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Stability Analysis of the ODE Model Representation of Amyloidogenic Processing in Alzheimer's Disease in the Presence of SORLA

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Abstract: Central to the pathology of Alzheimer's Disease (AD) is the proteolytic processing of amyloid precursor protein (APP) into amyloid plaques. SORLA (sorting protein-related receptor with A-type repeats) has a major influence in such process as it alters the form of the substrate APP that is preferred by the enzymes α- and β-secretases, therefore inhibiting the amyloidogenic processing. This paper analyzed the behaviour of the solutions of the autonomous system of ordinary differential equations (ODE) that models the biochemical system by performing a stability analysis of the system. The mathematical model consists of 20 ordinary differential equations, which made it difficult to analyze the solution of the system. The order of the system was reduced to 9 by considering only the coupled equations in the system and by imposing initial conditions on the system, which was done to facilitate better the analysis of the solutions. The equilibrium point of the reduced system was found to be hyperbolic. In turn, the Hartman-Grobman Theorem allows us to infer the local behaviour of the system around the steady-state solution from the local behaviour of the corresponding linearized system around the origin. Consequently, the nature of the real parts of the eigenvalues of the real matrix A representing the linearized system is the key to establish stability. The Routh-Hurwitz criterion was used to determine the nature of the eigenvalues of A. In the presence of SORLA, the steady-state solution of the reduced system is asymptotically stable. It was also found that the stability is local. Immediate consequence of the stability analysis of the reduced system to the solutions of the original system was also obtained.

Key Words: Alzheimer's disease; SORLA; stability analysis; Routh-Hurwitz criterion; Hartman-Grobman Theorem

1. INTRODUCTION

1.1 Background of the Study

Alzheimer's disease (AD) is an ultimately fatal disorder wherein neurons die or no longer function normally, which leads to impairment of bodily functions such as walking and swallowing (Alzheimer's Association, 2003), and loss of memory, among others. This disease affects not only the person afflicted with it, but also the lives of people close to him or her.

The exact origin of the disease is not yet fully understood, and the increasing incidence of the disease among the human population makes it imperative to continue and intensify efforts to better understand the nature of AD and hopefully find a

cure. A popular hypothesis among medical researchers is known as the *amyloid hypothesis*. According to the Alzheimer's Association (2013), there are two main changes in the brain tissues of a person with AD – the presence of amyloid plaques (also called Aβ plaques) and the presence of twisted strands of the protein tau (tangles). Among the proponents of the amyloid hypothesis, it is believed that the presence of amyloid plaques is a main contributor to AD (Hardy & Selkoe, 2002). The amyloidogenic process involves the proteolytic processing of amyloid precursor protein (APP) into the neurotoxins Aβ plaques. Thus, the amyloid hypothesis suggests that the extent of APP processing into amyloid plaques is central in the development of AD.

At present, efforts to prevent, interrupt, and cure AD are on the way, but drug trials are expensive and take a considerable amount of time since AD progresses very gradually and drug effectiveness can only be evaluated after a long period (Lao, 2012). Hence, one of the alternative measures towards understanding the disease is to mathematically represent the biochemical system involved in the amyloidogenic process. Modelling the system can provide researchers with a means to better understand various aspects of the process, as well as the cross-checking of experimental data.

One such model using a system of ordinary differential equations was formulated by Lao (2013). It represents the amyloidogenic processing in AD under the influence of sorting protein-related receptor with A-type repeats (also known as SORLA). This is the quantitative model presented in Schmidt, Baum, Lao, Rateitschak, Schmitz, Teichmann, Wiesner, Petersen, Nykjaer, Wolf, Wolkenhauer, and Willnow (2012). SORLA is believed to inhibit the processing of APP. Hence, its presence in the system may have a key role in the development and progress of AD.

In an effort to supplement the model presented in Schmidt et. al. (2012), the present study intends to conduct a stability analysis of the model. It is hoped that the results of the study can contribute to a better understanding of the biochemical processes that govern the development and progression of Alzheimer's disease.

1.2 The Biochemical Network and the Mathematical Model

In this section, we take a closer look at the biochemical model of amyloidogenic processing presented in Schmidt et. al. (2012). The biochemical network of the reactions involved in APP processing with the influence of SORLA is summarized in the figure below:

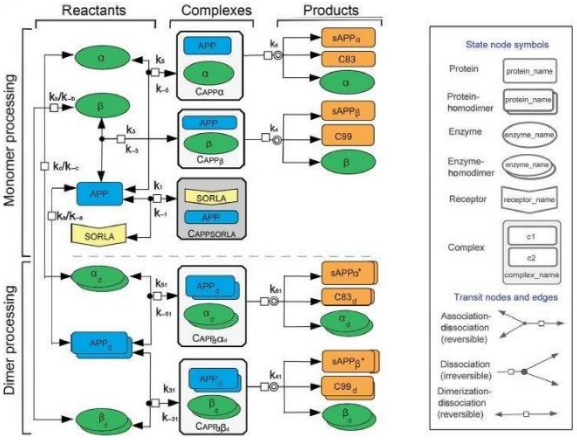

Fig. 1. Biochemical network of the interaction of the reactants APP (blue symbols) with α- and β-secretases (green symbols) and the formation of amyloidogenic and non-amyloidogenic products (orange symbols)

The k's appearing in the network are parameters associated with rates of reaction. Note that the chemical reactions in the system are evident from Figure 1. For instance, one such reaction is

$$\alpha + APP \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} C_{APP_\alpha}.$$

There are 8 reversible and 4 irreversible reactions shown in Figure 1. From these chemical reactions, the ordinary differential equations representing the mathematical model can be obtained by using the Law of Mass Action (Murray, 2001). We define first the key variables in the mathematical model in Table 1.

Table 1. Variables in the Mathematical Model

Notation	Concentration in fmol of	Notation	Concentration in fmol of
E_1	α-secretase	C_4	$C_{APP_d\beta_d}$

E_2	β-secretase	C_5	$C_{APPSORLA}$
E_3	α_d-secretase	P_1	$sAPP\alpha$
Notation	Concentration in fmol of	Notation	Concentration in fmol of
E_4	β_d-secretase	P_2	$sAPP\beta$
S_1	APP	P_3	$sAPP\alpha_d$
S_2	APP_d	P_4	$sAPP\beta_d$
X	$SORLA$	P_5	$C83$
C_1	$C_{APP\alpha}$	P_6	$C99$
C_2	$C_{APP\beta}$	P_7	$C83_d$
C_3	$C_{APP\alpha_d}$	P_8	$C99_d$

Denoting by $\dot{f}$ the derivative of f with respect to time t and applying the Law of Mass Action, we get the following system, which we will refer to as system (1).

$$\begin{aligned}
\dot{X} &= -k_1S_1X + k_{-1}C_5\\
\dot{S}_1 &= -k_1S_1X + k_{-1}C_5 - k_3S_1E_2 + k_{-3}C_2\\
&\quad -k_5S_1E_1 + k_{-5}C_1 + 2(k_{-1}S_2 - k_aS_1^2)\\
\dot{S}_2 &= -k_{31}S_2E_4 + k_{-31}C_4 - k_{51}S_2E_3\\
&\quad +k_{-51}C_3 - k_{-a}S_2 + k_aS_1^2\\
\dot{E}_1 &= -k_5S_1E_1 + (k_{-5} + k_6)C_1 + 2(k_{-c}E_3\\
&\quad - k_cE_1^2)\\
\dot{E}_2 &= -k_3S_1E_2 + (k_{-3} + k_4)C_2 + 2(k_{-b}E_4\\
&\quad - k_bE_2^2)\\
\dot{E}_3 &= -k_{51}S_2E_3 + (k_{-51} + k_{61})C_3 + k_cE_1^2\\
&\quad - k_{-c}E_3\\
\dot{E}_4 &= -k_{31}S_2E_4 + (k_{-41} + k_{41})C_4 + k_bE_2^2\\
&\quad - k_{-b}E_4\\
\dot{C}_1 &= k_5S_1E_1 - (k_{-5} + k_6)C_1\\
\dot{C}_2 &= k_3S_1E_2 - (k_{-3} + k_4)C_2\\
\dot{C}_3 &= k_{51}S_2E_3 - (k_{-51} + k_{61})C_3\\
\dot{C}_4 &= k_{31}S_2E_4 - (k_{-41} + k_{41})C_4\\
\dot{C}_5 &= -\dot{X}\\
\dot{P}_1 &= \dot{P}_5 = k_6C_1\\
\dot{P}_2 &= \dot{P}_6 = k_4C_2\\
\dot{P}_3 &= \dot{P}_7 = 2k_{61}C_3\\
\dot{P}_4 &= \dot{P}_4 = 2k_{41}C_4
\end{aligned}$$

2. METHODOLOGY

In this study, we will analyze the solutions of system (1), by performing a stability analysis of the model. However, the system consists of 20 differential equations which makes it difficult to accomplish this goal. Hence, we will reduce the order of the system. This will be done by (i) initially considering only the coupled equations in the system; that is, disregarding the uncoupled equations $\dot{P}_i$(i = 1, … , 8), since their solutions can be obtained by simple integration; and by (ii) imposing the initial conditions $X(0) = x_0 > 0$, $E_1(0) = \alpha > 0$, $E_2(0) = \beta > 0$, $E_3(0) = E_4(0) = 0$, and $C_i(0) = 0$, which enables us to solve for the particular solutions of the other variables. Through this strategy, the number of equations in the system can be reduced to 9. Meanwhile, x_0, α, and β become additional parameters to the model as a result of the reduction of the size of the system.

We will find the equilibrium points of the system obtained after reducing the number of equations. Only the equilibrium points with biological importance will be considered. The main problem that will be solved in this paper is determining the stability of the equilibrium points that were computed. To this end, linearization technique and Hartman-Grobman Theorem will be used. Through these, the stability problem can be solved by simply looking at the roots of the characteristic polynomial of the matrix representing the linearized system. In particular, the nature of the real parts of these roots will be evaluated. The Routh-Hurwitz criterion will be used towards this end so that there is no need to compute the roots; the nature of the real parts of the roots can be determined by looking at the coefficients of the polynomials and evaluating if these coefficients satisfy the criterion given by the Routh-Hurwitz test. Finally, if the equilibrium points enumerated in this study were found to be stable, we will determine whether the stability is local or global.

3. RESULTS AND DISCUSSION

3.1 Simplification of the Model

By using the initial conditions stated in the methodology, the system is reduced to

$$
\begin{aligned}
\dot{S}_1 &= -k_1 S_1(x_0 - C_5) + k_{-1}C_5 - k_3 S_1[\beta \\
&\quad -(C_2 + 2E_4 + 2C_4)] + k_{-3}C_2 - k_5 S_1[\alpha \\
&\quad -(C_1 + 2E_3 + 2C_3)] + k_{-5}C_1 \\
&\quad + 2(k_{-1}S_2 - k_a S_1^2) \\
\dot{S}_2 &= -k_{31}S_2E_4 + k_{-31}C_4 - k_{51}S_2E_3 \\
&\quad +k_{-51}C_3 - k_{-a}S_2 + k_a S_1^2 \\
\dot{E}_3 &= -k_{51}S_2E_3 + (k_{-51} + k_{61})C_3 \\
&\quad +k_c[\alpha - (C_1 + 2E_3 + 2C_3)]^2 - k_{-c}E_3 \\
\dot{E}_4 &= -k_{31}S_2E_4 + (k_{-41} + k_{41})C_4 \\
&\quad +k_b[\beta - (C_2 + 2E_4 + 2C_4)]^2 - k_{-b}E_4 \\
\dot{C}_1 &= k_5[\alpha - (C_1 + 2E_3 + 2C_3)]E_1 \\
&\quad - (k_{-5} + k_6)C_1 \\
\dot{C}_2 &= k_3 S_1[\beta - (C_2 + 2E_4 + 2C_4)] \\
&\quad - (k_{-3} + k_4)C_2 \\
\dot{C}_3 &= k_{51}S_2E_3 - (k_{-51} + k_{61})C_3 \\
\dot{C}_4 &= k_{31}S_2E_4 - (k_{-41} + k_{41})C_4 \\
\dot{C}_5 &= k_1 S_1(x_0 - C_5) - k_{-1}C_5
\end{aligned}
$$

which we will refer to as system (2). Note that the reduction of order gives rise to additional parameters x_0, α, and β, which from a biological perspective represent the total concentration of SORLA, α-secretase, and β- secretase, respectively, that are initially present in the system.

3.2 The Steady-state Solution and its Stability

In any dynamical system $\dot{x} = f(x)$ where $x \in \mathbb{R}^n$, a point $\xi \in \mathbb{R}^n$ is called *equilibrium point* if $f(\xi) = 0$. For system (2), the only biochemically meaningful equilibrium point is the point

$$\xi = (0,0,e_3,e_4,0,0,0,0,0)$$

where

$$
\begin{aligned}
e_3 &= (4K_c\alpha + 1 - \sqrt{8K_c\alpha + 1})/8K_c, \\
e_4 &= (4K_b\beta + 1 - \sqrt{8K_b\beta + 1})/8K_b,
\end{aligned}
$$

$K_c = k_c/k_{-c}$, and $K_b = k_b/k_{-b}$

under the assumption that $\alpha, \beta > 0$ and using the fact that the solutions of (2) are nonnegative for all time t whenever nonnegative initial conditions are imposed (Chellaboina, Bhat, Haddad, & Bernstein, 2009).

When studying stability, we are concerned with the behaviour of the *solutions* around an equilibrium point. A *solution* of the system $\dot{x} = f(x)$ through the point $y_o \in \mathbb{R}^n$ is a function $\phi_t(y_0)$ such that $\dot{\phi}_t(y_0) = f(\phi_t(y_0))$ and $\phi_0(y_0) = y_0$. When ξ is an equilibrium point, $\phi_t(\xi) = \xi$ for all time t is a solution, which is called a *steady-state solution.* By the Fundamental Existence-Uniqueness Theorem, system (2) has a unique solution through any point $y_0 \in \mathbb{R}^n$ since it is a polynomial system.

Let $\phi_t(y_0)$ denote the solution of system (2) through y_0 and let ξ be an equilibrium point. ξ is *stable* if for any choice of $\varepsilon > 0$, there exists some $\delta > 0$ such that for any y_0 with $|y_0 - \xi| < \delta$ and $t \geq 0$, $|\phi_t(y_0) - \xi| < \varepsilon$. If this condition is not satisfied, then it is *unstable*. If it is stable and if there exists some $\gamma > 0$ such that $\lim_{t\to\infty} \phi_t(y_0) = \xi$ for all points y_0 with $|y_0 - \xi| < \gamma$, then it is *asymptotically stable* (Perko, 2001). In other words, an equilibrium point ξ is stable if solutions starting near ξ stay near ξ for all time $t \geq 0$. It is asymptotically stable if solutions not only stay near ξ but also converges to ξ as $t \to \infty$ (Wiggins, 2003). Using only this definition, it is difficult to determine the stability. In the proof of the main result in this paper, the Hartman-Grobman Theorem and linearization were the main tools in establishing stability. Through these, it suffices to show that the real parts of the eigenvalues of the Jacobian matrix $A = Df(\xi)$, where

$f(S_1, S_2, E_3, E_4, C_1, \dots, C_5) = (\dot{S}_1, \dot{S}_2, \dot{E}_3, \dot{E}_4, \dot{C}_1, \dots, \dot{C}_5)$

are all negative, which is what will be shown in the proof of the following theorem.

Theorem: *When SORLA is present in the system, that is, when $x_0 > 0$, the equilibrium point*

$$\xi = (0,0,e_3,e_4,0,0,0,0,0)$$

is an asymptotically stable equilibrium point of system (2). The stability of ξ is not global.

Proof: The Jacobian of

$f(S_1, S_2, E_3, E_4, C_1, \dots, C_5) = (\dot{S}_1, \dot{S}_2, \dot{E}_3, \dot{E}_4, \dot{C}_1, \dots, \dot{C}_5)$

at the point ξ is

$$A = \begin{pmatrix} A_1 & A_2 & A_3 \\ A_4 & A_5 & A_6 \\ A_7 & A_8 & A_9 \end{pmatrix}$$

where

$$A_1 = \begin{pmatrix} a_{11} & 2k_{-a} & 0 \\ 0 & a_{22} & 0 \\ 0 & -k_{51}e_3 & a_{33} \end{pmatrix}, \quad A_2 = \begin{pmatrix} 0 & k_{-5} & k_{-3} \\ 0 & 0 & 0 \\ 0 & 2ak_c & 0 \end{pmatrix},$$

$$A_3 = \begin{pmatrix} 0 & 0 & k_{-1} \\ k_{-51} & k_{-31} & 0 \\ a_{37} & 0 & 0 \end{pmatrix}, \quad A_4 = \begin{pmatrix} 0 & -k_{31}e_4 & 0 \\ -k_5 a & 0 & 0 \\ -k_3 b & 0 & 0 \end{pmatrix},$$

$$A_5 = \begin{pmatrix} a_{44} & 0 & 2bk_b \\ 0 & K_1 & 0 \\ 0 & 0 & K_2 \end{pmatrix}, \quad A_6 = \begin{pmatrix} 0 & a_{48} & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$A_7 = \begin{pmatrix} 0 & k_{51}e_3 & 0 \\ 0 & k_{31}e_4 & 0 \\ k_1 x_0 & 0 & 0 \end{pmatrix}, \quad A_8 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$A_9 = \begin{pmatrix} K_3 & 0 & 0 \\ 0 & K_4 & 0 \\ 0 & 0 & -k_{-1} \end{pmatrix}, \quad \text{and}$$

$a = 2e_3 - \alpha$, $b = 2e_4 - \beta$,
$a_{44} = 4bk_b - k_{-b}$,
$a_{11} = ak_5 + bk_3 - k_1 x_0$,
$a_{22} = -(k_{-a} + k_{51}e_3 + k_{31}e_3 + k_{31}e_4)$,
$a_{33} = 4ak_c - k_{-c}$,
$a_{37} = k_{61} + k_{-51} + k_c(8e_3 - 4\alpha)$, and
$a_{48} = k_{41} + k_{-31} + k_b(8e_4 - 4\beta)$,

$K_1 = -(k_6 + k_{-5})$,
$K_2 = -(k_4 + k_{-3})$,
$K_3 = -(k_{61} + k_{-51})$,
$K_4 = -(k_{41} + k_{-31})$,

The characteristic polynomial $P(\lambda) = \det(A - \lambda I_9)$ of A is

$$P(\lambda) = -(\lambda - a_{33})(\lambda - a_{44})P_1(\lambda)P_2(\lambda)$$

where

$$\begin{aligned} P_1(\lambda) = \lambda^3 &+ (-a_{22} - K_3 - K_4)\lambda^2 \\ &+ (a_{22}K_3 + a_{22}K_4 + K_3K_4 - k_{31}k_{-31}e_4 \\ &- k_{51}k_{-51})\lambda - a_{22}K_3K_4 + k_{31}k_{-31}e_4K_3 \\ &+ k_{51}k_{-51}e_3K_4 \end{aligned}$$

and

$$\begin{aligned} P_2(\lambda) = \lambda^4 &+ (k_{-1} - K_1 - K_2 - a_{11})\lambda^3 \\ &+ (a_{11}K_1 + a_{11}K_2 - k_{-1}K_1 - k_{-1}K_2 \\ &- a_{11}k_{-1} + K_1K_2 + ak_5k_{-5} + bk_3k_{-3} \\ &- k_1k_{-1}x_0)\lambda^2 \\ &+ (k_{-1}K_1K_2 - a_{11}K_1K_2 + a_{11}k_{-1}K_1 \\ &+ a_{11}k_{-1}K_2 + ak_5k_{-1}k_{-5} + bk_3k_{-1}k_{-3} \\ &- ak_5k_{-5}K_2 - bk_3k_{-3}K_1 + k_1k_{-1}x_0K_1 \\ &+ k_1k_{-1}x_0K_2)\lambda - a_{11}k_{-1}K_1K_2 \\ &- k_1k_{-1}x_0K_1K_2 - ak_5k_{-1}k_{-5}K_2 \\ &- bk_3k_{-1}k_{-3}K_1. \end{aligned}$$

It can be shown by Routh-Hurwitz Criterion that the real parts of the roots of $P_1(\lambda)$ and $P_2(\lambda)$ are all negative. Since $a_{33} < 0$ and $a_{44} < 0$, then all the roots of $P(\lambda)$ have negative real parts. Thus, ξ is a locally asymptotically stable equilibrium point. Further, since

$$\xi^* = (0,0,e_3^+,e_4^+,0,0,0,0,0)$$

where

$e_3 = (4K_c\alpha + 1 + \sqrt{8K_c\alpha + 1})/8K_c$, and
$e_4 = (4K_b\beta + 1 + \sqrt{8K_b\beta + 1})/8K_b$,

is also an equilibrium point, then

$$\lim_{t\to\infty} \phi_t(\xi^*) = \xi^*.$$

Hence, the stability of ξ is not global. The claim of the theorem now follows. ■

3.3 Implications on the Original System

It follows from the above theorem that whenever SORLA is present in the system, then a solution of system (2) that starts in some neighbourhood of ξ has a C_5-component which approaches zero over time. Since from the original system (1), $\dot{X} + \dot{C}_5 = 0$ (that is, $X + C_5 = x_0$), then $X(t) \to x_0$ as $t \to \infty$.

Imposing the initial conditions $S_1(0) = s_0$, $S_2(0) = 0$, and $P_i(0) = 0$ for each $i = 1,2,3,4$ and using the identity

$$\sum_{i=1}^{4} \dot{P}_i + \dot{C}_1 + \dot{C}_2 + 2\dot{C}_3 + 2\dot{C}_4 + \dot{C}_5 + \dot{S}_1 + 2\dot{S}_2 = 0$$

from system (1), then

$$\sum_{i=1}^{4} P_i + C_1 + C_2 + 2C_3 + 2C_4 + C_5 + S_1 + 2S_2 = s_0.$$

It follows that

$$\lim_{t\to\infty} \sum_{i=1}^{4} P_i = s_0.$$

In a similar manner, we get

$$\lim_{t\to\infty} \sum_{i=5}^{8} P_i = s_0 + p_{50} + p_{60} + p_{70} + p_{80}$$

where $p_{i0} = P_i(0) \geq 0$ for $i = 5,6,7,8$.

Finally, if the region of attraction of ξ contains a point of the form $(x_1, x_2, 0, 0, x_5, \dots, x_9) \in \mathbb{R}^9$, then since

$$\dot{E}_1 + \dot{C}_1 + 2\dot{E}_3 + 2\dot{C}_3 = 0$$

that is, $E_1 + C_1 + 2E_3 + 2C_3 = \alpha$, then

$$E_1(t,\alpha) \to (\alpha - e_3) \text{ and } E_3(t,0) \to e_3$$

as $t \to \infty$ where $E_1(0,\alpha) = \alpha$ and $E_3(0,0) = 0$. Likewise,

$$E_2(t,\beta) \to (\beta - e_4) \text{ and } E_4(t,0) \to e_4$$

as $t \to \infty$.

4. CONCLUSIONS

The results indicate that SORLA persists in the system over time; that is, once SORLA is present in the system, it will return to its initial amount as time grows. Lao (2012) found out that as SORLA prevents APP dimerization, the high tendency of the substrates to form complexes with secretases is prevented. Consequently, despite the fact that $E_3(t,0) \to e_3$ and $E_4(t,0) \to e_4$ as $t \to \infty$, that is, inspite of the growth in concentration of the dimer enzymes α_d- and β_d-secretases, formation of complexes C_3 and C_4 is prevented as SORLA stays present in the system over time. Further, the decline in α- and β-secretases indicates the prevention of formation of the complexes C_1 and C_2. In turn, the formation of amyloidogenic products is inhibited, which is the primary factor in AD development.

In conclusion, the mathematical model suggests that SORLA has a very significant role in APP processing as it affects the enzymatic processes in both the monomeric and dimeric compartments. This supports the findings of Schmidt, et. al (2012) that SORLA prevents APP oligomerization. The stability analysis shows that this influence of SORLA to prevent proteolytic processing persists in the sytem through time. Therefore, the presence of SORLA is indicative of desirable long-time behaviour

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