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Fractional Derivatives in Mathematical Model of the Acute Inflammatory Response

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Abstract
Systems of differential equations are of basic importance in Acute Inflammatory Response because many biological laws and relations appear mathematically in the form of a ordinary differential equations systems. In this article we present some applications of mathematical models represented by differential equations systems in Acute Inflammatory Response.A reduced mathematical model of acute inflammatory response is taken into account in this paper. The mathematical model is based on delicate system of check and balance between the response of instigator (usually a pathogen) and the temporal pro-inflammatory mediators (early late action). A fractional derivative model is proposed to replace a classical one using Caputo approach. The results of simulations are presented along with a comparison between fractional and integer derivative approaches.

Keywords: Fractional Derivatives, Mathematical Modeling, Acute Inflammatory, Matlab

Introduction

Fractional calculus was started at the end of the seventeenth century and consists in development of derivatives and integrals of arbitrary real and complex order (Podlubny : 1999). In the last years, an intensive research in both theory and applications has been conducted to many publications. The main motivation for this intensive progress is that a fractional model can be a more realistic approach of natural phenomena. The applications are in various fields as viscoelasticity (Meral :2010), signal processing (Saptarshi :2012), Timoshenko theory in mechanics (Oskouie :2017) and epidemiology (Pinto : 2017).There are not so many mathematical models of acute inflammatory response and the most notable, in our opinion, are presented in what follows. The acute inflammatory phenomenon is the response of the human body to pathogens action against it and has as scope the restoration of the health (Kumara: 2004 and Reynolds: 2006). An uncontrolled evolution of acute inflammation due to an infection is named sepsis (clinical definition) and can conduct to organ failure or even death of patient. A model with three differential equations consisting of one pathogen and two inflammatory mediators is proposed in (Kumara: 2004). Five clinical scenarios are taken into account and applied to model: healthy response, recurrent infection, persistent infectious inflammation, non-infectious inflammation, and severe immunodeficiency (Kumara: 2004). The authors applied later the model to a mathematical simulation of the inflammatory response to anthrax infection (Kumara: 2008). The activated macrophages are the primary defense that fights against microbial infections followed by activation of classically activated macrophages (typically activated by IFN-γ).A mathematical model based on system of differential equations that describes the interactions among cells, bacteria, and cytokines for both processes is proposed in (Friedman: 2009). Individual variations in acute inflammation Endotoxin-induced are studies using a two compartmental model in (Nieman: 2012). A Bayesian probabilistic approach to inflammatory response for influenza A virus (H1N1) for predictions of survival is proposed in (Price: 2015).

Materials and Methods

The α-th fractional order Riemann-Liouville integration of one function denoted by $f(t)$ on the interval [t_0, t] is defined by:

$$ {}_{t_0}I_t^{\alpha} f(t) = {}_{t_0}D_t^{\alpha} = \frac{1}{\Gamma(\alpha)} \int_{t_0}^{t} \frac{f(\tau)}{(t-\tau)^{1-\alpha}} d\tau \qquad (1)$$

Where $\Gamma(\cdot)$ is the Gamma function?

The α-th fractional derivative order of α>0 in the Riemann-Liouville sense of a continuous function $f(t)$ is defined as the *n*th derivative of fractional integral (1) of order *n*-α:

$$ {}_{t_0}D_t^{\alpha} f(t) = \left(\frac{d}{dt}\right)^n I^{n-\alpha} f(t) = \frac{1}{\Gamma(n-\alpha)} \frac{d^n}{t^n} \int_{t_0}^{t} \frac{f(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau \qquad (2)$$

Where *n* is the smallest integer larger or equal toα.

Given a continuous function $f(t)$ the Caputo fractional derivative of order α>0 at a time instant t ≥0 is defined as an n derivative of fractional integral (1) of order *n*-α:

$$ {}_{t_0}D_t^{\alpha} f(t) = I^{n-\alpha} \left(\frac{d}{dt}\right)^n f(t) = \frac{1}{\Gamma(n-\alpha)} \int_{t_0}^{t} \frac{f^{n}(\tau)}{(t-\tau)^{\alpha-n+1}} d\tau \qquad (3)$$

The Caputo operator for fractional derivative is used a large scale in engineering, and it is advantageous for differential equations with initial values. In this paper we will use the Caputo approach for system of partial differential equations that models the acute inflammatory response.

Based on finite difference, Grünwald–Letnikov definition is proven to be an equivalent to the Riemann– Liouville definition. The approach provides an interpolation between the derivatives of integer order *m*−1 and *m* [12].Various numerical methods were proposed in pornographies (Podlubny: 1999) or papers (Diethelm: 2004 and Kumar: 2006). Numerical methods (implicit and explicit) must conserve the main properties of fractional differential equations: stability, convergence and error behavior. In this paper we will use the predictor corrector algorithm, described in (Kumar: 2006) with later implementation in Matlab.

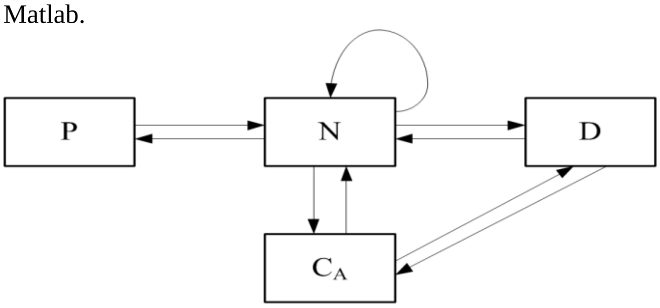

Fig.1: Four compartment model in acute model response. The arrows can be excitatory or inhibitory signals

The four equations for reduced model of acute immune response proposed in (Reynolds: 2006) are translated in fractional differential equations approach.

$$\begin{cases} \dfrac{d^{\alpha}P(t)}{dt^{\alpha}} = k_{pg}P(t)\left(1-\dfrac{P(t)}{P_{as}}\right) - \dfrac{k_{pm}s_m P(t)}{\mu_m + k_{mp}P(t)} - k_{pn}g(N)P(t) \\ \dfrac{d^{\alpha}N(t)}{dt^{\alpha}} = \dfrac{s_{nr}R(t)}{\mu_{nr}+R(t)} - \mu_n n(t) \\ \dfrac{d^{\alpha}D(t)}{dt^{\alpha}} = k_{dn}g_s(g(N)) - \mu_d D \\ \dfrac{d^{\alpha}C_A(t)}{dt^{\alpha}} = s_c + \dfrac{k_{cn}(N(t)+k_{cnd}D(t)}{1+g(N(t)+k_{cnd}D(t)} - \mu_c C \end{cases} \qquad (4)$$

Where

$$R(t) = g(k_{nn}N(t) + k_{np}P(t) + k_{nd}D(t)) \qquad (5)$$

$$g(X) = X/(1+(C_A/c_{as})^2) \qquad (6)$$

$$g_s(X) = X^6/(x_{dn}^6 + X^6) \qquad (7)$$

$$P_{as} = \lim_{t\to+\infty} P(t), \quad c_{as} = c_{\infty} \qquad (8)$$

The significations of variables are: P -activated phagocytes, N-activated neutrophils, D - tissue damage and C_A - anti-inflammatory mediators (cortical and interleukin-10). The other constants and functions g () and g_s() have the same significations as in (Reynolds: 2006).

Results & Discussion

The constants are set as in (Podlubny: 1999), and k_{pg} = 0.3/h. The initial conditions are set to P (0) =1, N (0) =0, D (0) = 0 and C_A=0. The saturation function g_s is expressed as Hill's equation with *n*=6.

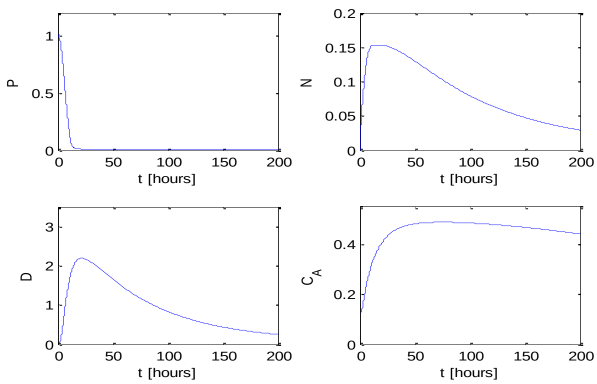

Fig.2: Healthy outcome, the curves for P(t), N(t), D(t) and C_A(t), model [7] based on fractional differential equations and α=0.9

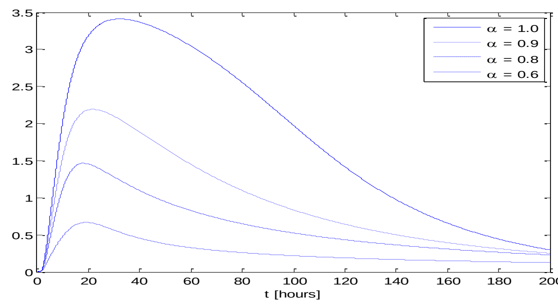

Fig.3: Healthy outcome, the curves for P (t), N (t), D (t) and C_A (t) and various α

In figure 1, we presented the graphics of P (t), N (t), D (t) and C_A (t) for healthy subject, with α=0.9, and in Figure 2.

The modification of shape of D (t) for various values of α. For α=1.0, the fractional differential equations (4) become as in (Reynolds: 2006), and the graphics have the same values.

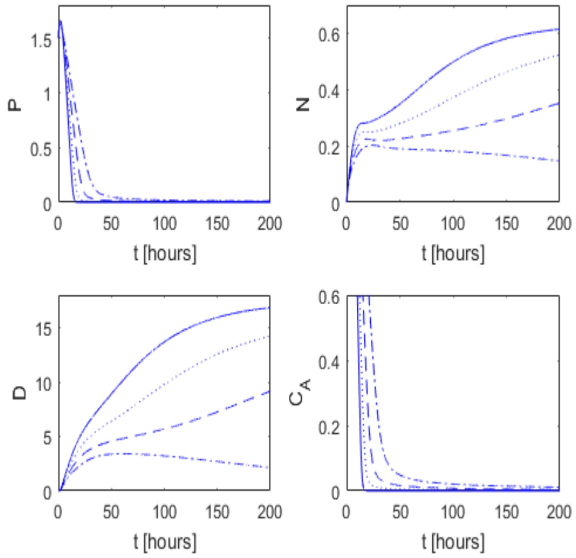

Fig.4: Aseptic death, k_{pg} = 0.3, initial conditions [P N D C_A] = [1.5 0 0 0.125]. The line patterns are: α = 1.0, normal differential equations, solid line; α = 0.9, dotted line; α = 0.8, dashed line; α = 0.6, dash-dot line.

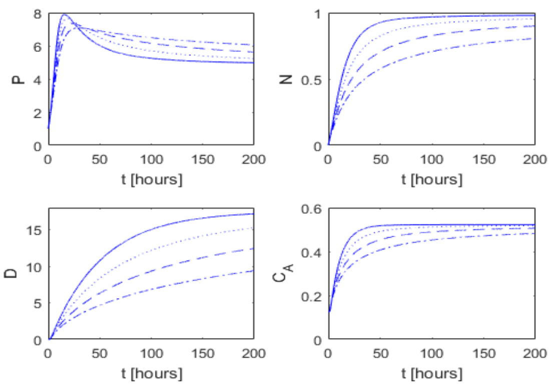

Fig.5: Septic death, k_{pg} = 0.6, initial conditions [P N D C_A] = [1.0 0 0 0.125]. The line patterns are: α = 1.0, normal differential equations, solid line; α = 0.9, dotted line; α = 0.8, dashed line; α = 0.6, dash-dot line.

Conclusions

In this paper we proposed to modify reduced mathematical model of acute inflammatory response to a fractional differential equation model. The model includes the differential equation model and fraction of differential. In some cases, this variant of model, taking into account the shape of functions, can fit better the experimental data. In the future we plan to extend the fractional differential equation model to more complex inflammatory models. In particular the numerical results suggest that the fractional differential equations play several important roles in the restoration of health.

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