International Journal of Current Research and Modern Education (IJCRME)
ISSN (Online): 2455 - 5428
(www.rdmodernresearch.com) Volume I, Issue I, 2016

A NEW BIO MATHEMATICAL MODEL TO ESTIMATE THE EFFECT OF RHIL-6 INFUSION ON GROWTH HORMONE BY USING FUZZY TRANSFORM

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Abstract:

Infusion of IL-6 (interlukin-6) has physiological effect on circulating components of growth hormone (GH). GH, the prototypical anabolic hormone, is released in large quantities form the pituitary during intense exercise but so is IL-6, a GH antagonist. In many practical applications, it turns out to be useful to use the notion of fuzzy transform: once we have functions $A_1(x) \geq 0 \ldots A_n \geq 0$, with $\sum_{i=1}^{n} A_i(x)=1$, we can represent each function f (x) by the coefficients. Once we know the coefficients F_i, we can (approximately) reconstruct the original function f(x) as $\sum_{i=1}^{n} F_i.A_i(x)$. The original motivation for this transformation came from fuzzy modeling, but the transformation itself is a purely mathematical transformation. Thus, the empirical successes of this transformation suggest that this transformation can be also interpreted in more traditional (non-fuzzy) mathematics as well. Such an interpretation is presented in this paper.

Key Words: Growth Hormone, IL-6, Fuzzy Transform

1. Introduction:

IL-6 stimulates GH secretion in bell-shaped dose-response manner [13]. The recombinant human (rh) IL-6 was infused intravenously for 3 h to healthy humans to achieve circulating IL-6 levels comparable to those observed during strenuous, prolonged exercise [11,14]. GH, the prototypical anabolic hormone, is released in large quantities form the pituitary during intense exercise [3], but so is IL-6, a GH antagonist [1]. IL-6 plays a major mechanistic role in the GH. IL-6 infusion led to a significant increase in GH, peaking 1 h after the beginning of infusion ($P<0.001$). The F-transform of function f is a vector with weighted local mean values of f as components. The first step in the definition of the Fuzzy transform of f: $X \rightarrow R$ is a selection of a fuzzy partition of universal set X by [6, 7].

2. Fuzzy Transform and the Need for Its probabilistic Interpretation:

The basic functions are called membership functions of respective fuzzy sets, or, alternatively, granules, information pieces, etc. Their choice reflects the type of uncertainty which is related to the knowledge of x. Once the basic functions are selected, we define the Fuzzy transform of a continuous function $f : X \rightarrow R$ as a vector $(F_1, \ldots, F_n)$,

F-transform satisfies the following properties [6, 7]:

(i) $y = F_i$ minimizes $\int_a^b (f(x)-y)^2 A_i(x)dx$

(ii) For a twice continuously differentiable function f, $F_i = f(x_i) + O(h_i^2)$, where h_i is the length of the support of A_i.

Fuzzy transform is used in applications as a "skeleton model" of f. This model provides a compressed image if f is an image [2], values of a trend if f is a time series [9], a numeric Model if f is used in numeric computations (integration, differentiation) [8], etc.

3. Example:

Twelve young (ages 26 ± 2 yr), healthy, active, but not specifically trained men participated in the study. The subjects were divided into two groups (n=6 in each group), receiving either albumin or rhIL-6 infusion. The rhIL-6 was infused in a dose lower than that reported to be safe in other studies. The IL-6 doses were chosen on the basis of pilot experiments. The aim is to reach plasma levels of IL-6 characteristic of intense exercise or low-grade inflammation [12]. The rate of rhIL-6 infusion was 5μg/h, with albumin used as a vehicle. In the control group, only albumin was infused during the trial. Blood samples were collected at baseline, 1,2,3,4 and 5 h after the beginning of the 3-h rhIL-6 infusion. GH serum concentrations were determined by ELISA with the use of the DSL-10-1900 Active kit. Intra-assay coefficient of variation (CV) was 3.3-4.3%, interassay CV was 6.3-6.5%, and the sensitivity was 0.03mg/ml. The effect of rhIL-6 infusion on GH levels is shown in the Fig.1. There was a significant increase in GH plasma level only in the IL-6 infused subjects (from 0.039 ± 0.008 ng/ml at baseline to 4.32 ± 0.96 ng/ml peak at 1 h, P<0.001).

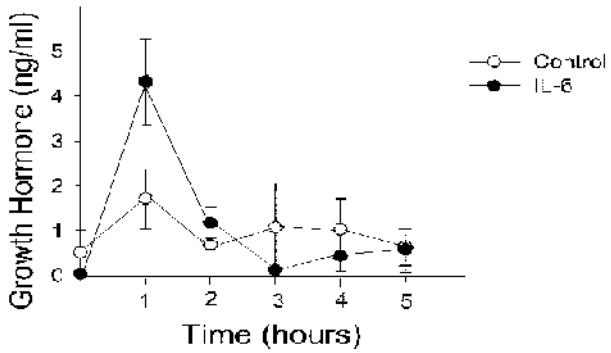

Figure: (1)

Let us give an example of the Fuzzy transform of

$$f_1(x)=\begin{cases}0.27x+0.11,\ x\in[0,1]\\ -0.23x+0.61,\ x\in[1,2]\\ 0.11x-0.07,x\in[2,3]\\ -0.045x+.41,x\in[3,4]\\ -0.14x+0.77,x\in[4,5]\end{cases}$$

$$f_2(x)=\begin{cases}x,x\in[0,1]\\ -0.73x+1.73,x\in[1,2]\\ -0.23x+0.73,x\in[2,3]\\ 0.07x-0.16,x\in[3,4]\\ -0.05x+0.3,x\in[4,5]\end{cases}$$

with respect A_1, A_2 …, A_5. For simplicity, we assume that basic functions A_1, …, A_5 are of triangular shape and constitute a uniform partition of (0,5). Their geometrical representation is as follows:

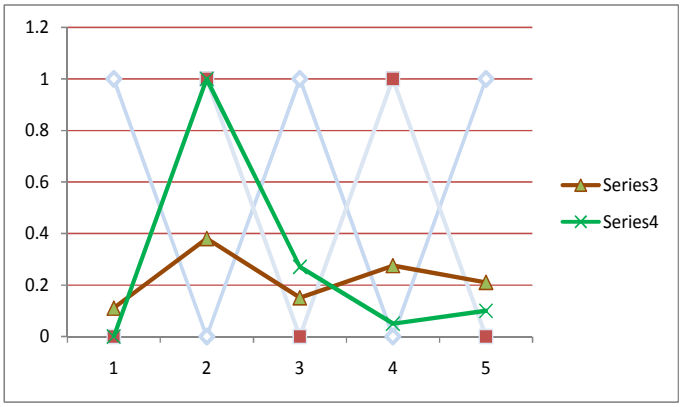

Figure: (2)
Series 3 = $f_1(x)$ & Series 4 = $f_2(x)$

Figure (2) provides a graphical representation of the basic functions $A_1, \ldots, A_5$, of the function f_1 (x) and $f_2(x)$ of its Fuzzy transform components $F_1, \ldots, F_5$, and of the inverse Fuzzy transform $F_1(x)$ and $F_2(x)$ (See Figure 3 to Figure 5)

4. Fuzzy Transform; Original Motivation:

The original motivation for Fuzzy transform came from fuzzy modeling [6,7]. For example, in the situation corresponding to the inverse Fuzzy transform, we have n rules

If x is A_1 then y = F_1,
.
.
If x is A_n then y = F_n …….. (4)

These rules are Takagi-Sugeno (TSK) rules with singleton (constant) right hand sides. For TSK rules, the value corresponding to a given input x is $\bar{f}$ (x) defined by in [7]. The purpose was to show that this type of modeling can be as useful in applications as more traditional techniques such as Fourier transform and wavelet transform. Moreover, Fuzzy transform has a potential advantage over Fourier and wavelet transforms: in contrast to the purely mathematical basic functions used in Fourier and wavelet transforms, the basic functions Ai in a fuzzy partition usually come from natural language terms like "low" or "high" [4, 5].

Just like any other tool of applied mathematics, Fuzzy transform is not a panacea. It is more successful in some problems, and in other problems, it is less successful. It is therefore desirable to combine Fuzzy transform with other mathematical tools, so as to combine relative advantages of different techniques. For combining Fuzzy transform with other mathematical tools, it is desirable to come up with a purely mathematical (non-fuzzy) interpretation for this transform. In particular, since most mathematical data processing tools are based on probability and statistics, it is desirable to come up with a probabilistic interpretation for F-transform.

5. The Known Probabilistic Interpretation of Fuzzy Modeling Leads to a Probabilistic Interpretation of Fuzzy Transform:

We have mentioned that Fuzzy transform was originally designed as a particular case of fuzzy modeling. A seminal paper [10] provided a reasonable probabilistic model

for a particular case of fuzzy modeling. Specifically, this paper shows that if we use piecewise constant probability density functions for describing the output, then we get a particular case of a fuzzy model, the case when we use product for "and" and sum for "or." Since Fuzzy transform corresponds to exactly this type of fuzzy modeling, we thus get a probabilistic model for Fuzzy transform as well.

In this paper, we show that a modification of the probabilistic interpretation from [10] enables us to justify formulas of Fuzzy transform without making any additional assumptions about the probability distributions. In mathematical terms, this modification consists of using Bayes formulas and making assumptions about prior distributions (a natural way to describe prior knowledge in statistics) instead of making assumptions about the actual distributions. Thus, we get an even more natural probabilistic interpretation of Fuzzy transform.

The values of the components F_1,... F_5 with respect to $f_1(x)$ of the Fuzzy transform are $F_1=0.2$, $F_2=0.297$, $F_3=0.203$, $F_4=0.24$, $F_5=0.2$ by using formula [6]

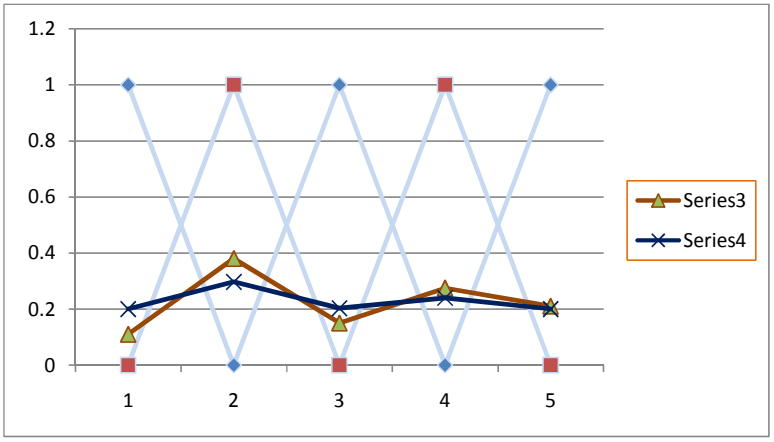

Figure: (3)

Series 3 = $f_1(x)$ & Series 4 = $\bar{f}_1(x)$

The values of the components F_1,... F_5 with respect to $f_2(x)$ of the Fuzzy transform are $F_1=0.34$, $F_2=0.71$, $F_3=0.357$, $F_4=0.097$, $F_5=0.09$ by using formula [6]

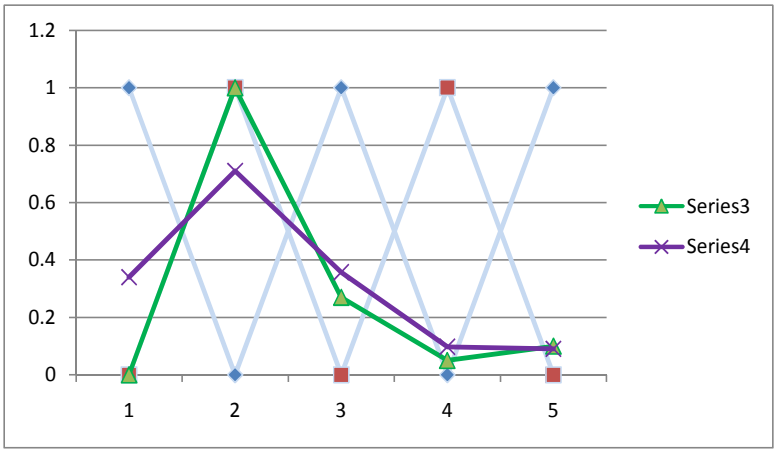

Figure: (4)

Series 3 = $f_2(x)$ & Series 4 = $\bar{f}_2(x)$

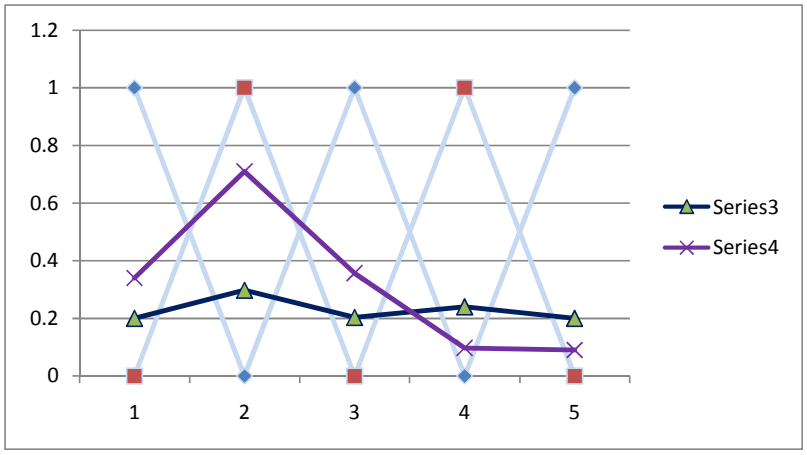

Figure: (5)

Series 3 = $\bar{f}_1(x)$ & Series 4 = $\bar{f}_2(x)$

6. Conclusion:

We describe a modification of a probabilistic interpretation described in [10]. In this modification, the corresponding probabilistic model uniquely leads to the formulas of the Fuzzy transform. A similar modification is described in a more general situation of fuzzy modeling. The results of these analyses, that infusion of IL-6 has effect on growth hormone, which are beautifully fitted with the Fuzzy transform. The results coincide with the mathematical and medical report.

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