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Mathematical Modeling of Pathological Processes in Alzherimer's Disease

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Abstract

Using kinetic differential equations and the Runge-Kutt algorithm, an analysis of the pathological processes occurring in the course of Alzherimer's disease was carried out. Thanks to the appropriately selected kinetic equations, the presented model allows to explain the time course of the growth of pathological proteins: beta-amyloid and tau protein and the related loss of nerve cells. The model is based on previous experimental knowledge of Alzherimer's diseas and is in good agreement with the experimental data.

Keywords: Alzherimer's disease; beta-amyloid and tau protein; mathematical modeling; differential kinetic equations; Runge–Kutta algorithm

Introduction

The first case of Alzherimer's disease was diagnosed and described by Alojz Alzherimer's in 1907 in a 51-year-old woman [1]. Alzherimer's disease (AD) is a chronic, progressive neurodegenerative disease of the brain causing the irreversible loss of nerve cells. Destruction of neurons in Alzherimer's disease (AD) is progressing rapidly, resulting in significant intellectual impairment, cerebral dementia - loss of memory, learning and thinking. It occurs mainly in those areas of the brain that are responsible for memory and cognitive processes. In the Alzherimer's disease, there are changes in intellectual performance, functioning and behavior as well as memory disorders. This is followed by speech disorders, characterized by forgetting words, significant behavioral and memory disorders, and hallucinations and delusion.

The main factor responsible for the development of Alzherimer's disease is the formation of two pathological proteins: beta-amyloid and the tau protein. Pathological beta-amyloid accumulates between axons, interfering with the transmission of nerve impulses between nerve cells. Phosphorylated tau protein wraps around cells, destroying them.

The data shows that Alzheimer's disease affects 5 to 10 percent patients over 65 years of age and 50 percent people over 80 years of age.

Proposed Hypothetical Mechanism of Pathological Changes Occurring in Alzheimer's Disease.

The mechanism of this disease is not fully understood. In most people, Alzherimer's disease (AD) is thought to be caused by a combination of genetic, environmental and lifestyle factors. In some families, Alzherimer's disease is inherited. However, most of the genetic mechanisms of Alzherimer's is unnown. To date, several genes associated with Alzherimer's have been identified. Two of them, located on chromosome 12 and 19, increase the risk of developing the disease, but do not cause it themselves. The apolipoprotein E (APOE) gene is located on chromosome 19. It comes in three forms - epsilon-2, epsilon-3 and epsilon-4. Having the epsilon-4 (APOE4) form in the genetic material increases the risk of Alzheimer's disease (AD) several times. disease remain unexplained. They are presumed to be complex. The gene associated with the production of amyloid was initially located on chromosome 21. However, it turned out that only the early-onset form of AD is associated with the presence of the gene on the long-term on the 21st arm of chromosome 21 and is inherited in an autosomal dominant fashion. Further studies have shown that in some cases the gene for amyloid precursor proteins (APP) is located on on chromosome 19. For other, more frequent, sporadic cases of AD, no gene responsible for the appearance of disease features has been foundAccording to current knowledge, 0.5-2 percent of people with Alzherimer's disease are caused by a known mutation in a known gene. This mutation causes the occurrence of toxic proteins in the brain tissue of the patient and from the moment of its inception is inherited by the next generations.

Based on the experimental data [2 - 38], the following hypothetical mechanism of changes occurring in the course of Alzherimer's disease has been proposed. The genetic defect of chromosome 21(or others) leads to an overload of the unknown constituting cell an amyloid precursor source (neuron, astroglial cell, microglia, vascular wall cell, or even blood serum). Then, as a result of pathological proteolysis (another genetic error or the only genetic error), or due to glial cell failure, the fibril form of amyloid is deposited in a diffuse form in the neuropil. Toxic effect of certain amyloid fragments on neurites leads to pathological transformations of cytoskeleton proteins, disturbances in tau protein phosphorylation, and slows down axonal flow. These Tau proteins are then ubiquitinated as a ubiquitin stimulates the production of amyloid. There is a feedback phenomenon. The death of numerous neurons results in a dramatic decrease in interneuronal connections, as well as a secondary deficit of neurotransmitters, including acetylcholine. During this period, it fades away the brain is already visible in radiological examinations. The aim of the model presented in this work is to show how the amount of pathological proteins: beta-amyloid and tau change over time, and how it affects the decline of nerve cells.

Methods

Based on the hypothetical mechanism of Alzherimer's disease, a mathematical description was used using kinetic differential equations depicting changes in time of pathological processes occurring in this disease. The set of kinetic equations have been numerically solved using the four-order Runge–Kutta algorithm.

Results

Model of Pathological Changes Occurring in Alzheimer Diseases

Based on the experimentally identified hypothetical mechanism of changes occurring in Alzherimer's disease, the following diagram was drawn up: (scheme 1)

$$pre\ Am\ \rightarrow^{k1} Am\ \ ^{k3}\leftrightarrow_{k2}\ Tau \rightarrow^{k3} Cell\ destruction$$

preAm- pre-amyloid

Am – beta-amyloid,

Tau – tau protein - total or phosphorylated,

k_1, k_2, k_3 – are the rate constants.

From the above scheme, we can draw the following system of kinetic equations showing changes in the pathological proteins: beta-amyloid and tau proteins, and quantitative changes in nerve cells.

$$\frac{dAm}{dt} = k_1\ preAm - k_2\ Am + k_3 Tau$$

$$\frac{dTau}{dt} = k_2 Am - k_3 Tau$$

$$\frac{dCell}{dt} = -(k_3 Tau)\ Cell$$

where:

Am – beta-amyloid,

Tau – phosphorylated tau protein,

Cell - number of nerve cells,

k_1, k_2, k_3 – are the rate constants.

The set of presented above kinetic equations can be numerically solved using the four-order Runge–Kutta algorithm. The calculations were performed with a step h = 0.01. The initial conditions for pathological beta-amyloid and tau protein were 1 for initial time t_0 = 0. The simulation parmeters are: $k_1 preAm$ = 0,05, 0.1, 0.2, k_2 = 0.12, 0.2, k_3 = 0.1, 0.21.

Figures 1 - 4 present obtained calculation results. Figure 1 generally shows how the amount of pre-amyloid, k_2 and k_3 values affect, the loss of nerve cells. Figure 2 shows the effect of pre-amyloid concentration on the increase in a concentration over time of beta amyloid and tau when k_2 is less than k_3: k_2 = 0,12 and k_3= 0,21 [a.u.]. Figure 3 shows the effect of pre-amyloid concentration on the increase in a concentration over time of beta-amyloid and tau when k_2 is greater than k_3: k_2 = 0,2,k_3 = 0,1 [a.u.], pre-amyloid values are: 0,05, 0,1, 0,2 [a.u.]. If we eliminate time, we can get a coordination matrix between tau protein and beta-amyloid. Figure 4 shows the coordination matrix beetween tau an beta-amyloid protein e.g. for k_2 = 0,12, k_3 = 0,21[a.u.].

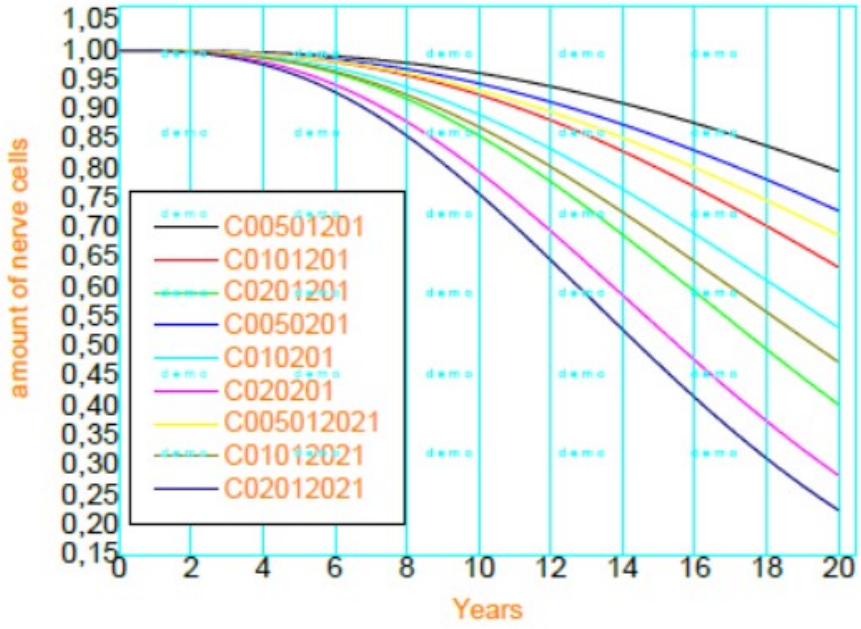

Figure 1: Influence of the amount of pre-amyloid, k_2 and k_3 values on the loss of nerve cells. The numbers represent respectively: $k_1$pre-Amyloid: 0.05, 0.1, 0.2, k_2: 0,12, 0.2, k_3: 0.1, 0.21, the number 1 on the y axis means 100%.

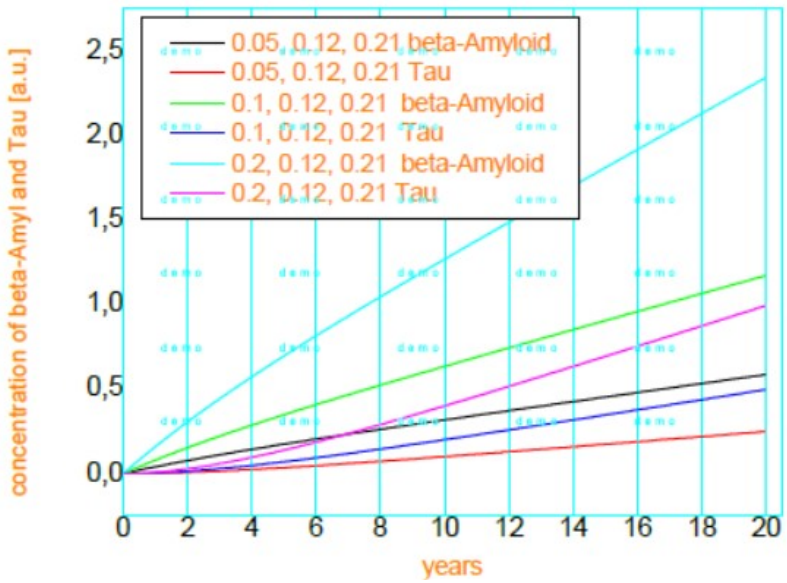

Figure 2: Effect of pre-amyloid concentration on the increase in a concentration over time of beta amyloid and tau when k_2 is less than k_3. The numbers represent respectively: $k_1$pre-Amyloid: 0.05, 0.1, 0.2, k_2: 0.12,, k_3: 0.21. a.u. - arbitrary units.

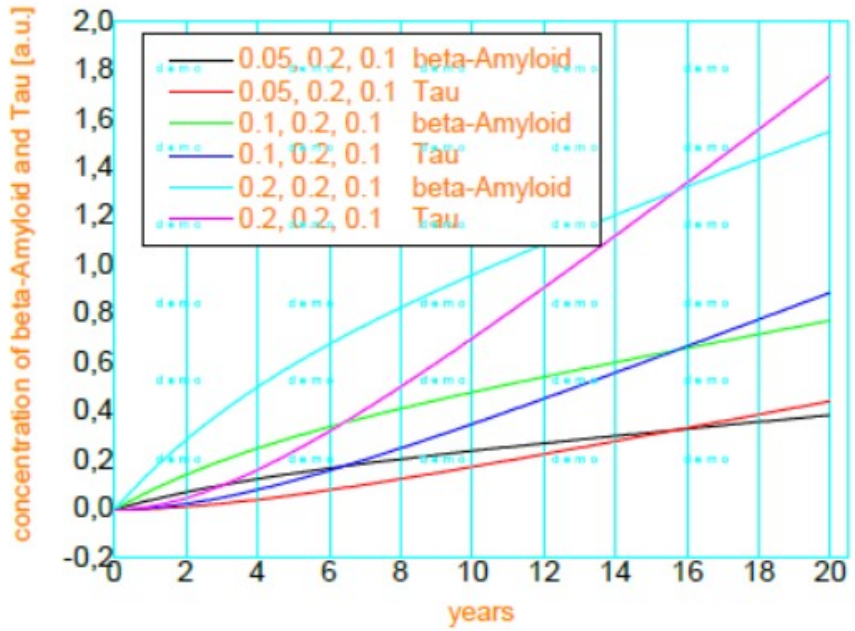

Figure 3: Effect of pre-amyloid concentration on the increase in a concentration over time of beta amyloid and tau when k_2 is greater than k_3. The numbers represent respectively: $k_1$pre-Amyloid: 0.05, 0.1, 0.2, k_2: 0.2, k_3: 0.1.a.u. - arbitrary units.

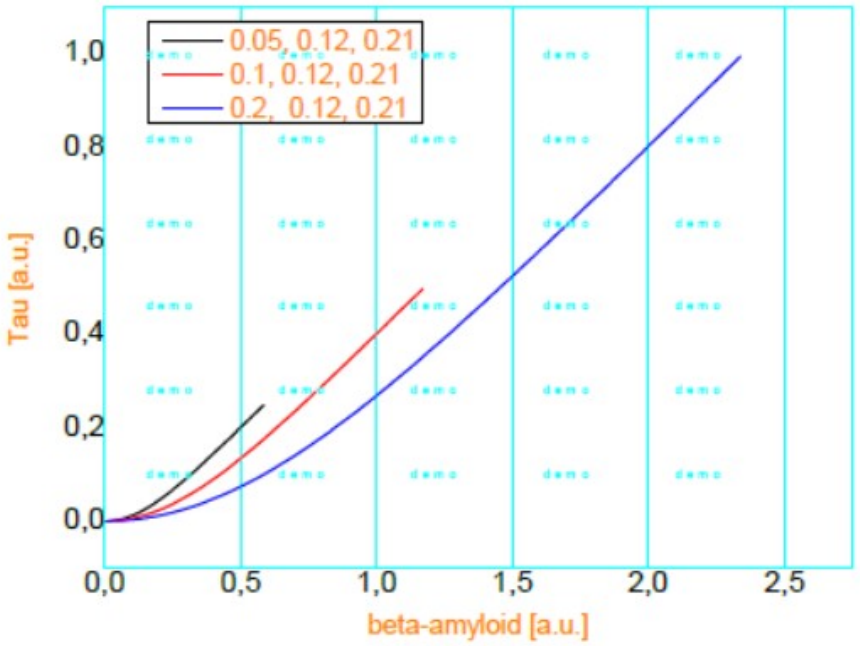

Figure 4: Coordination matrix beetween tau an beta-amyloid protein e.g. for k_2 = 0,12, k_3 = 0,21 a.u.- arbitrary units. The numbers represent respectively: $k_1$pre-Amyloid, k_2, k_3.

The charts show:

- The more pre-amyloid there is, the greater the increase with time of beta-amyloid and a phosphorylated, ubiquitous or total protein, and the greater the loss of brain cells over time. (at the same rate constants k_2 and k_3) (Figure 1, Figure 2, Figure 3).

- The greater the value of the k_2 rate constant, the greater the increase in beta-amyloid and tau protein (phosphorylated or

total) and the greater the loss of brain cells over time (Figure 1).

- The greater the value of the k_3 rate constant, the greater the growth of beta-amyloid, the slower the growth of tau protein (phosphorylated or total) and the greater the loss of brain cells over time (Figure 1). As the Figure 1 shows[i] up to about 2 years, this increase does not depend on the constant speed of k_3.

- If the constant k_2 is much larger than the constant k_3, then after about 16 years the advantage of the tau protein over the beta-amyloid is visible (Figure 3). If the constant k_2 is smaller than the constant k_3 then the proteins beta-amyloid and tau increase proportionally. Beta-amyloid is greater than that of tau (Figure 2).

- The coordination matrix (Figure 4) beetween tau an beta-amyloid protein shows shows how the amount of pre-amyloid affects the total increase of beta-amyloid and tau. The greater the amount of pre-amyloid, the greater the increase in beta-amyloid and tau with the same values of the constants k_2 and k_3.

Discussion

The presented model results seem to be in agreement with the experimental data. An mouse animal model of AD, called the Senescence-Accelerated Mouse-Prone and its control strain called Senescence-Accelerated Mouse-Resistant were used experiments [39]. In prone-mice there was an increase over time (after 6 and 8 months) in both beta-amyloid and tau (total and phosphorylated) in both the brain and red blood cells. In the brain of mice, a similar relationship is observed as in our model presented in Figure 3 (the constant k_2 is larger than the constant k_3) and in the red blood cells of mice, a relationship similar to that obtained in Figure 2 was observed (the constant k_2 is smaller than the constant k_3).

Association of tear fluid amyloid and tau levels with disease severity were investigated in neurodegenerative diseases such as Alzherimer's [40]. The analysis of dementia patients, which also includes Alzherimer's disease, shows relationships similar to those obtained in our model (taken only at one point in time). In some cases, beta-amyloid predominates over tau (total or phosphorylated), which corresponds to the of the case when k_2 rate constant is smaller than k_3 in our model (Figure 2), and in other cases, tau is superior to beta-amyloid, which corresponds to the case of constant k_2 is much larger than the constant k_3 in our model (Figure 3). But this only applies to one specific point in time in these studies. The obtained coordination matrix in our model between tau and beta-amyloid (Figure 4) seems to show a similar relationship to that obtained experimentally, covering only two points [40].

The method of electron paramagnetic resonance (EPR) with the use of spin markers in patients with Alzherimer's disease has been used [41]. Aggregation of amyloid peptides was investigated by EPR using a 40-residue variant of the alfa-beta amyloid peptide containing an N- terminal cysteine (cys-Ab) with a spin tag [1-oxyl-2,2,5,5-tetramethyl-Δ-pyrroline-3-methyl] MTSL methanethiosulfonate (SL-Ab). EPR signatures of aggregation in a prion protein were described. The potential of EPR to detect early stages of the aggregation of the alfa-beta amyloid peptide has been invastigated. After 5 min, the majority of the features are very short fibrils with a width of 5–10 nm and a length of 20–100 nm, in agreement with the dimensions of protofibrils has been found. After 15 min, very small fibrils as above and larger fibrils with a width of 5–10 nm and a length of 100 nm–1 μm appears. After 60 min, very small fibrils and more condensed clustered aggregates with a diameter of 200 nm–1 μm has been found. After several days of aggregation, the main structural features were clustered aggregates with a diameter of 200 nm–1 μm. [41]. These studies showed an increase in beta-amyloid aggregates in the early stage with time. The presented model also shows an increase in beta-amyloid concentration over time, also in the initial period.

The presented model allows to visualize the kinetics of pathological changes in nerve cells in the brain in the development of Alzherimer's disease. It shows the overall process of changes in Aitzhmeier's disease. It shows how the kinetic rate constants and the initial value of pre-amyloid influence the growth of pathological proteins: beta-amyloid and tau protein, and the loss of nerve

cells in the brain. The presented model allows for a better understanding of the pathology of Aitzhmeiere disease from the point of view of the kinetics of this process.

Some people may think so " A major problem […] in our epoch is that modeling disguises itself as science […] Lots of mathematics, of data, of calculations – then, it is scientific This snare, which is fear somely effective, works so efficiently that it becomes dangerous." [42]. I do not think that it is wrong to form mathematical models based on empirical premises, according to mathematical principles. A properly constructed mathematical model explains the course or essence of the process or phenomenon under study. Sometimes it allows you to predict the course of a given process or explain a phenomenon in more detail.

It may seem incomprehensible to some that it is inextricably embedded in three kinetic pseudo-constants, reducing complex biological phenomena to a simple sequence of basic enzymatic reactions. It turns out, however, that this is enough to model the essence of a given process, sometimes very complex. Ilya Prigogine - Nobel laureate in chemistry is convinced that physics explores the complexity of the system, and biology explores the elemental nature of the system [43]. For this reason he stated that simple physical processes are described by extremely complex mathematical equations, and complex biochemical and biological processes can be described by very simple equations.

Conflict of Interest

No conflict of interest.

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This article is dedicated to the memory of my Mother, who died of Alzherimer's disease.

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