Mathematics for Parkinson's Disease – Can It Help?

Manfred Sneps-Sneppe
Ventspils University of Applied Sciences, Latvia
Ventspils, Latvia
manfreds.sneps@gmail.com

***Abstract*— The goal is to attract mathematicians' interest in the neurodegenerative diseases research. Yoshinori Ohsumi received the Nobel Prize in 2016 in Physiology or Medicine for his discoveries of mechanisms for autophagy using yeast as a model organism. These uncovered secrets of nature initiated much in life science, including many mathematical models of Parkinson's disease: cell population dynamics, mitophagy, autophagic vesicle dynamics in single cells, dopaminergic nerve cell and terminal models, and glucose metabolism. The cause of PD – alpha-synuclein – potentially connects the gut-brain axis in PD patients. It is closely related to lipid metabolism and nutrition. Thus, a new science is emerging – neurogastroenterology.**

I. INTRODUCTION

Parkinson's disease (PD) is a common disorder, affecting more than 1% of the population over 60 years of age. Parkinson's disease is named after the French neurologist Jean Charcot (1825-1893). He proposed this name after the British physician and author of "An Essay on the Shaking Palsy" James Parkinson (1755-1824). In 1912, the German physician Friedrich Lewy (1885-1950) discovered specific cellular inclusions in brain stem cells characteristic of Parkinson's disease, later called Lewy bodies (Fig. 1).

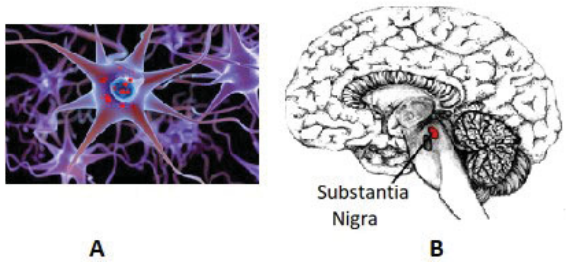

Fig. 1. Parkinson's disease: A) neurons contain small red spheres in Lewy bodies (in the region of substantia nigra) – deposits of a protein (alpha-synuclein) that accumulate in brain cells and lead to the death of neurons, B) The substantia nigra is a midbrain dopaminergic nucleus, which has a critical role in modulating motor movement

The normal aging process is associated with a decrease of dopamine levels (scientists know of at least 100 neurotransmitters, and dopamine is one of them). With age, the number and density of dopamine receptors decrease, and the dopamine concentration in the brain decreases also (Fig. 2).

Neurotransmitters transmit electrochemical impulses from a nerve cell through the synaptic gap between neurons. Each neuron forms at least 15,000 connections with other neurons. Note an amazing fact about how the brain functions. The brain spends 20% of the energy of our entire body, and of this large amount of energy, neurons spend 60-80% for transmitting impulses (Action potential) between neurons.

The main bioelectrical manifestation of nervous impulse action potential (AP) is a peak-shaped oscillation of the electrical potential associated with changes in the ionic permeability of the membrane (of the order of −70 to +40 mV). Increased permeability during AP leads to increased fluxes of cations (Na+ and Ca2+) into and out of the nerve fiber (K+). With moderate motor activity in motor nerve fibers, the discharge frequency is about 100 impulses per second.

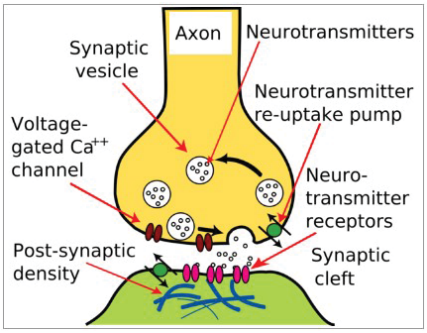

Fig. 2. How do neurotransmitters work?

A hallmark of PD pathology is the depletion of dopaminergic cells, but the etiology of PD neurodegeneration remains unclear. It is a complex, multifactorial disease resulting from aging, genetic predisposition, and exposure to environmental toxins.

Fig. 3. Signs of Parkinson's disease

Usual PD symptoms are tremors, slowness of movement, rigidity, and difficulty with balance, collectively known as parkinsonism. Parkinson's disease dementia, falls and neuropsychiatric problems such as sleep abnormalities,

psychosis, mood swings, or behavioral changes may arise in advanced stages (Fig. 3).

Google Scholar returns more than 2 million hits for the query "Parkinson's disease." Many works are also devoted to mathematical modeling of PD – 67,200; in 2024 alone, 4,450 works have already been completed.

Next, we will consider the possibility of transferring the achievements obtained in the study of yeast, a single-celled microorganism, to human diseases, including the treatment of Parkinson's disease. The idea concerns the mechanism of yeast starvation. It is clear in advance that this idea is likely unpromising, but it excites scientific thought.

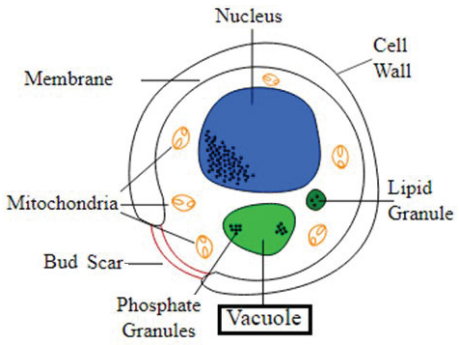

Fig. 4. Yeast. The first yeast originated hundreds of millions of years ago, at least 1,500 species are currently. Vacuoles of yeast are valuable models for trafficking processes to mammalian lysosomes. The bud scar is the chitin-containing ring on the cell wall of the mother cell.

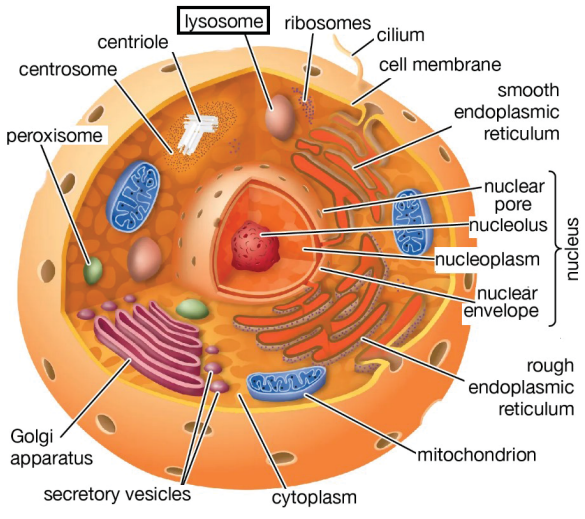

Fig. 5. Human cell diagram (Encyklopedia Britanica)

Lysosomes are single membrane-bound organelles found in many animal cells (Fig.5). Lysosomes contain more than 60 different enzymes and have more than 50 membrane proteins. How can we recognize the analogy between the yeast vacuole and the animal lysosome? How could it help in PD treatment?

The paper continues our previous research [1] and is the following. Section 2 is about the secrets of nature Y. Ohsumi received the Nobel prize in 2016. Section 3 contains a description of neurodegenerative diseases and leaky gut. Section 4 gives an insight into alpha-synucleinopathy explained by dopaminergic nerve cell and terminal models. Section 5 is devoted to brain metabolism. Section 6 concludes the paper with some discussion on the gut-brain axis in PD patients closely related to lipid metabolism and nutrition. Thus, a new science is emerging – neurogastroenterology.

II. Ohsumi's Nobel Prize: For What Secrets of Nature?

Yoshinori Ohsumi (born in 1945) is a Japanese cell biologist specializing in autophagy, process cells used to destroy and recycle cellular components. He received the 2016 Nobel Prize in Physiology or Medicine for his discoveries of mechanisms for autophagy using yeast as a model organism. The yeast species *Saccharomyces cerevisiae* (Ohsumi's study object) is widely used in our lives. It converts carbohydrates to carbon dioxide and alcohol through the process of fermentation.

Autophagy, self-eating, is a pivotal catabolic mechanism that ensures homeostasis and survival of the cell in the face of different stressors such as starvation, infection, or protein misfolding. In the autophagic type of cell death, all cell organelles are digested, leaving only cellular debris that is absorbed by macrophages. One of its seminal findings of Ohsumi was on the role of proteins in the double-membrane vesicle autophagosome formation, which is the functional unit of autophagy (Fig. 6).

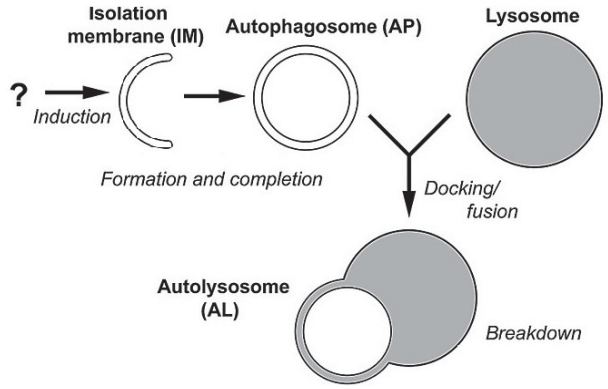

Fig. 6. Diagram of autophagosome formation: an insulating membrane (IM) surrounds cellular structures and creates an autophagosome (AP), which fuses with a lysosome to create an autophagolysosome (AL) [2]

Ohsumi began his work in 1988. Before that time, less than 20 papers per year were published on this subject. During the 1990s, Ohsumi's group described the morphology of autophagy in yeast and performed mutational screening on yeast cells that identified some genes capable of autophagy. Now Google Scholar returns 300,000 hits for the query "yeast autophagy", and the paper explaining Ohsumi's theory [2] is cited 7726 times.

Ohsumi's success story. In the yeast *Saccharomyces cerevisiae*, the vacuole of this microorganism is visible by phase contrast microscopy. The vacuole was assumed to be equivalent to the lysosome in mammals since it is an acidic compartment containing many hydrolytic enzymes. The vacuole is a fairly large compartment (3 μm in diameter). In a state of nitrogen starvation, the vacuole may become prominent by blocking normal degradation. Indeed, Y. Ohsumi discovered dramatic morphological changes in vacuoles during starvation [3]. After 30 min of starvation, energetically moving spherical bodies appeared in the vacuole, which gradually increased in number and finally filled the vacuole (averaging 500 nm in diameter and covering part of the cytoplasm).

The most important event in autophagy is the sequestration of these materials and how a new compartment forms as shown in Fig. 6. Autophagy leads to the de novo formation of isolated membranes in the cytoplasm called phagophores, which expand while becoming spherical and eventually seal to become double membrane-bound structures called autophagosomes [4].

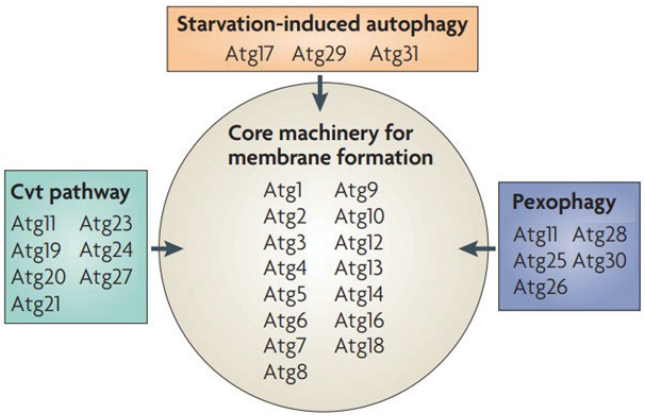

Fig. 7. Classification of autophagy-related (Atg) proteins as the core machinery for membrane formation [4]. Atg proteins are commonly required for three autophagy-related pathways: (1) starvation-induced autophagy, (2) the Cvt (cytoplasm-to-vacuole targeting) pathway, and (3) pexophagy (an autophagic degradation pathway for peroxisomes in yeast; peroxisomes are a type of microbodies found virtually in the cytoplasm)

During more than 10 years of continued experimental studies Y. Ohsumi and his group identified more than 30 proteins required for autophagy; however, the mechanism of action and regulation of these 30 proteins is incompletely understood. Furthermore, autophagy contributes to cell fate in a complex manner that is only beginning to be clarified.

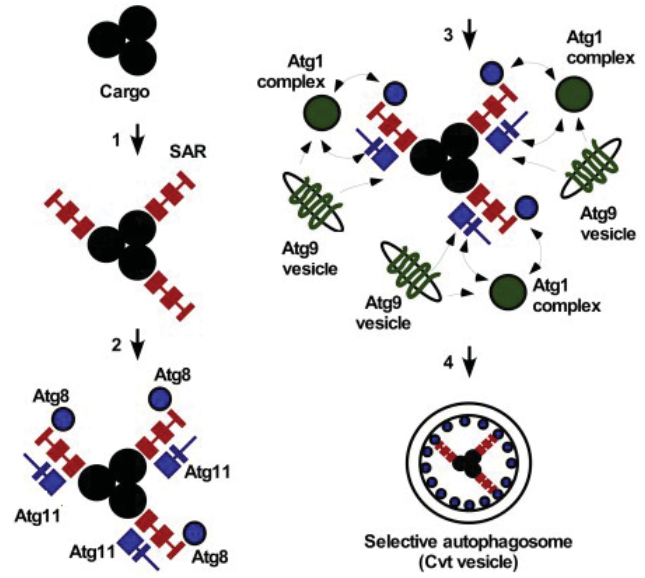

Fig. 8. A simplified model of selective autophagosome formation based on studies using yeast as a model organism [5]

The following four steps of selective autophagosome formation can be distinguished (Fig. 8):

(1) Cargo (some macromolecules) is labeled by SARs (selective autophagy receptors).

(2) SARs recruit the Atg1- and Atg9- binding adaptors Atg11 and Atg8 (Atg, autophagy-related proteins)

(3) Atg11 and Atg8 include the components of the Atg1 kinase complex.

(4) that leads to the production of the selective autophagosome in situ (Cvt, cytoplasm to vacuole transport).

Yeast population dynamics model. In [6], a mathematical model based on logistic growth studies the role of autophagy in yeast (Saccharomyces cerevisiae) cell population dynamics in response to starvation. Proper levels of autophagy promote cell survival by inhibiting cell death by autophagy and secretion of nutrients from autophagic cells, however, excessive autophagy can reduce the cell population due to autophagic cell death. This is a simple yeast population dynamics model without considering the details of autophagy.

Consider cells cultured in a container with fixed volume V. The cells are classified into the normal phase (population x) or autophagy phase (population y). The flow rates λ_1, k_1, k_2, k_3, a_3 depend on the average nutrient concentration per cell. Letting z be the concentration of nutrients in the container, $z_0(t)$ the nutrient concentration in the input flux, $\lambda_3(t) = V_0(t)/V$ the rate of nutrient loss by the output flux (dilution rate), $r = y/(x + y)$ the ratio of autophagic cells in the whole population, and $w = z/(x + y)$ the average nutrients per cell. Low-level autophagy can promote cell survival, while excessive autophagy can induce type II programmed cell death.

Fig. 9 illustrates the model of cell growth with nutrient delivery control and cell autophagy. Red squares represent nutrients, and cyanic and brown circles represent normal and autophagic cells, respectively. When the nutrient is sufficient, normal cells proliferate with intrinsic rate λ_1. Normal cells can turn into autophagic cells with a rate k_1 when nutrients are deficient.

Autophagy is reversible. Autophagic cells can return to their normal phase (with a rate k_2) when the nutrient level is restored. Normal and autophagic cells are removed randomly with rates δ_1 and δ_2, respectively. Dashed lines show nutrient fluxes. Nutrients are added and removed respectively with rates $\lambda_3 z_0$ and λ_3. Each cell consumes nutrients at a rate k_3, and each autophagic cell produces nutrients at a net production rate of a_3 per unit of time.

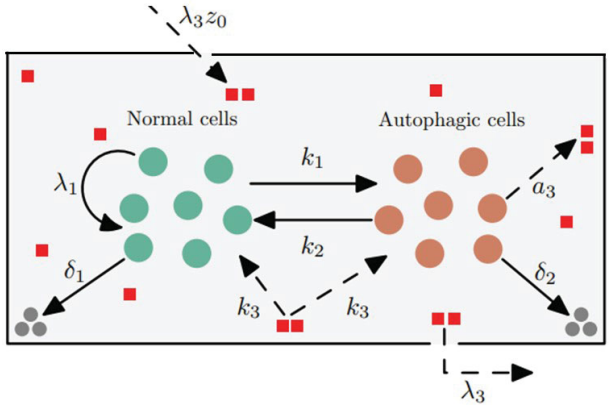

Fig. 9. Yeast population dynamics model [6]

The dynamics of cell populations can be modeled by the following logistic equations:

$$\begin{cases} \frac{dx}{dt} = \lambda_1(w)\left(1 - \frac{x+y}{M}\right)x - k_1(w)x + k_2(w)y - \delta_1 x \\ \frac{dy}{dt} = k_1(w)x - k_2(w)y - \delta_2(r)y \\ \frac{dz}{dt} = \lambda_3(t)(z_0(t) - z) - k_3(w)(x+y) + a_3(w)y \\ w = \frac{z}{x+y}, \quad r = \frac{y}{x+y}. \end{cases}$$

A deep mathematical analysis (including the existence and stability of equilibrium states) is carried out in [6]. It is shown that efficient autophagy might be sufficient to sustain a population during long periods of starvation. The model proposed is general and too simple – without details in yeast molecular-level regulations of autophagy.

A simple yeast autophagy model. In [7], a simple engineering approach was applied. The autophagy process is extremely complicated in reality but the very essence of starvation may be catched by a single ATG13 protein. The starvation-induced pathway utilizes a series of membrane rearrangements. It involves the hierarchical translocation of a series of relevant components into and out of forming autophagosomes and employs a large number of proteins and protein complexes. The paper [6] investigated one of the earliest steps in this pathway, the translocation of the ATG13 protein to the emerging autophagosomal structure, using mathematical models to gain insight into the mechanisms that regulate it.

This is a minimalistic model for the early steps of nonselective autophagy, where ATG13 aggregates and dissociates following mass-action reactions (Fig. 10A). ATG13 protein accumulation and disappearance are non-linear. That includes a dependency for the process on the concentration of aggregated ATG13. There are several biological terms used:

wortmannin – a natural product with anti-inflammatory and immunosuppressant effects

LC3 proteins – enable the engulfment of the targeted membrane

MTORC1 – a mechanistic target of rapamycin kinase complex 1 mTOR inhibitor (e.g., AZD8055)

To investigate the effect of wortmannin on these reactions, three models were investigated: 1) wortmannin regulating ATG13 aggregation, 2) wortmannin regulating ATG13 disappearance, and 3) wortmannin regulating both aggregation and disappearance.

Despite the modest knowledge about the mechanism of phagocytosis (only the ATG13 protein is considered), it was possible:

a) to analyze the strategy that allowed to exclude potential autophagosome formation on the mitochondrion surface. This selection of mitophagy events was then quantified,

b) the mathematical description of the nonselective autophagy model: synchronized time courses for ATG13 upon starvation and starvation plus wortmannin were simultaneously used for parameter estimation,

c) the mitophagy model extended the nonselective autophagy model (due to the inclusion of LC3) and oscillatory dynamics with delay for ATG13 were shown.

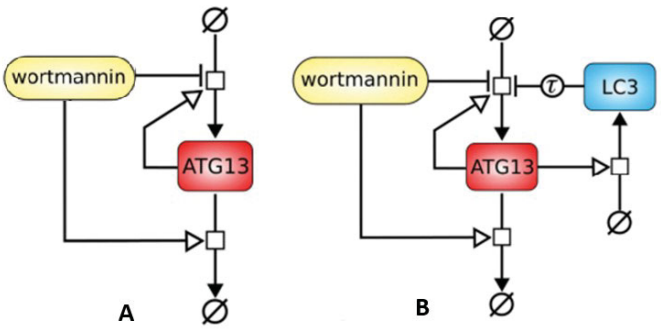

Fig. 10. (A) Schematic diagram of the mathematical model for nonselective autophagy. (B) Model diagram for mitophagy events. This model extends diagram A by including LC3 and the events regulating the delays τ between aggregations. The mitophagy model extended the nonselective autophagy model due to including LC3 and oscillatory dynamics with delay for ATG13 (LC3 inhibits ATG13 accumulation after a delay τ)

A stochastic model for single cell autophagy. This model, on the contrary, is too complicated. It considers the accumulated experience in autophagy [8]. In [9], the model utilizes stochastic simulation to reproduce observed autophagic vesicles as a whole considering many molecules mentioned in Fig. 7. This is one fundamental yeast autophagy model centered on explaining Oshumi's results in detail looking at parallels of autophagic vesicle dynamics in a very complex mammalian system. The model conceptualizes autophagy as a process consisting of four, in its order, complex stages: initiation, nucleation, maturation, and cargo delivery/ degradation.

Macroautophagy (autophagy) is a cellular recycling program essential for homeostasis and survival during cytotoxic stress. This process has an emergent role in disease etiology and treatment, it is executed in four stages through the coordinated action of more than 30 proteins.

Sophisticated studies in yeast and mammalian systems have identified more than 30 proteins required for autophagy; however, their mechanisms of action and regulation are incompletely truly speaking only partly understood. Furthermore, autophagy influences cell fate in a complex manner that is only beginning to be illuminated. Although autophagy acts as a survival mechanism to delay or prevent apoptosis during periods of stress, it can also participate in cell death when activated excessively or for prolonged periods.

Along these same lines, dysregulated autophagy has been found to contribute to the pathology of many serious diseases, including cancer and neurodegeneration. Thus, a greater knowledge of autophagy relating to the regulation, molecular underpinnings, and cellular consequences is crucial. It is important not only for understanding normal physiology but also for comprehending disease etiology and rationally designing therapies.

The report [9] describes a computational model that characterizes auto-phagic vesicle (AV) dynamics in single mammalian cells. The model contains 23 equations and 30 parameters. Fig. 11 displays an excerpt from [9].

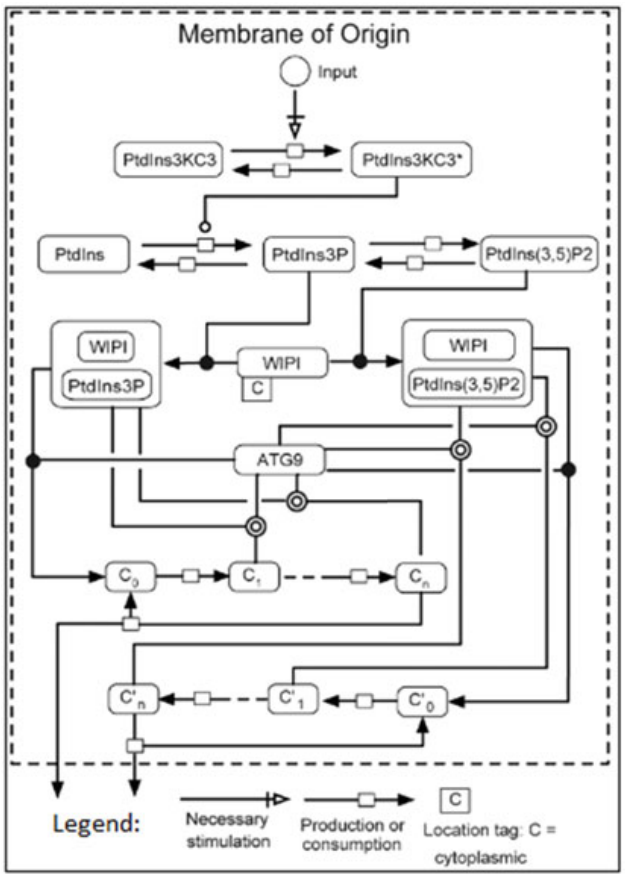

Fig. 11. Overview of key molecules included in the stochastic model of autophagic vesicle dynamics (excerpt from [9]. This model uses the conventions of Systems Biology Graphical Notation (SBGN). Dashed lines indicate compartments. Rounded rectangles represent chemical species. Arrows represent interactions as shown in the legend

Reactions considered in the model are listed in 23 equations (23 different reactions). As many as sixteen reactions involve chemical species in the membrane-of-origin compartment (Eqns. 1-16), i.e., the compartment from which all phagophores and mature autophagic vesicles arise. The other seven reactions (Eqns. 17-23) are associated with specific PGs or Avs.

Live-cell fluorescent microscopy was used to measure the synthesis and lysosomal turnover of LC3-positive AVs. (LC3 proteins enable the engulfment of the targeted membrane.)

The model accurately predicted vesicle dynamics observed in cells over different conditions. This computational model provides a framework from which comprehensive autophagy models can be built.

Besides, the following treatments are considered in this model:

(1) Bafilomycin A_1 (BafA1) as a treatment that inhibits lysosome function,

(2) mTOR (mammalian target of rapamycin) inhibitors, e.g. AZD8055, a class of drugs used to treat several human diseases, including cancer, autoimmune diseases, and neurodegeneration.

Using stochastical modeling, the goal was to understand the fluctuations and considerable dynamic range of behavior observed in single-cell experiments. A simulation algorithm (23 equations) characterizes the chemical kinetics of the reactions in the model.

What is new? The model generated an unforeseen prediction about vesicle size. The results were consistent with both published findings and experimental observations. Taken together, this model is accurate and useful. It can serve as the foundation for future efforts in the quantitative characterization of autophagy. The model discovered a positive correlation between LC3 level and AV size across single cells. Arguably the most important feature of a computational model is that it generates novel hypotheses that can be tested experimentally.

III. "THE MAIN REFUGE OF MADNESS IS THE STOMACH AND INTESTINES"

This is one old sentence said by
the "father" of modern psychiatry,
French psychiatrist Philippe Pinel (1745-1828),
back in 1807 (that is, more than 200 years ago).

Parkinson's disease is incurable, but hope doesn't die. Autophagy as a therapeutic target is considered central in PD treatment. The key goal is to understand the exact mechanisms by which autophagy may be compromised in neurodegeneration.

The wide Parkinson's disease analysis contains the survey [10]. Intracytoplasmic protein misfolding and aggregation are features of many late-onset neurodegenerative diseases called proteinopathies. These proteinopathies include Alzheimer's disease (AD), Parkinson's disease, tauopathies, and other neurodegenerative diseases.

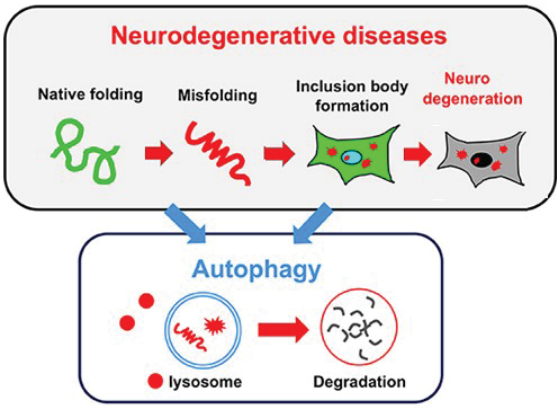

Fig. 13. Interconnections between neurodegenerative diseases and autophagy. A common pathology is exposed in several neurodegenerative diseases, namely, the accumulation of misfolded proteins and inclusion bodies. Autophagy may be useful for degrading both misfolded proteins and inclusion bodies [11]

Lysosomal storage disorders are the most common neurodegenerative diseases of childhood and comprise more than 50 diseases. The clinical phenotypes of these diseases vary; however, they frequently show progressive CNS defects. Because the final step in the autophagic process is the fusion of autophagic vesicles with lysosomes and the degradation of the contents of these autolysosomes, lysosomal defects are highly likely to affect the autophagic capacity of the cell.

Of course, reduction of α-synuclein aggregation and mitophagy by autophagy might be useful therapeutic approaches against PD. Unfortunately, there are no known ways to achieve this goal.

Good or bad gut bacteria. The term "gut microbiome" refers to the microorganisms living in our intestines. For example, Good bacteria are Bifidobacteria and lactic acid bacteria; Bad bacteria are Staphylococcus, clostridium perfringens, and E. coli (toxic strain).

Fig. 14 shows the microbial composition of the gut microbiota varies across the digestive tract. Our microbiome is extremely rich. It is estimated that the gut flora has around a hundred times as many genes in total as there are in the human genome.

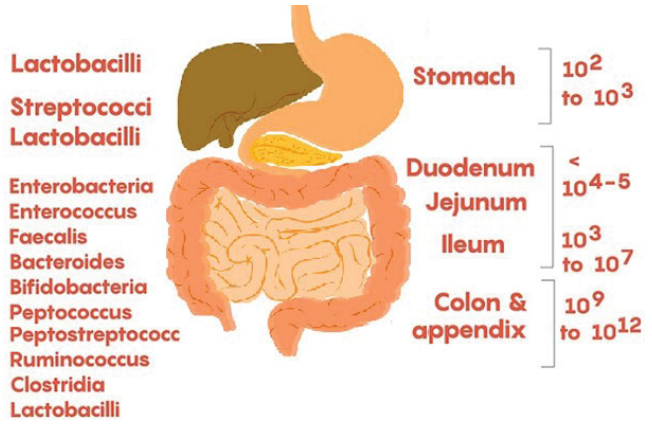

Fig. 14. Composition and distribution of gut microbiota in the human body [12]

Generally accepted nowadays gut bacteria are required to maintain epithelial integrity by regulating tight junction permeability. Lactobacillus plantarum, for example, was reported to regulate tight-junction proteins protecting chemical-induced disruption of the epithelial barrier.

Loss of gut epithelial integrity is crucial for a healthy life. It will allow bad bacteria, bacterial toxins, incompletely digested fats and proteins, and wastes to pass the epithelium into the bloodstream. As a result, it triggers inflammatory responses and leads to gastrointestinal problems, such as abdominal bloating, excessive gas and cramps, and food sensitivities. These symptoms indicate leaky gut syndrome, which exhibits intestinal hyperpermeability.

The gut microbiota will influence the host's immune system, inevitably affecting its health and disease. The gut microbiota could be potent biomarkers for disease diagnosis. However, identifying the precise changes in microbiota composition that are causally related remains a largely unrealized goal because the microbiota world is too rich.

Bacterial colonization processes are highly relevant for efficient CNS signaling. Indeed, a dysfunctional GBA accompanies disorders characterized by stress, depression, anxiety, irritable bowel syndrome, inflammatory bowel disease, and neurodevelopmental disorders.

North notes, that a high percentage of PD patients present with symptoms, such as abnormal salivation, dysphagia, nausea, constipation, and impaired defecation, altogether corresponding to physical functions associated with the gut. Although commonly accepted that a decrease in brain dopamine may mediate some gastrointestinal symptoms, peripheral organs (i.e., gut) are likely involved in the non-motor pathophysiology of PD.

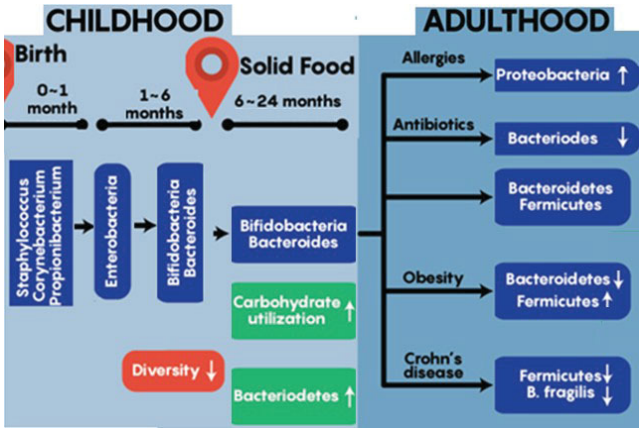

Fig. 15. The developmental colonization of gut microbiota [12]

Leaky gut. Disruption of the healthy flora (dysbiosis) has been implicated as a driver for a wide range of diseases such as irritable bowel syndrome, rheumatoid arthritis, obesity, diabetes, liver disease, and neurological disorders, including depression, anxiety, and Parkinson's disease. So far, treatments have been unable to stop this neurodegenerative disease. As scientists suggest nowadays, PD begins with bidirectional communication between the microbiota and the immune system, thus there is an exciting possibility that progression could be stopped before it reaches the brain [13].

"Leaky gut" is the name given to increased intestinal permeability. This is a generally recognized condition in which the spaces between the cells of the intestinal lining increase. The lining of a healthy intestine is semi-permeable, allowing water and nutrients from what you eat and drink to pass through.

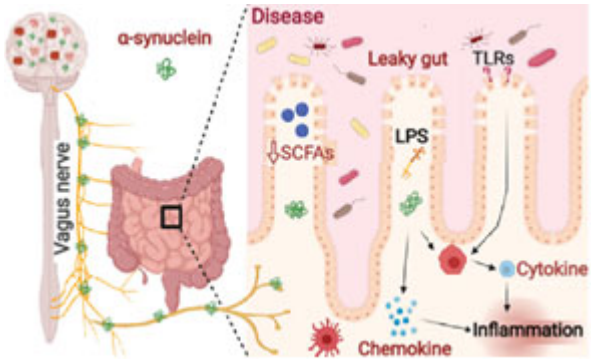

Fig.16. A schema illustrating the microbiota-gut-brain axis: how alterations in the microenvironment of the gut contribute to changes in the CNS in PD. North notes, that the alpha-synuclein propagates to the brain via the vagus nerve [14]

Comments to Fig. 16. *Positive side.* Short-chain fatty acids (SCFAs) are primarily produced by the fermentation of dietary fiber in the gut microbiome. Derived from intestinal microbial fermentation of indigestible foods, SCFAs in the human gut are acetic, propionic, and butyric acids. They are the main energy source of enterocytes, making them crucial to gastrointestinal health. Enterocytes in the colon, are the most numerous and function primarily for nutrient absorption. Examples of molecules taken up by enterocytes are ions, water, simple sugars, vitamins, lipids, peptides, and amino acids.

Toll-like receptors (TLRs) are found in various layers of the intestinal epithelium. They can recognize bacteria and are involved in establishing homeostasis in the intestine.

Negative side. Lipopolysaccharides (LPS) are bacterial toxins that can cause health problems if they enter the bloodstream. LPS is usually found safely in the intestines but can enter the bloodstream if you have an infection, leaky gut, or eat many fatty foods. Lipopolysaccharide, now more commonly known as Endotoxin, is a collective term for Gram-negative bacteria, such as E. coli and Salmonella.

The first characterizations of aSyn aggregates in the enteric nervous system (ENS) of PD patients were performed in the late 1980s. It is yet unclear whether microbiome changes are associated with Parkinson's disease, whether they are a consequence of the disease process per se, the basic reasons for underlying pathophysiology, or both. The systematic review of the current literature [15] on the role of the microbiota in the pathogenesis of alpha-synucleinopathies explores the hypothesis that the microbiota can modulate alpha-synuclein folding.

The clinical and pathological findings support the hypothesis that aSyn disease in PD occurs via a gut-brain pathway. For early diagnosis and early management, it is of utmost importance to identify pathogenic aSyn in the digestive system, for example, by gastrointestinal tract biopsies.

Intestinal dysbiosis may be a major factor in the development of Parkinson's disease by encouraging intestinal permeability, gastrointestinal inflammation, and the aggregation and spread of alpha-synuclein.

Parkinson's disease – microbiological explanation. By the time clinical symptoms of PD are evident, it is estimated that around 80% of dopaminergic neurons have been lost. The association of the microbiome with PD is of crucial interest since a healthy and dysbiotic microbiome can influence gut and brain homeostasis through complex two-way communication along the GBA (Gut-brain axis), the vagus nerve serves as a key communication channel (see Fig. 16). The intestinal microbiome is largely affected by the diet, at the same time serves as a source of disease pathology. Gastroenterology knowledge represents a therapeutic target in preventing, modifying, or stopping PD. Similarly, the components of the diet are closely related to the risk of suffering from PD since patients with this disease show a dysregulated intestinal microbiome (dysbiosis) characterized mainly by the loss of short-chain fatty acid bacteria and an increase in lipopolysaccharide bacteria (Fig. 17).

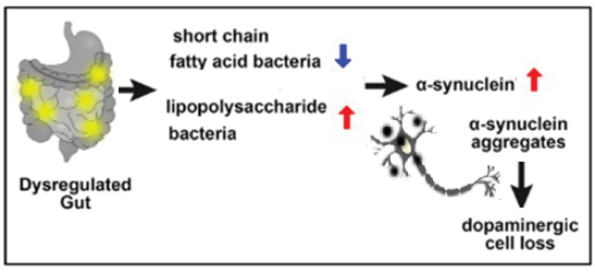

Fig. 17. Microbiological explanation of PD [14]

As noted above, a bidirectional communication in the gut-brain axis may preclude an initial excessive stimulation of the systemic innate immune system due to the dysregulation of the gastrointestinal system or bacterial overgrowth. This is one new aspect of immunology. Another important point considering GBA-induced neurodegenerative pathology is that gut bacteria synthesize many neurotransmitters and neuromodulators that mediate intracellular communication.

IV. Alpha-synuclein modeling

An insight into α-synucleinopathy. Alpha-synuclein (aSyn or α-syn) is a small cytosolic protein highly expressed in the brain and is mainly located in synaptic terminals. This neuronal protein regulates synaptic vesicle trafficking and subsequent neurotransmitter release. Alpha-synuclein is up to one percent of all proteins in the cytosol of brain cells. It has also been shown that alpha-synuclein is localized in neuronal mitochondria in its inner membrane. The alpha-synuclein may affect mitochondrial function, predisposing some neurons to degeneration [16].

Biophysical and lipidomic studies have demonstrated the wide harmful effects. Alpha-synuclein binds preferentially not only to specific lipid families but also to specific molecular species. These lipid-protein complexes enhance their interaction with synaptic membranes, influencing oligomerization and aggregation. They interfere with the catalytic activity of cytoplasmic lipid enzymes and lysosomal lipases, thereby affecting lipid metabolism (Fig. 18).

Parkinson's disease is associated with mutations in the alpha-synuclein gene SNCA. Yeast genome screening has found that several genes that deal with lipid metabolism and mitochondrial fusion play a role in alpha-synuclein toxicity.

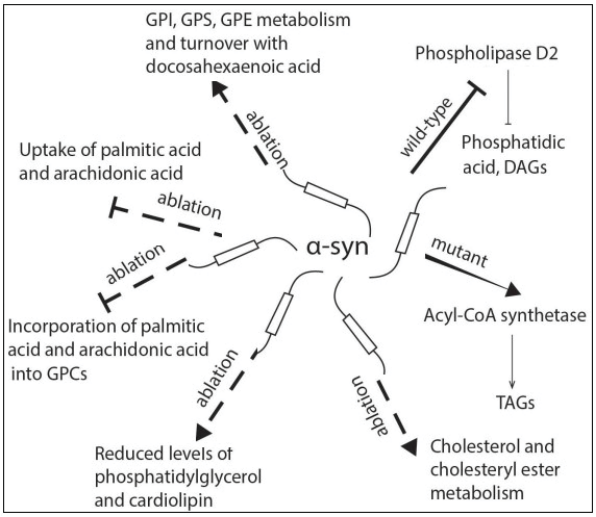

Fig.18. Schematic representation of the role of α-synuclein in lipid uptake and metabolism [16]

Comments to Fig 18: α-syn deficiency inhibits the uptake of palmitic acid and arachidonic acid and their further metabolism into GPE (glycerophosphocholine), while there is an increase in the incorporation of docosahexaenoic acid into GPE, GPI (glycerophosphoinositol), and GPS (glycerophosphoserine). The absence of α-syn also reduces levels of phosphatidylglycerol and cardiolipin in mitochondria. Mutant α-synuclein has been shown to enhance the activity of acyl-CoA synthetase and lead to an increased generation of triacylglycerols, wild-type α-synuclein may inhibit phospholipase D2, which hydrolyzes glycerophospholipids into diacylglycerols and phosphatidic acid. Notations: DAG, diacylglycerol; FA, fatty acid; GPC, glycerophosphocholine; TAG, triacylglycerol.

Note Google Scholar gives even 35,000 results on request for “Alpha-synuclein modeling”. Our goal is not in the survey. We refer only to two dopaminergic nerve cell models representing, in our view, the topic.

The dopaminergic nerve cell model. A Systems Biology Markup Language (SBML) model [17] of a whole dopaminergic nerve cell is built. The model is extremely complex. It includes, among others, dopamine (DA) metabolism and transport, oxidative stress, aggregation of α-synuclein (αSyn), lysosomal and proteasomal degradation, and mitophagy. This dopaminergic nerve cell model contains 111 metabolites (red and pink circles) and 139 reactions (rectangles) (Fig. 19). The different sub-models are labeled and indicated by different colors. The most strongly interconnected part of the model is in the middle and consists of αSyn, ROS, damaged proteins, and mitochondria.

The developed model consists of eleven sub-models. Let us call a few.

Sub-model 1, 2, and 3 – DA synthesis, metabolism, and transport: DA is synthesized from L-DOPA, which, in its order, is synthesized from L-tyrosine with the enzymes aromatic Lamino acid decarboxylase and tyrosine-hydroxylase (TH). The model includes the release of DA vesicles as well as the re-uptake via the dopamine transporter (DAT). The interaction of DA with αSyn, which enhances the protein aggregation and reaction with ROS, is also included in the SBML model.

Sub-model 7 – αSyn and LB formation. The nerve cell model includes the αSyn aggregation by the interaction of αSyn with DA and the aggregation enhanced by the interaction with ROS.

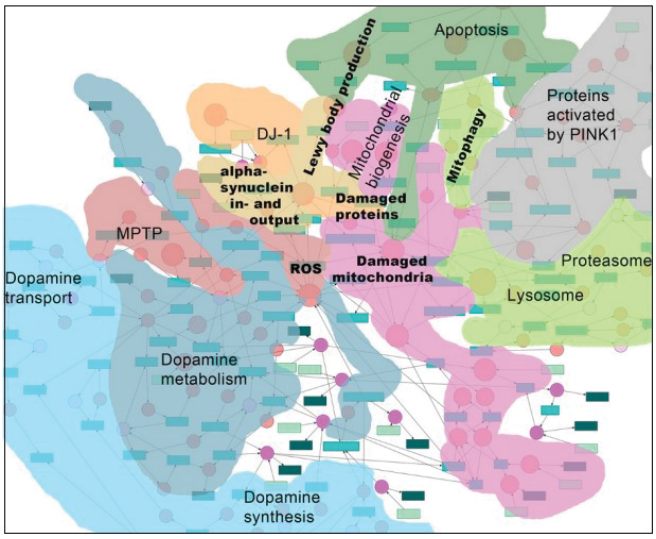

Fig. 19. Schema of the dopaminergic nerve cell model [17]

Six experiments were performed:

(i) modeling normal cell behavior,

(ii) the effect of increasing O2,

(iii) of increasing ATP,

(iv) the influence of neurotoxins,

(v) the increase of αSYN in the cell, and

(vi) the increase of dopamine synthesis.

This dopaminergic nerve cell model can serve as a basis for many future research groups to join efforts and to get a deep insight into Parkinson’s disease.

Dopaminergic neuron terminal model. This mathematical model imitates dopamine synthesis, release, reuptake, and use [18].

The model is much simpler than the previous model [17] and includes the following studies: (1) homeostasis in single dopaminergic neuron terminals, (2) investigation of the substrate inhibition of tyrosine hydroxylase by tyrosine, (4) the consequences of the rapid uptake of extracellular dopamine by the dopamine transporters, and (4) the effects of the autoreceptors on dopaminergic function. The main goal is to understand the regulation and control of synthesis and release and to interpret experimental findings.

It is known that the rate of the enzyme tyrosine hydroxylase (TH) limits dopamine synthesis, and tyrosine has the unusual property of being inhibited by its substrate. Cytosolic dopamine concentrations are normally quite low. Because most dopamine resides in vesicles from which it is released on the arrival of action potentials. After release, dopamine is rapidly taken up by dopamine transporters (DATs) on the terminal and it is thought that the DATs play an important role in extracellular dopamine homeostasis. Autoreceptors are found on most parts of dopaminergic neurons, in particular the neuron terminal.

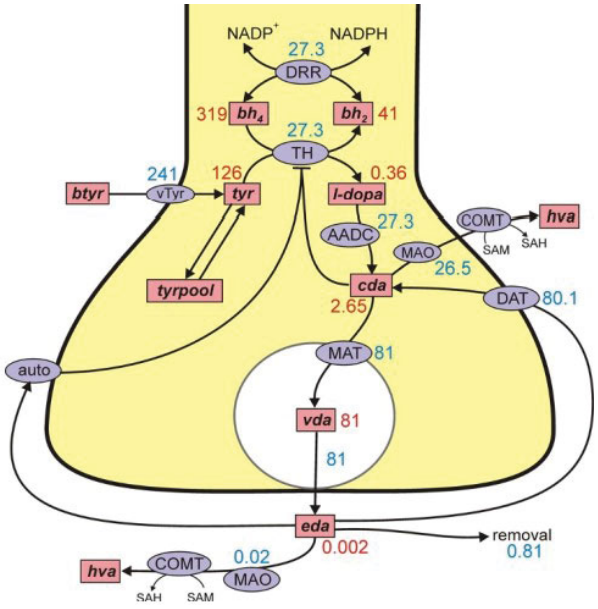

Fig. 20. Dopamine synthesis, release, and reuptake [18]

Comments to Fig. 20. Rectangular boxes indicate substrates and blue ellipses contain the acronyms of enzymes or transporters. The numbers indicate the steady-state concentrations and reaction velocities in the model. Full names for the substrates are shown in Table. Other acronyms: vTyr, neutral amino acid transporter; DRR, dihydrobiopterin reductase; TH, tyrosine hydroxylase; AADC, aromatic amino acid decarboxylase; MAT, vesicular monoamine transporter; DAT, dopamine transporter; auto, D2 dopamine autoreceptors; MAO monoamine oxidase; COMT, catecholamine O-methyl transferase.

TABLE. Variables in equations

bh2	dihydrobiopterin	cda	cytosolic dopamine
bh4	tetrahydrobiopterin	vda	vesicular dopamine
tyr	tyrosine	eda	extracellular dopamine
l-dopa	3,4-dihyroxyphenyl alanine (L-DOPA)	hva	homovanillic acid
		tyrpool	the tyrosine pool

The mathematical model [18] consists of nine differential equations:

$$\frac{d(bh2)}{dt} = V_{TH}(tyr, bh4, cda, eda) - V_{DRR}(bh2, NADPH, bh4, NADP)$$

$$\frac{d(bh4)}{dt} = V_{DRR}(bh2, NADPH, bh4, NADP) - V_{TH}(tyr, bh4, cda, eda)$$

$$\frac{d(tyr)}{dt} = V_{TYRin}(btyr(t)) - V_{TH}(tyr, bh4, cda, eda)$$
$$-k_1 \cdot tyr + k_{-1} \cdot tyrpool - k_{tyr}^{catab} \cdot tyr$$

$$\frac{d(l-dopa)}{dt} = V_{TH}(tyr, bh4, cda, eda) - V_{AADC}(l-dopa)$$

$$\frac{d(cda)}{dt} = V_{AADC}(l-dopa) - V_{MAT}(cda, vda) + V_{DAT}(eda) - k_{cda}^{catab} \cdot cda$$

$$\frac{d(vda)}{dt} = V_{MAT}(cda, vda) - fire(t) \cdot vda$$

$$\frac{d(eda)}{dt} = fire(t) \cdot vda - V_{DAT}(eda) - V_{CATAB}(eda) - k_{rem} \cdot eda$$

$$\frac{d(hva)}{dt} = k_{cda}^{catab} \cdot cda + V_{CATAB}(eda) - k_{hva}^{catab} \cdot hva$$

$$\frac{d(tyrpool)}{dt} = k_1 \cdot tyr - k_{-1} \cdot tyrpool - k_{tyrpool}^{catab} \cdot tyrpool$$

Results. It is shown that the substrate inhibition of tyrosine hydroxylase by tyrosine stabilizes cytosolic and vesicular dopamine against changes in tyrosine availability due to meals. It is found that the autoreceptors dampen the fluctuations in extracellular dopamine. It is caused by changes in tyrosine hydroxylase expression and, in its order, changes in the rate of firing. The short bursts of action potentials create significant dopamine signals against the background of tonic firing.

The observed time courses supported extracellular dopamine responses to stimulation in wild-type mice and mice having genetically altered dopamine transporter densities and the observed half-lives of extracellular dopamine under various treatment protocols.

Understanding quantitatively the effects of these homeostatic mechanisms in normal and pathological situations is crucial for the design of therapeutic strategies in several neurodegenerative diseases and neuropsychiatric disorders.

V. ENERGY FOR BRAIN

The brain consumes around 25% of the body's glucose. How does the energy in our brain distribute? The energetic demands for synaptic transmission are estimated at 50 %, 10-15 % for action potentials, and 9-18 % for other signaling-related processes, including calcium responses and glutamate/GABA recycling in neurons. Glutamate is the most abundant excitatory neurotransmitter in the vertebrate nervous system.

Brain glucose metabolism can produce adenosine triphosphate (ATP) to fulfill complex neurological functions (Fig. 21). Glucose metabolism is involved in oxidative stress modulation – an important feature (the source of ROS). Therefore, glucose metabolites support ATP production, supply the carbon for macromolecule synthesis, and modulate various functions of neurons and glial cells.

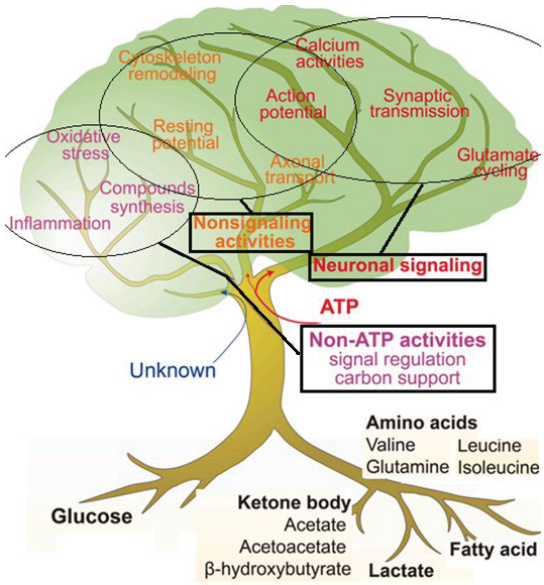

Fig. 21. How energetic fuels support the ATP-dependent and ATP-independent actions in the brain [19]

Comments to Fig. 21. Glucose is the most important fuel for the brain. It fulfills complex neurological functions: neuronal signal transmission (action potential, calcium activities, synaptic transmission, and glutamate cycling), and nonsignaling activities (axonal transport, resting potential, and cytoskeleton remodeling). Additionally, glucose metabolism provides the carbon to synthesize nucleic, fatty, and amino acids.

Modeling of glucose metabolism [20]. This paper aims to formulate a dynamic glucose metabolism with the brain-based regulatory mechanism (Fig. 22). To investigate the effect of the brain-centered glucoregulatory system on glucose metabolism of diabetes patients, the effectiveness and limitations of the combined therapy with insulin and leptin are evaluated.

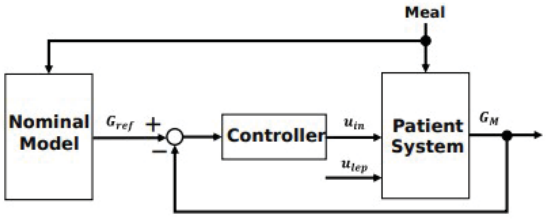

Fig. 22. A control system of dynamic glucose metabolism (key control parameters G_{ref} and G_M)

The article [20] presents a complex mathematical model of dynamic glucose metabolism considering insulin therapy and leptin therapy (Fig. 23). The model has three basic variables: d – the amount of carbohydrates (the main source of energy for the body), u_{in} – the rate of insulin supply, u_{lep} – the rate of leptin supply. The relationships between them are calculated using 48 formulas: Glucose system (equations 1-27), Insulin System (28-37), Glucagon System (38-40), Cortisol System (41-47), and the final formula (48) on combined feedback therapy for diabetes with constant leptin infusion u_{lep} and the

exogenous insulin infusion u_{in} composed of the basal insulin infusion u_b and at predictive insulin control:

$$u_{in}(t) = \max\left\{0, u_{in}^b + k_p\Big((G_{ref}(t) - G(t)) + k_i \int_0^t (G_{ref}(\tau) - G(\tau))d\tau + k_d \frac{d(G_{ref}(t) - G(t))}{dt}\Big)\right\}$$

Leptin is a protein hormone produced primarily by fat cells in the body, and in small quantities also by brain tissue. Its main role is probably to regulate long-term energy balance. Leptin levels influence appetite, satiety, and motivated behavior aimed at maintaining energy reserves (food seeking).

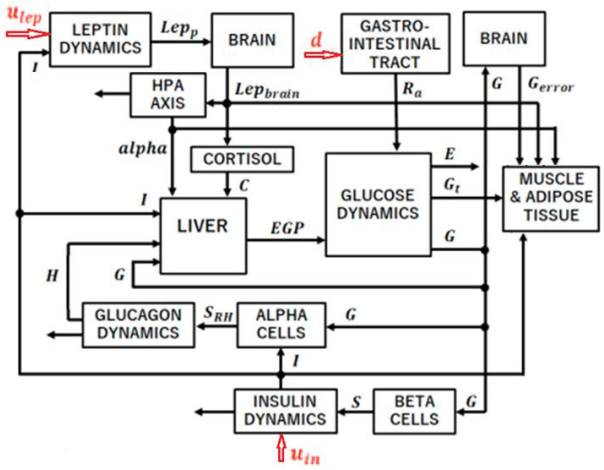

Fig. 23. Flowchart of a dynamic model of glucose metabolism [25]

The paper [20] has proposed an elaborate mathematical model of dynamic glucose metabolism. The aim was to integrate the brain-centered glucoregulatory system with leptin into the conventional US Food and Drug Administration-approved model for all human beings. The effectiveness and limitations of the proposed combined therapy with insulin and leptin for diabetes have been evaluated through in silico experiments. One of the future works is parameter identification and implementation to achieve a personalized treatment for diabetes patients.

The cause of PD should be sought in lipid metabolism. This is an important conclusion and is based on starvation studies. Starvation has been often used as a paradigm to modulate lipid and glucose metabolism. The changes in lipid and glucose metabolism during starvation occur gradually to guarantee substrate availability at all times. The approach can be summarized as follows (Fig. 24):

(1) Terminal glucose losses are decreased by changes in glucose, lipid fluxes, uptake, and oxidation. This may spare glucose for the brain to a limited degree but mainly conserves carbon for biosynthetic purposes and anaplerosis.

(2) Facid acids (FA) are the major fuel to yield energy. The human organism has tools to cope with metabolic challenges like starvation which are crucial for survival. The starvation response shows that the adaptation to energy deficit is very effective and coordinated in different organs.

During starvation, plasma fatty acid (FA) levels increase within 14 h after the last meal (Fig. 24) When the uptake of glucose decreases after the current meal, there is the orchestrated interplay of the decrease of insulin level, increased sympathetic nervous system activity, and increased growth hormone (GH) levels. The latter increases lipolysis of triglycerides stored in adipose tissue and plasma-free FA levels.

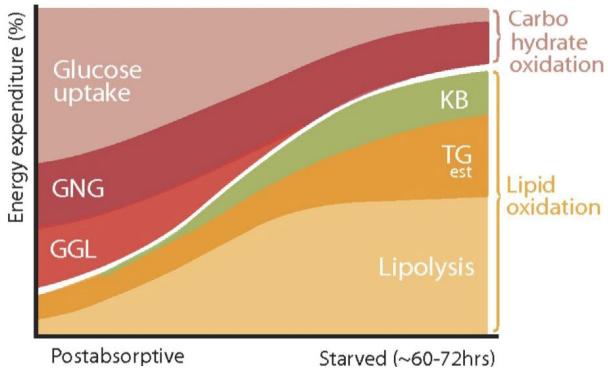

Fig. 24. The starvation diagram depicts the changes in metabolism [21]

During the fasting procedure, fuel oxidation gradually shifts from carbohydrates to lipids as an oxidative source. Lipolysis increases and provides the body with fatty acids. Due to liver fatty acid oxidation, ketone bodies (KB) are produced as an alternative energy source for the brain when glucose becomes less available. Also, increased lipid oxidation will decrease terminal glucose oxidation. In addition to the decrease of insulin concentrations during progressive starvation, there is substantial evidence that lipolysis is less sensitive to inhibition by insulin starvation, thereby enabling increased lipolysis.

What is the role of adipocytokines? Increasing experimental evidence suggests an association between the deterioration of the immune system due to metabolic changes and PD progression with dysregulation of central and peripheral neuroinflammatory networks mediated by circulating adipocytokines, particularly leptin.

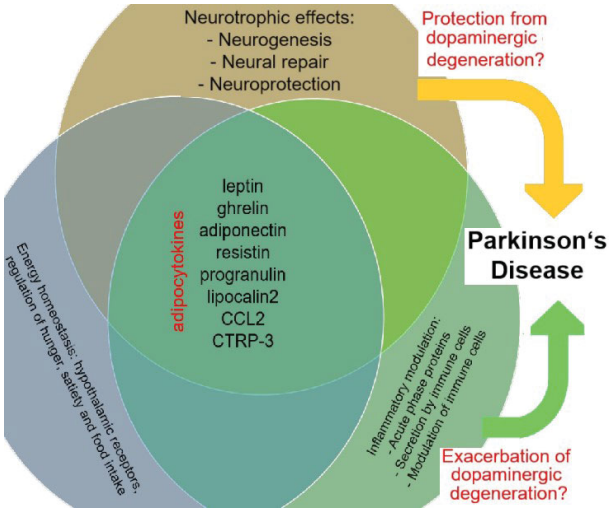

Fig. 25. Effects of adipocytokines in Parkinson's disease [22]. How does one keep in mind this diversity?

A better understanding of the homeostatic and neuroprotective roles of adipocytokines in PD may pave the way to developing disease-modifying therapies or evidence-based nutritional guidelines [22]. Recent evidence suggests that

leptin can cross the blood-brain barrier and stimulate receptors in the hypothalamus, thalamus, and other areas of the brain besides the sympathetic nervous system. It is even believed that adipose tissue is an endocrine organ that synthesizes a large number of biologically active substances – adipocytokines, which affect insulin resistance, glucose and lipid metabolism, and inflammation processes (Fig. 25). Representatives of adipocytokines (adiponectin, omentin, leptin, resistin, tumor necrosis factor-α, and interleukin-6) are divided into two groups: adipocytokines that reduce insulin resistance and adipocytokines that increase insulin resistance [23]. This is one hot topic in PD studies.

VI. CONCLUSION AND DISCUSSION

The goal is to attract mathematicians' interest in the neurodegenerative diseases research. Yoshinori Ohsumi received the Nobel Prize in 2016 in Physiology or Medicine for his discoveries of mechanisms for autophagy using yeast as a model organism. These uncovered secrets of nature initiated much in life science, including many mathematical models of Parkinson's disease: cell population dynamics, mitophagy, autophagic vesicle dynamics in single cells, microbiological explanations of Parkinson's disease, dopaminergic nerve cell and terminal models, and glucose metabolism.

Besides, there is a wide area in genetics, particularly, the mechanism of starvation of yeast and humans, is there an analogy? According to Yoshinori Ohsumi's viewpoint [4], "*For unicellular organisms such as yeast, depletion of nutrients must be the most frequent and crucial stress in nature. Therefore, a starvation-induced mode of autophagy would have been established first and has been conserved during evolution. All of the core ATG genes are conserved in mammals and plants*." Therefore, much research has been carried on. But… could it be successful?

The human genome contains 3 billion base pairs, but the size of the baker's yeast genome, a single-celled organism, has only 12 million base pairs, 250 times less. How does one find the correspondence between these genomes?

Autophagy is a major, conserved cellular pathway by which cells deliver cytoplasmic contents to lysosomes for degradation. Genetic studies have revealed extensive links between autophagy and neurodegenerative disease, and disruptions to autophagy may, hopefully, contribute to pathology in some cases.

Alpha-synuclein potentially connects the gut-brain axis in Parkinson's disease patients. And more. Asyn has been shown to play a role in many different lipid metabolic pathways, with significant consequent implications for its toxicity. The research [24] conducted a genome-wide screening study in yeast which supports the involvement of lipid metabolism in α-syn toxicity. The authors found that 18 out of 57 genes that modified the toxicity of α-syn were related to lipid metabolism and vesicle-mediated transport.

Honesty speaking, to date, the key PD standard therapy remains the combination of levodopa and carbidopa. Recently, the potential role of the microbiome-gut-brain axis in the pathogenesis and severity of PD has been identified. Disturbed gut microbiota could lead to gut barrier integrity disruption and cause neurodegeneration.

Clinical support of nutraceuticals in PD is often marginal or debatable. Nevertheless, they are gradually gaining ground. They can be considered as adjunctive treatment to first-line therapy [25]. Food components and nutraceuticals are acting on PD-related oxidative and mitochondrial stress. The main target of nutraceuticals as pharmacological treatment aims to clear misfolded proteins and reduce neurodegeneration (Fig. 26).

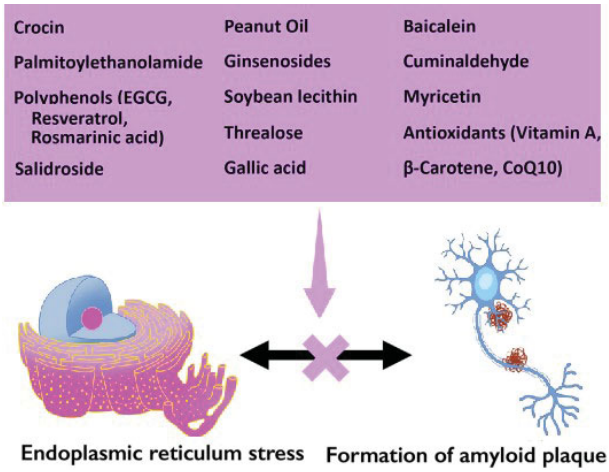

Fig. 26. Nutraceuticals as therapeutics for PD, able to limit endoplasmic reticulum stress and protein misfolding and aggregation [25]

The following are some examples of nutraceuticals having an essential impact on molecular mechanisms involved in PD [25].

Nutrients:

- Coenzyme Q10 counteracts against neurotoxicity;
- Resveratrol limits mitochondrial dysfunction and apoptosis in nigrostriatal cells;
- Lycopene reduces oxidative stress;
- Fish oil enriched in ω-3 fatty acids confers neuroprotective effects via multiple mechanisms.

Herbals and phytochemicals:

- Epigallocatechin-3-gallate protects against toxic dopamine metabolites through its properties of radical scavenger and chelator of iron ions;
- Ginsenosides block dopaminergic neuronal death, reducing glutamate-induced excitotoxicity and promoting synaptic transmission in the nigrostriatal nucleus;
- Vincamine has multiple mechanisms of action, including vasodilating effect, antioxidant, and chelating activity.

The novel emerging therapeutic and integrative approach with nutraceuticals has opened a new scenario to deal with such a complex neurodegenerative disease as Parkinsonism. Arises, is born a new science – neurogastroenterology.

In summary, looking back at the accumulated experience on PD, it should be recognized that scientists are at the beginning of their journey to knowledge of autophagy secrets. Mathematics for Parkinson's disease – can it help? There is no answer but this is an unimaginably wide and attractive field of

activity for mathematicians. For the initial study, one can recommend high-quality reading [26].

In conclusion, let us recall the analogy where mathematics meets physics. These are two closely related areas. For physicists, mathematics is a tool used to discover nature's secrets, for example, Newton invented calculus to help describe motion. For mathematicians, physics can be a source of inspiration, and theoretical concepts such as general relativity and quantum theory give mathematicians the impetus to develop new tools. Biologists are still far from mathematicians. Until now, they have not looked to mathematicians for answers.

There is still a long way ahead, a way of hopes and disappointments, and, I am sure, success.

REFERENCES

[1] M.A. Sneps-Sneppe, "On Parkinson's disease and its mathematical models". *The International Journal of Open Information Technologies (INJOIT)*, vol.12, Nr 7, 2024, pp. 51-64.

[2] Y. Kabeya, et al, "LC3, a mammalian homolog of yeast Apg8p, is localized in autophagosome membranes after processing". *The EMBO journal*. 2000.

[3] Y. Ohsumi, "Historical landmarks of autophagy research". *Cell Research*, *24*(1), 2014, pp. 9-23.

[4] H. Nakatogawa, et al. "Dynamics and diversity in autophagy mechanisms: lessons from yeast". *Nature Reviews Molecular cell biology*, *10*(7), 2009, pp. 458-467.

[5] V. Kirkin, "History of the selective autophagy research: how did it begin and where does it stand today?" *Journal of Molecular Biology*, *432*(1), 2020, pp. 3-27.

[6] H. Jin, and J. Lei, "A mathematical model of cell population dynamics with autophagy response to starvation". *Mathematical Biosciences*, *258*, 2014, pp. 1-10.

[7] P. Dalle Pezze, et al, "ATG13 dynamics in nonselective autophagy and mitophagy: insights from live imaging studies and mathematical modeling". *Autophagy*, *17*(5), 2020, pp. 1131–1141.

[8] D.J. Klionsky, "Autophagy: from phenomenology to molecular understanding in less than a decade". *Nat Rev Mol Cell Biol*; 8, 2007, pp. 931-7

[9] K.R. Martin, et al. "Computational model for autophagic vesicle dynamics in single cells". *Autophagy*, *9*(1), 2012, pp. 74–92.

[10] F.M. Menzies, A. Fleming, and D.C Rubinsztein, "Compromised autophagy and neurodegenerative diseases". *Nature Reviews Neuroscience*, *16*(6), 2015, pp. 345-357.

[11] N. Fujikake, M. Shin, and S. Shimizu, "Association between autophagy and neurodegenerative diseases". *Frontiers in neuroscience*, *12*, 2018, pp.337581.

[12] H. Wang, C.X. Wei, L. Min, and L.Y. Zhu, "Good or bad: gut bacteria in human health and diseases". *Biotechnology & Biotechnological Equipment*, *32*(5), 2018, pp.1075-1080.

[13] E. Fitzgerald, S. Murphy and H.A. Martinson "Alpha-Synuclein Pathology and the Role of the Microbiota in Parkinson's Disease". *Front. Neurosci.* 13:369, 2019.

[14] P. Bloomingdale, et al. "Hallmarks of neurodegenerative disease: A systems pharmacology perspective". *CPT: Pharmacometrics & Systems Pharmacology*, *11*(11), 2022, pp. 1399-1429.

[15] A.R.L Toledo, et al. "Gut-brain axis as a pathological and therapeutic target for neurodegenerative disorders". *International Journal of Molecular Sciences*, *23*(3), 2022, p. 1184.

[16] I. Alecu, and S.A. Bennett, "Dysregulated lipid metabolism and its role in α-synucleinopathy in Parkinson's disease". *Frontiers in neuroscience*, *13*, 2019, p. 328.

[17] F. Büchel, et al. "Parkinson's disease: dopaminergic nerve cell model is consistent with experimental findings of increased extracellular transport of α-synuclein". *Bmc Neuroscience*, *14*, 2013, pp.1-12.

[18] J.A Best, H.F. Nijhout, and M.C. Reed, "Homeostatic mechanisms in dopamine synthesis and release: a mathematical model". *Theoretical Biology and Medical Modelling*, *6*, 2009, pp. 1-20.

[19] S. Zhang, et al, "Glucose metabolic crosstalk and regulation in brain function and diseases". *Progress in neurobiology*, *204*, 102089, 2021.

[20] H. Ofuji, et al. "A Mathematical Modeling and Treatment Analysis of Dynamic Glucose Metabolism with Brain-based Regulatory Mechanism". *IFAC-PapersOnLine.* 56.2, 2023, pp. 3630-3635.

[21] M.R Soeters, et al, "Adaptive reciprocity of lipid and glucose metabolism in human short-term starvation". *American Journal of Physiology - Endocrinology and Metabolism,* 2012.

[22] M. Regensburger, et al, "Emerging roles of leptin in Parkinson's disease: chronic inflammation, neuroprotection, and more?" *Brain, Behavior, and Immunity*, *107*, 2023, pp.53-61.

[23] T.N Markova, K. Mishchenko, V. Petina, "Adipocytokines: a modern view of definition, classification, and role in the body". *Problemy endokrinologii.* Volume 68, No. 1. 2022.

[24] S. Willingham, et al, "Yeast genes that enhance the toxicity of a mutant huntingtin fragment or alpha-synuclein". *Science.* 302, 2003, pp. 1769-1772.

[25] A. Lama, et al, "Nutraceuticals: An integrative approach to starve Parkinson's disease". *Brain, Behavior, & Immunity-Health*, *2*, 2020, p.100037.

[26] A. Lerner, S. Neidhöfer, T. Matthias, "The Gut Microbiome Feelings of the Brain: A Perspective for Non-Microbiologists". *Microorganisms*, *5*, 66, 2017.