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Parameter Estimation for Subdiffusions within Proteins in Nanoscale Biophysics

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ABSTRACT
In this paper we study estimation of unknown parameter in the subdiffusion model based on discrete observations. We obtain consistency and asymptotic distribution properties of the estimator. The limit distributions are shown to be different in sub-critical, critical and super-critical cases.

KEYWORDS
Subdiffusion, fractional Brownian motion; method of moments; fractional Langevin equation; nanoscale biophysics; COVID-19

1. Introduction

Stochastic differential equation (SDE) has applications in biophysics, statistical physics, climate and weather sciences, interface growth, turbulence in fluid dynamics, polymer structure, finance and sports. The SDE can be used to model air pollution, dye dispersion or traffic flow with the solution representing the density of the pollutant (or dye or traffic). SDE can be useful for modeling long-range correlations of DNA sequences. Molecular motors play a key role for generation of movements and forces in cells. SDE can be useful for modeling in biophysis, e.g., what is the maximal excursion of a molecular motor against or in the average direction of the motor within a given time? How long does it take a motor to reach its maximum excursion against the chemical bias? What is the entropy production associated with an extreme fluctuation of a molecular motor? Other examples are microtubule catastrophes or a sperm winning a race against a billion competitors. Stochastic nonlinear differential equation has particular applications which involve a two-phase fluid flow, which has been used to study the flow of water through oil in a porous medium. For porous media flows, the spatial variations of porous formations occur on all length scales, but only variations at the largest length scales are reliably reconstructed from data. The heterogeneities occurring in the smaller lengths scales are incorporated stochastically.

Neurons express intrinsic bioelectrical activity which is known to be stochastic in nature. Hence parameter estimation in biological models of neurons and neural networks are very important problems. These can be treated as hidden Markov models.

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In particular, stochastic Hodgkin-Huxley type model is a very important biophysical model. In cellular biophysics, the mathematical reconstruction of nerve impulse was studied by Hodgkin and Huxley [1] which won them a Nobel prize in 1965. Hodgkin and Huxley [1] introduced a model for the membrane current of the squid giant axon. Their seminal work was immediately recognized as a breakthrough in the understanding of nerve excitation and their mathematical model of ion currents across the membrane of excitable cells have been used extensively.

The mammalian central nervous system consist of the brain and the spinal cord. The major component of the brain are the cerebral hemisphere which are linked with the millions of nerve fibers which constitute the corpus callosum. In man, each hemisphere, if laid out flat will would have an area of 1200 square cm and 3 mm thick. The nervous system consistent of discrete units called neurons. There are 0.25 billion neurons in a whole brain. Neurons are pyramidal cells and has a branching structure called dendrides and referred to as dendritic trees originates from a relatively compact cell body called soma. A typical soma dimension is 20 to 50 microns, typical dendride diameters range from a few to 10 microns. From a soma will usually project an action which transmits action potentials to its endings, called telodendria, these in turn make contact with other nerve cells or muscle cells.

Penetration of a neuron's membrane with a microelectrode shows that when a cell is in the resting state, the electrical potential is about -70mV inside relative to that of external medium. The membrane potential V_m is defined as the inside potential minus the outside potential. The latter is usually set arbitrarily zero, so the resting membrane potential is $V_{m,R} = -70mV$. The depolarization is defined as $V = V_m - V_{m,R}$. A cell is said to be excited (or depolarized) if $V > 0$ and inhibited (or hyperpolarized) if $V < 0$. In many neurons, when a sufficient (threshold) level of excitation is reached, an action potential may occur. The time interval between action potential, called the interspike intervals is random. The input current is a random process.

From their experimental results on ionic currents for squid axon under voltage clamp, Hodgkin and Huxley [1] formulated a system of nonlinear reaction diffusion equations with four components: voltage, potassium activation, sodium activation and sodium inactivation.

The stochastic version of Hodgkin-Huxley model is the following SDE: Let X be the gating process for the voltage dependent ion channel satisfying

$$dX_t = (\alpha(V_m)(1 - X_t) - \beta(V_m)X_t)dt + \sigma dW_t, \ t \geq 0$$

where α and β are the rate functions of activation or inactivation processes, W is a Brownian motion and σ is the intensity of random fluctuations. Here V_m is the change in the membrane potential in the intracellular calcium concentration. See Tuckwell [2] and Ermentrout and Terman [3]. For parameter estimation in Hodgkin-Huxley model, see Willms *et al.* [4].

Subdiffusion model is a very important to molecular biology, especially for particles in complicated solvent environments. Yang *et al.* [5] observed subdiffusion phenomenon while conducting single molecule experiments on a protein-enzyme system. The experiment studied a protein-enzyme compound called Fre, which is involved in the DNA synthesis of the bacterium *E. Coli.* In the reactions, Fre works as a catalyst. The crystal structure of Fre contains two smaller structures: FAD (an electron carrier) and Tyr (an amino acid). The 3D conformation (shape) of Fre spontaneously fluctuates, and consequently, the (edge-to-edge) distance between the two substructures FAD (flavin adenine dinucleotide) and Tyr (tyrosine) varies over time. It was found in the experiment that the stochastic distance fluctuation between FAD and Tyr undergoes a subdiffusion. A major class of anomalous diffusion is subdiffusion. The subdiffusion phenomenon is widespread in condensed phase system. The distance between a donor and an acceptor of electron transfer within a single protein molecule undergoes subdiffusion. The fluctuation of protein conformation results in dynamic disorder of enzymatic rates. In a living cell, many important biological functions are often carried out by single molecules. The model is non-Markovian and non-semimartingale. Adding a fractional Gaussian noise into a stochastic integro-differential equation framework governed by generalized Langevin equation gives subdiffusion. Kou [6] studied this model and gave a spectral analysis of the stochastic integro-differential equations along with a microscopic derivation of the model from a system of interacting particles. Sieve estimation in interacting particle systems of diffusions was studied in Bishwal [7]. Bernstein-von Mises Theorem and Bayes estimation in interacting particle systems of diffusions was studied in Bishwal [8]. Robust and efficient estimation in Gompertz diffusion model of tumor growth was studied in Bishwal [9]. Recently Baltazar-Larios *et al.* [10] studied maximum likelihood estimation for a stochastic SEIR (Susceptible-Exposed-Infected-Recovered) system with a COVID-19 application. A fractional anti-persistent model of stochastic SIRD type for COVID-19 pandemic was proposed in Alos *et al.* [11].

Parameter estimation of stochastic models is an inverse problem which is useful for any implementation. Here we study estimation in a theoretical model for subdiffusion based on generalized Langevin equation with fractional Gaussian noise with long memory. Under a harmonic potential this model describes a stationary Gaussian fluctuation at a broad range of time scales. Parameter estimation for directly observed stochastic differential equations was studied in Bishwal [12]. Minimum contrast estimation in fractional Ornstein-Uhlenbeck process was studied in Bishwal [13]. Wang *et al.* [14] estimated the parameter in the fractional Ornstein-Uhlenbeck process by the method of moments. Parameter estimation in partially observed SDE models including stochastic volatility models was studied in Bishwal [15]. In this paper, based on discrete observations, we estimate the unknown parameter in the bivariate subdiffusion cum displacement model by the method of moments and obtain consistency and asymptotic distribution property of the estimator.

2. Fractional Model and Preliminaries

Consider the bivariate displacement and subdiffusion model

$$
\begin{aligned}
dY_t &= X_t dt, \ t \geq 0, \\
m\, dX_t &= -\theta \left(\int_{-\infty}^{t} X_u K_H(t-u) du \right) dt - U'(Y_t) dt + \sqrt{2\theta \kappa_B T}\, dW_t^H, \ t \geq 0
\end{aligned}
$$

where $K_H(t) = 2H(2H-1)|t|^{2H-2}$ for $t \neq 0$, $(W_t^H, t \geq 0)$ is fractional Brownian motion with Hurst parameter $H \in (1/2, 1)$, $U(y)$ is an external potential and ψ is the strength of the potential, κ_B is the Boltzmann constant, T is the underlying temperature and $\theta > 0$ is the unknown parameter. Under harmonic potential $U(y) = m\psi y^2/2$, we have $U'(y) = m\psi y$ where m is the mass of the particle. The process (Y_t) is observed at discrete time points $t_i, i = 0, 1, 2, \ldots, n$ with $t_i - t_{i-1} = \Delta > 0$.

For the standard Langevin equation ($H = 1/2$),

$$m dX_t = -\theta X_t dt + \sqrt{2\theta \kappa_B T} dW_t,$$

$$E(X_t X_s) = \frac{\kappa_B T}{m} \exp(-\frac{\theta}{m}|t-s|),$$

$$Var(Y_t) = E(X_t^2) = \int_0^t \int_0^t E(X_u X_s) du ds = 2\frac{\kappa_B T}{\theta} t - 2\frac{\kappa_B T m}{\theta^2}(1 - \exp(-\frac{\theta}{m} t) \sim 2\frac{\kappa_B T}{\theta} t$$

for large t.

Diffusions in proteins are classified as: Subdiffusion ($1/2 < H < 1$), Superdiffusion ($0 < H < 1/2$), Diffusion ($H = 1/2$).

Subdiffusions are classified as follows: Weak Subdiffusion: ($1/2 < H < 3/4$), Critical Subdiffusion: $H = 3/4$, Strong Subdiffusion: ($3/4 < H < 1$).

The fractional Brownian motion (fBm) with Hurst index H is a centered Gaussian process with locally Hölder continuous paths of any order smaller than H and covariance function

$$E[W_t W_s] = \frac{1}{2}(|t|^{2H} + |s|^{2H} - |t-s|^{2H}), \ s, t \geq 0.$$

The parameter H with $0 \leq H \leq 1$ is the Hurst index which produces the Brownian motion when $H = 1/2$. The increments of fBm are positively correlated for $H > 1/2$ (persistent diffusion) and negatively correlated for $H < 1/2$ (rough diffusion). FBm is self similar (scale invariant) and it can be represented as a stochastic integral with respect to standard Brownian motion. For $H \neq \frac{1}{2}$, the fBm is not a semimartingale and not a Markov process, but a Dirichlet process. The parameter H which is also called the self similarity parameter, measures the intensity of the long range dependence. The ARIMA(p, d, q) with autoregressive part of order p, moving average part of order q and fractional difference parameter $d \in (0, \ 0.5)$ process converge in Donsker sense to fBm.

As a generalization of fractional Brownian motion we get the Hermite process of order k with Hurst parameter $H \in (\frac{1}{2}, 1)$ which is defined as a multiple Wiener-Itô integral of order k with respect to standard Brownian motion $(B(t))_{t \in \mathbb{R}}$

$$Z_t^{H,k} := c(H,k) \int_{\mathbb{R}} \int_0^t \prod_{j=1}^k (s - y_i)_+^{-(\frac{1}{2} + \frac{H-1}{2})} ds \ dB(y_1) dB(y_2) \cdots dB(y_k)$$

where $x_+ = \max(x, 0)$ and the constant $c(H,k)$ is a normalizing constant that ensures $E(Z_t^{H,k})^2 = 1$.

For $k = 1$ the process is fractional Brownian motion (W_t^H) with Hurst parameter $H \in (0,1)$. For $k = 2$ the process is Rosenblatt process. For $k \geq 2$, the process is non-Gaussian.

The Rosenblatt process is not a semimartingale and for $H > 1/2$, the quadratic variation is 0. The distribution of the process is infinitely divisible. It is unknown yet whether the process is Markov or not.

The covariance kernel $R(t,s)$ is given by

$$R(t,s) := E[Z_t^{H,k} Z_s^{H,k}] = c(H,k)^2 \int_0^t \int_0^s \left[(u-s)_+^{-(\frac{1}{2}+\frac{H-1}{2})} ds (v-y)_+^{-(\frac{1}{2}+\frac{H-1}{2})} dy\right]^k dudv.$$

A weighted fBm (wfBm) ξ_t has the covariance function

$$q(s,t) = \int_0^{s\wedge t} u^a[(t-u)^b + (s-u)^b]du, \quad s,t \geq 0$$

where $a > -1, \ -1 < b \leq 1, \ |b| \leq 1+a$. When $a = 0$, it is the usual fBm with Hurst parameter $(b+1)/2$ up to a multiplicative constant. For $b = 0$ it is a time-inhomogeneous Bm.

The function u^a is called the weight function of wfBm. For $a = 0$, this process is usual fBm with Hurst parameter $(b+1)/2$. For the case $b = 1$, this process has the covariance of the process $\int_0^t W_{r^a} dr$ where W is standard Brownian motion. For $b = 0$, this process is time-inhomogeneous Bm. The finite dimensional distributions of the process $(T^{-a/2}(\xi_{t+T} - \xi_T)), t \geq 0$ converge as $T \to \infty$ to those of fBm with Hurst parameter $(1+b)/2$ multiplied by $(2/(1+b)))^{1/2}$. The process has asymptotically stationary increments for long time intervals, but not for short time intervals. For $b \neq 0$, the process is neither a semimartingale nor a Markov process.

This process occurs as the limit of occupation time fluctuations of a particle system of independent particles moving in $\mathbb{R}^d$ with symmetric α-stable Levy process, $0 < \alpha \leq 2$, started from an inhomogeneous Poisson configuration with intensity measure $dx/(1+|x|^\gamma), 0 < \gamma \leq d = 1 < \alpha, a = -\gamma/\alpha, \ b = 1 - 1/\alpha, -1 < a < 0, 0 < b \leq 1+a$. The homogeneous case $\gamma = 0$ gives fBm.

The generalized Langevin equation is given by

$$m\frac{dX_t}{dt} = -\theta \int_{-\infty}^t X_u K(t-u)du + G_t$$

where G_t is a color noise and K is a kernel convoluted with the velocity makes the process non-Markovian.

The kernel K and and the noise G_t for any closed (equilibrium) physical system must satisfy the fluctuation-dissipation theorem which requires that

$$E[G_t G_s] = \kappa_B T \theta K(t-s).$$

We will consider the case $1/2 < H < 1$ which leads to subdiffusion given by

$$mdX_t = -\theta \left(\int_{-\infty}^t X_u K_H(t-u)du\right) dt - m\psi Y_t + \sqrt{2\theta\kappa_B T} dW_t^H,$$

$$Y_t = \int_0^t X_s ds$$

where $K_H(t) = 2H(2H-1)|t|^{2H-2}$ for $t \neq 0$.

The process $Y_t = \int_0^t X_s ds$ is the displacement with $Var[Y_t] \sim t^{2-2H}$ for large t. The harmonic potential pulls the particle back to the origin. In the limiting case of $\psi \to 0$, the harmonic potential becomes weaker and weaker and, the particle will behave more and more like a free particle. Under a harmonic potential,

$$E[X_s X_{s+t}] = E[X_0 X_t] = \frac{\kappa_B T}{m\psi} E_{2-2H}(-(t/\tau)^{2-2H})$$

where

$$\tau := \left(\frac{\theta\Gamma(2H+1)}{m\psi}\right)^{1/(2-2H)}$$

and $E_\alpha(z)$ is the Mittag-Leffler function defined by

$$E_\alpha(z) = \sum_{k=0}^{\infty} z^k/\Gamma(\alpha k + 1),$$

$$E_1(z) = \sum_{k=0}^{\infty} z^k/\Gamma(k+1) = \sum_{k=0}^{\infty} z^k/k! = \exp(z).$$

The Mittag-Leffler function generalizes the exponential function in a natural way. When $H \to 1$, the Mittag-Leffler function reduces to the exponential function and

$$E[X_0 X_t] = \frac{\kappa_B T}{m\psi} \exp(-(m\psi/\theta)t)$$

recovering the classical Brownian diffusion result.

The solution of the equation generalized Langevin equation with fractional Gaussian noise is given by

$$X_t = \sqrt{2\theta\kappa_B T} \int_{-\infty}^{\infty} \rho(t-u) dW_u^H,$$

$$Y_t = \sqrt{2\theta\kappa_B T} \int_{-\infty}^{\infty} \rho'(t-u) dW_u^H$$

where

$$\rho(t) = \frac{1}{2\pi} \int_{-\infty}^{\infty} e^{-itw} \frac{1}{m\psi - m\omega^2 - i\omega\theta \widetilde{K}_H^+(\omega)} d\omega,$$

$$\widetilde{K}_H^+(\omega) = \int_0^{\infty} e^{it\omega} K_H(t) dt = \Gamma(2H+1)|\omega|^{1-2H}[\sin(H\pi) - i\cos(H\pi)\text{sign}(\omega)],$$

$$\widetilde{K}_H(\omega) = \int_{-\infty}^{\infty} e^{it\omega} K_H(t)dt = \Gamma(2H+1)|\omega|^{1-2H}\sin(H\pi)|\omega|^{1-2H}$$

which are the Fourier transforms of the kernel $K_H(t)$ on the positive real line and the entire real line respectively.

The process (X_t, Y_t) is a stationary bivariate Gaussian process with zero means and covariance functions given by

$$E(X_s X_{s+t}) = \frac{\theta\kappa_B T}{2\pi}\int_{-\infty}^{\infty} e^{-itw}\frac{\omega^2\widetilde{K}_H(\omega)}{|m\psi - m\omega^2 - i\omega\theta\widetilde{K}_H^{+}(\omega)|^2}d\omega,$$

$$E(X_s Y_{s+t}) = \frac{\theta\kappa_B T}{2\pi}\int_{-\infty}^{\infty} e^{-itw}\frac{i\omega\widetilde{K}_H(\omega)}{|m\psi - m\omega^2 - i\omega\theta\widetilde{K}_H^{+}(\omega)|^2}d\omega,$$

$$E(Y_s X_{s+t}) = \frac{\theta\kappa_B T}{2\pi}\int_{-\infty}^{\infty} e^{-itw}\frac{i\omega\widetilde{K}_H(\omega)}{|m\psi - m\omega^2 - i\omega\theta\widetilde{K}_H^{+}(\omega)|^2}d\omega,$$

$$E(Y_s Y_{s+t}) = \frac{\theta\kappa_B T}{2\pi}\int_{-\infty}^{\infty} e^{-itw}\frac{\widetilde{K}_H(\omega)}{|m\psi - m\omega^2 - i\omega\theta\widetilde{K}_H^{+}(\omega)|^2}d\omega.$$

This gives

$$Var(X_0) = E(V_0^2) = \frac{\kappa_B T}{m}E_{2-2H}(0) = \frac{\kappa_B T}{m},$$

$$Var(Y_0) = \frac{\kappa_B T}{m\psi}E_{2-2H}(0) = \frac{\kappa_B T}{m\psi}.$$

3. Main Results

The process Y is observed at time points $t_i, i = 1, 2, \ldots, n$. We estimate θ by method of moments. Our equally spaced data set is $\{Y_{t_0}, Y_{t_1}, Y_{t_2}, \ldots, Y_{t_n}\}$. We assume that $t_i - t_{i-1} = \Delta > 0, i = 1, 2, \ldots, n.$ and Δ is fixed. The *method of moments estimator* of θ is given by

$$\hat{\theta}_n = \frac{m\psi\Delta^{2-2H}}{\Gamma(2H+1)\ln_{2-2H}\frac{\sum_{i=1}^n Y_{t_{i-1}}^2}{\sum_{i=1}^n Y_{t_{i-1}}Y_{t_i}}}.$$

When the process X is observed, the Hurst parameter H can be estimated by the change-of-frequency (COF) estimator based on the second-order difference of X_t:

$$\widehat{H} = \frac{1}{2}\log_2\left(\frac{\sum_{i=1}^{n-4}(X_{t_{i+4}} - 2X_{t_{i+2}} + X_{t_i})^2}{\sum_{i=1}^{n-2}(X_{t_{i+2}} - 2X_{t_{i+1}} + X_{t_i})^2}\right).$$

This estimator has asymptotic normality with the rate $\sqrt{n}$.
The following is the main result of the paper.

Theorem 3.1 *(Sub-critical case) Let $1/2 < H < 3/4$. Then*

$$\text{a)}\ \ \hat{\theta}_n \to^P \theta \ \text{ as } n \to \infty.$$

$$\text{b)}\ \ \sqrt{n}(\hat{\theta}_n - \theta) \to^D \mathcal{N}(0,\ I_H^{-1}(\theta)) \ \text{ as } n \to \infty$$

where $I_H(\theta)$ is the Fisher information given by

$$I_H(\theta) := \frac{2\theta^{2H} m\psi \Delta^{2-2H}}{\Gamma(2H+1)\kappa_B T}.$$

c) (Critical case) For the case $H = 3/4$, the limit distribution will be Gaussian with a rate $\sqrt{n}/\log n$:

$$\frac{\sqrt{n}}{\log n}(\hat{\theta}_n - \theta) \to^D \mathcal{N}\left(0,\ \frac{16\theta}{9\pi}\right) \ \text{ as } n \to \infty.$$

d) (Super-critical case) For the case $H > 3/4$, the limit distribution will be that of a non-Gaussian Rosenblatt process with the rate n^{2-2H}:

$$n^{2-2H}(\hat{\theta}_n - \theta) \to^D \frac{2\theta^{2H} m\psi \Delta^{2-2H}}{\Gamma(2H+1)\kappa_B T} R \ \text{ as } n \to \infty$$

where R is the Rosenblatt random variable.

Proof. Following the method in Masuda [16] along with Van der Vaart [17], and ergodicity and central limit theorem for second Wiener chaos under fourth moment condition in Nourdin and Peccati [18, 19], and delta method, the theorem follows. See also Wang *et al.* [14]. We omit the details. □

Concluding Remarks For the case $H > 3/4$, the limit distribution will be that of a non-Gaussian Rosenblatt process with the rate n^{2-2H}. For the case $H = 3/4$, the limit distribution will be Gaussian with a rate $\sqrt{n}/\log n$. Similar phenomenon occurs in maximum likelihood estimation for Feller [20] branching diffusion process with immigration, which are used in population biology, but for different parts of the parameter space, see Overbeck [21]. Models with $H < 1/2$ are useful for COVID-19 modeling, see Alos *et al.* [11].

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