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Analysis of granule cell generation system by lie symmetry method

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Abstract

In this paper, we study main headlines of brain development which is a major problem in neurobiology in present. Our aim here is to find the analytical solution of the equation that belongs to the brain development system. For this solution, the exchange of cerebellum granule cells in EGL (External granule layer of the cerebellum) is discussed. For this reason, Lie symmetry analysis is used. Obtaining solutions of this system means determining the behavior of the granular cell numbers at different stages. Knowing the behavior of these cells provides important information about the progression and development of diseases. Examples of these diseases are abnormal cerebellum development, cerebellum cancer. In this study, time dependent probability function related to division of two granule cells is examined. Then, analytical solutions are obtained for three different states of this function. Some tables and density graphics of these solutions are given.

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1. Introduction

A balance between granule cell precursor proliferation and differentiation is necessary to create the required number of granule cells in the ripe cerebellum. To describe this process mathematically, Leffler et al. [1] took into consideration the cellular behaviors in the external granule layer of the cerebellum (EGL).

It is important to understand the changes in the number of proliferations produced from granular cell precursors (gcps) in the outer layer of EGL (oEGL) and the number of differentiated granule cells in the inner layer of EGL (iEGL).

The cerebellum plays an important role in many motor, *cognitive* and emotional *processes*. At the cellular level, the granule cells and gcps in mice have been discussed almost 50 years in [1-3,4-8,9,10]. Recent studies of clonal analysis have been reported by Legue et al. [2] and Espinosa et al. [4].

In this paper, we have considered the following system of ordinary differential equations given by Leffler et al. [1]:

$$\frac{dN_o}{dt} = \alpha_p(1-\delta)N_o - \alpha_p\,\delta\,N_o \tag{1}$$

$$\frac{dN_i}{dt} = 2\alpha_p\delta N_o - \alpha_e\ N_i \tag{2}$$

where

$N_o(t)$: Time-dependent function expressing the number of cells in oEGL,

$N_i\,(t)$: Time-dependent function expressing the number of cells in iEGL,

α_p: Rate constant for the division of gcps,

α_e: Rate constant for the exit of granule cells from EGL,

$\delta(t)$: The time dependent probability function that a gcp divides terminally to generate two granule cells.

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Equations (1) and (2) provide predictions of initial number of gcps and gcp clone size. The model presented in [1] provides quantitative predictions about the granule cell properties and behaviors that can be compared to past and future data acquired from the developing mouse cerebellum. This mathematical model is very useful for us to explain how changes in these cell properties give rise to abnormal developments in mouse models of human neurodevelopmental diseases including cancer.

If the δ is a constant, the solutions of the Equation (1) and Equation (2) are easily found. For different values of δ, it is easy to determine the behavior of N_o as given by Leffler et al. [1]:

i) For $0 \leq \delta \leq 1/2$, $N_o(t)$: Increasing exponential function of time.

ii) For $\delta = ½$, $N_o(t)$: A constant.

iii) For $1/2 \leq \delta \leq 1$, $N_o(t)$: Decreasing exponential function of time.

Leffler et al. [1] conclude that δ must be a time-dependent function and the conditions of listed below must be satisfied:

"$\delta(t)$ must be less than 1/2 initially, and then greater than 1/2 after some time. Since $t = 0$ is the time just before gcps begin to differentiate into granule cells, it is assumed that $\delta(t) = 0$."

In this paper, three different $\delta(t)$ probability functions (linear, rational and exponential) are studied. Firstly, we will search the solutions of Equation (1) using Lie symmetry analysis and then we will find the general solution of Equation (2).

The rest of the paper is organized as follows: We will give some useful basic definitions and theorems about one parameter Lie group and the application of Lie symmetries to the ordinary equations in section two.

In the third section, there will be analytical solutions obtained by Lie symmetry method with different $\delta(t)$ probability functions which depend on time. In the fourth section, there will be some numerical simulations and the last section contains some discussions and conclusions.

2. Some Basic Definitions About Lie Symmetry Method

In this section, let us briefly sketch some basic elements of Lie group analysis of differential equations. The reader can find a more detailed exposition in [11-18,19-23,24-27].

2.1. One parameter lie group

Let

$$u: \mathbb{R}^2 \text{x } \varepsilon \rightarrow \mathbb{R}, \quad v: \mathbb{R}^2 \text{x } \varepsilon \rightarrow \mathbb{R} \tag{3}$$

where $\varepsilon \in \mathbb{R}$ is a parameter, u and v are analytical functions for Lie groups.

$$u(x, y, \varepsilon) = x_1, \quad v(x, y, \varepsilon) = y_1 \tag{4}$$

and using $Z_\varepsilon : \mathbb{R}^2 \rightarrow \mathbb{R}^2$,

$$(x, y) \rightarrow Z_\varepsilon(x, y) = \big(u(x, y, \varepsilon), v(x, y, \varepsilon)\big). \tag{5}$$

Then the set

$$H = [Z_\varepsilon \mid \varepsilon \in \mathbb{R}] \tag{6}$$

will be defined. It is called one parameter Lie group if the set (6) provides the group axioms. The analytic functions u and v are called global terms of the Lie group. For Equation (3), if we expand Taylor series about the point $\varepsilon = 0$, we get

$$x_1 = x + \varepsilon\, \xi(x,y) + O(\varepsilon^2) \tag{7}$$

$$y_1 = y + \varepsilon\; \eta(x,y) + O(\varepsilon^2), \tag{8}$$

where x_1 and y_1 are **infinitesimal transformations** of the Lie Group transformations. ξ and η are tangent vectors (infinitesimal of the group) and are defined by Oliver [24],

$$\xi(x,y) = \left(\frac{\partial x_1}{\partial \varepsilon}\right)_{\varepsilon=0} \tag{9}$$

$$\eta(x,y) = \left(\frac{\partial y_1}{\partial \varepsilon}\right)_{\varepsilon=0}. \tag{10}$$

We can use differential operator to observe a smooth function change under the influence of an infinitesimal form. The differential operator

$$G = \xi(x,y)\frac{\partial}{\partial x} + \eta(x,y)\frac{\partial}{\partial y} \tag{11}$$

is called **Lie operator.**

2.2 Lie group analysis of ODEs

We consider

$$y' = f(x,y). \tag{12}$$

A **first integral** of Equation (12) is a non-constant function $\phi(x,y)$ whose value is constant on any solution $y = y(x)$ of the ordinary differential equation. Symmetry transformations for differential equations move the points to new coordinates without changing them. So,

$$Z_\varepsilon : (x,y) \rightarrow (x_1,y_1) = \big(x_1(x,y,\varepsilon), y_1(x,y,\varepsilon)\big), \;\; \varepsilon \in \mathbb{R} \tag{13}$$

a transformation in (13) is symmetry for Equation (12). With the definition of this transformation,

$$\frac{dy_1}{dx_1} = f(x_1,y_1) \tag{14}$$

is called **symmetry condition** for Equation (12).

We have the equation

$$\frac{dy_1}{dx_1} = \frac{D_x y_1}{D_x x_1} = \frac{{y_1}_x + y'\,{y_1}_y}{{x_1}_x + y'\,{x_1}_y},$$

where D_x is total derivative operator in the x-direction.

That is, symmetry condition for Equation (12) will be

$$\frac{{y_1}_x + y'\,{y_1}_y}{{x_1}_x + y'\,{x_1}_y} = f(x_1,y_1). \tag{15}$$

Now we consider an orbit that is non-invariant for (x, y) point. Using the tangent vector with this orbit under the influence of Lie groups, we get

$$\frac{dx_1}{d\varepsilon} = \xi(x_1, y_1), \quad \frac{dy_1}{d\varepsilon} = \eta(x_1, y_1). \tag{16}$$

Using above conditions, we will obtain Equation (17) as linearized symmetry condition of ordinary differential equation:

$$\eta_x + (\eta_y - \xi_x)f - \xi_y f^2 = \xi f_x + \eta f_y . \tag{17}$$

2.3 Canonical coordinates for ODEs

Let's assume that we can find non-trivial symmetries of Equation (12) and these symmetries are just including translational Lie group in the y-direction.

In this case,

$$(r, s) = \big(r(x, y), s(x, y)\big), \quad r_x s_y - r_y s_x \neq 0 \tag{18}$$

shows with the new coordinates. These new coordinates are named **Canonical coordinates.** These new coordinates are symmetries of one-parameter Lie group**.** Then the tangent vector ($\left(\frac{d\hat{r}}{d\varepsilon}\right)_{\varepsilon=0} = 0, \left(\frac{d\hat{s}}{d\varepsilon}\right)_{\varepsilon=0} = 1$) is obtained with $(\hat{r}, \hat{s}) = (r, s + \varepsilon)$. When the chain rule is used at the tangent vector point, we will find

$$\xi(x, y)\, r_x + \eta(x, y) r_y = 0$$

$$\xi(x, y)\, s_x + \eta(x, y) s_y = 1 , \tag{19}$$

where the pair of canonical coordinates (r, s) is found as follows:

i) if $\xi \neq 0$, we see that the r is a first integral of

$$\frac{dy}{dx} = \frac{\eta(x,y)}{\xi(x,y)} . \tag{20}$$

Thus, $r = \phi(\mathrm{x}, \mathrm{y})$ is found by solving Equation (20). Here, r is an invariant canonical coordinate. So, by taking the first integral of Equation (20), there will be $r = \phi(\mathrm{x}, \mathrm{y}) = \mathrm{c}$, $\phi_y \neq 0$ (where c is an arbitrary constant) and

$$r = \phi(x, y), \quad s = \left(\int \frac{dx}{\xi(x, y(x, r))}\right)\Big|_{r=r(x,y)}.$$

ii) if $\xi = 0$ (if these symmetries are not trivial symmetries when $\eta = 0$), with the help of the first few Equations of (19), it is seen clearly that $r_y = 0$. Therefore, the canonical coordinates are found as

$$r = x, \quad s = \left(\int \frac{dy}{\eta(r,y)}\right)\Big|_{r=x} .$$

So, using the instruments of canonical coordinates, the analytical solution of the Equation (12) will be

$$s(x, y) - \left(\int \Omega(r) dr\right)\Big|_{r=r(x,y)} + c = 0 \tag{21}$$

where $\frac{ds}{dr} = \Omega(r, s)$.

3. Analytical Solutions for Different $\delta(t)$ Functions

In this section, we will find the analytical solutions of granule cell generation system with different time-dependent $\delta\ (t)$ functions using Lie symmetry analysis.

3.1 Case 1: $\boldsymbol{\delta(t) = at}$

In this case, we will deal with $\delta(t)$ being linear function. We take initial slope of $\delta(t)$ as a, that is $\delta(t) = at$. By using this substitution in Equation (1) and Equation (2), the system becomes,

$$\frac{dN_o}{dt} = \alpha_p(1 - at)N_o - \alpha_p\ at\ N_o \tag{22}$$

$$\frac{dN_i}{dt} = 2\alpha_p\ at\ N_o - \alpha_e\ \ N_i. \tag{23}$$

Considering Equation (22) and writing this equation under the influence of linearized symmetry conditions given by Equation (17) yields we obtain $(\xi, \eta) = (0, N_o)$. Since ξ = 0, is obtained, with the help of (ii) in subsection (2.3), it is also found that $r = t$, $s = (\int \frac{dt}{N_o})$ and by solving (20), N_o will be

$$N_o(t) = \frac{e^{\alpha_p\ t}\ c_1}{e^{at^2\ \alpha_p}}, \tag{24}$$

where c_1 is an arbitrary constant.

With writing down this solution in (23), we will have the equation for N_i,

$$\frac{dN_i}{dt} = 2\alpha_p\ at \frac{e^{\alpha_p\ t}\ c_1}{e^{at^2\ \alpha_p}}\ - \alpha_e\ \ N_i. \tag{25}$$

In the same way, with implementing symmetry condition which is the Equation (17), we will have $(\xi, \eta) = (0, e^{-\alpha_e t})$ as a tangent vector. Again, using subsection 2.3, we will have the canonical coordinates as $r = t$ and $s = (\int \frac{dt}{e^{-\alpha_e t}})$. Using the canonical coordinates, the analytical solution of N_i will be

$$N_i\ (\mathrm{t}) = \left[2\ \ c_1\ a\ \alpha_p \left(\frac{-1}{2}\ \frac{e^{-at^2\ \alpha_p + (\alpha_p+\alpha_e)t}}{a\ \alpha_p}\right) + \frac{1}{4}\frac{(\alpha_p+\alpha_e)\sqrt{\pi}e^{\frac{1}{4}\frac{(\alpha_p+\alpha_e)^2}{a\ \alpha_p}}\ \mathrm{erf}\,(\sqrt{a\ \alpha_p} t - 1/2\frac{(\alpha_p+\alpha_e)}{\sqrt{a\ \alpha_p}})}{a\ \alpha_p\sqrt{a\ \alpha_p}} + c_2\right] / e^{\alpha_e t} \tag{26}$$

where c_2 is an arbitrary constant.

3.2 Case 2: $\boldsymbol{\delta(t) = \frac{at}{1+at}}$

In this case we will examine the analytical solution if $\delta(t)$ will be chosen as rational expression. Therefore, if $\delta(t)$ is chosen as $\frac{at}{1+at}$, the new version of Equations (1) -(2) will be

$$\frac{dN_o}{dt} = \alpha_p \left(1 - (\frac{at}{1+at}\ )\right) N_o - \alpha_p\ (\frac{at}{1+at})\ N_o \tag{27}$$

$$\frac{dN_i}{dt} = 2\alpha_p\ \left(\frac{at}{1+at}\ \right)\ N_o - \alpha_e\ \ N_i. \tag{28}$$

As in the previous case, we will have the tangent vectors $(\xi,\eta)=(0,N_o)$, with implementing linear symmetry condition to Equation (27) and with the help of canonical coordinates the general solution of N_o will be

$$N_o(t)=\frac{(at+1)^{(\frac{\alpha_p}{a})^2}}{e^{\alpha_p t}(e^{(\frac{\alpha_p c_3}{a})})^2}, \tag{29}$$

where c_3 is an arbitrary constant. With writing down this analytical solution in Equation (28), differential equation for N_i will be

$$\frac{dN_i}{dt}=2\alpha_p\,(\frac{at}{1+at})(\frac{(at+1)^{\left(\frac{\alpha_p}{a}\right)^2}}{e^{\alpha_p t}\left(e^{\left(\frac{\alpha_p c_3}{a}\right)}\right)^2}-\alpha_e\ N_i\,. \tag{30}$$

By writing the expressions under the symmetry condition, we will find $(\xi,\eta)=(0,e^{-\alpha_e t})$ and using canonical coordinates the general solution of N_i can be given as:

$$N_i(t)=\frac{\int\left(\frac{2\alpha_p at(at+1)^{(\frac{2\alpha_p}{a}-1)}e^{\alpha_e t}}{e^{\alpha_p t}\left(e^{\left(\frac{\alpha_p c_3}{a}\right)}\right)^2}\right)dt+c_4}{e^{\alpha_e t}}\quad, \tag{31}$$

where c_4 is an arbitrary constant.

3.3 Case 3: $\boldsymbol{\delta(t)=1-e^{-at}}$

In the final case, we will examine the analytical solution of the model when $\delta\,(t)$ is an exponential expression. So, if we take $\delta(t)=1-e^{-at}$, Equations (1) -(2) will be

$$\frac{dN_o}{dt}=\alpha_p(1-(1-e^{-at}))N_o-\alpha_p\,(1-e^{-at})N_o \tag{32}$$

$$\frac{dN_i}{dt}=2\alpha_p(1-e^{-at})\,N_o-\alpha_e\ N_i. \tag{33}$$

If we apply the same procedures in the previous cases, we will have the general solutions as:

$$N_o(t)=\frac{c_5}{e^{\alpha_p t}(e^{(\frac{\alpha_p e^{-at}}{a})})^2} \tag{34}$$

and

$$N_i(t)=\left[\int\left(-2c_5\,\alpha_p\left(e^{-\left(\frac{at^2\alpha_e\,ta+at\alpha_p+2\alpha_p e^{-at}}{a}\right)}\right)+2c_5\,\alpha_p\left(e^{-\left(\frac{-\alpha_e\,ta+at\alpha_p+2\alpha_p e^{-at}}{a}\right)}\right)\right)dt+c_6\right]/e^{\alpha_e t}, \tag{35}$$

where c_5 and c_6 are arbitrary constants. As in the other cases, the tangent vectors are found as $(0,N_o)$ for N_o and $(0,e^{-\alpha_e t})$ for N_i .

4. Numerical Simulations

With the help of $N_o(t)$ and $N_i(t)$ functions, we can use a Equation (4.1) and Equation (4.2) to find changes in tissue area. Equation (36) and Equation (37) give us the cell numbers for granule cell generation systems. $A_o(t)$ means area of the oEGL and it is defined as,

$$A_o(t)=\frac{v_c\,N_o(t)}{L}. \tag{36}$$

$A_i(t)$ means area of the iEGL and it is defined as,

$$A_i(t) = \frac{v_c\, N_i(t)}{L} \tag{37}$$

where v_c is the volume of granule cell, assumed to be 300-μm^3 and L is the medial-lateral width of the vermis (central cerebellum), measured to be 1775-μm (∓%20). Now we will give some graphics to examine the change in tissue area with using this formula and measured values.
The table is constructed for the initial conditions $A_o(0) = 0$ and $A_i(0) = 0$. These values are gained in different biological observations that are studied in Leffler et al. [1].

Table 1. Values of δ(t) probability function.

$\delta(t) function$	Linear	Rational	Exponential
α_p	0.0348	0.0558	0.0473
α_e	0.0387	0.0588	0.0474
a	0.0029	0.0059	0.0041
$A_o(0)$	1994	1005	1411

For the linear case, if one considers the expressions in (24) and (26), the constants will be $c_1 = 11797$, $c_2 = 11797$. Using Table 1, the constants for rational and exponential case will be $c_3 = -0.4594$, $c_4 = 298.5502$, $c_5 = 0.2025723984 \times 10^{14}$ and $c_6 = 0$.

In Figure 1, the simulations which are obtained by taking account the constants for $A_o(t)$ can be seen. In Figure 2, the density simulations of $A_o(t)$ are plotted for linear, rational and exponential solutions.

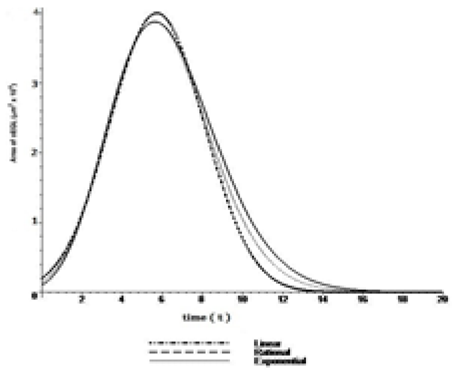

Figure 1. Solutions of $A_o(t)$ for linear, rational and exponential cases.

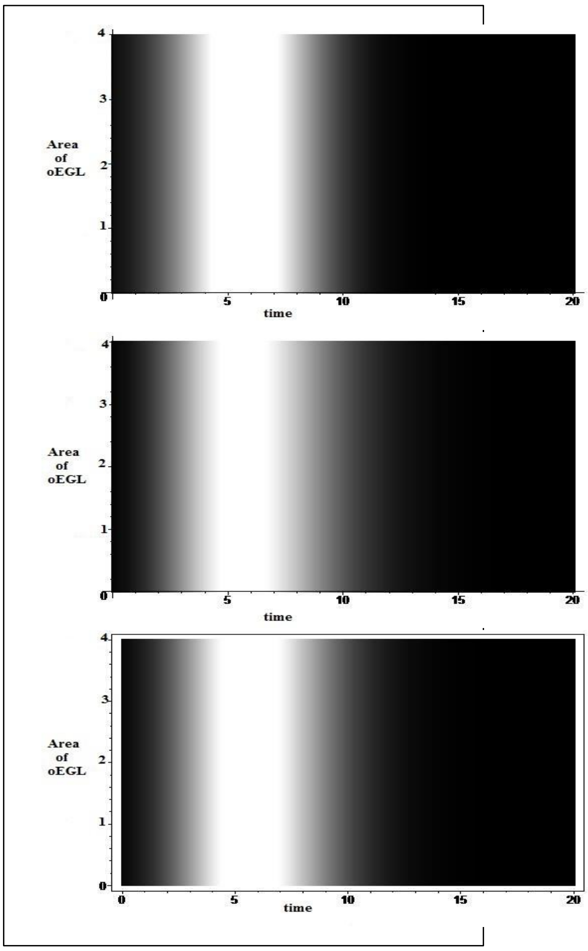

Figure 2. Density plot simulations of $A_0(t)$ for linear, rational and exponential cases respectively.

In Figure 3, we show the simulation for general solutions of $A_i(t)$ and in Figure 4, there are density plot graphics of the solutions of $A_i(t)$ for all three cases.

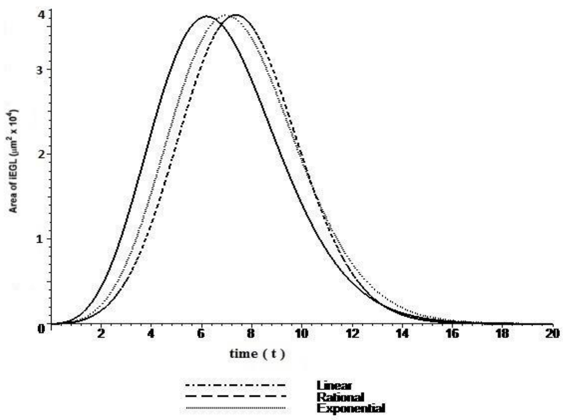

Figure 3. Solutions of $A_i(t)$ for linear, rational and exponential cases.

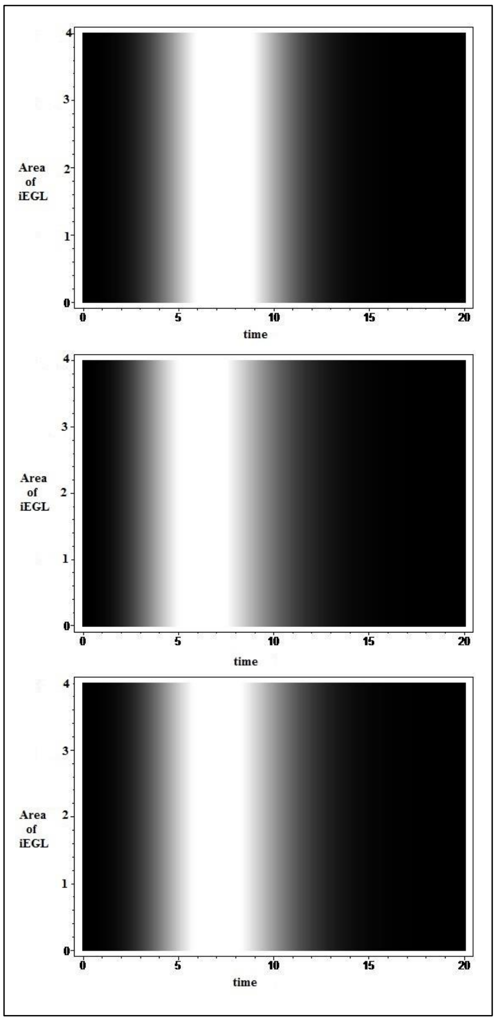

Figure 4. Density plot simulations of $A_i(t)$ for linear, rational and exponential cases respectively.

The density plot simulations are given for different values of $\boldsymbol{\alpha_p}$ in Figure 5 and Figure 6.

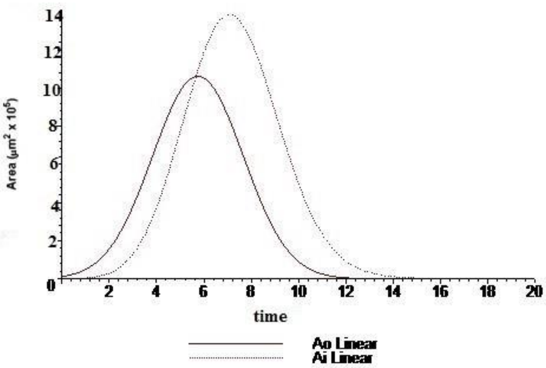

Figure 5. Solutions of $A_i(t)$ and $A_0(t)$ for $\alpha_p = 1.5 \times 0.0348$.

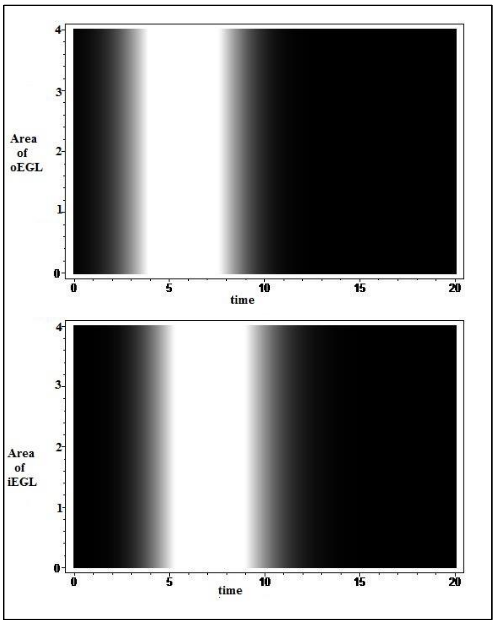

Figure 6. Density Plot simulations of $A_i(t)$ and $A_0(t)$ for different α_p.

Finally, Figure 7 and Figure 8 deal with linear case, but this time the different values of α_e are given for the simulation of granule cell change and density plot graphics.

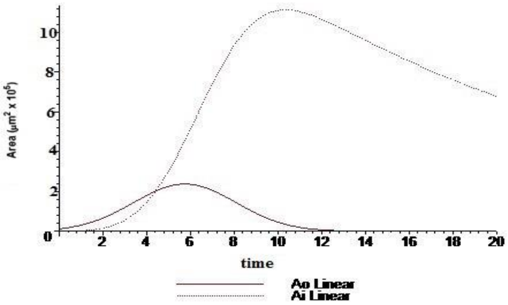

Figure 7. Solutions of $A_i(t)$ $a_0(t)$ for $\alpha_e = 0.5 \times 0.0387$.

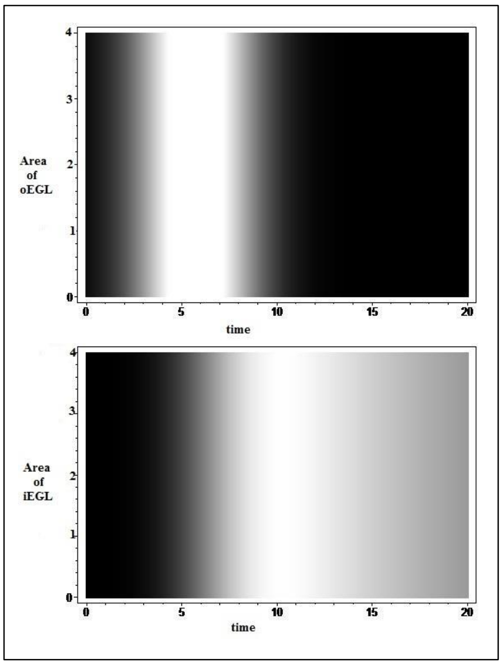

Figure 8. Density Plot simulations of $A_i(t)$ and $A_0(t)$ for different α_e.

In this work all numerical calculations and simulations carried out in Maple 18 package program.

5. Conclusions

In this study, analytic solutions are obtained by Lie symmetry analysis. Firstly, solutions of $N_o(t)$ and $N_i(t)$ are obtained using Equation (1) and Equation (2), respectively. Then, $A_o(t)$ and $A_i(t)$ functions which depend on time are found. Simulations about the monthly changes of these functions are given. Three different conditions have been investigated for $\delta(t)$. Estimating the number and distribution of granular cells are very important for nerve diseases. For this purpose, new and important contributions have been made in the field of nerve diseases.

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Conflicts of interest

Sample sentences if there is no conflict of interest: The outhors state that did not have conflict of interests

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