MODELING THE IMPACT OF DELAY ON THE AGGREGATION OF AD PROTEINS

Alessandro Nutini[1] · Ayesha Sohail[2] · Robia Arif[2] · Mudassar Fiaz[2] · O. A. Bég[3]

Abstract

Accumulation of the amyloid-β (Aβ) peptide in the brain gives rise to a cascade of key events in the pathogenesis of Alzheimer's disease (AD). It is verified by different research trials that the sleep-wake cycle directly affects Aβ levels in the brain. The catalytic nature of amyloidosis and the protein aggregation can be understood with the help of enzyme kinetics. During this research, the chemical kinetics of the enzyme and substrate are used to explore the initiation of Alzheimer's disease, and the associated physiological factors, such as the sleep wake cycles, related to this symptomatology. The model is based on the concentration of the Aβ fibrils, such that the resulting solution from the mathematical model may help to monitor the concentration gradients (deposition) during sleep deprivation. The model proposed here analyzes the existence of two phases in the production of amyloid fibrils in the sleep deprivation condition: a first phase in which the soluble form of amyloid Aβ is dominant and a second phase in which the fibrillar form predominates and suggests that such product is the result of a strong imbalance between the production of amyloid Aβ and its clearance. The time dependent model with delay, helps to explore the production of soluble Aβ amyloid form by a defective circadian cycle. The limitations of the time dependent model are facilitated by the artificial intelligence (AI) time series forecasting tools.

Keywords Amyloid aggregation · Alzheimer's disease (AD) · Reproductive number · Sensitivity analysis · Sleep deprivation · Circadian rhythm

✉ Ayesha Sohail
  ayeshasohail81@gmail.com

  Alessandro Nutini
  nutini@centrostudiattivitamotorie.it

[1] Centro Studi Attività Motore - Biology and Biomechanics Department, Via di tiglio 94, Lucca, Italy

[2] Department of Mathematics, Comsats University Islamabad, Lahore Campus, Lahore 54000, Pakistan

[3] Department of Mechanical/Aeronautical Engineering, SEE, University of Salford, Manchester, UK

1 Introduction

1.1 Background

Alzheimer's disease (AD) is actually promoted by the pathological accumulation of $A\beta$ amyloid in the brain. It is believed to initiate a cascade of key events that lead to the symptoms of the disease. The main mechanism underlying amyloid aggregation is an imbalance between "clearance" and production of $A\beta$ amyloid which results in synaptic and neuronal damage due to the accumulation of toxic amyloid aggregates [1]. Evidence is available in the literature that the sleep-wake cycle directly affects $A\beta$ levels in the brain [2]. Sleep and circadian rhythm disturbances often compromise the quality of life and safety of individuals with Alzheimer's disease (AD).

Nocturnal insomnia, restless behavior, and excessive sleep during the day affect 25–40% of patients with mild to moderate dementia due to community-based AD, and the intensity of these changes correlates with the severity of the dementia.

There is a decrease in the amplitude of the circadian rhythms and delayed phase is also reported, in people having dementia in advanced stages of AD. In experimental models, sleep deprivation increases soluble $A\beta$ concentration, that gives rise to chronic $A\beta$ accumulation.

Additionally, once $A\beta$ builds up, the following patterns develop:

- wakefulness
- disturbed sleep cycles

Individuals with early $A\beta$ deposition, who still show normal cognitive function, report sleep abnormalities as do individuals with very mild dementia due to AD [3].

Therefore, there is a correlation between the sleep cycle and the neuro-degenerative diseases. This relation can help to identify several ways for the accurate diagnosis and treatment of the Alzheimer disease.

1.2 Motivation

In the early stage of preclinical AD, soluble $A\beta$ amyloid becomes insoluble and aggregates into amyloid plaques, initially manifesting as a reduction in cerebrospinal fluid (CSF) soluble $A\beta$ levels [4].

Changes in sleep appear to precede the onset of cognitive symptoms in AD patients, and sleep quality or circadian function further declines in parallel with both cognitive dysfunction and disease progression. However, the time course of sleep changes, from preclinical AD to the clinical stages of dementia due to AD, is yet to be analyzed and defined.

In the work of Ju et'al. [2] linkage between Alzheimer's disease and disturbed sleep is reported. The data extracted from the guinea pigs experiments , as well as from the patients suffering from dementia (due to AD), indicated that the accumulation of amyloid disturbs sleep and the interrupted sleep increases the risk of $A\beta$ accumulation.

The motivation for the current research strategy is to explore the $A\beta$ form, under the assumption of delay. The hypothesis can be well understood with the aid of schematic depiction.
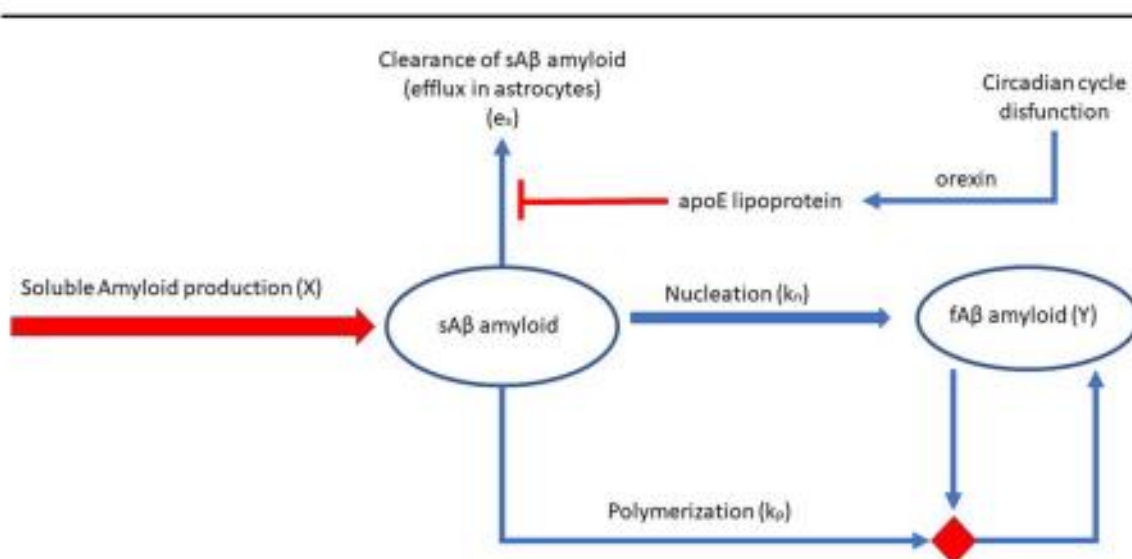
Fig. 1 The schematic of the soluble amyloid production and the neurodegeneration
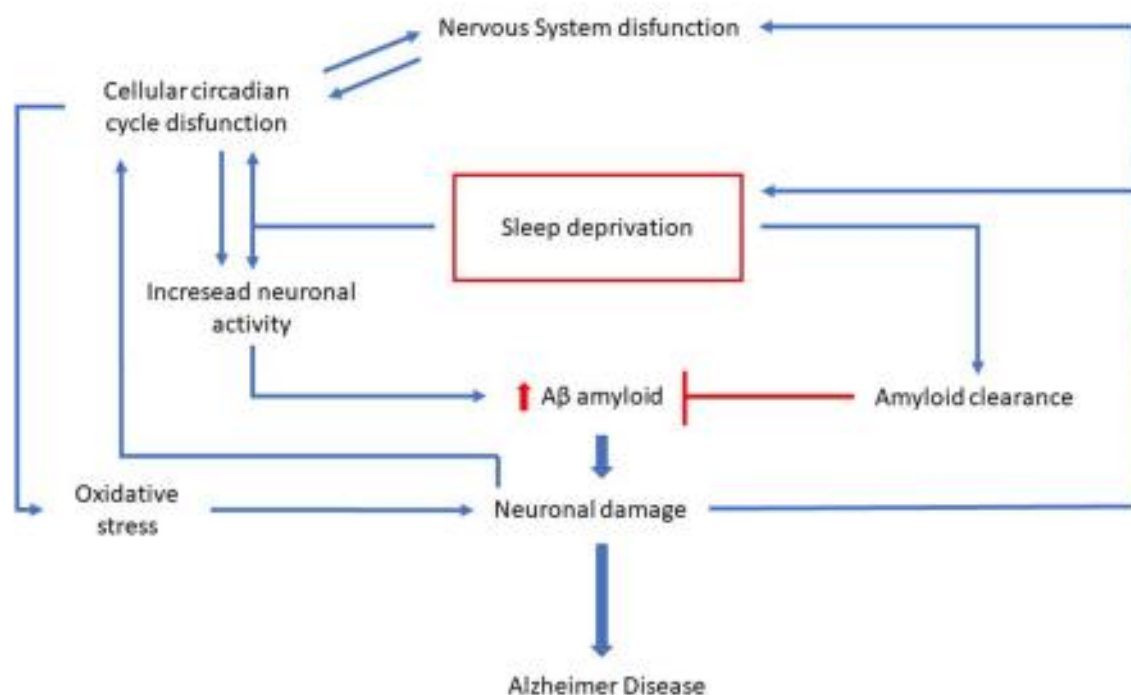

Fig. 2 Interaction between sleep deprivation and conditions facilitating Alzheimer's disease

Figure 1 shows the production cycle by nucleation of amyloid fibrils and the negative interaction of their clearance in the case of the dysfunction of "circadian cycle". This negative mediation is operated due to orexin which works by stimulating an overproduction of apoE, which inhibits the recovery of soluble amyloid by astrocytes. In this way the accumulation of soluble amyloid accelerates the formation of fibrils by nucleation.

Figure 2 shows the network of interactions that exists between sleep deprivation, due to the dysfunction of the circadian cycle, and the consequent increase in neuronal activity which leads, in turn, to a greater production of amyloid, to a cellular damage from oxidative stress and systemic dysfunction of the nervous system.
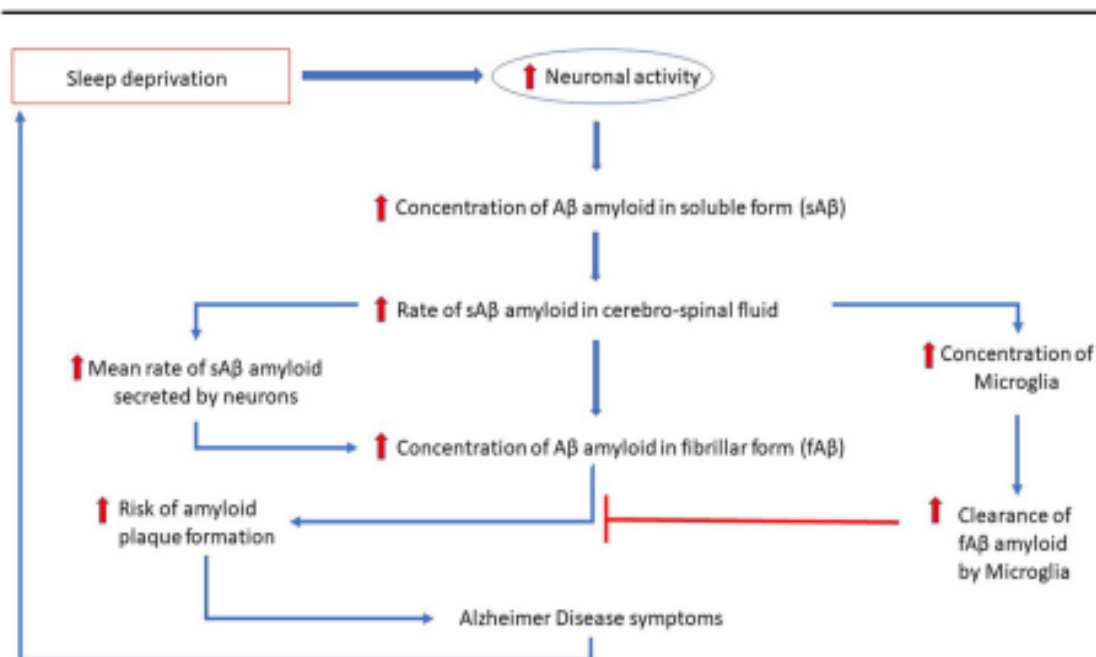
Fig. 3 The relationship of production of amyloid fibrils in relation to sleep deprivation

Figure 3 shows a general quantitative representation of the detectable amyloid concentrations and their increase in the case of sleep deprivation. Note the positive effect of increasing the concentration of microglia which could affect a greater clearance of the amyloid fibrils formed and decrease the risk of formation of amyloid plaques, "typical" of Alzheimer's disease.

The circadian cycle regulates sleep-wake activity over 24 hours and synchronizes the relative light-dark cycle. In Alzheimer's disease, the circadian cycle and sleep deprivation seem to be strongly linked to the disease through the accumulation of amyloid Aβ protein (the cause of this type of dementia).

Symptoms resulting from sleep-wake dysfunction are typical in Alzheimer's disease mainly these symptoms are related to lack of sleep during the night (on the contrary, excess sleep during the day) with reduced REM and slow-wave sleep loss.

Studies have shown that sleep-related symptoms are associated with an increased future risk of dementia over a period of one to nine years.

The sleep-wake cycle is linked to the accumulation of amyloid Aβ and parallel to the deprivation of sleep or the alteration of the sleep-wake cycle, there is a strong increase in amyloid Aβ fibrils. Parallel to this, there is a stress that induces further neuronal damage given by the phosphorylation of the amyloid proteins themselves, i.e. the synaptic lesions and mitochondrial oxidative stress that can induce neuronal death. A dysfunction of the circadian cycle and an abnormality in the secretion of melatonin are common symptoms in Alzheimer's disease.

Certainly, improving the quality of sleep in Alzheimer's patients is of undoubted benefit in a possible slowdown of the disease or in a possible form of prevention. Therefore, the Sleep and circadian function could represent the noteworthy parameters of the risk factors for the future development of Alzheimer's disease.

1.3 Current Research Strategy

In the fields of modeling, simulation and data science [25–31] computational tools have always helped to forecast the dynamics of the research problems in a realistic manner. During this research, to address the complex kinetics of the life threatening disease, the enzyme and substrate basic concepts of catalysis are modeled by keeping in view the delays associated with the production of the resulting products, the vicious cycles of Alzhimer, associated with the circadian cycles.

2 Model Development and Analysis

Nonlinear mathematical models play important role in understanding biological phenomena [5–12].

Inspired by the literature [13], data based studies [6, 8–11, 14–21], and the dynamics presented through the schematic description (Figs. 1, 2 and 3), the model presented here is highly non-linear. Let X be the concentration of Aβ oligomers in soluble form, and Y be their concentration in fibrillar form (see Fig. 1). Let S be the production rate of X per day, the mathematical model for the rate of change of these variables is presented as:

$$\frac{dX}{dt} = S - \gamma_g XY - \gamma_n X - \eta_X X,$$
$$\frac{dY}{dt} = \gamma_g XY + \gamma_n X - \eta_Y Y. \tag{1}$$

Where $\eta_X = Md_X + e_x$ and $\eta_Y = Md_p$. Description of variables and parameters is in Table 1.

2.1 Positivity

Theorem 2.1 *Assume that initial solution $X(0) \geq 0$ and $Y(0) \geq 0$, then the solution of model (1) are non-negative $\forall\, t > 0$, which satisfied*

$$\lim_{t \to \infty} \sup X(t) \leq \frac{S}{\gamma_n + \lambda_X},$$
$$\lim_{t \to \infty} \sup(X(t) + Y(t)) \leq \frac{S}{\eta}, \tag{2}$$

where $\eta = \min\{\eta_X, \eta_Y\}$.

Proof As $S > 0$, the first equation of model (1) gives

$$\frac{dX}{dt} \geq -\gamma_g XY - X\gamma_n - X\eta_X.$$

Thus, separating variable and integrating above inequality gives

$$X(t) \geq X(0) \exp\{(-\gamma_g Y - \gamma_n - \eta_X)t\} \tag{3}$$

which demonstrate that $X(t)$ will non-negative if $X(0)$ non-negative $\forall$ time t. The second equation of model (1) gives

$$\frac{dY}{dt} \geq -\eta_Y Y$$

by integrating both sides

$$Y(t) \geq Y(0) \exp\{-\eta_Y\} \tag{4}$$

It is demonstrated that $X > 0$ and $Y > 0$ $\forall$ $t > 0$. Now we proves boundedness of solution of model (1), from first equation

$$\frac{dX}{dt} = S - \gamma_g XY - \gamma_n X - \eta_X X$$
$$\leq S - (\gamma_n + \eta_X)X.$$

Integrate both sides

$$\lim_{t \to \infty} \sup X(t) \leq \frac{S}{\gamma_n + \eta_X}. \tag{5}$$

Now adding both equations of model (1)

$$\frac{d}{dt}(X + Y) \leq S - \eta_X X - \eta_Y Y$$

where $\eta = \min\{\eta_X, \eta_Y\}$ integrating both sides

$$\lim_{t \to \infty} \sup(X(t) + Y(t)) \leq \frac{S}{\eta}. \tag{6}$$

$\square$

2.2 Stability of equilibrium point

The model (1) has an equilibrium point, which is obtained by putting right-hand side of the equations in model equal to zero, given by

$$E = (X^*, Y^*) = \left(\frac{\beta + S\gamma_g}{2\gamma_g \eta_X}, \frac{S\gamma_g - \beta}{2\gamma_g \eta_X} \right). \tag{7}$$

Where:

$$\beta = \sqrt{(S\gamma_g + \eta_Y (\gamma_n + \eta_X))^2 - 4S\gamma_g \eta_X \lambda_Y} + \eta_Y (\gamma_n + \eta_X). \tag{8}$$

The endemic equilibrium point is exists if

$$S\gamma_g + \lambda_Y (\gamma_n + \lambda_X) > \sqrt{(S\gamma_g + \lambda_Y (\gamma_n + \lambda_X))^2 - 4S\gamma_g \lambda_X \lambda_Y}.$$

The linear stability of the model (1) is established by using method of the next-generation operator. It follow that basic reproduction number of model (1), represented by $\mathbb{R}$, is calculated as

$$F = \begin{pmatrix} \frac{\beta - S\gamma_g - 2(\gamma_n + \eta_X)\eta_Y}{2\eta_Y} & -\frac{\beta + S\gamma_g}{2\eta_X} \\ \frac{-\beta + S\gamma_g + 2(\gamma_n + \eta_X)\eta_Y}{2\eta_Y} & \frac{\beta + S\gamma_g - 2\eta_X\eta_Y}{2\eta_X} \end{pmatrix}, \quad V = \begin{pmatrix} 0 & \lambda_Y \\ \lambda_X & 0 \end{pmatrix},$$

$$\mathbb{R} = 1 - \frac{\sqrt{(S\gamma_g + \eta_Y (\gamma_n + \eta_X))^2 - 4S\gamma_g \eta_X \eta_Y}}{\eta_X \eta_Y}.$$

(9)

The equilibrium point E of the model (1) is locally asymptotically stable if and only if $\mathbb{R} > 1$. It is shown in following:

$$J_E = \begin{pmatrix} \frac{\beta - S\gamma_g}{2\eta_Y} - \gamma_n - \eta_X & -\frac{\beta + S\gamma_g}{2\eta_X} \\ \gamma_n - \frac{\beta - S\gamma_g}{2\eta_Y} & \frac{\beta + S\gamma_g}{2\eta_X} - \eta_Y \end{pmatrix}.$$

(10)

The quadratic equation of J_E is

$$P(\lambda) = \lambda^2 + (-A_1 - A_2)\lambda + \frac{1}{4}\left((A_1 + A_2)^2 - A_5^2\right) = 0$$

(11)

where:

$$A_1 = \frac{\beta - S\gamma_g}{2\eta_Y} - \gamma_n - \eta_X,$$

$$A_2 = \frac{\beta + S\gamma_g}{2\eta_X} - \eta_Y,$$

$$A_3 = \gamma_n - \frac{\beta - S\gamma_g}{2\eta_Y},$$

$$A_4 = -\frac{\beta + S\gamma_g}{2\eta_X},$$

$$A_5 = \sqrt{(A_1 - A_2)^2 + 4A_3 A_4}.$$

(12)

The model (1) is locally asymptotically stable if $\mathbb{R} > 1$.

2.3 Sensitivity Analysis

We can analyze sensitivity analysis by taking derivative with respect to each parameter of basic reproductive number

$$\mathbb{R}_0 = 1 - \frac{\sqrt{(S\gamma_g + \eta_Y (\gamma_n + \eta_X))^2 - 4S\gamma_g \eta_X \eta_Y}}{\eta_X \eta_Y}$$

that is defined as follows

$$\frac{d\mathbb{R}_0}{d\gamma_n} = -\frac{S\gamma_g + \eta_Y(\gamma_n + \eta_X)}{\eta_X\sqrt{(S\gamma_g + \eta_Y(\gamma_n + \eta_X))^2 - 4S\gamma_g\eta_X\eta_Y}} < 0,$$

$$\frac{d\mathbb{R}_0}{d\gamma_g} = -\frac{S(S\gamma_g + \eta_Y(\gamma_n - \eta_X))}{\eta_X\eta_Y\sqrt{(S\gamma_g + \eta_Y(\gamma_n + \eta_X))^2 - 4S\gamma_g\eta_X\eta_Y}} < 0,$$

$$\frac{d\mathbb{R}_0}{dS} = -\frac{\gamma_g(S\gamma_g + \eta_Y(\gamma_n - \eta_X))}{\eta_X\eta_Y\sqrt{(S\gamma_g + \eta_Y(\gamma_n + \eta_X))^2 - 4S\gamma_g\eta_X\eta_Y}} < 0, \tag{13}$$

$$\frac{d\mathbb{R}_0}{d\eta_X} = \frac{S\gamma_g\eta_Y(2\gamma_n - \eta_X) + S^2\gamma_g^2 + \gamma_n\eta_Y^2(\gamma_n + \eta_X)}{\eta_X^2\eta_Y\sqrt{(S\gamma_g + \eta_Y(\gamma_n + \eta_X))^2 - 4S\gamma_g\eta_X\eta_Y}} > 0,$$

$$\frac{d\mathbb{R}_0}{d\eta_Y} = \frac{S\gamma_g(S\gamma_g + \eta_Y(\gamma_n - \eta_X))}{\eta_X\eta_Y^2\sqrt{(S\gamma_g + \eta_Y(\gamma_n + \eta_X))^2 - 4S\gamma_g\eta_X\eta_Y}} > 0.$$

It is clearly shows that the basic reproductive number is increase with the increment of η_X and η_Y. It will decrease with mean rate of sAβ secretion by neurons, rate constant of Aβ fiber growth and rate constant of Aβ fiber nucleation.

2.4 Model with delay

$$\frac{dX}{dt} = -\gamma_g X_k Y_k - X_k \gamma_n + S - X\eta_X,$$

$$\frac{dY}{dt} = X(t - \tau)Y(t - \tau)\gamma_g + X\gamma_n - Y\eta_Y. \tag{14}$$

2.5 Stability of equilibrium point E

Theorem 2.2 *The model (14) is locally asymptotically stable if* $\mathbb{R} > 1$.

Proof Linearizing model (14) around equilibrium point E, the Jacobian matrix is

$$J = \begin{pmatrix} -\alpha_1 - \gamma_n - \eta_X & -\alpha_2 \\ (e^{-\tau\lambda} + 1)\alpha_1 + \gamma_n & (e^{-\tau\eta} + 1)\alpha_2 - \eta_Y \end{pmatrix}. \tag{15}$$

Where:

$$\alpha_1 = \frac{S\gamma_g - \beta}{2\eta_Y},$$

$$\alpha_2 = \frac{\beta + S\gamma_g}{2\eta_X}. \tag{16}$$

The transcendental characteristic equation of Jacobian matrix is

$$\lambda^2 + a_1\lambda + a_2 + (b_1\lambda + b_2)\, e^{-\lambda\tau} = 0 \tag{17}$$

where coefficients are

$$
\begin{aligned}
a_1 &= \alpha_1 - \alpha_2 + \gamma_n + \eta_X + \eta_Y, \\
a_2 &= \eta_Y\,(\alpha_1 + \gamma_n + \eta_X) - \alpha_2\,(2\,(\alpha_1 + \gamma_n) + \eta_X), \\
b_1 &= -\alpha_2, \\
b_2 &= -2\alpha_1\alpha_2 - \alpha_2\gamma_n - \alpha_2\eta_X.
\end{aligned}
\tag{18}
$$

For bifurcation analysis of model (14), first of all it is assume that $\tau = 0$, equation (17) give all the roots that are real negative. In this case theorem by Routh-Hurwitz can be use to find the roots. The equation (17) have negative roots if
$(a_1 + b_1) > 0$, and $(a_2 + b_2) > 0$
is holds, then it is stable. As delay is continuously increase from zero. The equation (17) have no real non-negative solutions for any value of τ. Suppose that for some values of τ there is exists a real number ψ such that $\lambda = i\psi$ is the root of (17), after simplify we have

$$\zeta^2 + c_1\zeta + c_2 = 0, \quad \psi^2 = \zeta \tag{19}$$

where the constants are

$$
\begin{aligned}
c_1 &= a_1^2 - 2a_2 - b_1^2, \\
c_2 &= a_2^2 - b_2^2.
\end{aligned}
\tag{20}
$$

According to the Descartes' rule of signs (20) has atleast one positive root if $a_1^2 - 2a_2 - b_1^2 > 0$ and $a_2^2 - b_2^2 < 0$ is hold. We have

$$\tau_j = \frac{1}{\psi_0}\arccos\{\frac{\psi_0^2\,(b_2 - a_1 b_1) - a_2 b_2}{b_1^2\psi_0^2 + b_2^2}\} + \frac{2\pi j}{\psi_0},\ j = 0,1,2,.... \tag{21}$$

Differentiate equation (17) with respect to τ at $\psi = \psi_0$, the transversality condition is obtain

$$Re\left(\frac{d\lambda}{d\tau}\right)^{-1} = \frac{-\psi_0^2\,(2b_2^2\,(\psi_0^2 - a_2) + b_1^2\,(a_1^2\psi_0^2 - a_2^2 + \psi_0^4))}{\psi_0^2\,((\psi_0^2 - a_2)^2 - a_1^2\psi_0^2)\,(b_1^2\psi_0^2 + b_2^2)}. \tag{22}$$

Hopf bifurcation occur for delay τ if $\left(\frac{d\lambda}{d\tau}\right)^{-1} > 0$. The above analysis is summarized in following theorem. $\qquad\square$

Theorem 2.3 *Assume that $\mathbb{R} > 1$ if either*
(I) $c_1 < 0$ or
(II) $c_1 \geq 0$ or $c_2 < 0$
is satisfied and ψ_0 is the largest positive number, then the equilibrium point E is asymptotically stable when $\tau < \tau'$ and unstable for $\tau > \tau'$ where $\tau' = \min\{\tau_j\}$.

Furthermore, the system is undergoes hopf bifurcation when $\tau = \tau'$ where

$$\tau' = \frac{1}{\psi_0} \arccos \left\{ \frac{\psi_0^2 (b_2 - a_1 b_1) - a_2 b_2}{b_1^2 \psi_0^2 + b_2^2} \right\}. \tag{23}$$

3 Results

The mathematical model and the associated parameters (the sources of the parametric values and the relevent units are provided in table 1 in detail), helped to generate the concentrations of the fibrils and the substrates for a limited time period. To forecast the dynamics further, we have used the time series forecasting tool. Forecasting of the key players of a model is an important step in the field of computational biology [22, 23]. We forecasted in time and fibrils concentration (Y) domains to see the rise in Y concentration with time to observe the fibrillization behaviour of Aβ oligomers. The numerical results are presented in Fig. 4, d.

Sleep deprivation is a very common condition in people with Alzheimer's disease. In the present work, based on the available literature, an assumption is made that Aβ amyloid fibrils accumulate, subject to the sleep-wake cycle defectiveness (the parameters of circadian control were not taken into account [2, 13].

The mathematical model is non-linear and its evolution admits the limiting values of the production of the soluble and fibril forms of the amyloid (Eq. 6). The underlying assumption was that the model is continuous. The important results are as follows:

- We analyze non negativity of model, behavior of equilibrium point and stability of model.
- Dynamics of the ordinary differential equations is analyzed via basic reproductive number R_0 as follows:
- If basic reproductive number $R_0 > 1$ the endemic equilibrium point is stable.
- Here we conclude criteria for Hopf bifurcation with the help of delay which is used as the bifurcation parameter.
- Endemic equilibrium point is asymptotically stable when delay parameter is small.
- Instability increases as delay parameter increases and Hopf bifurcation arises.
- With the help of Hopf bifurcation we can find a region or area of instability in zone of endemic equilibrium point.

We have given variation to the key parameters and obtained dynamics as shown in Figs. 5, d. From Fig. 5, we can see the variation in the dynamics, over time for the reduced rate of nucleation (γ_n). Next, the dynamics for with and without delay are presented in Fig. ?? and ??. We can see that the model with delay proved to be more realistic since it is anticipated that with the passage of time and for ascending values of γ_g (see dotted line for $0.4\gamma_g$ and thick line for γ_g for comparison), the concentration of the soluble form will reduce whereas the fibril form will increase in a diseased case. From Figs. 6 and d, we can understand the impact of delay on the change in the concentration of the two forms.

This is of fundamental importance since Alzheimer's disease is characterized by considerable fibrillar deposits of Aβ amyloid and understanding the dynamics of their
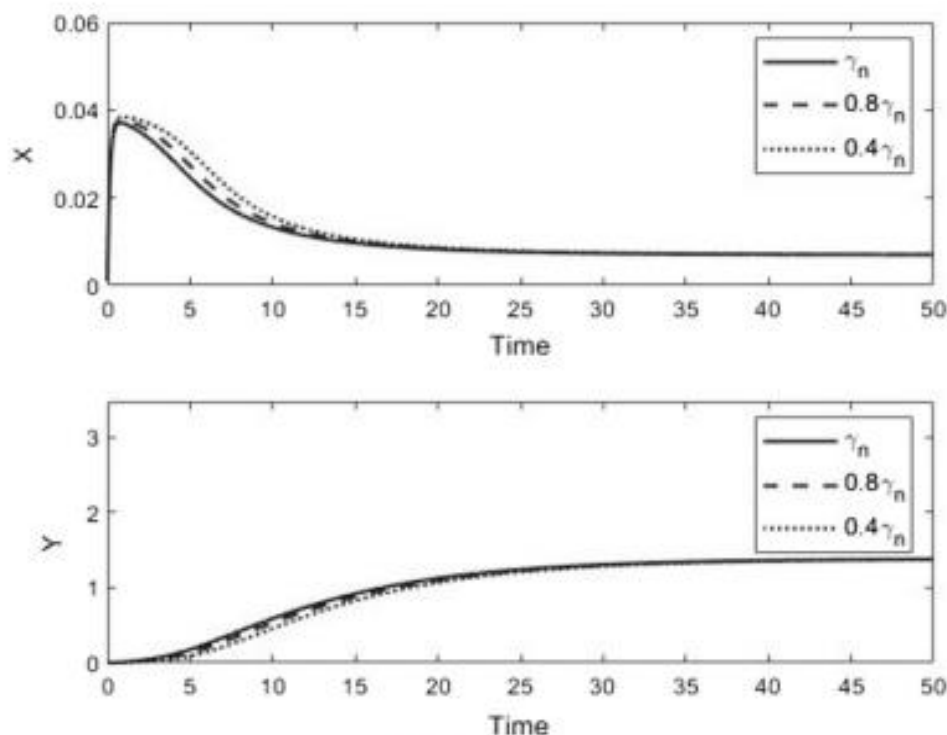
Fig. 4 Variation in X and Y concentrations relative to elevated transition rates of γ_n

Table 1 Summary of model variables and Parameters

Symbols	Description	Value	Ref
S	mean rate of $sA\beta$ secretion by neurons	$\mu M day^{-1}$	–
M	The number density of microglia	$6.7 \times 10^7 mL^{-1}$	
e_X	rate of $sA\beta$ efflux through the cerebro-spinal fluid	$1.9 day^{-1}$	–
d_X	rate of $sA\beta$ clearance by microglia	$5.3 \times 10^{-9} day^{-1} mL$	–
d_Y	clearance of $fA\beta$ by microglia	$\frac{d_X}{30} day^{-1} mL$	–
γ_g	$A\beta$ fiber growth rate	$2.1 \times 10^1 \, \mu M^{-1} \, day^{-1}$	[24]
γ_n	$A\beta$ fiber nucleation rate	$2.2 \times 10^{-1} \, \mu M^{-1} \, day^{-1}$	[24]

formation is one of the key points to fully understand the disease. The intervention of microglia in the control of amyloid fibril deposits induces a delay that quantifies the phenomenon in its complexity.

Furthermore, in the computation of the equilibrium state in the model, the coordinates relative to the same cannot be negative so that, although they identify an intrinsic instability, the steady state concentration of the amyloid fibrils depend on the rate of production of the soluble form of the amyloid $A\beta$ and any oscillation of the time-dependent parameters that somehow affect the production speed of the soluble form of the amyloid in some way. This result can have a significant impact on the quantity of amyloid fibrils produced allowing the quantification of the behavior in the production of fibrils themselves.
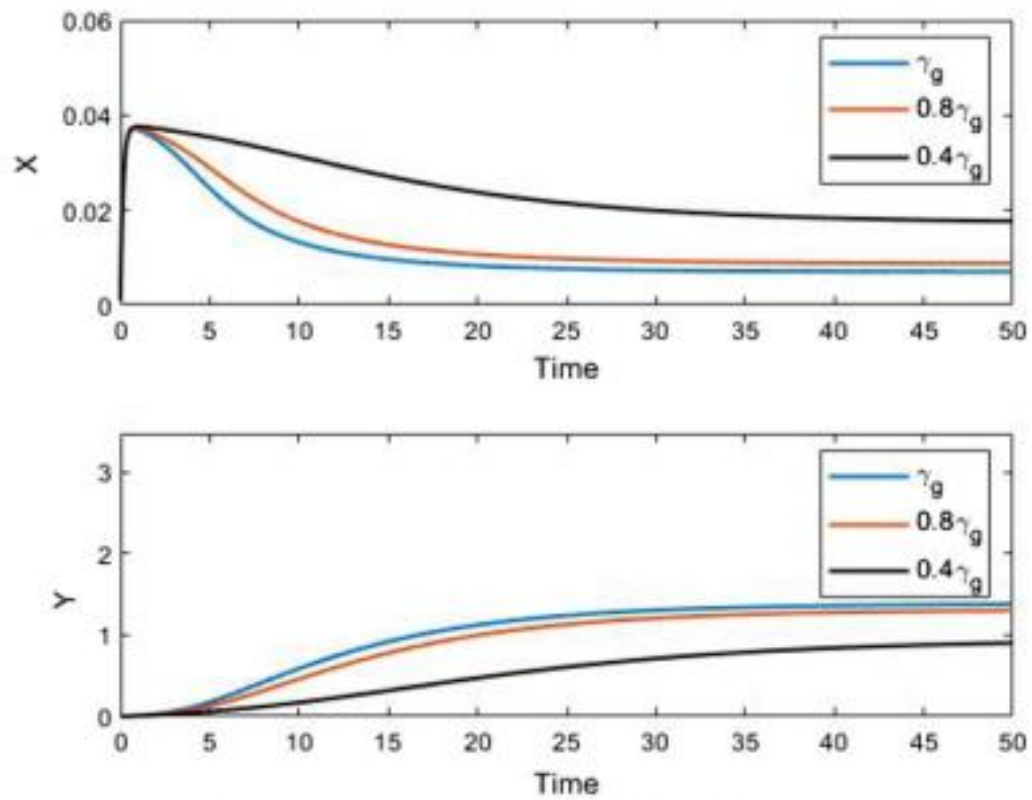
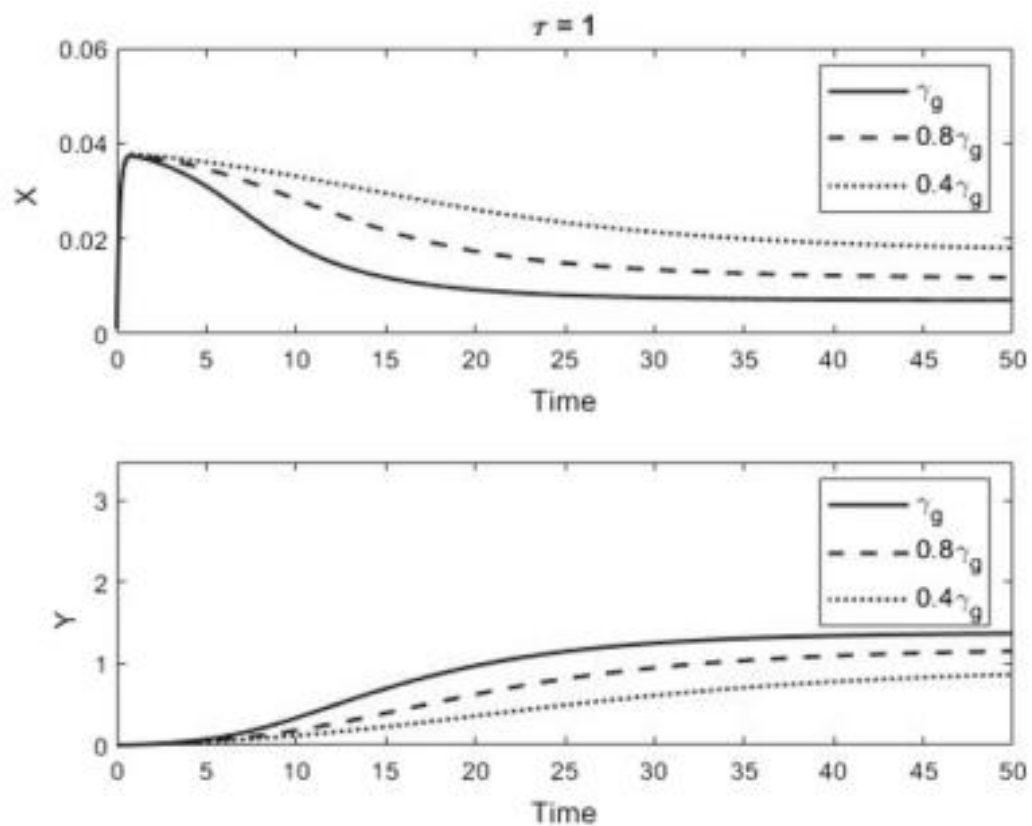**Fig. 5** Variation in X and Y concentrations relative to elevated transition rates γ_g

Fig. 6 Variation in X and Y concentrations relative to elevated transition rates γ_g for the model with delay $\tau = 1$
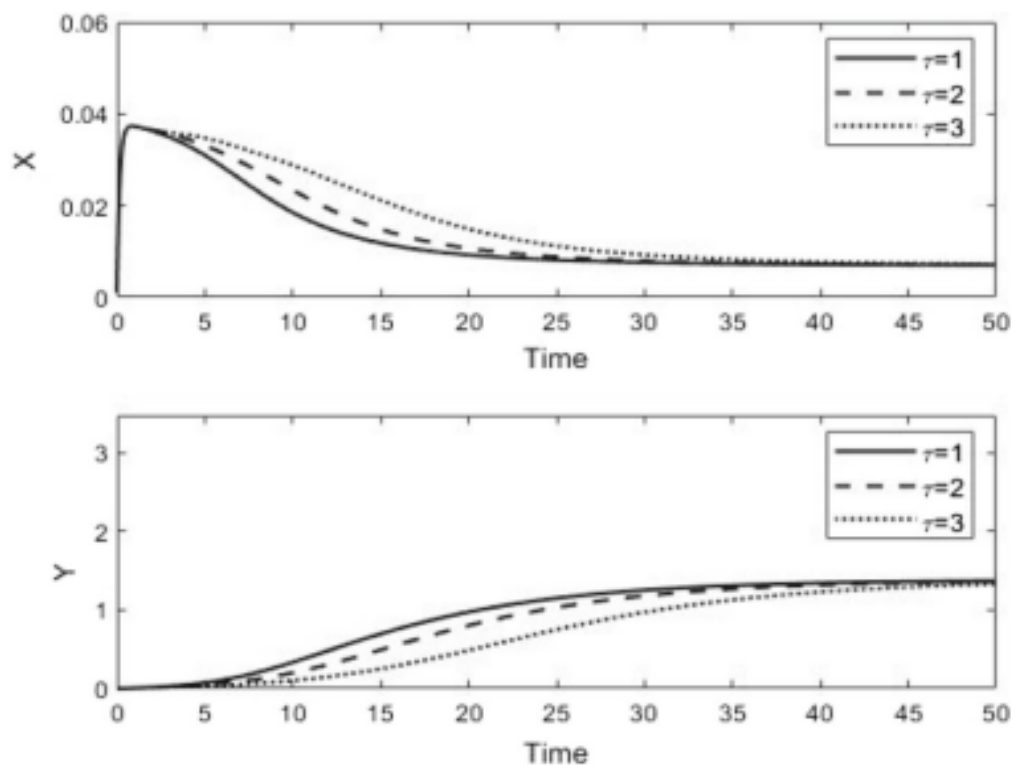
Fig. 7 Variation in X and Y concentrations for the model with delay. $\tau = 1, 2, 3$

4 Conclusions

The model proposed here analyzes the existence of two phases in the production of amyloid fibrils in the sleep deprivation condition:

- a first phase in which the soluble form of amyloid $A\beta$ is dominant
- a second phase in which the fibrillar form predominates and suggests that such product is the result of a strong imbalance between the production of amyloid $A\beta$ and its clearance

The results of the model provide a preliminary step toward the qualitative analysis of the physiology of AD. The study provides an insight of the formation of $A\beta$ amyloid in the disease and in conditions of sleep deprivation that however, account of the neuronal damage induced by this process.

It is really challenging to develop a compact model to demonstrate the spatial expansion of amyloids (a crucial parameter in the pathology). We have made a basic model, that is time dependent and also takes into account the delays. The resulting dynamics helps to understand both the pathogenesis of the disease and the disabling symptoms associated with it.

Declaration

Conflict of interest The authors declare that there is no conflict of interest.

Data Availability The work is based on numerical simulations. Parametric values and source of their values are cited in tabular form within the manuscript.

Code Availability Coding will be provided upon request. Standard algorithms for nonlinear systems are used during this research.

References

1. Nedergaard M (2013) Garbage truck of the brain. Science 340:1529
2. Ju YES, Lucey BP, Holtzman DM (2014) Sleep and Alzheimer disease pathology-a bidirectional relationship. Nature Reviews Neurology. 10(2):115–119
3. Huang Y, Potter R, Sigurdson W, Santacruz A, Shih S, Ju YE et al (2012) Effects of age and amyloid deposition on $A\beta$ dynamics in the human central nervous system. Archives of neurology 69:51
4. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM et al (2011) Toward defining the preclinical stages of Alzheimer's disease: Recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimer's & dementia 7(3):280
5. Sohail A, Ahmad Z, Bég OA, Arshad S, Sherin L (2017) A review on hyperthermia via nanoparticle-mediated therapy. Bull Cancer 104(5):452
6. Sohail A, Li ZW, Iftikhar M, Mohamed M, Beg OA (2017) Stochastic analysis of a deterministic and seasonally-forced SEI model for improved disease spread simulation. J Mech Med Biol 17:1750067
7. Sohail A (2019) Inference of biomedical data sets using Bayesian machine learning. Biomed Eng: Appl Basis Commun 31:1950030
8. Sohail A, Idrees M, Sajjad M, Iftikhar S, Tunc S (2020) Computational framework to explore impact of environmental stress on epidemics. Biomed Eng (Singapore) 32:2050047
9. Sohail A, Nutini A (2020) Forecasting the timeframe of coronavirus and human cells interaction with reverse engineering. Prog Biophys Mol Biol 155:29
10. Sohail A, Arif F (2020) Supervised and unsupervised algorithms for bioinformatics and data science. Prog Biophys Mol Biol 151:14
11. Iftikhar M, Sohail A, Ahmad N (2019) DETERMINISTIC AND STOCHASTIC ANALYSIS OF DENGUE SPREAD MODEL. Biomed Eng (Singapore) 31:1950008
12. Yu Z, Sohail A, Nutini A, Arif R (2020) Delayed Modeling Approach to Forecast the Periodic Behaviour of SARS-2. Frontiers in Molecular Biosciences 7:386
13. Hoore M, Khailaie S, Montaseri G, Mitra T, Meyer-Hermann M. Mathematical Model Shows How Sleep May Affect Amyloid-β Fibrillization;
14. Gramaje A, Thabtah F, Abdelhamid N, Ray SK (2019) Patient discharge classification using machine learning techniques. Ann Data Sci 1:1
15. Olson DL, Shi Y, Shi Y. Introduction to business data mining. vol. 10. McGraw-Hill/Irwin New York; 2007
16. Shi Y, Tian Y, Kou G, Peng Y, Li J (2011) Optimization based data mining: theory and applications. Springer Science & Business Media
17. Tien JM (2017) Internet of things, real-time decision making, and artificial intelligence. Ann Data Sci 4:149
18. Shi Y (2021) Advances in Big Data Analytics: Theory. Algorithms and Practices, Springer Nature
19. Olson DL, Shi Y, Shi Y (2007) Introduction to business data mining. vol. 10. McGraw-Hill/Irwin New York;
20. Sherin L, Sohail A, Shujaat S (2019) Time-dependent AI-modeling of the anticancer efficacy of synthesized gallic acid analogues. Comput Biol Chem 79:137
21. Nutini A, Sohail A, Farwa S (2021) BIOMEDICAL ENGINEERING OF SCLEROSTIN ACTION IN THE BONE REMODELING. Biomed Eng (Singapore) 31:2150016

22. Iftikhar M, Iftikhar S, Sohail A, Javed S (2020) AI-modelling of molecular identification and feminization of wolbachia infected Aedes aegypti. Prog Biophys Mol Biol 150:104

23. Sohail A, Iftikhar M, Arif R, Ahmad H, Gepreel KA, Iftikhar S (2021) Dengue control measures via cytoplasmic incompatibility and modern programming tools. Results Phys 21:103819

24. Cohen SI, Linse S, Luheshi LM, Hellstrand E, White DA, Rajah L et al (2013) Proliferation of amyloid-β42 aggregates occurs through a secondary nucleation mechanism. National Acad Sciences 24:9758

25. Yu Z, Sohail A, Arif R, Nutini A, Nofal TA, Tunc S (2022) Modeling the crossover behavior of the bacterial infection with the COVID-19 epidemics. Results in Physics 39, 105774. https://doi.org/10.1016/j.rinp.2022.105774

26. Sohail A, Yu Z, Nutini A (2022) COVID-19 variants and transfer learning for the emerging stringency indices. Neural Process Lett. https://doi.org/10.1007/s11063-022-10834-5

27. Sohail A, Arif R, Azim QUAA, Nutini A, Gepreel KA (2021) Piecewise fractional order modeling of the breast cancer epidemiology after the Atezolizumab Treatment. Fractals. https://doi.org/10.1142/S0218348X22401764

28. Wang F, Idrees M, Sohail A (2022) "AI-MCMC" for the parametric analysis of the hormonal therapy of cancer. Chaos Solitons Fractals. https://doi.org/10.1016/j.chaos.2021.111618

29. Yu Z, Abdel-Salam G. Abdel-Salam, Sohail A, Alam F (2021) Forecasting the impact of environmental stresses on the frequent waves of COVID19. Nonlinear Dyn 106(2):1509–1523. https://doi.org/10.1007/s11071-021-06777-6

30. Wang F, Sohail A, Tang Q, Li Z. Impact of fractals emerging from the fitness activities on the retail of smart wearable devices. Fractals. https://doi.org/10.1142/S0218348X22401120

31. Yu Z, Sohail A, Nofal TA, Tavares JMRS (2022) Explainability of Neural network clustering in interpreting the COVID-19 emergency data. Fractals. https://doi.org/10.1142/S0218348X22401223