ISSN : 2248-9622, Vol. 4, Issue 8(Version 2), August 2014, pp.29-33

RESEARCH ARTICLE OPEN ACCESS

Stochastic Model to Find the Gallbladder Motility in Acromegaly Using Exponential Distribution

P. Senthil Kumar*, A. Dinesh Kumar** & M. Vasuki***

*Assistant Professor, Department of Mathematics, Rajah Serfoji Government College (Autonomous), Thanjavur, Tamilnadu, India.

**Assistant Professor, Department of Mathematics, Dhanalakshmi Srinivasan Engineering College, Perambalur, Tamilnadu, India.

***Assistant Professor, Department of Mathematics, Srinivasan College of Arts and Science, Perambalur, Tamilnadu, India.

ABSTRACT

The purpose of the study was octreotide therapy in acromegaly is associated with an increased prevalence of gall stones, which may be the result of inhibition of gall bladder motility. Gall stone prevalence in untreated acromegalic patients relative to the general population is unknown, however and the presence of gall stones and gall bladder motility in these patients and in acromegalic patients receiving octreotide was therefore examined. Gall bladder emptying in untreated acromegalic subjects is impaired. Octreotide further increases post prandial residual gall bladder volume and this may be a factor in the increased gall stone prevalence seen in these patients.

The results of octreotide therapy in acromegalic and the normal controls were compared using the marginal distribution of a stretched Brownian motion $B(t^\alpha)$ as

$$f_*(x;t) = \frac{1}{\sqrt{4\pi t^\alpha}} exp\left\{\frac{-x^2}{4t^\alpha}\right\}$$

I. INTRODUCTION

The excessive and autonomous secretion of growth hormone in acromegaly may be reduced by the administration of somatostatin. The therapeutic value of somatostatin, however is limited by its very short plasma half life of 3 to 4 minutes. Octreotide, a long acting somatostatin analogue is now being used increasingly in the management of acromegalic patients. Patients with somatostatin producing tumours are known to have a high incidence of gallstone formation, possibly caused in part by impaired gallbladder emptying consequent upon inhibition of cholecystokinin and motilin, allowing a stasis of bile and thence crystal and subsequently stone formation. An increased prevalence of gall stones in acromegalic patients being treated with octreotide has been reported by several groups and it has been postulated that this may also be the result of impaired gall bladder contraction [1].

The master equation approach to model anomalous diffusion is considered. Anomalous diffusion in complex media can be described as the result of superposition mechanism reflecting in homogeneity and non stationary properties of the medium. For instance, when this superposition is applied to the time fractional diffusion process, the resulting master equation emerges to be the governing equation of the Erdelyi-Kober fractional diffusion, which describes the evolution of the marginal distribution of the Brownian motion, as

$$f_*(x;t) = \frac{1}{\sqrt{4\pi t^\alpha}} exp\left\{\frac{-x^2}{4t^\alpha}\right\}$$

This motion is a parametric class of stochastic processes that provides models for both fast and slow anomalous diffusion: it is made up of self similar processes with stationary increments and depends on two real parameters. The class includes the fractional Brownian motion, the time fractional diffusion stochastic processes, and the standard Brownian motion. In this frame work, the M-Wright function emerges as a natural generalization of the Gaussian distribution, recovering the same key role of the Gaussian density for the standard and the fractional Brownian motion.

II. NOTATIONS

$D_1(x)$	-	Drift Coefficient
$D_2(x)$	-	Diffusion Coefficient
$F(x)$	-	External Force Field
$K(x,t)$	-	Integral Operator
$L_\theta^{-\theta}(\xi)$	-	Stable Density
$P(D,x,t)$	-	Spectrum of Values of D
$B_H(t)$	-	Brownian Motion
C_α	-	Dimension
t	-	Assuming Time
x	-	Scale Parameter

III. THE MASTER EQUATION APPROACH

Statistical description of diffusive processes can be performed both at the microscopic and at the macroscopic levels. The microscopic level description concerns the simulation of the particle trajectories by opportune stochastic models. Instead, the macroscopic level description requires the derivation of the evolution equation of the probability density function of the particle displacement (the Master Equation) which is, indeed, connected to the microscopic trajectories. The problem of microscopic and macroscopic descriptions of physical systems and their connection is addressed and discussed in a number of cases.

The most common examples of this microscopic to macroscopic dualism are the Brownian motion process together with the standard diffusion equation and the Ornstein Uhlenbeck stochastic process with the Fokker Planck equation [2] & [8]. But the same coupling occurs for several applications of the random walk method at the microscopic level and the resulting macroscopic description provided by the Master Equation for the probability density function [10].

In many diffusive phenomena, the classical flux gradient relationship does not hold. In these cases anomalous diffusion arises because of the presence of nonlocal and memory effects. In particular, the variance of the spreading particles does no longer grow linearly in time. Anomalous diffusion is referred to as fast diffusion, when the variance grows according to a power law with exponent greater than 1, and is referred to as slow diffusion; when that exponent is lower than 1. It is well known that a useful mathematical tool for the macroscopic investigation and description of anomalous diffusion is based on Fractional Calculus.

A fractional differential approach has been successfully used for modelling purposes in several different disciplines, for example, statistical physics, neuroscience, economy and finance, control theory, and combustion science**.** Further applications of the fractional approach are recently introduced and discussed by [5].

Moreover, under a physical point of view, when there is no separation of time scale between the microscopic and the macroscopic level of the process, the randomness of the microscopic level is transmitted to the macroscopic level and the correct description of the macroscopic dynamics has to be in terms of the Fractional Calculus for the space variable [4]. On the other side, fractional integro / differential equations in the time variable are related to phenomena with fractal properties [9].

In this paper, the correspondence microscopic to macroscopic for anomalous diffusion is considered in the framework of the Fractional Calculus.

Making use of the grey noise theory, introduced a class of self similar stochastic processes termed grey Brownian motion. This class provides stochastic models for the slow anomalous diffusion and the corresponding Master Equation turns out to be the time fractional diffusion equation. This class of self similar processes has been extended to include stochastic models for both slow and fast anomalous diffusion and it is named generalized grey Brownian motion. Moreover, in a macroscopic framework, this larger class of self similar stochastic processes is characterized by a Master Equation that is a fractional differential equation in the Erdelyi Kober sense. For this reason, the resulting diffusion process is named Erdelyi Kober fractional diffusion [7].

IV. THE MASTER EQUATION AND ITS GENERALIZATION

The equation governing the evolution in time of the probability density function (pdf) of particle displacement $P(x;t)$, where $x \in R$ is the location and $t \in R_0^+$ the observation instant, is named Master Equation (ME). The time t has to be interpreted as a parameter such that the normalization condition $\int P(x;t)dx = 1$ holds for any t. In this respect, the Master Equation approach describes the system under consideration at the macroscopic level because it is referred to as an ensemble of trajectories rather than a single trajectory.

The most simple and more famous Master Equation is the parabolic diffusion equation which describes the normal diffusion. Normal diffusion, or Gaussian diffusion, is referred to as a Markovian stochastic process whose probability density function satisfies the Cauchy problem:

$$\frac{\partial P(x;t)}{\partial t} = D\frac{\partial^2 P(x;t)}{\partial x^2}, \quad P(x;0) = P_0(x) \tag{1}$$

where $D > 0$ is called diffusion coefficient and has physical dimension $[D] = L^2T^{-1}$. The fundamental solution of (1), also named Green function, corresponds to the case with initial condition $P(x;0) = P_0(x) = \delta(x)$ and turns out to be the Gaussian density:

$$f(x;t) = \frac{1}{\sqrt{4\pi Dt}} exp\left\{-\frac{x^2}{4Dt}\right\} \tag{2}$$

In this case, the distribution variance grows linearly in time, that is, $\langle x^2 \rangle = \int_{-\infty}^{+\infty} x^2 f(x;t)dx = 2Dt$. The Green function represents the propagator that allows to express a general solution through a convolution integral involving the initial condition $P(x;0) = P_0(x)$, that is,

$$P(x;t) = \int_{-\infty}^{+\infty} f(\xi;t)P_0(x-\xi)d\xi$$

Diffusion equation (1) is a special case of the Fokker Planck equation [8]

$$\frac{\partial P}{\partial t} = \left(-\frac{\partial}{\partial x}D_1(x) + \frac{\partial^2}{\partial x^2}D_2(x)\right)P(x;t) \tag{3}$$

where coefficients $D_1(x)$ and $D_2(x) > 0$ are called drift and diffusion coefficients, respectively. The Fokker Planck equation, also known as Kolmogorov forward equation, emerges naturally in the context of Markovian stochastic diffusion processes and follows from the more general Chapman Kolmogorov equation [2], which also describes pure jump processes.

A non Markovian generalization can be obtained by introducing memory effects, which means, from a mathematical point of view, that the evolution operator on the right hand side of (3) depends also on time, that is,

$$\frac{\partial P}{\partial t} = \int_0^t \left[\frac{\partial}{\partial x} D_1(x, t-\tau) + \frac{\partial^2}{\partial x^2} D_2(x, t-\tau)\right] P(x;\tau) d\tau$$

A straight forward non Markovian generalization is obtained, for example, by describing a phase space process (v, x), where v stands for the particle velocity, as in the Kramers equation for the motion of particles with mass m in an external force field $F(x)$, that is,

$$\frac{\partial P}{\partial t} = \left[-\frac{\partial}{\partial x} v + \frac{\partial}{\partial v}\left(v - \frac{F(x)}{m}\right) + \frac{\partial^2}{\partial v^2}\right] P(v, x; t) \qquad (4)$$

In fact, due to the temporal correlation of particle velocity, eliminating the velocity variable in (4) gives a non Markovian generalized ME of the following form [8]:

$$\frac{\partial P}{\partial t} = \int_0^t K(x, t-\tau) \frac{\partial^2}{\partial x^2} P(x;\tau) d\tau \qquad (5)$$

where the memory kernel $K(x, t)$ may be an integral operator or contain differential operators with respect to x, or some other linear operator.

If the memory kernel $K(x, t)$ were the Gelfand Shilov function

$$K(t) = \frac{t_+^{-\mu-1}}{\Gamma(-\mu)}, \quad 0 < \mu < 1$$

where the suffix $+$ is just denoting that the function is vanishing for $t < 0$, then ME (5) would be

$$\frac{\partial P}{\partial t} = \int_{0_-}^{t^+} \frac{(t-\tau)^{-\mu-1}}{\Gamma(-\mu)} \frac{\partial^2}{\partial x^2} P(x;\tau) d\tau = D_t^{\mu} \frac{\partial^2 P}{\partial x^2}$$

that is, the time fractional diffusion equation [5]**.** The operator D_t^{μ} is the Riemann Liouville fractional differential operator of order μ in its formal definition according to [3] and it is obtained by using the representation of the generalized derivative of order n of the Dirac delta distribution: $\delta^{(n)}(t) = t_+^{-n-1}/\Gamma(-n)$ with proper interpretation of the quotient as a limit if $t = 0$. It is here reminded that, for a sufficiently well behaved function $\varphi(t)$, the regularized Riemann Liouville fractional derivative of non integer order $\mu \in (n-1, n)$ is

$$D_t^{\mu} \varphi(t) = \frac{d^n}{dt^n}\left[\frac{1}{\Gamma(n-\mu)} \int_0^t \frac{\varphi(\tau) d\tau}{(t-\tau)^{\mu+1-n}}\right]$$

For any $\mu = n$ non negative integer, it is recovered the standard derivative

$$D_t^{\mu} \varphi(t) = \frac{d^n}{dt^n} \varphi(t)$$

Now consider a Physical Mechanism for Time Stretching Generalization, It is well known that the "Stretched" exponential $exp(-t^{\theta})$ with $t > 0$ and $0 < \theta < 1$, being a completely monotone function, can be written as a linear superposition of elementary exponential functions with different time scales T. This follow directly from the well known formula of the Laplace transform of the unilateral extreme stable density $L_{\theta}^{-\theta}(\xi)$ [6], that is,

$$\int_0^{\infty} e^{-t\xi} L_{\theta}^{-\theta}(\xi) d\xi = e^{-t^{\theta}}, t > 0, 0 < \theta < 1$$

Where

$$L_{\theta}^{-\theta}(\xi) = \frac{1}{\pi} \sum_{n=1}^{\infty} \frac{(-1)^{n-1}}{n!} \Gamma(1+n\theta) \sin(n\pi\theta) \xi^{-\theta n-1}$$

Putting $\xi = 1/T$, it follows that

$$\int_0^{\infty} e^{-t/T} L_{\theta}^{-\theta}\left(\frac{1}{T}\right) \frac{dT}{T^2} = e^{-t^{\theta}}, t > 0, 0 < \theta < 1 \qquad (6)$$

and $T^{-2} L_{\theta}^{-\theta}(1/T)$ is the spectrum of time scales T.

In the framework of diffusion processes, the same superposition mechanism can be considered for the particle probability density function. In fact, anomalous diffusion that emerges in complex media can be interpreted as the resulting global effect of particles that along their trajectories have experienced a change in the values of one or more characteristic properties of the crossed medium, as, for instance, different values of the diffusion coefficient, that is, particles diffusing in a medium that is disorderly layered.

This mechanism can explain, for example, the origin of a time dependent diffusion coefficient. Consider, for instance, the case of a classical Gaussian diffusion (1) where different, but time independent, diffusion coefficients are experienced by the particles. In fact, let $\rho(D, x, t)$ be the spectrum of the values of D concerning an ensemble of Gaussian densities (2) which are solutions of (1), that is,

$$f(x; t, D) = \frac{1}{\sqrt{4\pi Dt}} exp\left(-\frac{x^2}{4Dt}\right) \qquad (7)$$

where the dependence on the diffusion coefficient D is highlighted in the notation, then, taking care about physical dimensions, in analogy with (6):

$$\begin{aligned} \int f(x; t, D) \rho(D, x, t) dD &= \frac{1}{\sqrt{4\pi C_{\alpha}^{1-\alpha/2} t^{\alpha}}} exp\left\{-\frac{x^2}{4C_{\alpha}^{1-\alpha/2} t^{\alpha}}\right\} \\ &= f\left(x; \frac{C_{\alpha}^{1-\alpha/2} t^{\alpha}}{D_0}, D_0\right) \qquad (8) \\ &= f_*(x; t) \end{aligned}$$

where $0 < \alpha < 2$, D_0 is a reference diffusion coefficient according to notation adopted in (7) and

$$\rho(D, x, t) = \frac{x^{2-4/\alpha} t^{3/2-\alpha/2}}{(4C_{\alpha})^{1-2/\alpha} C_{\alpha}^{(1-\alpha/2)/2} D^{3/2}} L_{\alpha/2}^{-\alpha/2}\left[\frac{x^{2-4/\alpha} t}{(4C_{\alpha})^{1-2/\alpha} D}\right]$$

Hence, the superposition mechanism corresponds to a "Time Stretching" in the Gaussian distribution of the form $t \to C_{\alpha}^{1-\alpha/2} t^{\alpha}/D_0$ and the additional parameter C_{α} has dimension: where $[C_{\alpha}] = [L^2 T^{-\alpha}]^{1/(1-\alpha/2)}$. From now on, in order to lighten the notation, it is set that $D_0 = 1$ and $C_{\alpha} = 1$.

Note that the Gaussian probability density function in (8)**,** that now reads

$$f_*(x;t) = \frac{1}{\sqrt{4\pi t^\alpha}} exp\left(-\frac{x^2}{4t^\alpha}\right) \quad (9)$$

can be seen as the marginal distribution of a "Stretched" Brownian motion $B(t^\alpha)$. Such a process is actually a stochastic Markovian diffusion process and it is easy to understand that the "Anomalous" behavior of the variance comes from the power like time stretching. However, the Brownian motion stationarity of the increments is lost due to just the nonlinear time scaling. One can preserve the stationarity on the condition to drop the Markovian property. For instance, the probability density function given in (9) is also the marginal density function of a fractional Brownian motion $B_H(t)$ of order $H = \alpha/2$. Such a process is Gaussian, self similar, and with stationary increments.

V. EXAMPLE

Fifty one patients with acromegaly were studied. The clinical diagnosis of acromegaly was confirmed by a $75g$ glucose tolerance test during which circulating growth hormone failed to fall below $2mu/I$. The average basal serum growth hormone obtained in each patient from a five point day curve performed on samples drawn through an indwelling venous cannula over 12 hours ranged from 5 to $1135mu/I$, and no sample was $< 2mu/I$. Nine of the acromegalic patients had gall bladder motility studies performed before and after treatment with octreotide, and the effect on gall bladder fasting and residual volume is shown in figure (1). Fasting volume increased with octreotide in seven of the nine patients. This was not statistically significant. Residual volume however increased in all but one of the patients [1].

Figure (1): Gall Bladder fasting and residual volumes in acromegalic patients before and after treatment with octreotide.

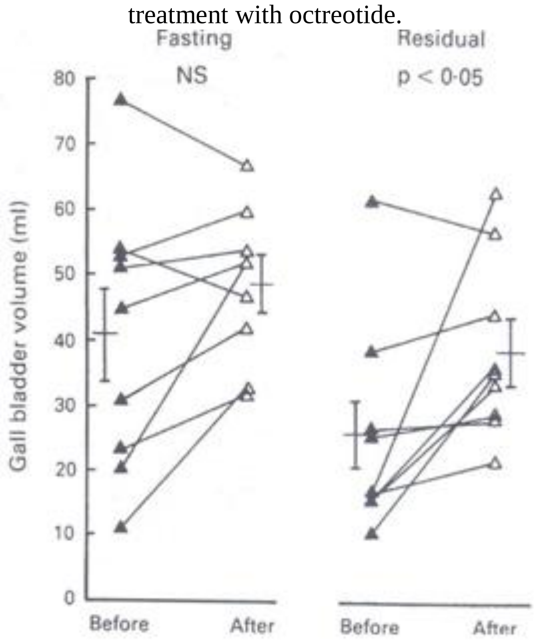
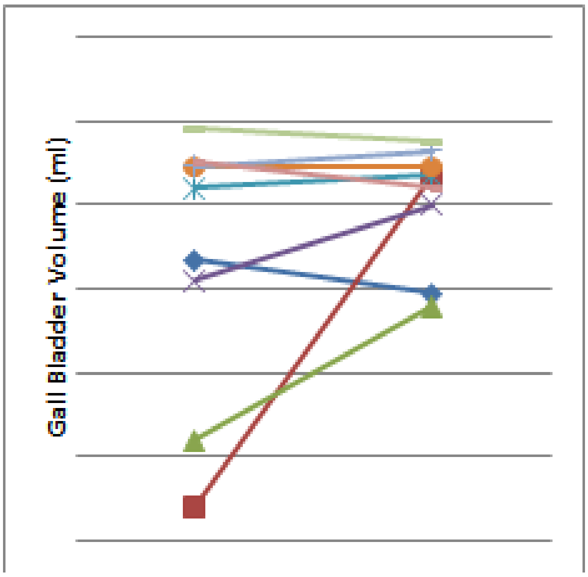
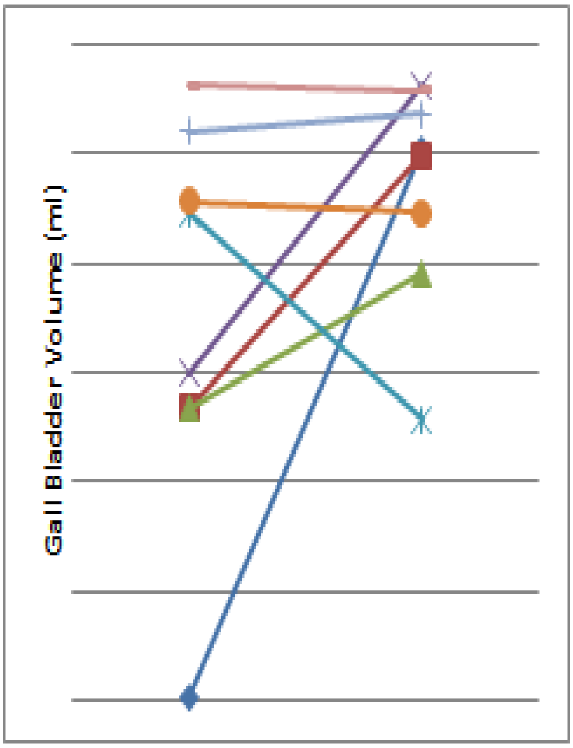


Figure (2): Gall Bladder fasting volume in acromegalic patients before and after treatment with octreotide.



Fasting

Figure (3): Gall Bladder residual volume in acromegalic patients before and after treatment with octreotide.



Residual

VI. CONCLUSION

The mathematical model also stresses the same effect of acromegalic patients and non acromegalic patient's conditions, which are beautifully fitted with the marginal distribution of a stretched Brownian motion. The results of these analysis shows that octreotide therapy is associated with an increased prevalence of gall stones and that duration of treatment seems to be important. Impaired gall bladder emptying is associated with this increased risk. It also shows that acromegalic patients not treated with octreotide have abnormal gall bladder which empty poorly. The medical report {Figure (1)} is beautifully fitted with the mathematical models {Figure (2) and Figure (3)}; $(i.e)$ the results coincide with the mathematical and medical report.

REFERENCES

[1] Catnach S M, Anderson J V, Fairclough P D and Trembath R C, "*Effect of Octreotide on Gall Stone prevalence and Gall Bladder motility in Acromegaly*", Gut 1993, 34: 270-273.

[2] Gardiner C W, "*Handbook of Stochastic Methods for Physics, Chemistry and the Natural Sciences*", Springer, Berlin, Germany, 2nd Edition, 1990.

[3] Gorenflo R and Mainardi F, "*Fractional Calculus: Integral and Differential Equations of Fractional Order*", in Fractals and Fractional Calculus in Continuum Mechanics, A. Carpinteri and F.Mainardi, Eds., 223-276, Springer, 1997.

[4] Grigolini P, Rocco A and West B J, "*Fractional Calculus as a Macroscopic Manifestation of Randomness*", Physical Review E, Volume 59, Number 3, 2603-2613, 1999.

[5] Klafter J, Lim S C and Metzler R, "*Fractional Dynamics*", Recent Advances, World Scientific, Singapore, 2012.

[6] Mainardi F, Luchko Y and Pagnini G, "*The Fundamental Solution of the Space-Time Fractional Diffusion Equation*", Fractional Calculus and Applied Analysis, Volume 4, Number2, 153-192, 2001.

[7] Pagnini G, "*Erdelyi Kober Fractional Diffusion*", Fractional Calculus and Applied Analysis, Volume 15, Number 1, 117-127, 2012.

[8] Risken H, "*The Fokker Planck Equation: Methods of Solution and Applications*", Springer, Berlin, Germany, 2nd Edition, 1989.

[9] Rocco A and West B J, "*Fractional Calculus and the Evolution of Fractional Phenomena*", Physica A, Volume 265, 535-546, 1999.

[10] Wesis G H, "*Aspects and Applications of the Random Walk*", North Holland Publishing, Amsterdam, The Netherlands, 1994