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Research article

Stationary distribution and extinction of a stochastic Alzheimer's disease model

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Abstract: In this paper, a stochastic Alzheimer's disease model with the effect of calcium on amyloid beta is proposed. The Lyapunov function is constructed, followed by the feasibility and positivity and the existence of a stationary distribution for the positive solutions of the proposed model. The sufficient conditions for the extinction of the stochastic Alzheimer's disease model are derived through the Lyapunov function. This indicates that beta-amyloid plaque and the complex of beta-amyloid oligomers with prion protein may go extinct and there is a possibility of a cure for the disease. Furthermore, our numerical simulations show that as the intensity of the random disturbance increases, the time it takes for the disease to go extinct decreases.

Keywords: Alzheimer's disease; stochastic model; extinction; stationary distribution
Mathematics Subject Classification: 60G10, 34F05, 92B05

1. Introduction

Alzheimer's disease (AD), a major form of dementia, is accompanied by cognitive decline, memory impairment, impaired ability to learn new information and language dysfunction. As one of the top 10 causes of death worldwide today, it will severely affect the daily life of the patient [1]. According to the global burden of disease study in 2019 (GBD 2019), the number of people with Alzheimer's-like dementia has 50 million in 2018 and it will reach 152 million by 2050 [2]. In the USA, total payments for medicare, long-term care, and hospice services for dementia are estimated to be up to $335 billion in 2021 [3]. With no reliable and effective treatment, dementia will affect the patient's ability to perform daily live by impairing cognitive function and pose an increasing challenge to health care systems worldwide [4–6].

In the earliest phase of Alzheimer's disease (cellular phase), amoid beta ($A\beta$) accumulate in the brain, along with the spread of tau pathology [7]. The peptide $A\beta$, obtained by amyloid precursor protein (APP), can form $A\beta$ oligomers (two main $A\beta$ forms, $A\beta_{40}$ and $A\beta_{42}$), which will reduce the

number of synapses and decrease glucose metabolism in the brain. This process will finally lead to brain atrophy [8]. To discuss how $A\beta$ peptide aggregates into $A\beta$ oligomers, Masoud Hoore et al. [9] developed a model of $A\beta$ fibrillation on a minimal scale. The results showed that $A\beta$ monomers rapidly increased once $A\beta$ oligomers produced. Furthermore, by considered $A\beta_{40}$ and $A\beta_{42}$ as two forms of $A\beta$ oligomers, Li and Zhao [10] proved that the targeted therapeutic drug Aducanumab of $A\beta$ cannot completely cure AD. However, many studies have found that the prion protein (PrP^C) inhibits the activity of the protease that cleaves APP and slows the proliferation of $A\beta$ [11, 12]. To understand the dynamics of PrP^C, Helal et al. [13] devised an in vitro model to study the role of protein and analyzed the kinetics of $A\beta$ plaques, $A\beta$ oligomers, PrP^C and $A\beta-\mathrm{x}-PrP^C$ complex. Considering the process of diffusion of these substances, Hu et al. [14] focused on the dynamic behaviors of the system in a finite time interval and under what conditions the state value may exceed a certain value.

Various factors are involved in the transmission of neural signals. For example, in the cerebrospinal fluid, the level of $A\beta$ oligomers is affected by Ca^{2+}, microglia activity, reactive oxygen species and Na^+ concentration etc. [15–18]. For example, Caluwé and Dupont [19] designed a positive loop between $A\beta$ and Ca^{2+} to explore the role of Ca^{2+} on $A\beta$ oligomers during the progression of a healthy pathological state to a severe pathology. All the factors always fluctuate in a small range over long periods which will affect the level of $A\beta$ oligomers and the pathological status of AD. Therefore, stochastic perturbations cannot be ignored and parameters are often assumed in biomathematics to be perturbed by linear functions of white noise, a phenomenon described by stochastic differential equations (SDE) [20–23]. Hu et al. [24] formulated a stochastic model of the in vivo progression of AD incorporating the role of prions derived from Helal et al. [13] and discussed the existence of the ergodic stationary distribution of the model.

Studies have been done on minimizing the concentrations of $A\beta$ plaques and $A\beta-\mathrm{x}-PrP^C$ complex in Alzheimer's disease models, but the conditions are complex and not well measured in many practical situations [14]. And the random factors in the interstitial fluid (ISF) cannot be neglected, therefore it is necessary to study stochastic models of Alzheimer's disease to explore the convergence to extinction in a probabilistic sense. For this purpose, we introduce calcium ions into the system based on Helal et al. [12] and consider the effect of random noise on Brownian motion in the environment. The main contributions of this paper are as follows:

(i) A stochastic Alzheimer's disease model is formulated by taking the influence of calcium ions and environmental noise on $A\beta$ oligomers into account.
(ii) The sufficient conditions for extinction of the model are established.

The remaining paper is organized as follows. In the next section, the mathematical model of Alzheimer's disease with Ca^{2+} is established. Section 3 shows the existence, uniqueness and boundedness of the solution of the model. The conditions for the existence of a steady state distribution are derived in Section 4. Section 5 focuses on the threshold conditions for the extinction of plaques and complex and shows how random noise affects the development of Alzheimer's disease. In Section 6, a numerical simulation is performed to prove the validity of the theoretical derivation. In the ending section, we present our conclusion.

2. Mathematical model

In this section, we introduce the model and then give the necessary definitions and lemmas.

2.1. Model formation

To explore the role of prions in memory impairment, Helal et al. [13] introduced a mathematical model of in vivo Alzheimer's disease progression that explains the relationship between $A\beta$ plaque, $A\beta$ oligomers, PrP^C and $A\beta$−x−PrP^C complex. The model is as follows

$$\begin{cases} \dot{A} = \alpha u^n - \eta A, \\ \dot{u} = \lambda_2 - \tau u p + \sigma b - \alpha n u^n - \rho u A - k_2 u, \\ \dot{p} = \lambda_3 - \tau u p + \sigma b - k_3 p, \\ \dot{b} = \tau u p - \sigma b - k_4 b. \end{cases} \tag{2.1}$$

Where $A(t)$, $u(t)$, $p(t)$ and $b(t)$ represent the concentration of $A\beta$ plaque, $A\beta$ oligomers, PrP^C and $A\beta$−x−PrP^C complex. Where α is the rate of formation of oligomers, η is the rate of degradation of a plaque, τ is the rate of binding of $A\beta$ oligomers to PrP^C, σ is the rate of unbinding of $A\beta$−x−PrP^C, ρ is the conversion rate of oligomers to plaque, $k_i (i = 2, 3, 4)$ is the degradation of $A\beta$ oligomers, PrP^C and $A\beta$−x−PrP^C complex, $\lambda_i (i = 2, 3)$ is the source of PrP^C and $A\beta$ oligomers.

In this paper, by considering that the presence of PrP^C can optimize and control Ca^{2+} input [11] and this process is affected by the level of Ca^{2+}, it can be assumed to be a bilinear model [25, 26]. Furthermore, there is positive feedback between the level of Ca^{2+} and the level of $A\beta$ [19], so Ca^{2+} is introduced into the model. Moreover, due to the randomness of real life, especially in the neurobiological environment, there exist various random factors involved in signaling. In many stochastic models of infectious diseases, factors such as noise, Brownian motion, pollution, etc. have been considered [27–29]. Then, we assume that the white noise in the environment is proportional to the variables $C(t)$, $u(t)$, $p(t)$, $b(t)$, and $A(t)$. The stochastic differential model can be written as

$$\begin{cases} \mathrm{d}C = (\lambda_1 + v_2 u - v_3 p C - k_1 C)\,\mathrm{d}t + \xi_1 C dB_1(t), \\ \mathrm{d}u = (\lambda_2 - \tau u p + \sigma b + v_1 \frac{C}{k+C} - \alpha n u^n - \rho u A - k_2 u)\,\mathrm{d}t + \xi_2 u\,\mathrm{d}B_2(t), \\ \mathrm{d}p = (\lambda_3 - \tau u p + \sigma b - k_3 p)\,\mathrm{d}t + \xi_3 p\,\mathrm{d}B_3(t), \\ \mathrm{d}b = (\tau u p - \sigma b - k_4 b)\,\mathrm{d}t + \xi_4 b\,\mathrm{d}B_4(t), \\ \mathrm{d}A = (\alpha u^n - \eta A)\,\mathrm{d}t + \xi_5 A\,\mathrm{d}B_5(t). \end{cases} \tag{2.2}$$

Where λ_1 is the source of Ca^{2+}, v_2 is the acceleration of Ca^{2+} due to $A\beta$, v_3 is the limitation of Ca^{2+} due to PrP^C, k_1 is the degradation of Ca^{2+}, $v_1$is the maximal rate of the positive feedback of Ca^{2+} on $A\beta$ and k is half-saturation constant, $B_i(t)$ denote independent and standard Brownian motions and ξ_i^2 are the intensities of the white noise, $i = 1, 2, 3, 4, 5$. The other parameters in model (2.2) have identical significance as in model (2.1). Our main purpose is to explore the threshold related to epidemic transmission and try to establish the threshold dynamics of model (2.2).

2.2. Preliminaries

Throughout this paper, we let $(\Omega, \mathcal{F}, \{\mathcal{F}\}_{l\geqslant 0}, \mathbb{P})$ be a complete probability space with filtration $\{\mathcal{F}\}_{l\geqslant 0}$ satisfying the usual conditions (that is to say, it is increasing and right continuous while $\mathcal{F}_0$ contains all $\mathbb{P}$ -null sets). Let $B_i(t)(i = 1, 2, 3...)$ denote the independent standard Brownian motions defined on this probability space. We also denote $\mathbb{R}_+^d = \left\{x \in \mathbb{R}^d : x_i > 0 \text{ for all } 1 \leqslant i \leqslant d\right\}$ and $a \wedge b = \min\{a, b\}$.

Generally speaking, consider the d-dimensional stochastic differential equation (SDE)

$$\mathrm{d}x(t) = f(x(t), t)\,\mathrm{d}t + g(x(t), t)\,\mathrm{d}B_t, \tag{2.3}$$

where $f(t, x(t))$ is a function in $\mathbb{R}^d$ defined in $[t_0, \infty] \times \mathbb{R}^d$ and $g(x(t), t)$ is a $d \times m$ matrix, f, g are locally Lipschitz functions in x. B_t denotes an m-dimensional standard Brownian motion ($B_t = (B_1(t), B_2(t), ..., B_m(t))^T$, $B_i(t)(i = 1, 2, ..., m)$ is standard normal distribution and $B_i(t) \sim N(0, t)$) defined on the complete probability space $(\Omega, \mathcal{F}, \{\mathcal{F}\}_{t\geq 0}, \mathbb{P})$. Denote by $C^{2,1}\left(\mathbb{R}^d \times [t_0, \infty]; \mathbb{R}_+\right)$ the family of all nonnegative functions $V(x(t), t)$ defined on $\mathbb{R}^d \times [t_0, \infty]$ such that they are continuously twice differentiable in x and once in t.

We define the differential operator L of Eq (2.3) by [30]

$$\mathrm{L} = \frac{\partial}{\partial t} + \sum_{i=1}^{d} f_i(x, t)\frac{\partial}{\partial x_i} + \frac{1}{2}\sum_{i,j=1}^{d}\left[g^T(x, t)g(x, t)\right]_{ij}\frac{\partial^2}{\partial x_i \partial x_j}. \tag{2.4}$$

If L acts on a function $V \in C^{2,1}\left(\mathbb{R}^d \times [t_0, \infty], \mathbb{R}_+\right)$ then

$$\mathrm{L}V(x, t) = V_t(x, t) + V_x(x, t)f(x, t) + \frac{1}{2}\,\mathrm{trace}\left[g^T(x, t)V_{xx}(x, t)g(x, t)\right] \tag{2.5}$$

where $V_t(x, t) = \frac{\partial V}{\partial t}$, $V_x(x, t) = \left(\frac{\partial V}{\partial x_i}, \ldots, \frac{\partial V}{\partial x_d}\right)$, $V_{xx}(x, t) = \left(\frac{\partial^2 V}{\partial x_i \partial x_j}\right)_{d\times d}$. From Itô's formula, if $x(t) \in \mathbb{R}^d$, then

$$\mathrm{d}V(x, t) = \mathrm{L}V(x, t)\,\mathrm{d}t + V_x(x, t)g(x, t)\,\mathrm{d}B_t. \tag{2.6}$$

Here are some definitions and lemmas what we will use in the following text.

Definition 1. *[21] (Fokker-Plank equation) The respective Fokker-Plank equation for an unknown probability density function (PDF) in variables $x(t)$ can be assigned to Eq (2.3):*

$$\frac{\partial}{\partial t}p(t, x) = -\frac{\partial}{\partial x}(f p(t, x)) + \frac{\partial^2}{\partial x^2}\left(\frac{1}{2}g^2 p(t, x)\right),$$

where $p(t, x)$ means the probability density function of $x(t)$ at t.

Definition 2. *[30] For a set Ω_k composed of elementary random events ω, the indicator function of Ω_k, denoted by 1_{Ω_k}, is the random variable, where*

$$1_{\Omega_k} = \begin{cases} 1 & \text{if } \omega \in \Omega_k, \\ 0 & \text{if } \omega \notin \Omega_k. \end{cases}$$

Definition 3. *[31] The SDE (2.3) is said to be stochastically ultimately bounded if for any $\varepsilon \in (0, 1)$, there is a positive constant $\chi = \chi(\varepsilon)$ such that for any initial data $\{x(t) : -\tau \leqslant t \leqslant 0\} \in C\left([-\tau, 0]; \mathbb{R}^d_+\right)$, the solution $x(t)$ of Eq (2.3) has the property that*

$$\limsup_{t\to\infty} \mathbb{P}\{|x(t)| > \chi\} < \varepsilon. \tag{2.7}$$

Definition 4. *[30] For the Markov process $\{X(t), t \geqslant 0\}$, the state space is $S = \{1, 2, ..., T\}$, if there exists a positive integer m such that*

$$p_{ij}(m) > 0 \quad \text{for every} \quad i, j \in S,$$

then $X(t)$ has the ergodic feature.

Definition 5. *[23, 24, 27] The diffusion matrix of system (2.3) is defined as follows:*

$$A(x) = \left(a_{i,j}(x)\right),\ a_{i,j}(x) = \sum_{r=1}^{k} g_r^i(x).g_r^j(x).$$

Definition 6. *[23] Let $N(t) = (N_i(t))^T$ $(i = 1, 2, ..., d)$ be the solution of model (2.2) with initial value $N(0) \in \mathbb{R}_+^d$. If for any $0 < \varepsilon < 1$, there exists a pair of positive constants $\theta = \theta(\varepsilon)$ and $\chi = \chi(\varepsilon)$ such that*

$$\liminf_{t\to\infty} \mathbb{P}\{N_i(t) \geqslant \theta\} \geqslant 1 - \varepsilon, \quad \liminf_{t\to\infty} \mathbb{P}\{N_i(t) \leqslant \chi\} \geqslant 1 - \varepsilon$$

then the species i is said to be stochastically permanent.

Definition 7. *[20, 22, 28] For model (2.3), the infected individuals $x_i(t)$ are said to be extinctive if $\lim_{t\to\infty} x_i(t) = 0$, almost surely (a.s.).*

Lemma 1. *[23] (Chebychev inequality) Let $X = \{X_t\}_{t\geqslant 0}$ be a nonnegative random variable, its mean value is noted as $\mathbb{E}(X)$, for a given $r > 0$. Then,*

$$\mathbb{P}(X \geqslant r) \leqslant \frac{1}{r}\mathbb{E}(X) \quad \text{for every} \quad r > 0.$$

Lemma 2. *[21, 28] The Markov process $X(t)$ has a unique ergodic stationary distribution $\mu(\cdot)$ if there exists a bound $D \subset \mathbb{R}^d$ with regular boundary Γ and the following conditions:*

(1) In the domain D and some neighborhood thereof, the smallest eigenvalue of the diffusion matrix A(x) is bounded away from zero.

(2) There exists a nonnegative C^2-function V such that $\mathrm{L}V$ is negative for any $\mathbb{R}_d \backslash D$. Then,

$$\mathbb{P}_x\left\{\lim_{T\to+\infty} \frac{1}{T}\int_0^T f(X(t))dt = \int_{E_d} f(x)\mu(dx)\right\} = 1$$

for all $x \in \mathbb{R}^d$, where f is a function integrable with respect to the measure μ.

Lemma 3. *[20] (Strong Law of Large Number) Let $M = \{M\}_{t\leqslant 0}$ be continuous and real-valued local martingale, which vanishes as $t \to 0$, then*

$$\lim_{t\to\infty}\langle M, M\rangle_t = \infty, a.s., \Rightarrow \lim_{t\to\infty}\frac{M_t}{\langle M, M\rangle_t} = 0, a.s.$$
$$\limsup_{t\to\infty}\frac{\langle M, M\rangle_t}{t} < 0,\ a.s., \Rightarrow \lim_{t\to\infty}\frac{M_t}{t} = 0, a.s.$$

3. Existence and uniqueness of the solution

Theorem 1. *For any initial value*

$$X(0) = (C(0), u(0), p(0), b(0), A(0)) \in \mathbb{R}_+^5,$$

there exists a positive salutation $X(t) = (C(t), u(t), p(t), b(t), A(t))$ of the stochastic model (2.2) for $t \geqslant 0$ and the solution will hold in $\mathbb{R}_+^5$ with probability one.

Proof. We can easily know that the coefficients of model (2.2) are locally Lipschitz continuous. Then, for any given initial value $(C(0), u(0), p(0), b(0), A(0)) \in \mathbb{R}_+^5$, there exists a unique local solution $(C(0), u(0), p(0), b(0), A(0))$ on $t \in [0, \tau_e)$, where τ_e is the explosion time (see [20]). To prove that

the solution is global, all you have to do is to prove $\tau_e = \infty$ almost surely. Let $k_0 \geqslant 0$ be sufficiently large so that $(C(0), u(0), p(0), b(0), A(0))$ all lie within the interval $\left[\frac{1}{k_0}, k_0\right]$. For each integer $k \geqslant k_0$, define the following stopping time:

$$\tau_k = \inf\{t \in [0, \tau_e) : \min\{(C(0), u(0), p(0), b(0), A(0))\} \leqslant \frac{1}{k} \text{ or } \max\{(C(0), u(0), p(0), b(0), A(0)) \geqslant k\}\}.$$

Where throughout this paper, we set $\inf \emptyset = \infty$ (as usual $\emptyset$ denotes the empty set). According to the definition of the stopping time, τ_k is increasing as $k \to \infty$. Set $\tau_\infty = \lim_{t\to\infty} \tau_k$ with $\tau_\infty \leqslant \tau_e$ almost surely. Namely, we need to show that $\tau_\infty = \infty$ almost surely. If $\tau_\infty \neq \infty$, we assumed that there exists a pair of constants $T > 0$ and $\epsilon \in (0, 1)$ such that

$$P\{\tau_\infty \leqslant T\} > \epsilon. \tag{3.1}$$

As a result, there is an integer $k_1 \geqslant k_0$ such that

$$P\{\tau_k \leqslant T\} > \epsilon, \text{ for all } k \geqslant k_1.$$

Now, we define a C^5-function $V(C, u, p, b, A) \in \mathbb{R}^5_+$ as follows

$$\begin{aligned} V(C, u, p, b, A) =& m_1(A - 1 - \ln A) + C - 1 - \ln C + m_2 u - 1 - \ln u \\ &+ m_3 P - 1 - \ln P + m_4(b - 1 - \ln b), \end{aligned}$$

where $m_i (i = 1, 2, 3, 4)$ are positive constants to be determined below. Then, by using the Itô's formula, we have

$$\begin{aligned} \mathrm{d}V =& \mathrm{L}V\,\mathrm{d}t + m_1(A - 1)\xi_5\,\mathrm{d}B_5(t) + (C - 1)\xi_1\,\mathrm{d}B_1(t) \\ &+ (m_2 u - 1)\,\xi_2\,\mathrm{d}B_2(t) + (m_3 p - 1)\,\xi_3\,\mathrm{d}B_3(t) + m_4(b - 1)\xi_4\,\mathrm{d}B_4(t), \end{aligned}$$

where

$$\begin{aligned} \mathrm{L}V =& m_1\left(1 - \frac{1}{A}\right)(\alpha u^n - \eta A) + \frac{m_1\xi_5^2}{2} + \left(1 - \frac{1}{C}\right)(\lambda_1 + v_2 u + v_3 pC - k_1 C) + \frac{\xi_1^2}{2} \\ &+ \left(m_2 - \frac{1}{U}\right)\left(\lambda_2 - \tau up + \sigma b + v_1\frac{C}{k + C} - \alpha n u^n - \rho uA - k_2 u\right) + \frac{\xi_2^2}{2} \\ &+ \left(m_3 - \frac{1}{p}\right)(\lambda_3 - \tau up + \sigma b - k_3 p) + \frac{\xi_3^2}{2} + m_4\left(1 - \frac{1}{b}\right)(\tau up - \sigma b - k_4 b) + \frac{m_4\xi_4^2}{2} \\ =& m_1\alpha u^n - m_1\eta A + m_1\eta - \frac{m_1}{A}\alpha u^n + \frac{m_1\xi_5^2}{2} \\ &+ \lambda_1 + v_2 u + v_3 pC - k_1 C + k_1 - v_3 p - \frac{1}{C}(\lambda_1 + v_2 u) + \frac{\xi_1^2}{2} \\ &+ m_2\lambda_2 - m_2(\tau up - \sigma b) + m_2 v_1\frac{C}{k + C} - m_2\alpha n u^n - m_2\rho uA - m_2 k_2 u \\ &+ \tau p + \alpha n u^{n-1} + \rho A + k_2 - \frac{1}{u}\left(\lambda_2 + \sigma b + v_1\frac{C}{k + C}\right) + \frac{\xi_2^2}{2} \end{aligned}$$

$$
\begin{aligned}
&+ m_3\lambda_3 - m_3(\tau up - \sigma b) - m_3k_3p + \tau u + k_3 - \frac{1}{p}(\lambda_3 + \sigma b) + \frac{\xi_3^2}{2} \\
&+ m_4(\tau up - \sigma b) - m_4k_4b + m_4(\sigma + k_4) - \frac{m_4}{b}\cdot\tau up + \frac{m_4\xi_4^2}{2} \\
\leqslant &-(m_2n - m_1)\alpha u^n + \alpha n u^{n-1} + (v_2 - m_2k_2 + \tau)u - (m_1\eta - \rho)A \\
&+ (\tau - m_3k_3)p + m_1\eta + \frac{m_3\xi_5^2}{2} + \lambda_1 + k_1 + \frac{\xi_1^2}{2} + m_2\lambda_2 + m_2v_1 + k_2 + \frac{\xi_2^2}{2} \\
&+ m_3\lambda_3 + k_3 + \frac{\xi_3^2}{2} + m_4(\sigma + k_4) + \frac{m_4\xi_4^2}{2} + (m_4 - m_2 - m_3)(\tau up - \sigma b).
\end{aligned}
$$

Choosing

$$
m_1 = \frac{\rho}{\eta},\ \ m_2 = \max\left\{\frac{v_2 + \tau}{k_2} + 1, \frac{m_1}{n} + 1\right\},
$$
$$
m_3 = \frac{\tau}{k_3} + 1,\ \ m_4 = m_3 + m_2,
$$

such that

$$
v_2 - m_2k_2 + \tau < 0,\ \ m_2n - m_1 > 0,\ \ \tau - m_3k_3 < 0.
$$

And there exists a constant K such that $LV \leqslant K$, where K is define as follows

$$
\begin{aligned}
K := \max\Bigg\{&-(m_2n - m_1)\alpha u^n + \alpha n u^{n-1} + m_1\eta + \frac{m_3\xi_5^2}{2} + \lambda_1 + k_1 + \frac{\xi_1^2}{2} + m_2\lambda_2 \\
&+ m_2v_1 + k_2 + \frac{\xi_2^2}{2} + m_3\lambda_3 + k_3 + \frac{\xi_3^2}{2} + m_4(\sigma + k_4) + \frac{m_4\xi_4^2}{2}\Bigg\}.
\end{aligned}
$$

Integration of the above inequality from 0 to $\tau_k \wedge T$ and taking the expectation on both sides, we get the following inequality

$$
\begin{aligned}
&E\left(V\left(C\left(\tau_k \wedge T\right), u\left(\tau_k \wedge T\right), p\left(\tau_k \wedge T\right), b\left(\tau_k \wedge T\right), A\left(\tau_k \wedge T\right)\right)\right) \\
&\qquad \leqslant V\left(C(0), u(0), p(0), b(0), A(0)\right) + TK.
\end{aligned} \tag{3.2}
$$

Now, we set $\Omega_k = \{\tau_k \leqslant T\}$, $k \geqslant k_1$. It follows from the inequality (3.1) that $P(\Omega_k) \geqslant \varepsilon$. Note that for each $\omega \in \Omega_k$, $C(\tau_k, \omega)$, $u(\tau_k, \omega)$, $p(\tau_k, \omega)$, $b(\tau_k, \omega)$, $A(\tau_k, \omega)$ equals either k or $\frac{1}{k}$. Consequently,

$$
\begin{aligned}
&V\left(V\left(C\left(\tau_k \wedge T\right), u\left(\tau_k \wedge T\right), p\left(\tau_k \wedge T\right), b\left(\tau_k \wedge T\right), A\left(\tau_k \wedge T\right)\right)\right) \\
&\qquad \geqslant \min\left\{k - 1 - \ln k, \frac{1}{k} - 1 + \ln k\right\}.
\end{aligned} \tag{3.3}
$$

From (3.2) and (3.3) we get

$$
\begin{aligned}
&V\left(C(0), u(0), p(0), b(0), A(0)\right) + TK \\
&\qquad \geqslant E\left(1_{\Omega_k}(\omega)V\left(C\left(\tau_k, \omega\right), u\left(\tau_k, \omega\right), p\left(\tau_k, \omega\right), b\left(\tau_k, \omega\right), A\left(\tau_k, \omega\right)\right)\right) \\
&\qquad \geqslant \varepsilon \min\left\{k - 1 - \ln k, \frac{1}{k} - 1 + \ln k\right\},
\end{aligned}
$$

where 1_{Ω_k} is the indicator function of Ω_k. Letting $k \to \infty$ leads to

$$\infty > V\left(C(0), u(0), p(0), b(0), A(0)\right) + TK = \infty.$$

This is a contradiction. As a consequence, $\tau_\infty = \infty$ a.s. The proof is completed. □

Theorem 2. *For any initial value $X(0) = (C(0), u(0), p(0), b(0), A(0)) \in \mathbb{R}^5_+$, the solutions of the model (2.2) are stochastically ultimately bounded and permanent.*

Proof. For facilitate calculation, define $N = nA + mC + u + p + 2b$, choosing $\Lambda = \min\{\eta, k_1, k_2 - mv_2, k_3 + mv_3, k_4\}$, $0 < m < \min\left\{\frac{k_2}{v_2}, \frac{k_3}{v_3}\right\}$ and define

$$V = \frac{1}{N} + N.$$

By using the Itô's formula, we have

$$\begin{aligned}
\mathrm{L}V =& m\lambda_1 + \lambda_2 + \lambda_3 - \eta nA + mv_2u - mv_3p - mk_1C + \frac{v_1C}{k+C} - \rho uA - k_2u - k_3p \\
&- 2k_4b - \frac{1}{N^2}(m\lambda_1 + \lambda_2 + \lambda_3 - \eta nA + mv_2u - mv_3p - mk_1c + \frac{v_1C}{k+C} - \rho uA) \\
&+ \frac{1}{N^2}(-k_2u - k_3p + 2k_4b) + \frac{1}{N^3}(\xi_5^2n^2A^2 + \xi_1^2m^2C^2 + \xi_2^2u^2 + \xi_3^2p^2 + 4\xi_4^2b^2) \\
\leqslant& m\lambda_1 + \lambda_2 + \lambda_3 + v_1 - \eta nA - mk_1C - (k_2 - mv_2)u - (k_3 + mv_3)p - 2k_4b \\
&- \frac{1}{N^2}(m\lambda_1 + \lambda_2 + \lambda_3 + v_1) - \frac{1}{N^2}(-\eta nA - mk_1C - (k_2 - mv_3)u) \\
&+ \frac{1}{N^2}(-(k_3 - mv_3)p + 2k_4b) + \frac{1}{N^3}(\xi_5^2n^2A^2 + \xi_1^2m^2C^2 + \xi_2^2u^2 + \xi_3^2p^2 + 4\xi_4^2b^2) \\
\leqslant& m\lambda_1 + \lambda_2 + \lambda_3 + v_1 - \Lambda(nA + mC + u + p + 2b) - \frac{1}{N^2}(m\lambda_1 + \lambda_2 + \lambda_3 + v_1) \\
&+ \frac{1}{N^2}(-\eta nA - mk_1C - (k_2 - mv_3)u - (k_3 - mv_3)p - 2k_4b) \\
&+ \frac{1}{N}(\Lambda + \xi_5^2 + \xi_1^2 + \xi_2^2 + \xi_3^2 + \xi_4^2) \\
\leqslant& G - \Lambda V,
\end{aligned}$$

where

$$G = \frac{4(m\lambda_1 + \lambda_2 + \lambda_3 + v_1)^2 + (\Lambda + \xi_5^2 + \xi_1^2 + \xi_2^2 + \xi_3^2 + \xi_4^2)^2}{4(m\lambda_1 + \lambda_2 + \lambda_3 + v_1)}.$$

Then, by a similar proof of Theorem 4.3 in literature [32] we can get the $X(t)$ of model (2.2) is V-geometrically ergodic. And through a simple calculation we have

$$\begin{aligned}
E\left[e^{\Lambda t}V\right] &= E[V(0)] + E\left[\int_0^t e^{\Lambda s}\left(\Lambda V(s) + LV(s)\right)ds\right] \\
&\leqslant E[V(0)] + GE\left[\int_0^t e^{\Lambda s}ds\right] \\
&= E[V(0)] + \frac{G}{\Lambda}\left(e^{\Lambda t} - 1\right).
\end{aligned}$$

It follows that

$$E[V(t)] \leqslant e^{-\Lambda t}E[V(0)] + \frac{G}{\Lambda}\left(1 - e^{-\Lambda t}\right) \leqslant E[V(0)] + \frac{G}{\Lambda} := H.$$

Thus, $\limsup_{t\to\infty} \mathbb{E}[V(t)] \leqslant H$, we chose a constant χ which is sufficiently large, such that $\frac{H}{\chi} < 1$. By using Chebychev inequality in Lemma 1,

$$\mathbb{P}\{V(t) > \chi\} \leqslant \frac{1}{\chi}\mathbb{E}[V(t)] \leqslant \frac{H}{\chi} := \varepsilon.$$

Note that,

$$1 - \varepsilon \leqslant \mathbb{P}\{V(t) \leqslant \chi\} \leqslant \mathbb{P}\left\{\frac{1}{\chi} \leqslant N \leqslant \chi\right\}.$$

That means,

$$\mathbb{P}\{N > \chi\} + \mathbb{P}\left\{N < \frac{1}{\chi}\right\} < \varepsilon.$$

Thus,

$$\mathbb{P}\{|\, A(t), C(t), u(t), p(t), b(t) \,| > \chi\} \leqslant \mathbb{P}\{N > \chi\} < \varepsilon.$$

According to Definition 3 and Definition 6, model (2.2) is stochastically ultimately bounded and permanent. The proof is completed. □

4. The stationary distribution of Alzheimer's disease model

In this section, we will consider whether there is a unique stationary distribution of the model (2.2) that allows the disease to persist rather than die off.

Theorem 3. *If there exist constants c_i $(i = 1, 2, 3)$ such that inequality (4.1) holds then for any initial value*

$$X(0) = (C(0), u(0), p(0), b(0), A(0)) \in \mathbb{R}^5_+,$$

the model (2.2) admits a unique stationary distribution $\mu(\cdot)$ and it has the ergodic feature.

$$\begin{cases} c_1\eta n - \rho > 0, \\ c_2k_2 - v_2 - \tau > 0, \\ c_3k_3 - \tau > 0, \\ c_2 - c_1 > 0. \end{cases} \tag{4.1}$$

Proof. According to Lemma 5, the diffusion matrix of model (2.2) is given by

$$a(x) = \begin{bmatrix} \xi_1^2C^2 & 0 & 0 & 0 & 0 \\ 0 & \xi_2^2u^2 & 0 & 0 & 0 \\ 0 & 0 & \xi_3^2p^2 & 0 & 0 \\ 0 & 0 & 0 & \xi_4^2b^2 & 0 \\ 0 & 0 & 0 & 0 & \xi_5^2A^2 \end{bmatrix}.$$

Choose

$$G = \min_{(C,u,p,b,A)\in D_\delta\subset\mathbb{R}^4_+} \left\{\xi_1^2C^2, \xi_2^2u^2, \xi_3^2p^2, \xi_4^2b^2, \xi_1^2A^2\right\},$$

we can get that

$$\sum_{i,j=1}^{4} a_{ij}(C,u,p,b,A)\theta_i\theta_j = \xi_1^2C^2\theta_2^2 + \xi_2^2u^2\theta_2^2 + \xi_3^2p^2\theta_3^2 + \xi_4^2b^2\theta_4^2 + \xi_5^2A^2\theta_5^2 \geqslant G\|\theta\|^2,$$

for any $(C,u,p,b,A) \in D$, $\theta = (\theta_1,\theta_2,\theta_3,\theta_4,\theta_5) \in \mathrm{R}^5_+$. Then the condition (1) in Lemma 2 is satisfied.

To prove condition (2) of Lemma 2 is fulfilled, we need to develop a non-negative C^5-function V: $\mathrm{R}^5_+ \to \mathrm{R}$. To do this, we first define

$$V_1(C,u,p,b,A) = c_1nA + C + c_2u + c_3p + (c_2+c_3)b.$$

By using the Itô's formula in the proposed model (2.2), we obtain

$$\begin{aligned}
\mathrm{L}(-\ln C) &= -\frac{\lambda_1}{C} - \frac{v_2u}{C} - \frac{v_3P}{C} + k_1 + \frac{\xi_1^2}{2},\\
\mathrm{L}(-\ln u) &= -\frac{\lambda_2}{u} + k_2 + \tau p - \frac{\sigma b}{u} - v_1\frac{C}{(k+C)u} + \alpha n u^{n-1} + \rho A + \frac{\xi_2^2}{2},\\
\mathrm{L}(-\ln p) &= -\frac{\lambda_3}{p} + k_3 + \tau u - \frac{\sigma b}{p} + \frac{\xi_3^2}{2},\\
\mathrm{L}(-\ln b) &= -\frac{\tau up}{b} + \sigma + \delta + \frac{\xi_4^2}{2},\\
\mathrm{L}(-\ln nA) &= -\frac{\alpha u^n}{A} + \eta + \frac{n^2\xi_5^2}{2}.
\end{aligned}$$

Therefore, we have

$$\begin{aligned}
\mathrm{L}V_1 &= \mathrm{L}(c_1nA + C + c_2u + c_3p + (c_2+c_3)b)\\
&= c_1\alpha n u^n - c_1\eta nA + \lambda_1 + v_2u - v_3pC - k_1C + c_2\lambda_2 + c_2v_1\frac{C}{k+C}\\
&\quad - c_2\alpha n u^n - c_2\rho uA - c_2k_2u - c_3k_3p - (c_2+c_3)k_4b\\
&\leqslant -(c_2-c_1)\alpha n u^n - c_1\eta nA - k_1C - (c_2k_2 - v_2)u - c_3k_3p - (c_2+c_3)k_4b\\
&\quad + \lambda_1 + c_2\lambda_2 + c_2v_1.
\end{aligned}$$

Let

$$V_2(C,u,p,b,A) = V_1 - \ln nA - \ln C - \ln u - \ln p - \ln b.$$

In addition, we can obtain

$$\begin{aligned}
\mathrm{L}V_2 = \mathrm{L}V_1 &- \frac{\alpha u^n}{A} + \eta + \frac{n^2\xi_5^2}{2} - \frac{\lambda_1}{C} - \frac{v_2u}{C} - \frac{v_3P}{C} + k_1 + \frac{\xi_1^2}{2}\\
&- \frac{\lambda_2}{u} + k_2 + \tau p - \frac{\sigma b}{u} - v_1\frac{C}{(k+C)u} + \alpha n u^{n-1} + \rho A + \frac{\xi_2^2}{2}\\
&- \frac{\lambda_3}{p} + k_3 + \tau u - \frac{\sigma b}{p} + \frac{\xi_3^2}{2} - \frac{\tau up}{b} + \sigma + \delta + \frac{\xi_4^2}{2}
\end{aligned}$$

$$\begin{aligned}
&\leqslant -(c_1\eta n-\rho)A-k_1C-(c_2k_2-v_2-\tau)u-(c_3k_3-\tau)p-(c_2+c_3)k_4b\\
&-\frac{\alpha u^n}{A}-\frac{1}{C}(\lambda_1+v_2u+v_3P)-\frac{1}{u}(\lambda_2+\sigma b)-\frac{1}{p}(\lambda_3+\sigma b)-\frac{\tau up}{b}\\
&-(c_2-c_1)\alpha nu^n+\alpha nu^{n-1}+\lambda_1+c_2\lambda_2+c_2v_1+\eta+k_1+k_2+k_3+\sigma+\delta\\
&+\frac{n^2\xi_5^2}{2}+\frac{\xi_1^2}{2}+\frac{\xi_2^2}{2}+\frac{\xi_3^2}{2}+\frac{\xi_4^2}{2}.
\end{aligned}$$

For the sake of simplicity, we define

$$\begin{aligned}
F=\max\Big\{&-(c_2-c_1)\alpha nu^n+\alpha nu^{n-1}+\lambda_1+c_2\lambda_2+c_2v_1+\eta\\
&+k_1+k_2+k_3+\sigma+\delta+\frac{n^2\xi_5^2}{2}+\frac{\xi_1^2}{2}+\frac{\xi_2^2}{2}+\frac{\xi_3^2}{2}+\frac{\xi_4^2}{2}\Big\}.
\end{aligned}$$

Also,

$$M=\max\{F,\ v_2+v_3,\ \sigma\}.$$

Now we define a C^5-function $V(C,u,p,b,A)\in\mathbb{R}^5_+$ as follows

$$V(C,u,p,b,A)=V_2(C,u,p,b,A)-V_2(C_0,u_0,p_0,b_0,A_0).$$

Applying the Itô's formula and using the proposed model, we get

$$\begin{aligned}
\mathrm{L}V\leqslant&-(c_1\eta n-\rho)A-k_1C-(c_2k_2-v_2-\tau)u-(c_3k_3-\tau)p-(c_2+c_3)k_4b\\
&-\frac{\alpha u^n}{A}-\frac{1}{C}(\lambda_1+v_2u+v_3P)-\frac{1}{u}(\lambda_2+\sigma b)-\frac{1}{p}(\lambda_3+\sigma b)-\frac{\tau up}{b}+M.
\end{aligned}$$

The next step is to define the set

$$D=\left\{\varepsilon\leqslant C\leqslant\frac{1}{\varepsilon},\varepsilon\leqslant u\leqslant\frac{1}{\varepsilon},\varepsilon\leqslant p\leqslant\frac{1}{\varepsilon},\varepsilon^3\leqslant b\leqslant\frac{1}{\varepsilon^3},\varepsilon^{n+1}\leqslant A\leqslant\frac{1}{\varepsilon^{n+1}}\right\},$$

where $0<\epsilon<1$ is a constant that is sufficiently small and satisfies the following Eq (4.2)

$$\begin{aligned}
\varepsilon=\frac{1}{2}\min\Big\{&\frac{\alpha}{M},\frac{\lambda_1}{M-c_2-c_3},\frac{\lambda_2}{M-\sigma},\frac{\tau}{M},\frac{c_1\eta n-p}{M},\\
&\frac{k_1}{M},\frac{c_2k_2-v_2-\tau}{M},\frac{c_2k_3-\tau}{M},\frac{(c_2+c_3)\,k_4}{M}\Big\}.
\end{aligned}\tag{4.2}$$

We divide the domain $\mathbb{R}^5_+\backslash D$ into the ten regions is follows

$$D_1=\left\{(C,u,p,b,A)\in R^5_+,0<C<\varepsilon\right\},\ D_6=\left\{(C,u,p,b,A)\in R^5_+,C>\frac{1}{\varepsilon}\right\},$$

$$D_2=\left\{(C,u,p,b,A)\in R^5_+,0<u<\varepsilon\right\},\ D_7=\left\{(C,u,p,b,A)\in R^5_+,u>\frac{1}{\varepsilon}\right\},$$

$$D_3=\left\{(C,u,p,b,A)\in R^5_+,0<p<\varepsilon\right\},\ D_8=\left\{(C,u,p,b,A)\in R^5_+,p>\frac{1}{\varepsilon}\right\},$$

$$D_4 = \left\{(C,u,p,b,A) \in R_+^5, 0 < b < \varepsilon^3\right\},\ D_9 = \left\{(C,u,p,b,A) \in R_+^5, b > \frac{1}{\varepsilon^3}\right\},$$
$$D_5 = \left\{(C,u,p,b,A) \in R_+^5, 0 < A < \varepsilon^{n+1}\right\},\ D_{10} = \left\{(C,u,p,b,A) \in R_+^5, A > \frac{1}{\varepsilon^{n+1}}\right\}.$$

Obviously, $\Theta_\varepsilon^c = \mathbb{R}_+^5/\Theta^c = D_{i=1}^{10}\Theta_i$. In what follows, we will prove that

$$\mathrm{L}W(C,u,p,b,A) < 0, \text{ for any } (C,u,p,b,A) \in \mathbb{R}_+^5.$$

We divide the proof into ten cases.

Case 1: If $(C,u,p,b,A) \in D_1$, we can derive that

$$\begin{aligned}\mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2u + v_3P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau up}{b} + M \\ \leqslant & -\frac{1}{\varepsilon}(\lambda_1 + v_2\varepsilon + v_3\varepsilon) + M \leqslant -\frac{\lambda_1}{\varepsilon} + M - v_2 - v_3.\end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C,u,p,b,A) < 0, \text{ for any } (C,u,p,b,A) \in D_1.$$

Case 2: If $(C,u,p,b,A) \in D_2$, we can derive that

$$\begin{aligned}\mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2u + v_3P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau up}{b} + M \\ \leqslant & -\frac{1}{\varepsilon}(\lambda_2 + \sigma\varepsilon) + M \leqslant -\frac{\lambda_2}{\varepsilon} + M - \sigma.\end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C,u,p,b,A) < 0, \text{ for any } (C,u,p,b,A) \in D_2.$$

Case 3: If $(C,u,p,b,A) \in D_3$, we can derive that

$$\begin{aligned}\mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2u + v_3P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau up}{b} + M \\ \leqslant & -\frac{1}{\varepsilon}(\lambda_3 + \sigma\varepsilon) + M \leqslant -\frac{\lambda_3}{\varepsilon} + M - \sigma.\end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C,u,p,b,A) < 0, \text{ for any } (C,u,p,b,A) \in D_3.$$

Case 4: If $(C, u, p, b, A) \in D_4$, we can derive that

$$\begin{aligned} \mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1 C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4 b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2u + v_3P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau up}{b} + M \\ \leqslant & -\frac{\tau\varepsilon^2}{\varepsilon^3} + M \leqslant -\frac{\tau}{\varepsilon} + M. \end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in D_4.$$

Case 5: If $(C, u, p, b, A) \in D_5$, we can derive that

$$\begin{aligned} \mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1 C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4 b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2u + v_3P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau up}{b} + M \\ \leqslant & -\frac{\alpha\varepsilon^n}{\varepsilon^{n+1}} + M \leqslant -\frac{\alpha}{\varepsilon} + M. \end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in D_5.$$

Case 6: If $(C, u, p, b, A) \in D_6$, we can derive that

$$\begin{aligned} \mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1 C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4 b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2u + v_3P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau up}{b} + M \\ \leqslant & -\frac{k_1}{\varepsilon} + M. \end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in D_6.$$

Case 7: If $(C, u, p, b, A) \in D_7$, we can derive that

$$\begin{aligned} \mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1 C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4 b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2u + v_3P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau up}{b} + M \\ \leqslant & -\frac{1}{\varepsilon}(c_2k_2 - v_2 - \tau) + M. \end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in D_7.$$

Case 8: If $(C, u, p, b, A) \in D_8$, we can derive that

$$\begin{aligned} \mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1 C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4 b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2 u + v_3 P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau u p}{b} + M \\ \leqslant & -\frac{1}{\varepsilon}(c_3k_3 - \tau) + M. \end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in D_8.$$

Case 9: If $(C, u, p, b, A) \in D_9$, we can derive that

$$\begin{aligned} \mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1 C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4 b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2 u + v_3 P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau u p}{b} + M \\ \leqslant & -\frac{1}{\varepsilon}(c_2 + c_3)k_4 + M. \end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in D_9.$$

Case 10: If $(C, u, p, b, A) \in D_{10}$, we can derive that

$$\begin{aligned} \mathrm{L}W \leqslant & -(c_1\eta n - \rho)A - k_1 C - (c_2k_2 - v_2 - \tau)u - (c_3k_3 - \tau)p - (c_2 + c_3)k_4 b \\ & - \frac{\alpha u^n}{A} - \frac{1}{C}(\lambda_1 + v_2 u + v_3 P) - \frac{1}{u}(\lambda_2 + \sigma b) - \frac{1}{p}(\lambda_3 + \sigma b) - \frac{\tau u p}{b} + M \\ \leqslant & -\frac{c_1\eta n - \rho}{\varepsilon} + M. \end{aligned}$$

According to (4.2),

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in D_{10}.$$

Including the analysis from Cases 1 to 10, we can derive that

$$\mathrm{L}W(C, u, p, b, A) < 0, \text{ for any } (C, u, p, b, A) \in R_+^5.$$

Consequently, condition (2) in Lemma 2 is satisfied. This finishes the proof. □

5. Stochastic extinction dynamics

In this section we are going to discuss under what conditions the disease will be extinct, for convenient, we define $\langle X(t)\rangle = \frac{1}{t}\int_0^t x(r)dr$, and define another threshold parameter as follows:

$$R_1 = \frac{(\sigma + k_4)(\lambda_2 + v_1)}{k_4(\sigma + k_4 + \frac{\xi_4^2}{2})}, \quad R_2 = \frac{\lambda_2 + v_1}{\eta + \frac{\xi_5^2}{2}}.$$

Theorem 4. *If $R_1 < 1$ and $R_2 < 1$ hold, the $b(t)$ and $A(t)$ will die out with probability one, moreover*

$$\lim_{t\to\infty} A(t) = 0,$$
$$\lim_{t\to\infty} p(t) = \frac{\lambda_3}{k_3},$$
$$\lim_{t\to\infty} b(t) = 0, a.s.$$

Proof. By using the Itô's formula to the equation of model (2.2), we can get

$$\mathrm{d}\left(\frac{\sigma}{\sigma+k_4}b+u\right)=\left[\lambda_2-\frac{k_4}{\sigma+k_4}\tau up+v_1\frac{c}{k+c}-\alpha nu^n-\rho\mu A-k_2\mu\right]\mathrm{d}t + \xi_2 u\,\mathrm{d}B_2(t)+\frac{\sigma}{\sigma+k_4}\xi_4 b\,\mathrm{d}B_4(t).$$

Integration both sides of the equation above from 0 to t, we get

$$\begin{aligned}&\frac{\sigma}{\sigma+k_4}\frac{b(t)-b(0)}{t}+\frac{u(t)-u(0)}{t}\\ =&\lambda_2-\frac{k_4}{\sigma+k_4}\langle\tau up\rangle+v_1\langle\frac{c}{k+c}\rangle-\langle\alpha nu^n\rangle-\rho\langle uA\rangle\\ &-k_2\langle u\rangle+\frac{\xi_2}{t}\int_0^t u(s)\,\mathrm{d}B_2(s)+\frac{\sigma\xi_4}{(\sigma+k_4)\,t}\int_0^t b(s)\,\mathrm{d}B_4(s).\end{aligned}$$

By simple calculation, we can obtain

$$\langle\tau up\rangle=\frac{\sigma+k_4}{k_4}(\lambda_2+v_1\langle\frac{c}{k+c}\rangle)-\frac{\sigma+k_4}{k_4}\left(\langle\alpha nu^n\rangle+\rho\langle uA\rangle+k_2\langle u\rangle\right)+\phi_1(t),$$

where the value of $\phi_1(t)$ is defined via the subsequent equation

$$\phi_1(t)=\frac{\sigma_1 k_4}{k_4}\cdot\frac{\xi_2}{t}M_1(t)+\frac{\sigma\xi_4}{k_4 t}M_2(t)-\frac{\sigma}{k_4}\frac{b(t)-b(0)}{t}-\frac{\sigma+k_4}{k_4}\frac{u(t)-u(0)}{t}.$$

With the large number theorem as stated in Lemma 3 and local martingales, $\lim_{t\to\infty}\phi_1(t)=0$. Similarly, we also can get

$$\langle\alpha nu^n\rangle=\lambda_2+v_1\langle\frac{c}{k+c}\rangle-(\frac{k_4}{\sigma+k_4}\langle\tau up\rangle+\rho\langle uA\rangle+k_2\langle u\rangle)+\phi_2(t),$$

where $\phi_2(t)$ is defined by

$$\phi_2(t)=\frac{\xi_2}{t}M_1(t)+\frac{\sigma\xi_4}{(\sigma+k_4)\,t}M_2(t)-\frac{\sigma}{\sigma+k_4}\frac{b(t)-b(0)}{t}-\frac{u(t)-u(0)}{t}.$$

Similarly, $\lim_{t\to\infty}\phi_2(t)=0$.

Likewise, we integrate both sides of the last two equations of the proposed model (2.2), yielding these equations

$$\mathrm{d}(p+b)=\lambda_3-k_3p-k_4b+\xi_3p\,\mathrm{d}B_3(t)+\xi_3b\,\mathrm{d}B_4(t)$$

and

$$\frac{p(t)-p(0)}{t}+\frac{b(t)-b(0)}{t}=\lambda_3-k_3\langle p\rangle-k_4\langle b\rangle+\frac{\xi_3}{t}\int_0^t p(s)\,\mathrm{d}B_3(t)+\frac{\xi_4}{t}\int_0^t b(s)\,\mathrm{d}B_4(t).$$

With a simple calculation, we can get

$$\langle p\rangle = \frac{\lambda_3}{k_3} - \frac{k_4}{k_3}\langle b\rangle + \phi_3(t),$$

where

$$\phi_3(t) = \frac{1}{k_3}\left[-\frac{p(t)-p(0)}{t} - \frac{b(t)-b(0)}{t} + \frac{\xi_3}{t}\int_0^t p(s)\,\mathrm{d}B_3(s) + \frac{\xi_4}{t}\int_0^t b(s)\,\mathrm{d}B_4(s)\right].$$

Clearly, $\lim\limits_{t\to\infty}\phi_3(t) = 0$.

By using the Itô's formula on the fourth equation of model (2.2), we have

$$\begin{aligned}
\mathrm{d}\ln b(t) =& \langle\frac{\tau up}{b}\rangle - (\sigma + k_4) - \frac{\xi_4^2}{2} + \frac{\xi_4}{t}\int_0^t B_4(t)\\
\leqslant& \frac{\sigma+k_4}{k_4}\left(\lambda_2 + v_1\langle\frac{c}{k+c}\rangle\right) - \frac{\sigma+k_4}{k_4}\left(\langle\alpha n u^n\rangle + \rho\langle uA\rangle + k_2\langle u\rangle\right) + \phi_1(t)\\
&- (\sigma + k_4) - \frac{\xi_4^2}{2} + \frac{\xi_4}{t}\int_0^t B_4(t)\\
\leqslant& \frac{(\sigma+k_4)(\lambda_2+v_1)}{k4} + \phi_1(t) - \left(\sigma + k_4 + \frac{\xi_4^2}{2}\right) + \frac{\xi_4}{t}\int_0^t B_4(t)\\
=& \left(\sigma + k_4 + \frac{\xi_4^2}{2}\right)(R_1 - 1) + \phi_1(t) + \frac{\xi_4}{t}\int_0^t B_4(t).
\end{aligned}$$

Obviously,

$$\limsup_{t\to\infty}\frac{\xi_4}{t}\int_0^t B_4(t) = 0, a.s.$$

Therefore when $R_1 < 1$, we obtain

$$\limsup_{t\to\infty}\frac{\ln b(t)}{t} \leqslant \left(\sigma + k_4 + \frac{\xi_4^2}{2}\right)(R_1 - 1) < 0.$$

That implies that,

$$\lim_{t\to\infty} b(t) = 0, a.s.$$

In the same way, by applying the Itô's formula to the last equation of model (2.2), we can obtain,

$$\begin{aligned}
\mathrm{d}\ln nA =& \langle\frac{\alpha n u^n}{nA}\rangle - \eta - \frac{\xi_5^2}{2} + \frac{\xi_5}{t}\int_0^t B_5(t)\\
\leqslant& \langle\alpha n u^n\rangle - \eta - \frac{\xi_5^2}{2} + \frac{\xi_5}{t}\int_0^t B_5(t)\\
=& \lambda_2 + v_1\langle\frac{c}{k+c}\rangle - \left(\frac{k_4}{\sigma+k_4}\langle\tau up\rangle + \rho\langle uA\rangle + k_2\langle u\rangle\right) + \phi_2(t)\\
&- \eta - \frac{\xi_5^2}{2} + \frac{\xi_5}{t}\int_0^t B_5(t)\\
\leqslant& \lambda_2 + v_1 - \left(\eta + \frac{\xi_5^2}{2}\right) + \phi_2(t) + \frac{\xi_5}{t}\int_0^t B_5(t)
\end{aligned}$$

$$= \left(\eta + \frac{\xi_5^2}{2}\right)(R_2 - 1) + \phi_2(t) + \frac{\xi_5}{t}\int_0^t B_5(t).$$

Obviously,

$$\limsup_{t\to\infty} \frac{\xi_5}{t}\int_0^t B_5(t) = 0, a.s.$$

Therefore when $R_2 < 1$, we obtain

$$\limsup_{t\to\infty} \frac{\ln nA(t)}{t} \leqslant \left(\eta + \frac{\xi_5^2}{2}\right)(R_2 - 1) < 0.$$

It implies that,

$$\lim_{t\to\infty} nA(t) = 0, a.s.$$

That is to say

$$\lim_{t\to\infty} A(t) = 0, a.s.$$

With $\langle p\rangle = \dfrac{\lambda_3}{k_3} - \dfrac{k_4}{k_3}\langle b\rangle + \phi_3(t)$ above, we can get that

$$\lim_{t\to\infty} p(t) = \frac{\lambda_3}{k_3}, a.s.$$

This completes the proof. □

Remark 1. *Theorem 4 reveals that the extinction or not of the disease depends on the sign of R_1 and R_2. With $R_i < 1(i = 1, 2)$, both the Aβ oligomers and Aβ-x-PrP^C complex incline to go extinct. That is, stochastic perturbations of the environment are beneficial to the extinction of both materials. This means that in real life, it is useful to pay attention to the physical condition of the patient and improve the internal environment of the body [33]. A more interesting result is that such random perturbations may lead to disease extinction. This provides a theoretical basis for disease cure.*

6. Numerical simulations

To illustrate the theoretical results obtained, we give some examples in this section. Using the Milstein's higher order method developed in [34], we present our results. Let us consider the corresponding discretizing equations,

$$\begin{cases} C_{i+1} = C_i + (\lambda_1 + v_2 u_i - v_3 p_i C_i - k_1 C_i)\,\Delta t + \xi_1 \varpi_{1,i} C_i \sqrt{\Delta t} + \frac{1}{2}\xi_1^2 C_i \left(\varpi_{1,i}^2 - 1\right)\Delta t, \\ u_{i+1} = u_i + (\lambda_2 - \tau u_i p_i + \sigma b_i + v_1 \frac{C_i}{k + C_i} - \alpha n u_i^n - \rho u_i A_i - k_2 u_i)\Delta t + \xi_2 \varpi_{2,i} u_i \sqrt{\Delta t} \\ \qquad + \frac{1}{2}\xi_2^2 u_i \left(\varpi_{2,i}^2 - 1\right)\Delta t, \\ p_{i+1} = p_i + (\lambda_3 - \tau u_i p_i + \sigma b_i - k_3 p_i)\,\Delta t + \xi_3 \varpi_{3,i} p_i \sqrt{\Delta t} + \frac{1}{2}\xi_3^2 p_i \left(\varpi_{3,i}^2 - 1\right)\Delta t, \\ b_{i+1} = b_i + (\tau u_i p_i - \sigma b_i - k_4 b_i)\,\Delta t + \xi_4 \varpi_{4,i} b_i \sqrt{\Delta t} + \frac{1}{2}\xi_4^2 b_i \left(\varpi_{4,i}^2 - 1\right)\Delta t, \\ A_{i+1} = A_i + (\alpha u_i^n - \eta A_i)\,\Delta t + \xi_5 \varpi_{5,i} A_i \sqrt{\Delta t} + \frac{1}{2}\xi_5^2 A_i \left(\varpi_{5,i}^2 - 1\right)\Delta t. \end{cases}$$

Where $\varpi_{j,i}$ $j = 1, 2, 3, 4, 5$ are the realization of five independent Gaussian random variables with distribution $N(0, 1)$ and time step $\Delta t = 0.01$. Using MATLAB, numerical simulations were performed on the proposed stochastic Alzheimer's disease model (2.2) and an approximate solution of the model is obtained. In addition, it is shown that noise intensity has a significant influence. By assuming numerical values of the parameters related to their biological feasibility, we verified the extinction of the disease and the existence of a stationary distribution.

First, we choose $\lambda_1 = 0.2$, $v_1 = 1$, $v_2 = 0.6$, $v_3 = 0.4$, $k_1 = 7$, $\xi_1 = 0.1$, $k = 0.3$, $k_2 = 0.35$, $\rho = 0.5$, $\xi_2 = 0.25$, $\lambda_3 = 0.5$, $k_3 = 0.2$, $\xi_3 = 0.2$, $\tau = 0.85$, $\sigma = 0.6$, $\eta = 0.8$, $\alpha = 0.3$, $n = 3$, $\xi_5 = 0.5$, $\xi_4 = 0.1$. Furthermore, we consider the initial size of population density as $X(0) = (C(0), u(0), p(0), b(0), A(0)) = (0.2, 0.5, 0.5, 1.2, 1)$. These assumptions satisfy the Theorem 3, which implies that model (2.2) has a unique stationary distribution as shown in Figure 1 and means the disease will be persistent.

Next, based on the previous assumptions, we change λ_1, v_1, ξ_1, k_2, ξ_2, λ_3, ξ_3, η, ξ_4, ξ_5 to be $\lambda_1 = 0.02$, $v_1 = 0.08$, $\xi_1 = 2.8$, $k_2 = 3$, $\xi_2 = 4$, $\lambda_3 = 0.85$, $\xi_3 = 5$, $\eta = 0.12$, $\xi_4 = 0.6$ and $\xi_5 = 1.6$. We can easily calculate the basic reproduction number $R_1 = 0.8556 < 1$ and $R_2 = 0.2357 < 1$. And according to Theorem 4 the solution of model (2.2) must obey

$$\limsup_{t\to\infty} \frac{\ln b(t)}{t} \leqslant \left(\sigma + k_4 + \frac{\xi_4^2}{2}\right)(R_1 - 1) < 0$$

and

$$\limsup_{t\to\infty} \frac{\ln nA(t)}{t} \leqslant \left(\eta + \frac{\xi_5^2}{2}\right)(R_2 - 1) < 0.$$

This means that the disease will die out in this case and the numerical simulation of Figure 2 confirms our theoretical results. Figure 2 shows that the stochastic equation (2.2) and the deterministic equation have differences in their behavior. By this, we can point out that the disease tends towards the extinction with environmental noise. The numerical simulation shows that the surrounding noise have a very large effect on the mentioned disease. That is, the environmental interference will cause the $A\beta$ plaque and $A\beta-\mathrm{x}-PrP^C$ complex to disappear.

Finally, to simulate the effect of different intensities of environmental interference, we fix the parameters above except ξ_4 and ξ_5. We change the values of ξ_4 and ξ_5 in Figure 3. As the intensity of white noise increases, $A\beta$ plaques and $A\beta$-x-PrP^C complex will accelerate extinction.

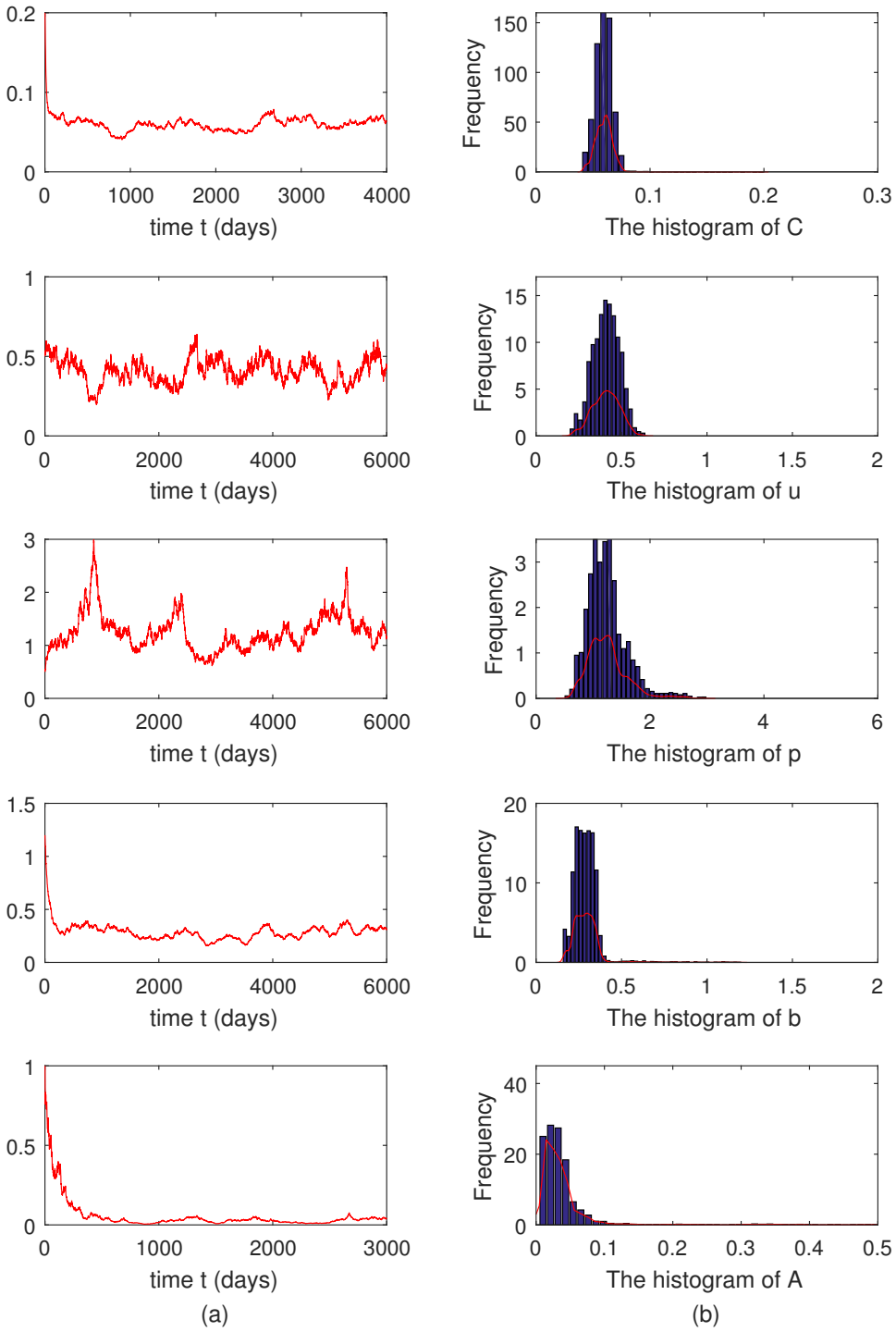

Figure 1. The stationary distribution of the Alzheimer's disease, five small images of (a) show the changes of C, u, p, b and A number over a period of time. (b) are the number histogram of C, u, p, b and A, respectively.

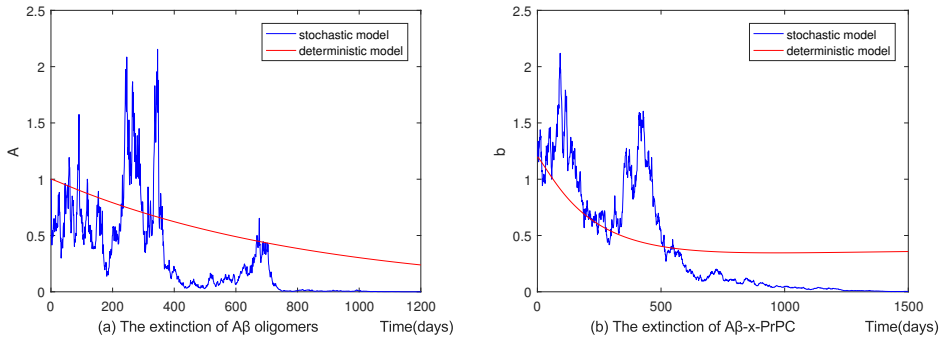

Figure 2. The extinction of $A\beta$ plaques and $A\beta$-x-PrP^C complex on the stochastic model (2.2) along with its corresponding deterministic model ($\xi_i = 0,\ i = 1, 2, ..., 5$).

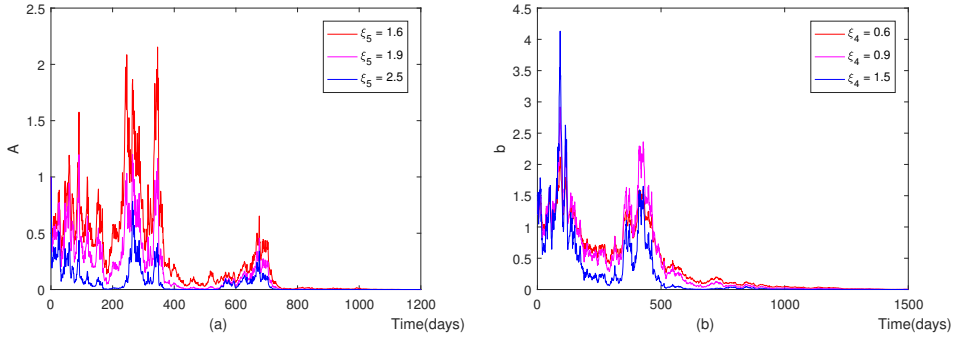

Figure 3. The effects of the environmental random disturbance on $A\beta$ plaques and $A\beta$-x-PrP^C complex.

7. Conclusions

During neural signaling, the concentration of $A\beta$ is influenced by a number of stochastic factors. For example, calcium ions can regulate of $A\beta$ levels in the interstitial fluid (ISF) by affecting the permeability of the cell membrane. We established a random Alzheimer's disease model containing Ca^{2+} and investigated the transmission dynamics with changing biological environment. Using the stochastic Lyapunov functions theory, the existence and positivity were proved. The extinction and the stationary distribution were also discussed, the related conditions implied that the random parameters such as the random of Ca^{2+} concentration will lead to disease's extinction. In contrast to the optimal control conditions proposed by Hu et al. [14], this paper directly derives more explicit and simple conditions for the extinction of $A\beta$ plaques and $A\beta-\text{x}-PrP^C$ complex, which will form the basis in formulating novel therapeutic solutions for control strategies regarding AD pathology. In the future, the model can be further extended by adding drugs. One can also talk about the drug-target kinetics of the model by adding drugs and the influence of toxicological effects of drugs on therapeutic efficacy.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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Conflict of interest

The authors declare that they have no conflicts of interest related to this article.

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