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An Allee Threshold Model for a Glioblastoma(GB)-Immune System(IS) Interaction with Fuzzy Initial Values

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Abstract

In this paper, we adopt the model of [12] by including fuzzy initial values to study the interaction of a monoclonal brain tumor and the macrophages for a condition of extinction of GB(Glioblastoma) by using Allee threshold. Numerical simulations will give detailed information on the behavior of the model at the end of the paper. We perform all the computations in this study with the help of the Maple software.

Keywords: Fuzzy number, Fuzzy derivative, Fuzzy differential equations (FDE), Fuzzy initial values.

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1 Introduction

Fuzzy set theory was introduced by Zadeh [34]. Kandel and Byatt [23] studied fuzzy differential equations, where other studies about fuzzy differential equations and the concept of the strongly generalized derivative of higher order fuzzy differential equation can be shown in [6, 7, 21, 24]. Many terms we use randomly in daily life often have a fuzzy structure. Verbal and numerical expressions that we use when describing something, explaining an event, commanding and in many other cases contain fuzziness. As for the fuzzy set, it has two basic features. The first is the modeling of systems whose mathematical model is uncertain or whose behavior can be estimated approximately. The second can decide when there is incomplete and uncertain information. Because of these features, new mathematical concepts have emerged, new research issues have emerged and engineering practices have been designed. Especially interesting applications in the field of medicine and artificial intelligence began to emerge. Nowadays, diseases can now be expressed and solved mathematically. This leads to better ways to treat diseases. Fuzzy numbers can give closer results than classical mathematics. For this reason,

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in our study, we have more accurate results by using these numbers and to be more effective in the diagnosis and treatment of the disease. One of these diseases is cancer that is one of the greatest killers in the world. The control of tumor growth requires special attention [17] and interdisciplinary studies, like biology, medicine and mathematics, many fields are attracted by modeling the spread of this disease. The typical approach for treating GBM (Glioblastoma Multiforme) involves surgical resection, that is followed by radiation treatment and chemotherapy [20]. Works about modeling of multi subpopulations can be shown in [7, 9, 15, 27, 29, 31]. Differential equations have high importance in biological modeling. In the last years and through the use of different type of models, F. Bozkurt has used a system of differential equations as a model for the brain tumor, and its interaction with the immune system (IS) of the human body [10, 11]. Also, another interesting model is the GBM model constructed by F. Bozkurt [12], which explains the interaction between cancer and the human body. Furthermore, in [2], Ö. Akın and Ö. Oruç have studied a predator-prey model with fuzzy initial values. Then, by considering a second-order initial values Ö. Akın, T. Khaniyev, Ö. Oruç and I. B. Turksen [3] have generalized the model. Works about the prey-predator model of fuzzy numbers can be seen in [1, 26, 28]. Lastly, Benli and Keskin [8] considered a model which has a predator-prey structure between the monoclonal tumor and the macrophages. In this study, a new model upon the work of F. Bozkurt [12] is modeled, where fuzzy initial values are used. Furthermore, Allee threshold functions are embedded in the system to investigate the threshold effect on the system and to explain the extinction conditions. A novel multi-resolution method proposed by Seyedi [35] for solving partial differential equations. He tested this method for the solution of well-known viscous Burger's equation and the obtained results showed superior accuracy in comparison to the finite difference and boundary element methods. Owing to the importance of studying some of equations, several distinct techniques have been proposed that some of them are: 3D-block-pulse functions method [36], homotopy method [37, 38], Hirota bilinear method [39], and Dynamic buckling in lamina plates and dynamic analysis [40, 41].

The paper is constructed as follows: The model and the preliminary definitions are in Section 2., in Section 3 nonlinear fuzzy differential equations are given, a numerical study of the model are given in Section 4. The last Section we have the conclusion part to summarize the study in this paper.

2 The Model and Preliminary Definitions

The model is constructed as follows:

$$\begin{cases} \frac{dx}{dt} = \left(\frac{x}{E+x}\right)(px + r_1x(K_1 - \alpha_1x) - d_1x - \tau_1xy) \\ \frac{dy}{dt} = r_2y(K_2 - \beta_1y) - d_2y - \tau_2xy \end{cases} \quad (1)$$

where $t \geq 0$ denotes the time and E is an Allee constant, the parameters $\alpha_1, \beta_1, \tau_1, \tau_2, p, d_1, d_2, K_1, K_2, r_1$ and r_2 (see Table 1) are positive numbers. $x(t)$ is used for the GB which represents the monoclonal brain tumor, $y(t)$ denotes the activated macrophages in the system [18]. Differential equations are indispensable for modeling real-world phenomena, unfortunately, every time uncertainty can intervene with real worlds problems the uncertainty can arise from deficient data, measurement errors or when determining initial conditions. Fuzzy set theory is a powerful tool to overcome these problems. Followings are some definitions that are needed to have a fundamental idea of the work.

Definition 1. A fuzzy set A in a universe set X is a mapping $A : X \rightarrow [0, 1]$. We think of A as assigning to each element $x \in X$ a degree of membership, $0 \leq A(x) \leq 1$. Let us denote by $\mathcal{F}$ the class of fuzzy subsets of the real numbers, $A : X \rightarrow [0, 1]$ satisfying the following properties:

1. A is a convex fuzzy set, i.e. $A(r\lambda + (1 - \lambda)s) \geq \min[A(r), A(s)]$, $\lambda \in [0, 1]$ and $r, s \in X$;
2. A is normal, i.e. $\exists x_0 \in X$ with $A(x_0) = 1$;
3. A is upper semicontinuous, i.e. $A(x_0) \geq \lim_{x \rightarrow x_0^-} A(x)$;

4. $[A]^0 = \overline{\sup p(A)} = \overline{\{x \in R | A(x) \geq 0\}}$ is compact, where $\bar{A}$ denotes the closure of A .

Then $\mathcal{F}$ is called the space of fuzzy numbers.

If A is a fuzzy set, we define $[A]^\alpha = \{x \in X | \mu_A \geq \alpha\}$, the α -level (cut) of A , with $0 < \alpha \leq 1$. For $u, v \in \mathcal{F}$ and $\lambda \in R$ the sum $u \oplus v$ and the product $\lambda \odot u$ are defined by $[u \oplus v]^\alpha = [u]^\alpha + [v]^\alpha$, $\lambda \odot u = \lambda[u]^\alpha$, $\forall \alpha \in [0, 1]$. Additionally, $u \oplus v = v \oplus u$, $\lambda \odot u = u \odot \lambda$. Also if $u \in \mathcal{F}$ the α -cut of u , denoted by $[u]^\alpha = [\underline{u}^\alpha, \bar{u}^\alpha]$, $\forall \alpha \in [0, 1]$.

Definition 2. Let $D: \mathcal{F} \times \mathcal{F} \rightarrow R_+ \cup \{0\}$, $D(u, v) = \sup_{\alpha \in [0, 1]} \max\{|[\underline{u}^\alpha, \underline{v}^\alpha]|, |[\bar{u}^\alpha, \bar{v}^\alpha]|\}$ be a Hausdorff distance between fuzzy numbers, where $[u]^\alpha = [\underline{u}^\alpha, \bar{u}^\alpha]$ and $[v]^\alpha = [\underline{v}^\alpha, \bar{v}^\alpha]$.

The following properties are well-known [18, 33].

$$D(u \oplus \omega, v \oplus \omega) = D(u, v), \forall u, v, \omega \in \mathcal{F},$$

$$D(k \odot u, k \odot v) = |k| D(u, v), \forall k \in R, u, v \in \mathcal{F},$$

$$D(u \oplus v, \omega \oplus e) \leq D(u, \omega) + D(v, e), \forall u, v, \omega, e \in \mathcal{F},$$

and $(\mathcal{F}, D)$ is a complete metric space.

Definition 3. (H- Difference) Let $\forall u, v \in \mathcal{F}$. If there exists $\omega \in \mathcal{F}$ such that $u = v \oplus \omega$, then ω is called the H- difference of u and v and is denoted by $u \ominus v$.

Definition 4. (Hukuhara Derivative) [29] Consider a fuzzy mapping $F: (a, b) \rightarrow \mathcal{F}$ and $t_0 \in (a, b)$. We say that F is H-differentiable at $t_0 \in (a, b)$ if there exists an element $F'(t_0) \in \mathcal{F}$ such that for all $h > 0$ sufficiently small $F(t_0 + h) \ominus F(t_0)$, $F(t_0) \ominus F(t_0 - h)$, and the limits (in the metric D)

$$\lim_{h \rightarrow 0^+} \frac{F(t_0 + h) \ominus F(t_0)}{h} = \lim_{h \rightarrow 0^-} \frac{F(t_0) \ominus F(t_0 - h)}{h},$$

exist and are equal to $F'(t_0)$.

Note that the definition of the derivative above is restrictive; for instance in [6, 7] it is shown that, if $F(t) = c.g(t)$ where c is a fuzzy number and $g: [a, b] \rightarrow R^+$ is a function with $g'(t) < 0$, then F is not differentiable. To avoid this difficulty, a more general definition of the derivative for fuzzy mappings are given in [6, 7] which is as following:

Definition 5. (Generalized Fuzzy Derivative) [6, 7] Let $F: (a, b) \rightarrow \mathcal{F}$ and $t_0 \in (a, b)$. We say that F is strongly generalized differentiable at t_0 if there exists an element $F'(t_0) \in \mathcal{F}$ such that

1. for $h > 0$ sufficiently small $\exists F(t_0 + h) \ominus F(t_0)$, $F(t_0) \ominus F(t_0 - h)$ and the limits satisfy

$$\lim_{h \rightarrow 0} \frac{F(t_0 + h) \ominus F(t_0)}{h} = \lim_{h \rightarrow 0} \frac{F(t_0) \ominus F(t_0 - h)}{h} = F'(t_0),$$

2. for $h > 0$ sufficiently small $\exists F(t_0) \ominus F(t_0 + h)$, $F(t_0 - h) \ominus F(t_0)$ and the limits satisfy

$$\lim_{h \rightarrow 0} \frac{F(t_0) \ominus F(t_0 + h)}{(-h)} = \lim_{h \rightarrow 0} \frac{F(t_0 - h) \ominus F(t_0)}{(-h)} = F'(t_0),$$

or

3. for $h > 0$ sufficiently small $\exists F(t_0 + h) \ominus F(t_0), F(t_0 - h) \ominus F(t_0)$, and the limits satisfy

$$\lim_{h \rightarrow 0} \frac{F(t_0 + h) \ominus F(t_0)}{h} = \lim_{h \rightarrow 0} \frac{F(t_0 - h) \ominus F(t_0)}{(-h)} = F'(t_0),$$

or

4. for $h > 0$ sufficiently small $\exists F(t_0) \ominus F(t_0 + h), F(t_0) \ominus F(t_0 - h)$ and the limits satisfy

$$\lim_{h \rightarrow 0} \frac{F(t_0) \ominus F(t_0 + h)}{(-h)} = \lim_{h \rightarrow 0} \frac{F(t_0 - h) \ominus F(t_0)}{h} = F'(t_0),$$

Definition 5 is equivalent to the Definition 6 that we will use in the paper.

Definition 6. Let $F : (a, b) \rightarrow \mathcal{F}$ and $t_0 \in (a, b)$.

1. for $h > 0$ sufficiently small $\exists F(t_0 + h) \ominus F(t_0), F(t_0) \ominus F(t_0 - h)$ and

$$\lim_{h \rightarrow 0^+} \frac{F(t_0 + h) \ominus F(t_0)}{h} = \lim_{h \rightarrow 0^+} \frac{F(t_0) \ominus F(t_0 - h)}{h} = F'(t_0),$$

or

2. for $h > 0$ sufficiently small $\exists F(t_0 + h) \ominus F(t_0), F(t_0) \ominus F(t_0 - h)$ and

$$\lim_{h \rightarrow 0^-} \frac{F(t_0 + h) \ominus F(t_0)}{h} = \lim_{h \rightarrow 0^-} \frac{F(t_0) \ominus F(t_0 - h)}{h} = F'(t_0),$$

The following theorem is very important for us to solve fuzzy differential equations.

Theorem 1. [14, 22] Let $F : T \rightarrow \mathcal{F}$ be a function and set $[F(t)]^\alpha = [f_\alpha(t), g_\alpha(t)]$ for each $\alpha \in [0, 1]$. Then

1. If F is differentiable following the form (1) in Definition 6 then $f_\alpha(t)$ and $g_\alpha(t)$ are differentiable functions and $[F'(t)]^\alpha = [f'_\alpha(t), g'_\alpha(t)]$.
2. If F is differentiable following the form (2) in Definition 6 then $f_\alpha(t)$ and $g_\alpha(t)$ are differentiable functions and $[F'(t)]^\alpha = [g'_\alpha(t), f'_\alpha(t)]$.

3 Solving Fuzzy Differential Equations with Fuzzy Initial Values

Consider the following equation with fuzzy initial values

$$x'(t) = F(t, x(t)), x(0) = x_0, \quad (2)$$

where $F : [0, \alpha] \times \mathcal{F} \rightarrow \mathcal{F}$ and x_0 is a fuzzy number, $[x(t)]^\alpha = [u_\alpha(t), v_\alpha(t)]$, $[x_0]^\alpha = [u_\alpha^0, v_\alpha^0]$ and $[F(t, x(t))]^\alpha = [f_\alpha(t, u_\alpha(t), v_\alpha(t)), g_\alpha(t, u_\alpha(t), v_\alpha(t))]$.

Then, we get the following alternatives for solving the initial value problem (2):

1. If we consider $x'(t)$ by using the derivative in the first form (1), then from Theorem 1 $[x'(t)]^\alpha = [u'_\alpha(t), v'_\alpha(t)]$. So we have the following equalities:

$$\begin{aligned} u'_\alpha(t) &= f_\alpha(t, u_\alpha(t), v_\alpha(t)), u_\alpha(0) = u_\alpha^0 \\ v'_\alpha(t) &= g_\alpha(t, u_\alpha(t), v_\alpha(t)), v_\alpha(0) = v_\alpha^0. \end{aligned}$$

By solving the above system for u_α and v_α , we get the fuzzy solution $[x(t)]^\alpha = [u_\alpha(t), v_\alpha(t)]$. Finally we ensure that $[x(t)]^\alpha = [u_\alpha(t), v_\alpha(t)]$ and $[x'(t)]^\alpha = [u'_\alpha(t), v'_\alpha(t)]$ are valid level sets.

2. If we consider $x'(t)$ by using the derivative in the second form (2), then from Theorem 1 $[x'(t)]^\alpha = [u'_\alpha(t), v'_\alpha(t)]$. So we get following:

$$\begin{aligned} u'_\alpha(t) &= g_\alpha(t, u_\alpha(t), v_\alpha(t)), u_\alpha(0) = u_\alpha^0 \\ v'_\alpha(t) &= f_\alpha(t, u_\alpha(t), v_\alpha(t)), v_\alpha(0) = v_\alpha^0. \end{aligned}$$

Solving the above system for u_α and v_α , we get the fuzzy solution $[x(t)]^\alpha = [u_\alpha(t), v_\alpha(t)]$. Finally we ensure that $[x(t)]^\alpha = [u_\alpha(t), v_\alpha(t)]$ and $[x'(t)]^\alpha = [u'_\alpha(t), v'_\alpha(t)]$ are valid level sets.

4 Numerical Study with Allee Threshold For A GB-IS Interaction with Fuzzy Initial Values

Important research for population models by the Allee [4], who demonstrated that Allee effect occurs when the population growth rate is reduced at low population size. It is well known that the logistic model assumes that per-capita growth rate declines monotonically when the density increase; however, it is shown that for population subjected to an Allee effect, per-capita growth rate gives a humped curve increasing at low density, up to a maximum intermediate density and then declines again [32]. Many theoretical and laboratory studies have demonstrated the importance of the Allee effect in the dynamics of small populations, see for example [5, 16, 19, 25, 30]. This section presents the numerical study for the following Allee threshold tumor model, which considers fuzzy initial values. Since the critical point $x = 0$ is unstable, we need a threshold to explain the extinction of the tumor population. Biological facts led to assume the Allee function as follows:

1. If $N = 0$, then $\alpha(N) = 0$; that is, there is no reproduction without partners, α is the Allee function and N is the populations density at time t ,
2. $\alpha'(N) > 0$ for $N \in (0, \infty)$; that is, Allee effect decreases as density increases,
3. $\lim_{N \rightarrow \infty} \alpha(N) = 1$; that is, Allee effect vanishes at high density [13].

Considering system (3), we can see that we embed to the monoclonal tumor population on Allee threshold model.

$$\begin{aligned} \frac{dx}{dt} &= \left(\frac{x-1.23}{x}\right)[0.148x + 0.55x(4.704 - 0.25x) - 0.55x - 0.01xy], \\ \frac{dy}{dt} &= 0.5y(1.132 - 0.25y) - 0.06y - 0.01xy, \\ x(0) &= 1.6 \text{ ml}, y(0) = 0.2 \text{ ml}. \end{aligned} \quad (3)$$

where $x(t)$ and $y(t)$ are the density of the tumor and macrophages at time t , respectively. Table 1 shows the values of the parameters in Equation (1), which gives us (4).

Table 1 Values of the parameter of system (1).

E	Allee constant	1.23
r_1	The growth rate of the macrophage	0.55
r_2	The growth rate of the macrophage	0.5
p	Division rate of the sensitive cells	0.148
K_1	Carrying capacity of the tumor cells	4.704
K_2	Carrying capacity of the macrophages	1.132
α_1	Logistic population rate of tumor cell population	$\alpha_1 \in [0.5; 0.95]$
τ_i	Destroying rate caused from the interaction	0.01
d_1	Causes of drug treatment to the tumor cells	0.55
d_2	Causes of drug treatment to the macrophages	0.06
β_1	Logistic population rate of macrophages	$\beta_1 \in [0.05; 0.25]$

By ordering and simplifying system (3), we have

$$\begin{aligned}\frac{dx}{dt} &= 2.3543x - 0.1375x^2 - 0.01xy + 0.0123y - 2.6878 \\ \frac{dy}{dt} &= 0.506y - 0.125y^2 - 0.01xy \\ x(0) &= 1.6 \text{ ml}, y(0) = 0.2 \text{ ml}.\end{aligned}\quad (4)$$

The crisp solutions for the problem (4) are shown in Figure 1.

Fig. 1 Crisp solution for (4)

Let the initial values be fuzzy, that is, $x(0) = \widetilde{1.6}$, $y(0) = \widetilde{0.2}$ and let their α -level sets be as follows;

$$x(0) = [\widetilde{1.6}]^\alpha = [1.2 + 0.4\alpha, 2 - 0.4\alpha]$$

$$y(0) = [\widetilde{0.2}]^\alpha = [0.1 + 0.1\alpha, 0.3 - 0.1\alpha]$$

Let the α -level sets of $x(t, \alpha)$ be $[x(t, \alpha)]^\alpha = [u(t, \alpha), v(t, \alpha)]$ and for simplicity denote them as $[u, v]$, similarly $[y(t, \alpha)]^\alpha = [r(t, \alpha), s(t, \alpha)] = [r, s]$

If $x(t, \alpha)$ and $y(t, \alpha)$ are (1) differentiable according to Definition 6, system (4) becomes

$$[u', v'] = 2.3543[u, v] - 0.1375[u, v] \cdot [u, v] - 0.01[u, v] \cdot [r, s] + 0.0123[r, s] - [2.6878, 2.6878],$$

$$[r', s'] = 0.506[r, s] - 0.125[r, s] \cdot [r, s] - 0.01[u, v] \cdot [r, s].$$

Hence for $\alpha = 0$ the following initial value problem derives from (4) :

$$u' = 2.3543u - 0.1375v^2 - 0.01vs + 0.0123r - 2.6878,$$

$$v' = 2.3543v - 0.1375u^2 - 0.01ur + 0.0123s - 2.6878,$$

$$r' = 0.506r - 0.125s^2 - 0.01vs,$$

$$s' = 0.506s - 0.125r^2 - 0.01ur.$$

$$u(0) = 1.20 \text{ ml}, v(0) = 2 \text{ ml}, r(0) = 0.10 \text{ ml}, s(0) = 0.30 \text{ ml}.$$

$u(0), v(0), r(0), s(0)$ are fuzzy initial conditions for the system. Now if $x(t, \alpha)$ and $y(t, \alpha)$ are (2) differentiable according to Definition 6, system (4) becomes:

$$v' = 2.3543u - 0.1375v^2 - 0.01vs + 0.0123r - 2.6878,$$

$$u' = 2.3543v - 0.1375u^2 - 0.01ur + 0.0123s - 2.6878,$$

$$s' = 0.506r - 0.125s^2 - 0.01vs,$$

$$r' = 0.506s - 0.125r^2 - 0.01ur.$$

$$u(0) = 1.20 \text{ ml}, v(0) = 2 \text{ ml}, r(0) = 0.10 \text{ ml}, s(0) = 0.30 \text{ ml}.$$

In Figure 2, we can see the graphical solution of all cases for $\alpha = 0$.

Fig. 2 Fuzzy solution of (4) for $\alpha = 0$.

In Figure 2; according to Definition 6, (a) means that $x(t, \alpha)$ and $y(t, \alpha)$ are (1) differentiable, (b) means that $x(t, \alpha)$ is (1) differentiable and $y(t, \alpha)$ is (2) differentiable, (c) means that $x(t, \alpha)$ is (2) differentiable and $y(t, \alpha)$ is (1) differentiable and (d) means that $x(t, \alpha)$ and $y(t, \alpha)$ are (2) differentiable. Now, if Figure 2 is analyzed, we see that when $x(t, \alpha)$ and $y(t, \alpha)$ are (2) differentiable graphical solution (Fig.(d)) is biologically meaningful.

In addition, the graphical solution is compatible with a crisp solution. In contrast, when $x(t, \alpha)$ and $y(t, \alpha)$ are differentiable as in (a), (b) and (c), the graphical solutions are incompatible with biological facts. $x(t)$ and $y(t)$ are the density of tumors and macrophages at time t respectively. Being compatible with biological facts means that the tumor is increasing or decreasing and the macrophages are increasing or decreasing. It does not give us information about tumors and macrophages when it is differentiated as in (a), (b) and (c), so these conditions are biologically meaningless.

Now, we will focus on the situation when $x(t, \alpha)$ and $y(t, \alpha)$ are (2) differentiable. When the crisp graphical solution and the fuzzy graphical solution $x(t, \alpha)$ and $y(t, \alpha)$ are (2) differentiable, we will plot their graphs on the same graph for $\alpha = 0$ and $\alpha \in [0, 1]$. The fuzzy solution for $\alpha = 0$ and the crisp solution are given in Table 2 and Figure 3.

Fig. 3 Crisp solution and fuzzy solution for $\alpha = 0$.

Table 2 Numerical values of Figure 3.

Time(t)	v	x	u	s	y	r
0.0	2.0000	1.6000	1.2000	0.3000	0.2000	0.10000
0.1	1.9800	1.6800	1.3762	0.3037	0.20950	0.11499
0.2	2.0005	1.7767	1.5461	0.30812	0.2194	0.13010
0.3	2.0589	1.8931	1.7179	0.31326	0.22972	0.14535
0.4	2.1543	2.0329	1.8995	0.31909	0.24046	0.16078
0.5	2.2876	2.2001	2.0980	0.3256	0.25164	0.17639
0.6	2.4605	2.3992	2.3203	0.33279	0.26324	0.19222
0.7	2.6760	2.6350	2.5731	0.34064	0.27528	0.20826
0.8	2.9375	2.9123	2.8626	0.34914	0.28775	0.22454
0.9	3.2487	3.2361	3.1948	0.35826	0.30065	0.24105
1.0	3.6133	3.6107	3.5750	0.36799	0.31397	0.25780

5 Conclusion

In this paper, we consider a model which has a predator-prey structure between the monoclonal tumor and the macrophages. Building upon the work of F. Bozkurt [12], we include fuzzy initial values to study about the interaction of a monoclonal brain tumor and the macrophages to see the extinction conditions for the tumor population. And also by including on Allee threshold function to the model we have seen that by using fuzzy initial values, the uniqueness of the solution is lost. Furthermore, using the strongly generalized derivative biologically we obtain more realistic behavior that explains the interaction phenomena. In Figure 2, the graphical solution is compatible with a crisp solution. Being compatible with biological facts means that the tumor is increasing or decreasing and the macrophages are increasing or decreasing. It does not give us information about tumors and macrophages when it is differentiated as in Figure 2 (a), (b) and (c), so these conditions are biologically meaningless.

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