Multistep Transformation Method for Discrete and Continuous Time Enzyme Kinetics

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***Abstract*— In this paper we develop the new physical-mathematical time scale kinetic approach-model applied on organic and non-organic particles motion. Concretely, here, at first, this new research approach is based on enzyme particles dynamics results. At the beginning, a time scale is defined to be an arbitrary closed subset of the real numbers *R*, with the standard inherited topology. Mathematical examples of time scales include real numbers *R*, natural numbers *N*, integers *Z*, the Cantor set (i.e. fractals), and any finite union of closed intervals of *R*. Calculus on time scales (TSC) was established in 1988 by Stefan Hilger. TSC, by construction, is used to describe the complex process. This method may utilized for description of physical (classical mechanics), material (crystal growth kinetics, physical chemistry kinetics - for example, kinetics of barium-titanate synthesis), (bio)chemical or similar systems and represents major challenge for contemporary scientists. In this sense, the Michaelis-Menten (MM) mechanism is the one of the best known and simplest nonlinear biochemical network which deserves appropriate attention. Generally speaking, such processes may be described of discrete time scale. Reasonably it could be assumed that such a scenario is possible for MM mechanism. In this work, discrete time MM kinetics (dtMM) with time various step h, is investigated. Instead of the first derivative by time used first backward difference h. Physical basics for new time scale approach is a new statistical thermodynamics, natural generalization of Tsallis non-extensive or similar thermodynamics. A reliable new algorithm of novel difference transformation method, namely multi-step difference transformation method (MSDETM) for solving system of nonlinear ordinary difference equations is proposed. If h tends to zero, MSDETM transformed into multi-step differential transformation method (MSDTM). In the spirit of TSC, MSDETM describes analogously MSDTM.**

Keywords—kinetics, enzymes, materials, ceramics, $BaTiO_3$, MSDETM .

I. INTRODUCTION

TSC, as a relatively new physical-mathematical method, is shown in [1], [2], [3]. Therefore,in scientific records we have analyzed that is evident a relatively small number appropriate applications or numerical methods for solving such nonlinear problems. One good choice, in this way, for solving numerical or practical problems, is the MSDTM [4], [5].

As we know, that in nature exists several examples of kinetics: classical mechanics (as a synonym of dynamics), fluid equations, plasma and chemical kinetics, particularly in chemical physics and physical chemistry and biology kinetics [6-13]. The well known is the fact that in medicine and biology holds a special position enzyme kinetics (**Figure 1**).

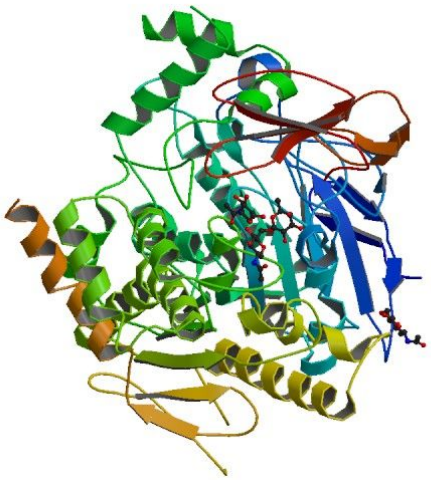

Figure 1. One example of enzyme: acetylcholinesterase (AChE). It is known that this enzyme catalyzes the breakdown of acetylcholine and of some other choline esters that function as neurotransmitters.

Kinetics, therefore, in principle, research many different materials, especially ceramics phenomena.

From the other side, in the area of a non-organic materials, we performed the investigations on BaTiO3 - ceramics [14-22] as an complex material example that is often used in different applications. Barium-titanate, as a crystallography, of the grains monocristals is a part of cubic "perovskite family". The perovskite structure is adopted by many oxides that have the chemical formula ABO_3 (**Figure 2 (a)**).

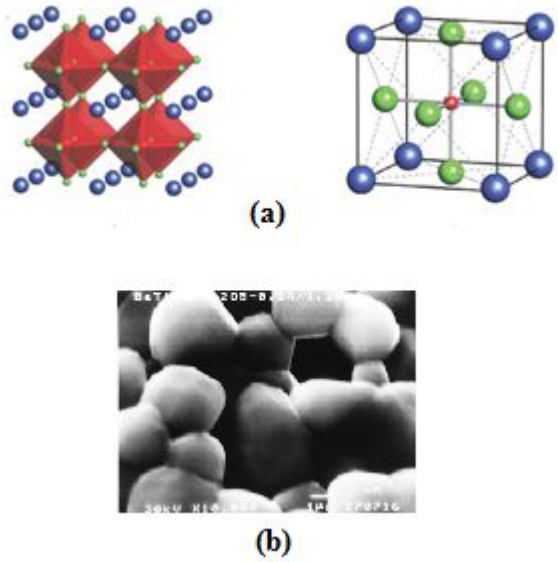

Figure 2. (a) Cubic perovskite-type structure ABO_3 [18]. **(b)** SEM micrograph of domain structure in sintered samples of $BaTiO_3$ sintered at 1300°C for 2h .

The growth kinetics process of single crystals is usually time-consuming business while the complexities of ceramic micro structures renders the prediction of properties of the ceramic from those of the corresponding single crystal very uncertain. Consequently, empirical observation has usually led to the establishment of new devices based on ceramics before there is more than a partial understanding of the underlying physical mechanisms. Barium-titanate ceramics (**Figure 2. (b)**) synthesis methods were mentioned in a lot of papers, introduces these are just some: conventional solid-state reaction, sol-gel, hydrothermal, coprecipitation, polymeric precursor and other consolidation methods as wel as mechanic- activated synthesis. All of these, are the subject of the future research and analysis which are, simultaneously, on the way.

In this article the modeling of synthesis of materials (ceramics) will be treated inversely. Due to the complexity of the material we will assume that the kinetics of the various natural process described with non-Boltzmann statistics [8], [9].

Similar, but extreme systems, in this context exists in biology [24-27]. However, this means that will be expands the theories of [3] and [24], in the sense that it will assume the existence of TSC processes, and, especially, their discrete time scale. In other words, it is assumed that the time sequences of events during the synthesis of materials - ceramics, is essential for its features.

From the point of, organic-non organic electronics ceramics higher level microelectronics miniturizations and integration new frontiers, view, we are opening the gate towards the new perspectives.

In the literature are known two approaches to the concept of discrete time for nature systems [23], [24].

The first approach is a primary physical, and it is assumed the existence of time particles - chronons. The second approach is biological, and then the discrete time is understood as a time crystal. Under second approach, here accepted, the meaning of the general TSC may be that the some processes in complex materials are understood, by definition, as a non-crystal, time depended. At the moment, it does not exist method of synthesis ceramics described by means of TSC. In this paper one simple and essential biophysical model - the discrete time MM reaction model will be considered. It is necessary to note that, mathematically speaking, this model may be applied to any time scale, and the same goes for the corresponding numerical method. In the paper [3], authors found that with discrete time as an independent variable in fractional continuous and discrete models as a generalization of corresponded ordinary calculi, of the cancer growth rate, and the best observation fit is provided when using appropriate fractional discrete Caputo operator and the discrete fractional Gompertz curve. However, tumor growth models using continuous fractional or ordinary calculus [25], [26] are also known in the literature. By example, the paper [25] used MM substrate model for the time growth description on the cellular population in multicellular organisms. Model in [25] describe micro environmental influence in tumorigenesis independent of genomic changes in the neoplastic populations. Next research shall consist in how to develop appropriate TSC software tool that would practically automatically extract kinetic parameters from experimental data, especially parameter h.

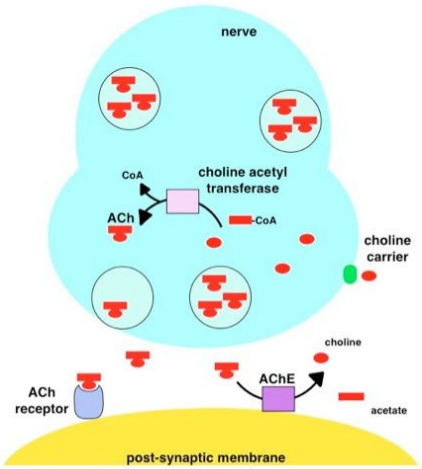

Figure 3 Example of kinetic: AChE mechanism of action [28]. Each molecule of AChE degrades about 25000 molecules of acetylcholine (ACh) per second, approaching the limit allowed by diffusion of the substrate [29].

The modern notion of enzymatic catalysis [27], was elaborated by Linus Pauling in 1946: in order to catalyze reactions, an enzyme must be complementary to the reaction transition state. MM kinetics is one of the best-known models of enzyme kinetics. It involves an enzyme E binding to a substrate S to form a ES is the enzyme–substrate complex, EP

enzyme–product intermediate complex, which in turn is converted into a product P and the enzyme. This may be represented schematically as

$$E + S \leftrightarrow ES \rightarrow EP \rightarrow P + E \qquad (1)$$

The symbols ↔ and → denote the reversible (equilibrium) and irreversible (one way) reaction steps. Applying the law of mass action, which states that the rate of a reactions are proportional to the products of the concentrations of the reactants, gives a system of four non-linear ordinary differential equations that define the rate of change of reactants with time t ("velocities"), for notation $s = [S]$, $e = [E]$, $c = [SE]$, $p = [P]$

$$\begin{aligned} \frac{ds}{dt} &= -k_1 es + k_{-1} c, \\ \frac{de}{dt} &= -k_1 es + (k_{-1} + k_2) c, \\ \frac{dc}{dt} &= k_1 es - (k_{-1} + k_2) c, \\ \frac{dp}{dt} &= k_2 c, \end{aligned} \qquad (2)$$

where the parameters k_1, k_{-1}, and k_2 are positive rate constants, with initial conditions $e(0)=e_0$, $s(0)=0$, $c(0)=0$, $p(0)=0$.

The assumptions for modeling the system of equations (2) are : (1) ES complex is in steady-state, which means that during the initial reaction phase concentration of the ES does not change, even when a large amount of substrate converted to product by using the ES complex; (2) under conditions of complete saturation of all the enzyme substrate is converted to a complex EC (no free enzyme molecules), a condition for this is that the high concentration of the substrate; (3) if all of the enzyme complex ES, then the rate at which the product generates a maximum and can be expressed by the equation: $v_{max} = k_3 [ES]$.

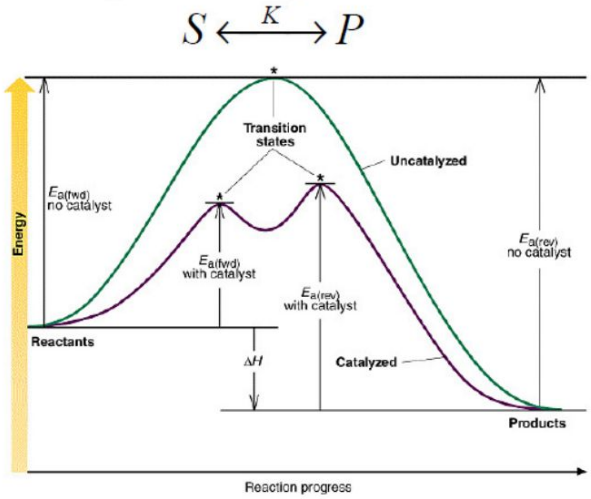

Figure 4. Continuous time chemical reaction. Enzymatic lowering the activation energy E_a.

Thermodynamic description mechanism of continuous time catalysis presents in **Figure 4**: activation energy is a equal the difference of entalpy of the system $E_a = \Delta H$ - basic feature of the enzyme is that it decreases activation energy for chemical reactions. Was established to assume: if the characteristic time scale chemical process that it is discreet, the previous graphics must be discreet. Thermodynamic description of such a system, by definition, is extension of Boltzmann approach .

In this paper, authors, consequently, numerically considering the nonlinear ordinary difference MM dynamics model, by analogy with [4] and [5]. To begin, DTM is one of the semi-numerical analytic methods for fractional, ordinary and partial differential equations that uses the form of generalized Taylor's polynomials as approximations of the exact solutions. The approximate solutions obtained by using DTM are valid only for a short time, while the ones obtained by using the MSDTM [4] are valid for wider time intervals. MSDTM may be treated as an algorithm in a sequence of small intervals (i.e., time steps Δt) for finding accurate approximate solutions to the corresponding systems. This method is one of the tools for solving different classes of nonlinear problems. In these work presents generalization of MSDTM - MSDTEM in the case discrete of the time scale $h\boldsymbol{Z}$ for nonlinear discrete time MM reaction model.

II. EXPERIMENTAL PROCEDURE

Based on bio-medical research results, we developed enough general experimental-theoretical models [3], [5], [24-33]. In [30] given is complete experimental procedure. Here is that experiment examines only conceptually.

The reaction scheme of enzymatic hydrolysis of the substrate S (i.e. ACH or ATCH) by the enzyme E (i.e. ACHE or BCHE) to products P (i.e. CH or TCH) and HA can be expressed by the steps: (1) E+S↔ES; (2) ES↔EA+P; (3) EA+H_2O→E+HA. If last reaction (due to the water excess) is very fast, it holds first part in (1) and ES+H_2O→E+P+HA with rate constant k_2. A steady state for the reaction components E and ES exists during the whole reaction course under condition that the initial molar concentration $[S]_0$ $[E]_0$ and the initial concentrations of all other components are zero. For such hydrolysis of S the classic MM (Briggs-Haldane) equation holds under given conditions (temperature, pH value, ionic strength etc.), and $[S]$, $[P]$ and $[HA]$ are molar concentrations with the relation $[S]=[S]_0-[P]=[S]_0-[HA]$.

The importance of this biochemical reaction is the following. Acetylcholine (ACh) hydrolysis by acetylcholinesterase (AChE) or butyrylcholinesterase (BChE) plays an important role at cholinergic synapses in electric impulse transmission, i.e., surplus of these enzymes in brain cells is considered as one possible reason of Alzheimer disease [30].

III. RESULTS AND DISCUSSION

In this section, with better understanding idea, we, at first, demonstrated and explained **discrete time Michaelis-Menten model** (dtMM) as our new contribution.

1. Model

If first backward difference of discrete real function $f_D(t)$: $h\mathbf{Z}\rightarrow\mathbf{R}$ defined by

$$\left(\nabla_h f_D\right)(t) := f_D(t) - f_D(t-h), \tag{3}$$

then dtMM reaction model reduced to the three non-linear ordinary difference equations

$$\begin{aligned}
\nabla_h s_D(t) &= -k_1 \cdot (es)_D(t) + k_{-1} c_D(t),\\
\nabla_h e_D(t) &= -k_1 \cdot (es)_D(t) + (k_{-1} + k_2) c_D(t),\\
\nabla_h p_D(t) &= k_2 c_D(t),
\end{aligned} \tag{4}$$

Of course, (4) satisfy the law of mass action. This system of equations is a subject of initial conditions: $e(0)=e_0$, $s(0)=0$, $p(0)=0$. System of equations (1) and the initial conditions can be represented in dimensionless form as follows [5]:

$$\begin{aligned}
\nabla_h u_D &= -\varepsilon \cdot u_D + \varepsilon(u_D + k_3 - \lambda) v_D,\\
\nabla_h v_D &= u_D + (u_D + k_3) v_D(t),\\
\nabla_h w_D(t) &= k_2 v_D(t)
\end{aligned} \tag{5}$$

with a initial conditions: $u_D(0)=1$, $v_D(0)=0$, $w_D(0)=0$ ($s\rightarrow u$, $e\rightarrow v$, $p\rightarrow w$). When $h\rightarrow 0$, then $u_D(t)\rightarrow u(t)$, $v_D(t)\rightarrow v(t)$, $w_D(t)\rightarrow w(t)$ (discrete tends to continuous functions: $\mathbf{R}\rightarrow\mathbf{R}$) and backward difference exceeding in the ordinary derivation; where λ, k_3, and ε are dimensionless parameters.

Discrete time scale approach, in the physical point of view, probably is a new, extended, statistical thermodynamics, natural generalization of non-extensive or similar thermodynamics [8], [9]. However, it is important to emphasize, in [3] and [24], exists experimental evidence or theoretical explanation to the concept of discrete time in biological systems.

1.1. Multi-step differential transformation method

Description of MSDTM follows. In this context, the following nonlinear initial value problem for one differential equation first order considered

$$f'(t) = G(t, f), \tag{6}$$

subject to the initial condition $f(0) = c_0$; $G(t, f)$ and $f(t)$ are real functions.

The ordinary differential transformation of the k-th derivative of time function $f(t)$ is defined as follows:

$$F(k) := \frac{\left(f^{(k)}(t_0)\right)}{k!}. \tag{7}$$

Where $f(t)$ is the original function and $F(k)$ is the transformed function (Taylor's coefficents at the point $t=t_0$). For implementation purposes, the function $f(t)$ is expressed by a finite series (inverse transfomation), for non-negative values of K,

$$f(t) = \sum_{k=0}^{K} F(k)(t-t_0)^k \tag{8}$$

as inverse transformation.

Let $[0, T]$ be the interval over which we want to find the solution of the initial value problem. MSDTM assume that the interval $[0,T]$ is divided into M subintervals $[t_{m-1}, t_m]$, $m=1,2,...,M$ of equal step size $\Delta t = T/M$ by using the nodes $t_m = m\Delta t$, $t_0 = 0$. A sequence of approximate solutions $f_m(t)$, $m = 1, 2, ..., M$, for the solution $f(t)$ expressed by

$$f(t) = \begin{cases} f_1(t) \text{ } t \in [0, t_1], \\ f_2(t) \text{ } t \in [t_1, t_2], \\ \vdots \\ f_M(t) \text{ } t \in [t_{M-1}, t_M], \end{cases} \tag{9}$$

in the sense

$$f_m(t) = \sum_{k=0}^{K} F(k, m)(t - t_{m-1})^k, \tag{10}$$

with the initial conditions: for $k = 2, 3, \ldots, M$,

$$f_k(t_{k-1}) \equiv F(0, k) \tag{11}$$

The main steps of the MSDTM, are the following: (1) We apply the differential transformation to the problem (5), and then the result is a recurrence relation for $F(k, m)$; (2) Solving this relation over each time subinterval $[t_{m-1}, t_m]$, $m = 1, 2, ..., M$, bearing in the mind initial conditions, and using the differential inverse transformation we can obtain the solution of the problem. If $\Delta t = T$, then MSDTM reduces to the classical DTM.

It is proved that, the approximated solutions obtained using DTM are not valid for large t for some systems. As demonstrated in the work [6], MSDTM is comparable with Runge-Kutta fourth order approximate solutions.

1.2. Multi-step difference transformation method

In discrete version of calculus [2], for $h > 0$, Equation (5) replaces with

$$\nabla_h f_D(t) = G_D(t, f_D) \tag{12}$$

and exists analog of Taylor's series and appropriate transformations are

$$F_D(k) = \frac{\left(\nabla_h^k f_D(t_0)\right)}{k!}. \quad (13)$$

Where is

$$(t-t_0)_h^{(k)} := h^k \frac{\Gamma\left(\frac{t-t_0}{h}+1\right)}{\Gamma\left(\frac{t-t_0}{h}+1-k\right)} \quad (14)$$

h-factorial function and

$$f_D(t) = \sum_{k=0}^{K} F_D(k)(t-t_0)_h^{(k)}, \quad (15)$$

For $h \to 0+$, Eqs. (13) and (15), tends to, respectively, (7) and (8), and $(t-t_0)_h^{(k)} \to (t-t_0)^k$.

Besides, in relation to (9), instead intervals used the corresponding discrete sets and valid

$$f_{Dm}(t) = \sum_{k=0}^{K} F_D(k,m)(t-t_{m-1})_h^{(k)} \quad (16)$$

and for $k = 2, 3, \ldots, M$, $M > 1$, $f_{Dk}(t_{k-1}) \equiv F_D(0, k)$.

2. Implementation MSDTM and MSDETM on a continuous and discrete time MM model

The specific parameters for the simulation of continuous and discrete enzyme kinetics are taken from [29]. The main reason for this, is the methodology of extraction parameters of a given experiment. Based on the model of discrete TSC, namely, it is possible to write a software tool for a similar, but extensive analysis of various processes in the time domain.

Basic extracted parameters from [29] are: $k_1=16847\ M^{-1}s^{-1}$, $k_{-1}=7\ s^{-1}$, $k_2=12\ s^{-1}$; $s_0=2.5\cdot10^{-3}\ M$, $e_0=5.4\cdot10^{-8}\ M$. Discussed a chemical reaction is a hydrolysis of ACH + ACHE2, HXA method. Normalized parameters are: $\lambda=0.2849$, $k_3=0.4511$ and $\varepsilon=2.16\cdot10^{-5}$.

To the **Figure 5**, basic parameters are: $\Delta t = 0.7$, $h = 0.01$, $M = 28$, $N = 20$. Nevertheless, the approximate solutions obtained using the fourth-order Runge-Kutta method (ode45 in Matlab) and MSDTM of concentrations of substrate u, enzyme-substrate complex v, and product w for fixed values of dimensionless reaction parameters k_3, ε, and λ, and MSDETM for the discrete case (u_D, v_D, w_D) , gives the same result.

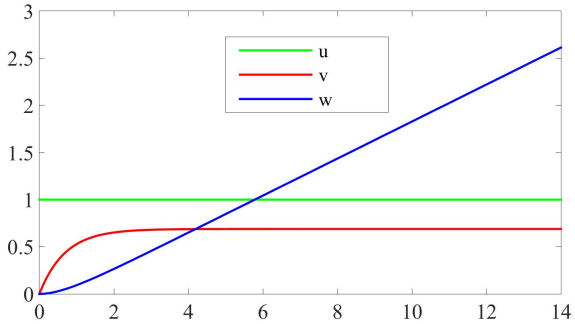

Figure 5. Profile of the normalized concentrations of the substrate *u*, enzyme-substrate complex *v*, and product *w* for $\lambda=0.2849$, $k_3=0.4511$ and $\varepsilon=2.16\cdot10^{-5}$. MSDETM, MSDTM solutions and Runge-Kutta method solution corresponds to the same lines.

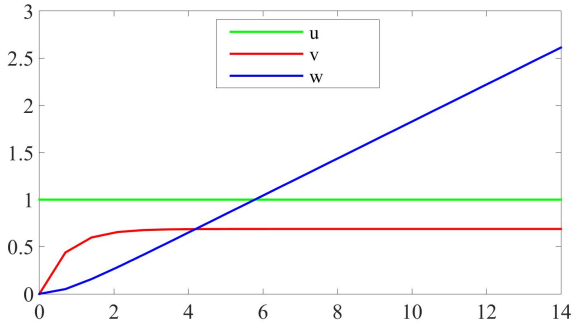

Figure 6. Profile of the normalized concentrations of the substrate *u*, enzyme-substrate complex *v*, and product *w* for $k\lambda=0.2849$, $k_3=0.4511$ and $\varepsilon=2.16\cdot10^{-5}$. MSDTM and Runge-Kutta method solution for $\Delta t = 1.4$, $h = 0.7$, $M = 10$, $N = 20$.

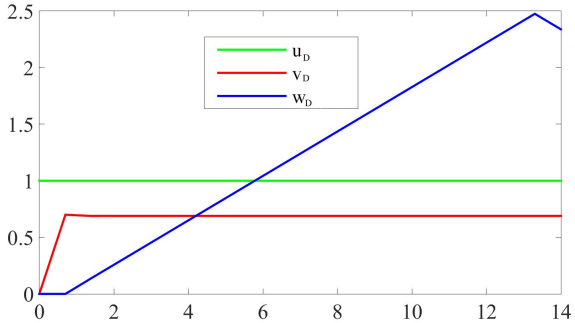

Figure 7. Profile of the normalized concentrations of the substrate u_D, enzyme-substrate complex v_D, and product w_D for $\lambda=0.2849$, $k_3=0.4511$ and $\varepsilon=2.16\cdot10^{-5}$. MSDETM solution for $\Delta t = 1.4$, $h = 0.7$, $M = 10$, $N = 20$.

Figure 6 and **Figure 7** corresponded, respectively, MSDTM and MSDETM solutions. It is easy to observe the significant differences between graphs, which means that it is important different kinetic models. Against this background, relatively new and good example for possible (fractional) time discretization or TSC is a kinetic model of barium-titanate ceramics aqueous and hydrothermal synthesis method in [15].

3. TSC new model dtMM Results and Discussion

At the end of these researched results reports, we would like to consider, discuss and to stress some points for future scientific investigations.

Nowadays, we are faced with new scientific goals and results, with intentions to sortout many bio medical problems and challenges, for example in DNA nanotechnology, bio design [34], new anticancer frontiers and solutions [35], growing and developing transplantations and replacements the human body organs and tissues with new design and developed high integrated components and devices like electronic (pump) heart, ice lenses, bones and her acceptance with the nature body, new complex human-robotics integrations and, generally, in all substitutions in human body natural materials with new advanced properties prognosis designed materials substitution. So, these results in lighting and trace the new processing and technologies.

IV. Conclusion

In this research, the application of MSDETM was introduced to obtain explicit and numerical solutions of a discrete and continuous time enzyme AChE kinetics. The multi-step DETM, as a new method for solving difference equations was meticulously proposed. MSDETM represents generalization on the MSDTM, in the sense of TSC. Bio-medical- physical-mathematical model provides immediate and visible analytic symbolic terms solutions, as well as numerical approximate solutions to nonlinear ordinary difference or differential equations.

Besides the biophysics and chaos in overall nature reality, there might be other applications of this difference-differential calculus. One of examples, in this sense, is the advanced materials, in particular ceramics, kinetics and, in general, bio-fluid dynamics creations. Also, all of these considered and discussed above, is our next research step on the way, of electronics ceramics materials consolidation and there is one additional possibility on the field of catalytic-electrochemical, electrolytic bulks, increasingly important for new and renewable battery storage and energy sources to.

At the end, we will not miss, one, also very excitingly increasing fractal nature materials, specifically ceramics structures, analysis Brownian particles motions, with fractals, thermodynamics fundamental parameters (temperature, entropy) and chaotic structures by fractals transformations from disorder to controlled order scientific results.

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