Multiscale fuzzy modeling and Mathematical problems Related To Tumor Evolution and Medical Therapy

R. Pakzad¹, M. Keshavarz¹*, M. Pakzad²

(1) Department of Mathematics, Science and Research Branch, Islamic Azad University, Tehran, Iran.
(2) Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran

Copyright 2016 © R. Pakzad, M. Keshavarz and M. Pakzad. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract
Many mathematical models have presented for preventing different diseases such as cancers. But the question often asked is why the suggested models are not effective for all people suffering from a special disease. Researchers have mentioned patients’ mental and physical conditions not considered by such models. In this article by consideration of special fuzzy factors, we attempt to present a model which can show the progress and dis-progression of cancer cells with attention to anatomical and physiological conditions of the body.

Keywords: Multiscale modelling, Distribution functions, Tumor evolution, Medical therapy, fuzzy Differential.

1 Introduction

Regarding mathematical modeling scientists, like Adam and Bellomo [1] Preziosi [8] raised significant issues. Considering these issues show that in less than one decade many changes have been made in mathematical modeling specially the interaction between mathematics and medicine. Similar discussions were presented by Chaplain [4] and Bellomo which are noteworthy. Other studies were conducted by Gatenby and Maini [7] in which mathematical symbols in cancer modeling are visible. Application of kinetic theory of mathematic methods for modeling the interaction between tumor cells and immune systems was introduced by Bellomo and Forni [2]. This research was based on the hypothesis of centralized interaction, which means that engagement between cells only happens if pair hub cells are in contact with each other. Another hypothesis was proposed by De Angelis and Mesi which showed the interaction of cells with all other cells.

In section 2, we present some basic definitions. In section 3, we propose our fuzzy method to solve a cancer modeling, and conclusions are drawn in section 4.
2 Preliminaries

Definition 2.1. A fuzzy number is a function such as \( u : \mathbb{R} \rightarrow [0, 1] \) satisfying the following properties:

1. \( u \) normal, i.e. \( \exists x_0 \in \mathbb{R} \) with \( u(x_0) = 1 \),
2. \( u \) is a convex fuzzy set i.e. \( u((1-\lambda)x + \lambda y) \geq \min \{u(x),u(y)\}, \forall x, y \in \mathbb{R}, \lambda \in [0,1] \),
3. \( u \) is upper semi-continuous on \( \mathbb{R} \),
4. \( \{x \in \mathbb{R} : u(x) > 0\} \) is compact, where \( \overline{A} \) denotes the closure of \( A \).

Definition 2.2. Let \( A, B \in \mathbb{R}_f \). If there exists \( C \in \mathbb{R}_f \) such that \( A = B + C \), then \( w \) is called the Hukuhara difference of \( A \) and \( B \), and it is denoted by \( A \ominus B \).

Definition 2.3. The generalized Hukuhara difference of two fuzzy number \( A, B \in \mathbb{R}_f \) is defined as follows

\[
A \ominus_{gH} B = C \iff \begin{cases} (i) & A = B + C, \\ (ii) & B = A + (-1)C. \end{cases}
\]

Please note that a function \( f : [a, b] \rightarrow \mathbb{R}_f \) is so called fuzzy-valued function. The parametric representation of fuzzy-valued function \( f : [a, b] \rightarrow \mathbb{R}_f \) is expressed by \( f_\alpha(t) = [f^-_\alpha(t), f^+_\alpha(t)] \), \( t \in [a, b] \), \( \alpha \in [0,1] \).

Definition 2.4. The generalized Hukuhara derivative of a fuzzy-valued function \( f : [a, b] \rightarrow \mathbb{R}_f \) at \( t_0 \) is defined as

\[
(f')_{gH}(t_0) = \lim_{h \to 0} \frac{f(t_0 + h) \ominus_{gH} f(t_0)}{h}
\]

If \( (f')_{gH}(t_0) \in \mathbb{R}_f \), we say that \( f \) is generalized Hukuhara differentiable (\( gH \)-differentiable) at \( t_0 \). Also we say that \( f \) is \( (i)-gH \)-differentiable at \( t_0 \) if

\[
\left( (f')_{gH} \right)_\alpha(t_0) = \left[ (f^-_\alpha)'(t_0), (f^+_\alpha)'(t_0) \right], \quad 0 \leq \alpha \leq 1.
\]

and that \( f \) is \( (ii)-gH \)-differentiable at \( t_0 \) if

\[
\left( (f')_{gH} \right)_\alpha(t_0) = \left[ (f^+_\alpha)'(t_0), (f^-_\alpha)'(t_0) \right], \quad 0 \leq \alpha \leq 1.
\]

3 Main section

Reference [3] offers a mathematical model and simulation of cancer cells behavior to deal with various factors. These models are presented in the same way for all patients with physiological, anatomic, psychological and environmental conditions. Often patients’ situations and their test did not confirm the model in this work we intend to deal with some parameters which are near to reality. The interaction between immune cells and neoplastic and environmental factors, is characterized by a situation and internal microscopic conditions which are completely different for various cells. This microscopic situation is a scalar \( \tilde{u} \in [0, \infty) \) (triangular fuzzy number) and it shows the progress for cancer cells and defense ability for immune cells and nutrition ability for environmental cells. We show the evolution of distribution function...
with normal distribution \( f_i = f_i(t, u) \) on \( U \) microscopic situation with mathematic models in which \( i=1 \) refers to tumor cells and \( i=2 \) refers to immune system and \( i=3 \) refers to environmental cells.

Mathematical modeling and evolution equation:

In this section we probe the interaction between test cells and field cells. These interaction cause a change in cells situation or quantities. The mathematical model is based on the following assumptions:

- \( f_i \) is a function with normal distribution \( W \) (crisp)
- \( U \) (fuzzy triangular)

\[
A[f_i] = \int_0^{\infty} wf_i(t, w)dw.
\]

\( \tilde{f}_i = \tilde{f}_i(t, \tilde{u}) \)

\[
f_i = (\tilde{u}, \mu, \sigma^2) = \frac{1}{\sqrt{2\pi}\sigma^2} \exp\left\{-\frac{1}{2\sigma^2} (\tilde{u} - \mu)^2\right\}
\]

\( \tilde{u} \in R_f, \mu, \sigma \in R \)

\[
f_{-i}(\tilde{u}, \mu, \sigma^2) = \min\left\{ \frac{1}{\sqrt{2\pi}\sigma^2} \exp\left\{-\frac{1}{2\sigma^2} (u - \mu)^2\right\}, u \in \tilde{u}[\alpha]\right\}
\]

\[
f_{+i}(\tilde{u}, \mu, \sigma^2) = \max\left\{ \frac{1}{\sqrt{2\pi}\sigma^2} \exp\left\{-\frac{1}{2\sigma^2} (u - \mu)^2\right\}, u \in \tilde{u}[\alpha]\right\}, \alpha \in [0, 1]
\]

- The action of the field cells with state \( w \) belonging to the \( k \)-th population on the test cells of the \( i \)-th population with state \( u \) is modeled by the superposition of two different actions: a conservative action which modifies the state of the particles, but not their number; and a non-conservative action which generates a birth or death process in the states of the interacting pair.

- Conservative actions are modeled by the function.

Assuming that \( U \) is a fuzzy number near to zero with membership function 1, \( \tilde{\phi}_{ik} \equiv \tilde{\phi}_{ik}(\tilde{u}, w) \)

\[
(3.1)
\]

such that its resultant action is

\[
\tilde{f}_i(t, \tilde{u}) = \frac{\partial}{\partial u} \left[ \tilde{f}_i(t, \tilde{u}) \sum_{k=1}^{3} \int_0^{\infty} \tilde{\phi}_{ik}(\tilde{u}, w)f_k(t, w)dw \right]
\]

\[
(3.2)
\]

- Non-conservative actions are modeled by the function.

Assuming that \( U \) is a fuzzy number but stable near to zero with membership function 1, \( \tilde{\kappa}_{ik}(\tilde{u}, w) \delta(v - \tilde{u}) \)

\[
(3.3)
\]

such that its resultant action is

\[
\sigma_i(t, \tilde{u}) = \tilde{f}_i(t, \tilde{u}) \sum_{k=1}^{3} \int_0^{\infty} \tilde{\kappa}_{ik}(\tilde{u}, w)f_k(t, w)dw
\]

\[
(3.4)
\]

- A source term can be added to model the inlet from the outer environment into the control volume.

The balance scheme which generates the model is reported in Fig. 1. Accordingly, the resultant structure of the evolution model, in the absence of inlet from the outer environment, is the following:

\[
\frac{\partial}{\partial t} \tilde{f}_i(t, \tilde{u}) + \frac{\partial}{\partial \tilde{u}} \left[ \tilde{f}_i(t, \tilde{u}) \sum_{k=1}^{3} \int_0^{\infty} \tilde{\phi}_{ik}(\tilde{u}, w)f_k(t, w)dw \right] = \tilde{f}_i(t, \tilde{u}) \sum_{k=1}^{3} \int_0^{\infty} \tilde{\kappa}_{ik}(\tilde{u}, w)f_k(t, w)dw
\]

\[
(3.5)
\]
In many cases when cancer cells stay next to immune cells, their progress will be low, but the important point which we should note is the extent of weakness of cancer cells progress beside immune cells and vice versa. So with fuzzy match of $\alpha_{ik}$ we can distinguish the range of progressing or disprogressing cells.

- $\alpha_{12}$ refers to the quality of weakening in progression of neoplastic cells due to encounters with active immune cells;
- $\alpha_{13}$ refers to the quality of increase in progression of neoplastic cells due to encounters with endothelial cells;
- $\alpha_{21}$ is the parameter corresponding to the quality ability of tumor cells to inhibit the active immune cells;
- $\alpha_{31}$ refers to the quality of weakening in the feeding ability of endothelial cells due to encounters with neoplastic cells.

Thus, the linear function resulting from the interaction of different cells types with each other would be as follows:

$$\bar{\varphi}_{11} = 0 \quad \bar{\varphi}_{12} = -\bar{\alpha}_{12} \mu \quad \bar{\varphi}_{13} = \bar{\alpha}_{13} \mu$$  
(3.6)

$$\bar{\varphi}_{21} = -\bar{\alpha}_{21} \mu \quad \bar{\varphi}_{22} = \bar{\varphi}_{23} = 0$$  
(3.7)

$$\bar{\varphi}_{31} = -\bar{\alpha}_{31} \mu \quad \bar{\varphi}_{32} = \bar{\varphi}_{33} = 0$$  
(3.8)

The interaction of similar cells with each other does not change their conditions but when one cancer cell interacts with immune cells or vice versa, it cause weakness in the status of the cells. Besides, when one environmental cell interacts with cancer cell it causes weakening of the progress of cancer cell, but the impact of cancer cells on environmental cells cause weakening the situation of environmental cell. Immune cells and environmental cells in contrast with each other do not make any changes in the status of each other. The models which show the proliferation or destruction of interacted cells are as follows:

$$\kappa_{11} = 0 \quad \kappa_{12} = -\beta_{12} \mu \quad \bar{\kappa}_{13} = \beta_{13} \mu$$  
(3.9)

$$\bar{\kappa}_{21} = \beta_{21} \mu \quad \kappa_{22} = \kappa_{23} = 0$$  
(3.10)

$$\kappa_{31} = -\beta_{31} \mu \quad \kappa_{32} = \kappa_{33} = 0$$  
(3.11)

$\beta_{ik}$ refers to proliferation and destruction interactions. In the model proposed in reference [3], changes in distribution function are considered as crisp while cells growth depends on the changes in cells situation and depend on their proliferation conditions. However, these changes are all qualitative. Thus, considering changes in the distribution function.

We write the gh- difference for type 1 and 2:

$$\frac{\partial \tilde{f}_I}{\partial t} = \frac{\partial}{\partial t}\left[\tilde{\alpha}_{12} \tilde{u}_I(t, \tilde{u})A[f_2](t) \odot_{gh} \tilde{\alpha}_{13} \tilde{u}_I(t, \tilde{u})A[f_2](t)\right]$$

$$+ \tilde{B}_{13} \tilde{u}_I(t, \tilde{u})A[f_3](t) \odot_{gh} \tilde{B}_{12} \tilde{f}_I(t, \tilde{u})A[f_2](t)$$

(i)

$$\frac{\partial \tilde{f}_I}{\partial t} = \frac{\partial}{\partial t}\left[\tilde{\alpha}_{12} \tilde{u}_I(t, \tilde{u})A[f_2](t) \odot_{h} \tilde{\alpha}_{13} \tilde{u}_I(t, \tilde{u})A[f_2](t)\right]$$

$$+ \tilde{B}_{13} \tilde{u}_I(t, \tilde{u})A[f_3](t) \odot_{h} \tilde{B}_{12} \tilde{f}_I(t, \tilde{u})A[f_2](t)$$
Considering the first and second derivatives of the situations described above.

(i) \[
\frac{\partial \tilde{f}_1}{\partial t} = \frac{\partial}{\partial t} \left[ \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) \cap \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) \right] \\
+ \tilde{B}_{12} \tilde{f}_1(t,u) A[f_2](t) \cap \tilde{\nu}_1 \tilde{B}_{12} \tilde{f}_1(t,u) A[f_2](t)
\]

Derivative type (1):

\[
\frac{\partial \tilde{f}_1}{\partial t} = \frac{\partial}{\partial u} \left[ \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) - \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) \right] \\
+ B_{12} \tilde{f}_1(t,u) A[f_2](t) - B_{12} \tilde{f}_1(t,u) A[f_2](t)
\]

Derivative type (2):

\[
\frac{\partial \tilde{f}_1}{\partial t} = \frac{\partial}{\partial u} \left[ \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) - \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) \right] \\
+ B_{12} \tilde{f}_1(t,u) A[f_2](t) - B_{12} \tilde{f}_1(t,u) A[f_2](t)
\]

(ii) \[
\frac{\partial \tilde{f}_1}{\partial t} = \frac{\partial}{\partial u} \left[ \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) \cap \tilde{\alpha}_{12} \tilde{\nu}_1(t,u) A[f_2](t) \right] \\
+ \beta_{12} \tilde{f}_1(t,u) A[f_2](t) \cap \beta_{12} \tilde{f}_1(t,u) A[f_2](t)
\]

Derivative type (1):

\[
\frac{\partial f}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{12} f_1(t,u) A[f_2](t) - \alpha_{12} f_1(t,u) A[f_2](t) \right] + \beta_{12} \tilde{f}_1(t,u) A[f_2](t) \\
- \beta_{12} \tilde{f}_1(t,u) A[f_2](t)
\]

\[
\frac{\partial \tilde{f}}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{12} f_1(t,u) A[f_2](t) - \alpha_{12} f_1(t,u) A[f_2](t) \right] + \beta_{12} \tilde{f}_1(t,u) A[f_2](t) \\
- \beta_{12} \tilde{f}_1(t,u) A[f_2](t)
\]

Derivative type (2):

\[
\frac{\partial \tilde{f}}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{12} f_1(t,u) A[f_2](t) - \alpha_{12} f_1(t,u) A[f_2](t) \right] + \beta_{12} \tilde{f}_1(t,u) A[f_2](t) \\
- \beta_{12} \tilde{f}_1(t,u) A[f_2](t)
\]
Given the gh difference for type 1 and 2 then for the derived types

Derivative type (1):

\[
\frac{\partial \hat{f}_2}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{31} u f_3(t) - \alpha_{12} u f_1(t) A[f_2](t) + \beta_{12} f_1(t) A[f_3](t) - \beta_{13} u f_1(t) A[f_3](t) \right]
\]

There are models for \( \hat{f}_2 \) as follows:

\[
\frac{\partial \hat{f}_2}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{21} u \hat{f}_2(t) A[f_1](t) + \beta_{21} u \hat{f}_2(t) A[f_2](t) \right]
\]

Examine the types of derivative for it.

Derivative type (1):

\[
\frac{\partial \hat{f}_1}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{21} u \hat{f}_1(t) A[f_1](t) + \beta_{21} u \hat{f}_1(t) A[f_2](t) \right]
\]

Derivative type (2):

\[
\frac{\partial \hat{f}_2}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{21} u f_2(t) A[f_1](t) + \beta_{21} u f_2(t) A[f_1](t) \right]
\]

Given the gh difference for type 1 and 2 then for the derived types

(1) \( \frac{\partial \hat{f}_3}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{31} u \hat{f}_3(t) A[f_1](t) \right] \bigotimes \beta_{31} \hat{f}_3(t) A[f_1](t) \)}

Derivative type (1):

\[
\frac{\partial \hat{f}_3}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{31} u \hat{f}_3(t) A[f_1](t) \right] \bigotimes \beta_{31} \hat{f}_3(t) A[f_1](t)
\]

Derivative type (2):

\[
\frac{\partial \hat{f}_3}{\partial t} = \frac{\partial}{\partial u} \left[ \alpha_{31} u f_3(t) A[f_1](t) \right] - \beta_{31} f_3(t) A[f_1](t)
\]
Derivative type (2):
\[
\frac{df_3}{dt} = \frac{\partial}{\partial u} \left[ \beta_3 f_3(t,u) A[f_1](t) \right] - \alpha_3 u f_3(t,u) A[f_1](t)
\]
\[
\frac{\partial f_3}{\partial t} = \frac{\partial}{\partial u} \left[ \beta_3 f_3(t,u) A[f_1](t) \right] - \alpha_3 u f_3(t,u) A[f_1](t)
\]

4 Conclusion

The problems of non-fuzzy function models that have different results in different patients was resolved by fuzzy models.

References


http://dx.doi.org/10.1016/0895-7177(94)90223-2

http://dx.doi.org/10.1080/1027336042000288633

http://dx.doi.org/10.1201/9780203494899.ch10

http://dx.doi.org/10.1142/S0218202501001501

http://dx.doi.org/10.1016/S0895-7177(03)00125-0

http://dx.doi.org/10.1038/421321a

http://dx.doi.org/10.1201/9780203494899