Preface of the Conference Proceeding of the 2nd International Conference on Mathematics, its Applications, and Mathematics Education (ICMAME) 2024

We are pleased to present the proceedings of the 2nd International Conference on Mathematics, its Applications, and Mathematics Education (ICMAME) 2024. This esteemed event was a collaborative effort organized by the Department of Mathematics, Faculty of Science and Technology, and the Department of Mathematics Education, Faculty of Teacher Training and Education, Universitas Sanata Dharma, Yogyakarta, Indonesia.

The conference was held on September 21, 2024, at Universitas Sanata Dharma, Indonesia, under the theme *"21st Century Mathematics and Mathematics Education."* This theme reflects the urgent need for innovative approaches to mathematics and mathematics education, aligned with the demands and opportunities of the 21st century. ICMAME 2024 brought together mathematicians, educators, and researchers to discuss emerging trends and share insights in these critical areas.

We were privileged to have distinguished keynote and invited speakers who enriched the conference with their expertise and perspectives. Our heartfelt thanks go to:

- **Assoc. Prof. Dr. Wanty Widjaya** (Deakin University, Australia)
- **Dr. rer. nat. Wolfgang Bock** (Linnaeus University, Sweden)
- **Dr. Martianus Frederic Ezerman** (Nanyang Technological University, Singapore)
- **Asst. Prof. Dr. Parkpoom Phetpradap** (Chiang Mai University, Thailand)
- **Veronica Fitri Rianasari, M.Sc., Ph.D.** (Universitas Sanata Dharma, Indonesia)

We extend our deepest gratitude to the organizing committee for their dedication and hard work, to the authors for their invaluable contributions, and to the reviewers for their diligent evaluations and constructive feedback. Without their combined efforts, this conference would not have been possible.

We hope this collection of proceedings, featuring contributions from authors across various countries (Indonesia, Philippines, Thailand, Japan, etc.), serves as a significant resource for researchers, educators, and practitioners. May it inspire future innovations, foster collaboration, and contribute to the advancement of mathematics and mathematics education for the betterment of our global community.

Thank you for being a part of the 2nd ICMAME 2024. We look forward to continuing this journey together and to exploring new horizons in the fascinating realms of mathematics and mathematics education.

Yogyakarta, 15 January 2025
Eko Budi Santoso
Chair, The 2nd ICMAME 2024

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Volume 71 (2025)

International Conference on Mathematics, its Applications and Mathematics Education (ICMAME 2024)

Yogyakarta, Indonesia, September 21, 2024

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Numerical Investigation of β-Amyloid Aggregation Process In Alzheimer's Disease

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Abstract. The process of β-amyloid (Aβ) protein aggregation in Alzheimer's disease can be represented by a mathematical model. The model is built based on several groups representing the concentrations of a number of monomer and the concentration of oligomer, which is presented as a system of nonlinear ordinary differential equations. In this paper, the extinction and interior equilibrium point are also determined. The model will be solved numerically by the fourth-order Runge-Kutta method and it is shown that the solution will lead to the equilibrium point obtained. Some numerical investigations are done by analyzing the effect of monomer number that occur. It can be concluded that the greater the number of monomers considered, the lower the concentration of oligomers, so that it can reduce the symptoms of Alzheimer's disease. Moreover, for the greater capacity of the Aβ protein, the faster monomers aggregation process occurs.

1 Introduction

Degenerative disease is a disease in which the function or structure of tissues or organs deteriorates over time. The disease is classified into three main groups, namely cardiovascular, neoplastic, and nervous system. Some degenerative diseases cannot be cured, even in some countries, degenerative diseases are the main cause of death [1]. These diseases are caused not by bacteria or viruses but rather by protein abnormalities. Proteins are essential for the organism because they participate in virtually every process within the cell. Therefore, if they do not function normally, the consequences can be devastating [2]. One example of a degenerative disease in the nervous system group is Alzheimer. Alzheimer's disease (AD) is the most common form of dementia. This disease causes a gradual decline in cognitive abilities, often starting with memory loss. This disease attacks the elderly who are usually 65 years of age or older, and twice more women than men [3]. Currently, there is no cure for AD or stop its progression. Many clinical trials of drugs aimed at preventing or eliminating symptoms of protein aggregation in the brain have failed to show efficacy. For now, the only treatment for AD is with drugs used to treat the symptoms of AD. This makes the cost of care and treatment quite large for patients and their families, also for the government, and for researchers. For example, in 2015, there were more than 5 million people in the United States with AD and the cost of caring for AD patients in the U.S. was estimated at $226 billion for 2015 [3]. Several factors that trigger the high cost of care and treatment are due to a lack of

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understanding about this disease which results in a lack of resources and training for caregivers of people with dementia.

AD is characterized by several things, one of which is the abnormal aggregation of Aβ protein in the brain. This process of aggregation start when Aβ split and form a single piece (monomer). Then monomers thought to combine and form Aβ oligomers, and finally the oligomers will form insoluble fibrils. These fibrils continue to aggregate and become plaques, which is one of the causes of the symptoms of AD [4]. Therefore, a clearer understanding of the this aggregation process of Aβ is needed, in order to understand the disease and find alternative treatments to reduce the symptoms of the disease.

The process of this aggregation can be studied with a mathematical model. Hao and Friedman developed a mathematical model of AD to investigate the effect of drugs in clinical trials. The model consists of partial differential equations and consider Aβ aggregation and hyperphosphorylated tau proteins [3]. Dayeh, et al. proposed a discrete-time mathematical model for the aggregation of Aβ monomers into oligomers based on chemical kinetics and population dynamics concepts, and construct a formula to derive the number of monomers which produce oligomers [5]. Using the same concepts, Ackleh, et al. developed a continues mathematical model for the aggregation of Aβ, which consits of ordinary differential equations and compare the two-discrete time approximation with numerical solutions of the model [4].

In this paper, we will investigate numerically the continues mathematical model of the Aβ protein aggregation in AD, which only consider the formation of oligomers. The model is solved using the fourth order Runge-Kutta method. The effect of monomer number on oligomer formation and capacity of the Aβ protein are investegeted.

2 Governing Equations

The basic continues model of the Aβ protein aggregation considered in this paper based on some assumptions, as follows: The modeled phase is a slower nucleation phase according to the structured size, considering the concentration of 1-monomer (M_1), 2-monomers (M_2), ..., 6-monomers (M_6); Oligomers are formed from at least 7 monomers; Aggregation (nucleation and elongation) occurs through the addition of monomers; Dissociation (reduction of monomers from natural aggregation or drug effects) is ignored; Fibril fragmentation, which will produce many fibrils and further accelerate their spread, is ignored; Monomer production is represented by a saturation function which is a logistic differential equation [4]; There is monomer degradation with rates $\mu_i, i = 1,2,\ldots,6$ and oligomer degradation with rates μ_0; From these assumptions, the Aβ aggregation process can be illustrated with diagram as follows:

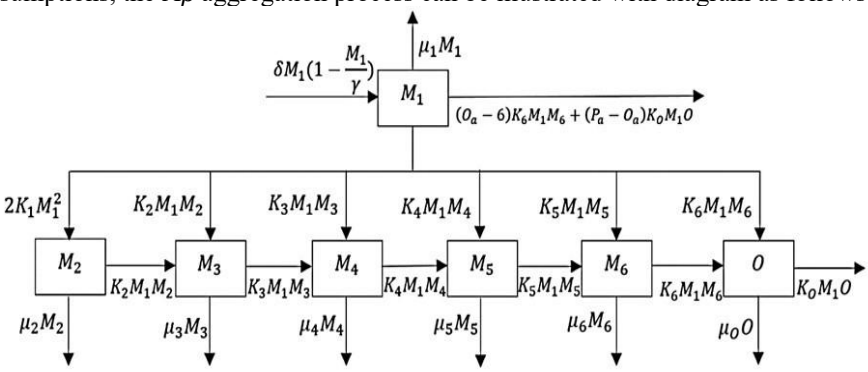

Fig. 1. The Aβ aggregation process.

where $K_i, i = 1,2,\ldots,6$ denote nucleation rate for i monomers, K_O is elongation rate, O_a and P_a are average of oligomer and fibril size, respectively, δ is the growth rate of monomers and γ denotes the carrying capacity.

From Fig. 1, it can be developed a system of ordinary differential equations, i.e.

$$\frac{dM_1}{dt} = \delta M_1\left(1 - \frac{M_1}{\gamma}\right) - 2K_1M_1^2 - M_1(K_2M_2 + K_3M_3 + K_4M_4 + K_5M_5) - (O_a - 6)K_6M_1M_6 - (P_a - O_a)K_OM_1O - \mu_1M_1 \quad (1)$$

$$\frac{dM_2}{dt} = K_1M_1^2 - K_2M_1M_2 - \mu_2M_2 \quad (2)$$

$$\frac{dM_3}{dt} = K_2M_1M_2 - K_3M_1M_3 - \mu_3M_3 \quad (3)$$

$$\frac{dM_4}{dt} = K_4M_1M_4 - K_4M_1M_4 - \mu_4M_4 \quad (4)$$

$$\frac{dM_5}{dt} = K_5M_1M_5 - K_5M_1M_5 - \mu_5M_5 \quad (5)$$

$$\frac{dM_6}{dt} = K_6M_1M_6 - K_6M_1M_6 - \mu_6M_6 \quad (6)$$

$$\frac{dO}{dt} = K_6M_1M_6 - K_OM_1O - \mu_OO \quad (7)$$

The factors $(O_a - 6)$ and $(P_a - O_a)$ in Eq. (1) represent the average number of monomers which is needed M_6 to form an oligomer ad the average number of monomers which is needed an oligomer to form a fibril, respectively [4].

3 Existence of Equilibrium Points

Following [4], the existence of equilibrium points of the model is stated in the following theorem:

Theorem 1. Consider the model stated in Eqs. (1)-(7).

(1) If $\delta - \mu_1 \leq 0$, then the model has only the extinction equilibrium.

(2) If $\delta - \mu_1 > 0$, then the model can also have a unique positive interior equilibrium.

The extinction equilibrium point occurs when the monomer stops aggregating. In this condition, there is no more oligomer formation or it can be said that the concentration of oligomer is heading towards zero. Whereas the positive single interior equilibrium point occurs when there is still growth of monomers that aggregate.

The equilibrium points can be obtained by setting the Eqs. (1)-(7) as

$$\delta M_1\left(1 - \frac{M_1}{\gamma}\right) - 2K_1M_1^2 - M_1(K_2M_2 + K_3M_3 + K_4M_4 + K_5M_5) - (O_a - 6)K_6M_1M_6 - (P_a - O_a)K_OM_1O - \mu_1M_1 = 0 \quad (8)$$

$$K_1M_1^2 - K_2M_1M_2 - \mu_2M_2 = 0 \quad (9)$$

$$K_2M_1M_2 - K_3M_1M_3 - \mu_3M_3 = 0 \quad (10)$$

$$K_4M_1M_4 - K_4M_1M_4 - \mu_4M_4 = 0 \quad (11)$$

$$K_5M_1M_5 - K_5M_1M_5 - \mu_5M_5 = 0 \quad (12)$$

$$K_6M_1M_6 - K_6M_1M_6 - \mu_6M_6 = 0 \quad (13)$$

$$K_6M_1M_6 - K_OM_1O - \mu_OO = 0 \quad (14)$$

Suppose the extinction equilibrium point is $E^0 = (M_1^0, M_2^0, M_3^0, M_4^0, M_5^0, M_6^0, O^0)$. In the case of extinction, no more M_1 is added to the monomer aggregation, so we get that $M_1 = 0$. Substitute the value into Eqs. (8)-(14) we can obtained $E^0 = (0,0,0,0,0,0,0)$. Suppose the interior equilibrium point is $M^* = (M_1^*, M_2^*, M_3^*, M_4^*, M_5^*, M_6^*, O^*)$ The interior equilibrium

point indicates a condition where the monomer concentration is heading towards a value greater than zero. This condition occurs because the monomer continues to increase due to the aggregation process, but also decreases due to the degradation processes. From Eqs. (9), we can derived the component of interior equilibrium for M_2^*, that is

$$M_2^* = \frac{K_1(M_1^*)^2}{(K_2M_1^* + \mu_2)} \tag{15}$$

Substitute Eq. (15) into Eqs. (10)-(14) we can obtain the component of interior equilibrium for $M_3^*, M_4^*, M_5^*, M_6^*, O^*$ as follows

$$M_3^* = \frac{K_1K_2(M_1^*)^3}{(K_2M_1^* + \mu_2)(K_3M_1^* + \mu_3)} \tag{16}$$

$$M_4^* = \frac{K_1K_2K_3(M_1^*)^4}{(K_2M_1^* + \mu_2)(K_3M_1^* + \mu_3)(K_4M_1^* + \mu_4)} \tag{17}$$

$$M_5^* = \frac{K_1K_2K_3K_4(M_1^*)^5}{(K_2M_1^* + \mu_2)(K_3M_1^* + \mu_3)(K_4M_1^* + \mu_4)(K_5M_1^* + \mu_5)} \tag{18}$$

$$M_6^* = \frac{K_1K_2K_3K_4K_5(M_1^*)^6}{(K_2M_1^* + \mu_2)(K_3M_1^* + \mu_3)(K_4M_1^* + \mu_4)(K_5M_1^* + \mu_5)(K_6M_1^* + \mu_6)} \tag{19}$$

$$O^* = \frac{K_1K_2K_3K_4K_5K_6(M_1^*)^7}{(K_OM_1^* + \mu_O)(K_2M_1^* + \mu_2)(K_3M_1^* + \mu_3)(K_4M_1^* + \mu_4)(K_5M_1^* + \mu_5)(K_6M_1^* + \mu_6)} \tag{20}$$

The value $M_1^*$of can be determined by substituting Eqs. (15)-(20) into Eq. (8) and solve it for M_1^*. Moreover, from those equations, it can be concluded that the component of interior equilibrium for $M_2^*, M_3^*, \dots, M_n^*$ have formula:

$$M_i^* = \frac{K_{i-1}M_1^*M_{i-1}^*}{\prod_{j=2}^{i}(K_jM_1^* + \mu_j)} \tag{21}$$

for i = 2,3,...,n.

4 Numerical Simulations and Discussions

4.1 Case of extinction

In this subsection, we will simulate the numerical solution of the mathematical model of Aβ protein aggregation in AD, in case of extinction. The model solved numerically using the fourth-order Runge-Kutta method [6]. For this simulation, we use the initial values as follows: $M_1(0) = 10, M_2(0) = M_3(0) = M_4(0) = M_5(0) = M_6(0) = O(0) = 0$. Since it is expected that the degradation rate will decrease as the monomer stack size increases, while the nucleation rate will increase as the monomer aggregation size increases, to select the values of μ_i and K_i, for i = 2, 3, 4, 5, 6, the relationship that meets these criteria is chosen, i.e. $\mu_i = \mu_{i-1}$ and $K_i = K_{i-1} + \epsilon$, with $\epsilon > 0$ [4]. Consider $\delta = 10^{-4}$, $\epsilon = 10^{-3}$, $K_1 = 10^{-4}$, $K_O = 10^{-1}$, $\gamma = 75$, $O_a = 10$, $P_a = 100$, $\mu_1 = 10^{-3}$, $\mu_O = 10^{-5}$. The solution of the model can be seen in Fig. 2.

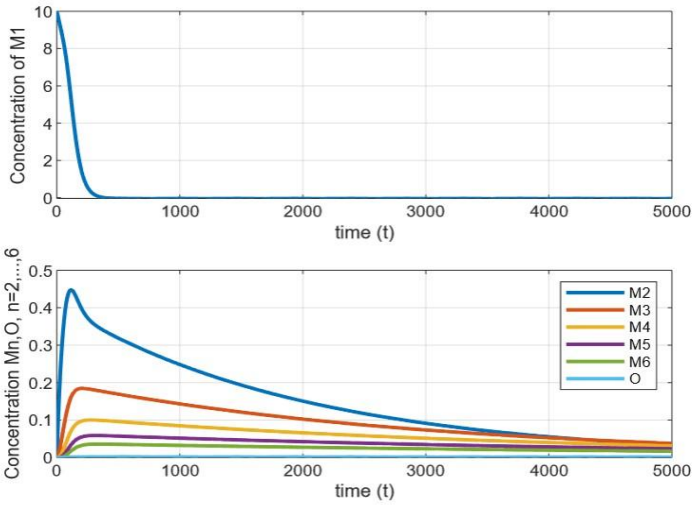

Fig. 2. Numerical solution of Aβ aggregation process, in case of extinction.

From Fig. 2, it can be seen that, with the value of $\delta - \mu_1 < 0$, the concentrations of M_1 decrease relatively quickly towards 0. Whereas, the $M_i, i = 1,2,...,6$ and O concentration all initially increase but then go towards 0, which shows that for a long time there will be no more aggregation of Aβ protein.

4.2 Case of interior equilibrium

Suppose we set the value $\delta = 40$, and the other parameter values are the same as those used in the extinction case. Then $\delta - \mu_1 > 0$. The solution graph for this case can be seen in Fig. 3. Based on Fig. 3(left), concentration of M_1 increase rapidly at $t = 0$ to $t = 0.44$ and a fairly slow decrease when $t = 0.441$ to $t = 100$. This increase occurs because of the aggregation of 1-monomer with other monomers which will form other aggregation. While the decrease occurs due to monomer degradation. After sustain an increase, it will then have a decrease towards the equilibrium point component for the concentration M_1, that is $M_1^* = 73.9$. Furthermore, from Fig. 3(right) it can be seen that the concentrations of $M_2 - M_6$ and O increase until they finally reach their interior equilibrium point, according to Eqs. (15)-(20). This increasing occurs because of the aggregation of 1-monomer with other monomers from each group. It can also be seen that the longer the aggregation of monomers, the lower it will be.

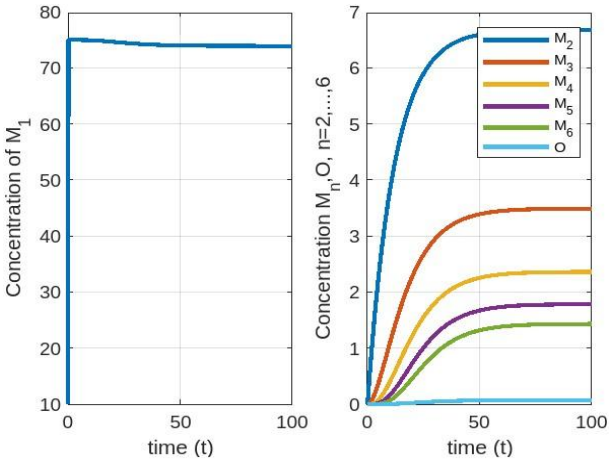

Fig. 3. Numerical solution of Aβ aggregation process, in case of interior equilibrium.

4.3 Number of monomers's effect

In the Aβ aggregation process, the formation of oligomer depends on number of monomers. Reixach, et.al. [7] showed that oligomers are formed from the aggregation of at most six monomers. In this subsection, we investigate the effect of the number of monomers in oligomers forming. The basic model is modified by reducing differential equations related to $M_2 - M_5$, denotes oligomers are formed from the aggregation of 2-monomers until 5-monomers, respectively. The effect of the number of monomers can be seen in Fig. 4. The larger the value of n, the less oligomers will be formed.

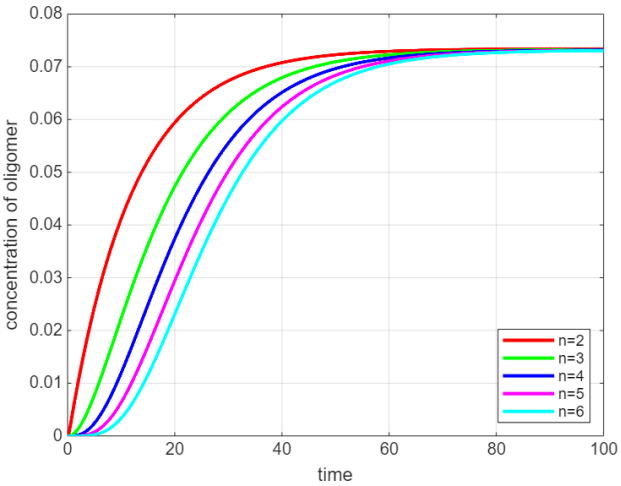

Fig. 4. Concentration of oligomers with various number of monomers.

4.4 Capacity of the Aβ protein

In this section, the effect of the capacity of the β-amyloid protein (γ) on the monomer aggregation process will also be investigated. By using several values of γ, changes in monomer concentration can be observed in Fig. 5. It can be seen that for the greater γ, it makes the concentration of M_1 more higher.

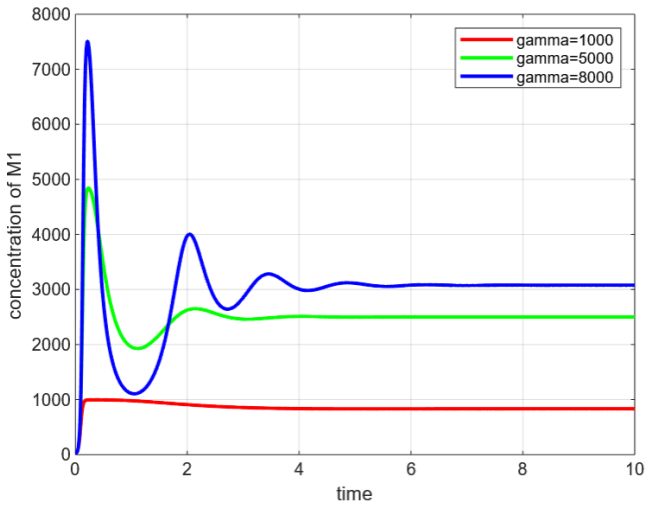

Fig. 5. Concentration of M_1 with various capacity of the β-amyloid.

5 Conclusion

Numerical investigations were conducted on the model of β-amyloid aggregation in Alzheimer's disease. It can be observed that the number of monomers required to form oligomers will affect the concentration of the oligomers themselves. The more monomers required, the lower the concentration of oligomers. In addition, the greater the capacity of the beta amyloid protein, the faster the monomer aggregation process occurs.

References

1. O. F. Voropaeva, T. V. Bayadilov, S. V. Leontiev, S. D. Senotrusova, C. A. Tsgoev, and Y. I. Shokin, "Mathematical modeling of degenerative diseases," in AIP Conference Proceedings, November 2018. https://doi.org/10.1063/1.5065169
2. E. Reynaud, "Protein Misfolding and Degenerative Diseases," Nature Education, vol. **3**, p. 28, 2010.
3. W. Hao and A. Friedman, "Mathematical model on Alzheimer's disease," BMC Systems Biology, vol. **10**, p. 1, 2016. https://doi.org/10.1186/s12918-016-0348-2
4. A. S. Ackleh, et al., "A continuous-time mathematical model and discrete approximations for the aggregation of β-Amyloid," Journal of Biological Dynamics, vol. **15**, p. 109, 2021. https://doi.org/10.1080/17513758.2020.1869843
5. M. A. Dayeh, G. Livadiotis, and S. Elaydi, "A discrete mathematical model for the aggregation of β-Amyloid," PLOS ONE, vol. **13**, e0196402, 2018. https://doi.org/10.1371/journal.pone.0196402
6. J. H. Mathews and K. D. Fink, Numerical Methods Using MATLAB (3rd ed., Upper Saddle River, NJ: Prentice Hall, 2004).
7. N. Reixach, S. Deechongkit, X. Jiang, J. W. Kelly, and J. N. Buxbaum, "Tissue damage in the amyloidoses: Transthyretin monomers and nonnative oligomers are the major cytotoxic species in tissue culture," Proceedings of the National Academy of Sciences, vol. **101**, no. 9, pp. 2817–2822, 2004. https://doi.org/10.1073/pnas.0400062101