS bacteria, a lower number of SCFA and a higher level of permeability.

Thus, the environment Env_m is a triple:

$$Env_m = \{M, m_0, \tau\}$$

where M is the set of our environment states, m_0 is the initial state and τ is a transformation function that map the run to a subset of M .

The system has one run contained in R^{Ac_m} :

$$r_1 : m_0 \xrightarrow{\text{microbiotaDysbiosis}} m_1 \xrightarrow{\text{probioticAssumption}} m_2 \xrightarrow{\text{LPStransport}} m_3$$

As written before, the Microbiota system includes four agents: SCFA, Ephitelial cells, Probiotic and LPS bacteria. Each agent is a reactive agent and they can be described using this strategy:

- *SCFA*

see: $m_0 \rightarrow SCFAdecrease$

action: $SCFAdecrease \rightarrow MicrobiotaDysbiosis$

do: $MicrobiotaDysbiosis \times SCFAdecrease \rightarrow m_1$

- *Epithelial cell*

see: $m_0 \rightarrow IncreasePermeability$

action: $IncreasePermeability \rightarrow MicrobiotaDysbiosis$

do: $MicrobiotaDysbiosis \times IncreasePermeability \rightarrow m_1$

- *Probiotic*

see: $m_1 \rightarrow EnhancementIntestinalBarrier$

action: $EnhancementIntestinalBarrier \rightarrow DecreaseDevelopingDysbiosis$

do: $DecreaseDevelopingDysbiosis \times EnhancementIntestinalBarrier \rightarrow m_2$

- *LPS*

see: $m_2 \rightarrow UnstableMicrobiota$

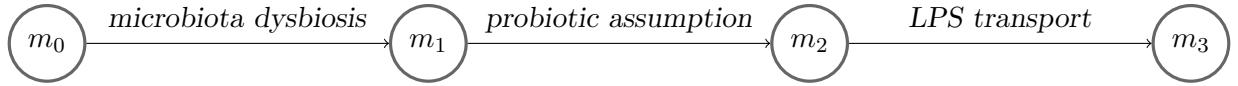
action: $UnstableMicrobiota \rightarrow LPStransport$

do: $LPStransport \times UnstableMicrobiota \rightarrow m_3$

The set of action is:

$$Ac_m = \{MicrobiotaDysbiosis, ProbioticAssumption, LPStransport\}$$

The evolution of microbiota is represented using this model:



The rest of the model remains unchanged.

8. Experimentation

After completing the experimental procedures for each environment and saving the outcomes in a CSV file, we employ the Matplotlib library [14] to visualize the data from this file through plotted graphs. The resulting visual representations are presented in the following sections, illustrating key findings and trends derived from our experiments.

Microbiota System Result

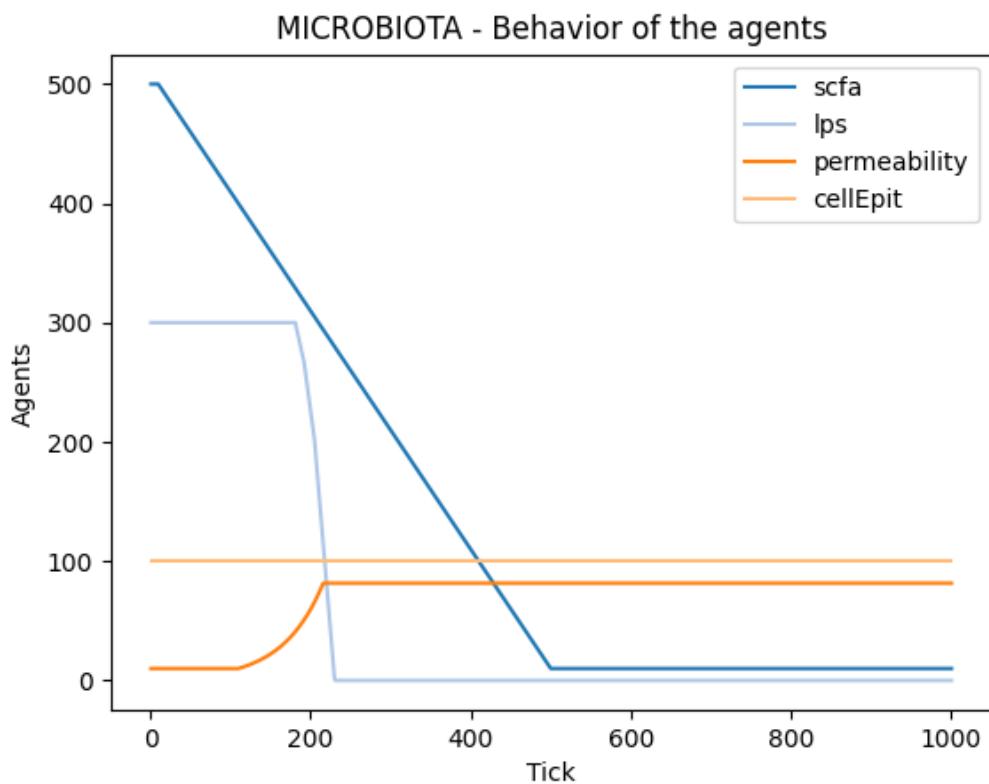


Figure 8.1: Microbiota system result

As depicted in the image 8.1, over time (as indicated by the ticks), the number of SCFA agents will gradually decrease, representing the Microbiota dysbiosis or "leaky gut". Once the threshold of SCFA agents is surpassed, the permeability of the barrier will increase, facilitating the transport of LPS agents into the intestinal lumen.

Intestinal Lumen System Result

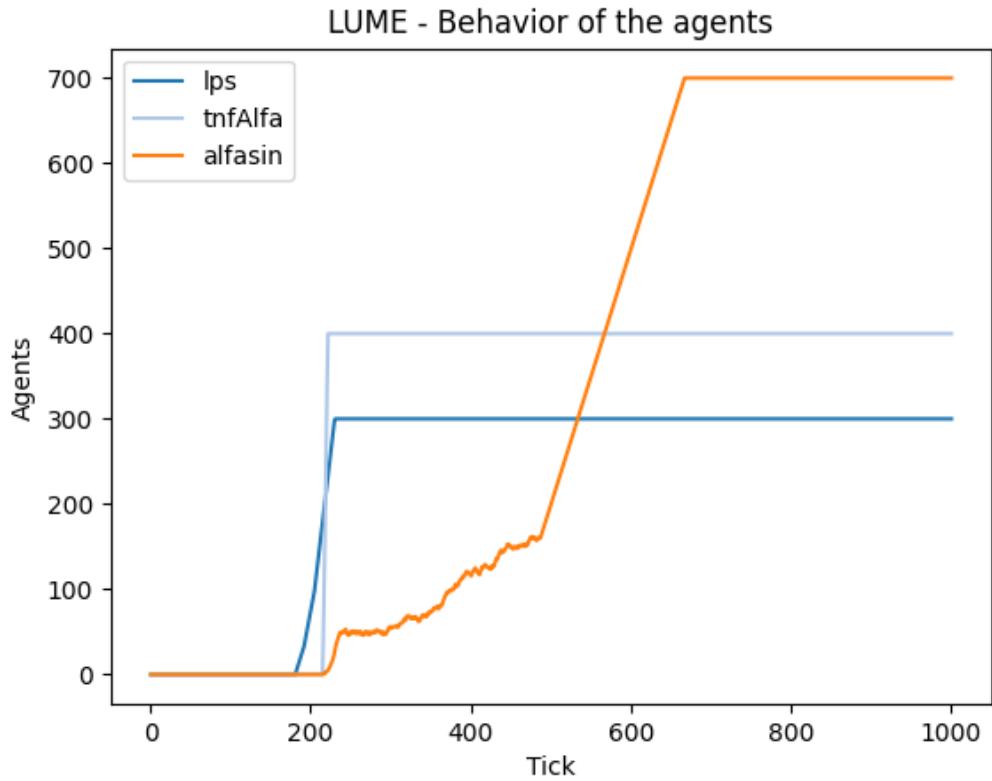


Figure 8.2: Lumen system result

As depicted in the image 8.2, the entry into the actual intestinal lumen occurs around tick 150, following the arrival of LPS from the microbiota due to partial or near-total breakdown of the intestinal barrier. Subsequently, the system enters an inflammatory state by activating TNF- α agents. This inflammation leads to the production of α -synuclein which, from a theoreric point of view, via the vagus nerve in the enteric system, gradually transports the α -synuclein produced in the central nervous system.

CNS system result

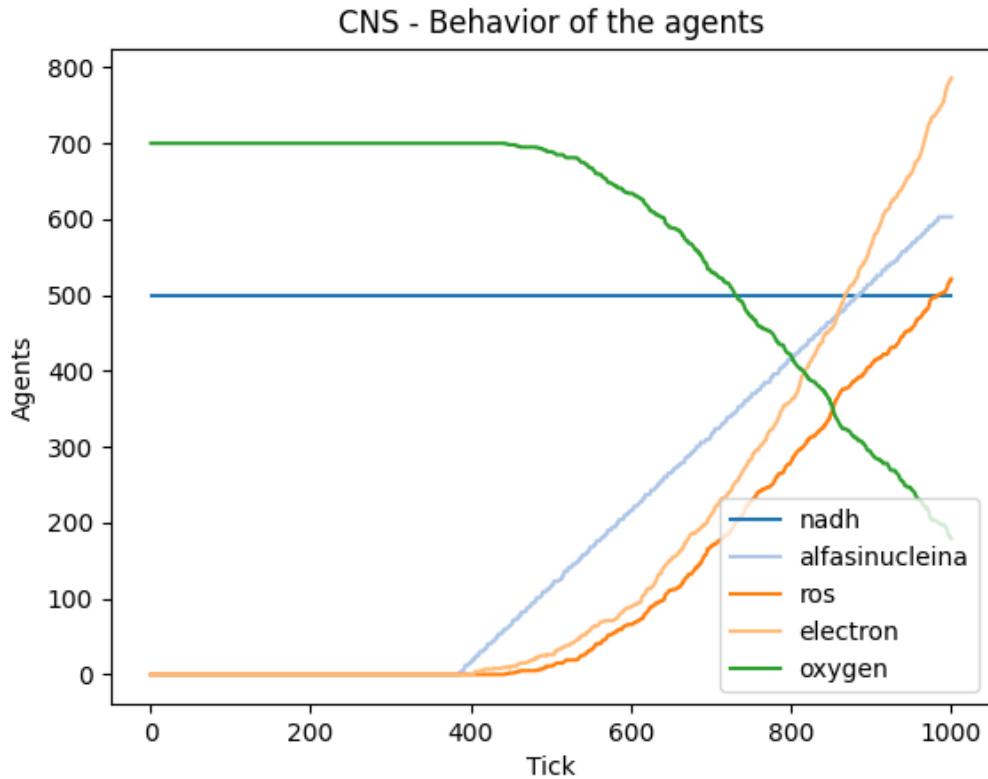


Figure 8.3: CNS system result

As depicted in the figure above (Figure 8.3), the involvement of the Mitochondrial system commences around tick 400, subsequent to the transportation of α -synuclein from the intestinal lumen to the vagus nerve and subsequently to the mitochondria. As discussed in Section 4, the aggregation of α -synuclein results in damage to the Electron Transport Chain (ETC), leading to a release in the number of electrons. ETC damage causes the generation of Reactive Oxygen Species (ROS) through the leakage of electrons that react with molecular oxygen, forming ROS. We can observe that the number of ROS agents increases as the number of oxygen agents starts to decrease. This image represents the oxidative stress occurring in the mitochondria and subsequent mitochondrial dysfunction.

9. Conclusions

Working on this project has been very stimulating and challenging. Learning a new modeling language like Repast4py has been interesting and certainly useful for the future. We encountered difficulties in understanding some concepts of Repast4py that are different from Repast Symphony, such as the implementation of agents and the ability to add and communicate multiple contexts.

Continuing to delve into the study of Parkinson's disease done in the Distributed Calculus and Coordination course was an optimal choice, especially because we were able to study the development of the disease in a different environment from the nervous system. Studying how Parkinson's evolves within the gastrointestinal system has led us to both a greater understanding of how the disease works and to understand how our body behaves in case of "malfunction".

There could be many future developments for this project: One of them is to represent the model in a more detailed way, with a lesser degree of abstraction compared to the current one. This would certainly result in a higher computational cost, but with a more realistic model, we could better understand the development of the disease. Of course, to best represent the model, we should delve deeper into the study and analysis of the system.

With more time available, implementing a graphical interface, similar to the one used in the Repast Symphony project, could show the interaction and movement of agents in the various environments clearly.

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