Robust Estimation in Gompertz Diffusion Model of Tumor Growth

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Abstract

Stochastic Gompertz diffusion model describes the in vivo tumor growth. The drift parameter describes the intrinsic growth rate (mitosis rate) of the tumor. The paper introduces some new approximate minimum contrast estimators of the tumor growth acceleration parameter in the Gompertz diffusion model based on discretely sampled data which are robust and studies their asymptotic distributional properties with precise rates of convergence.

Keywords: Itô stochastic differential equation; Gompertz diffusion process; Black-Karasinski model; Discrete observations; Approximate minimum contrast estimators; Robustness; efficiency; Berry-Esseen bound

Model and Estimators

The Gompertz diffusion process has been used in tumor growth modeling, Ferrante et al. [1]. Lo [2] considered a Gompertz diffusion model in which the size of the tumor cells is bounded and used Lie-algebraic method to derive the exact analytical solution of the functional Fokker-Planck equation obeyed by the density function of the size of the tumor. Giorno et al. [3] proposed a non-homogeneous time dependent Gompertz diffusion process with jumps to describe the evolution of a solid tumor subject to an intermittent therapeutic program. Moummou et al. [4] obtained explicit expressions for the maximum likelihood estimators with discrete sampling from the Gompertz diffusion model by using functional optimization orthogonal projections. However, the statistical properties of the model were not studied.

Ferrante et al. [1] studied maximum likelihood estimation of natural growth parameters of tumor for such models. However, they did not study distributional properties of the estimators. The knowledge of the distribution of the estimator may be applied to evaluate the distribution of other important growing parameters used to access tumor treatment modalities. We study distributional properties of approximate minimum contrast estimators of the unknown parameters in the model from discrete data with precise rates of convergence which are robust and efficient.

Let $(\Omega, F, \{F_t\}_{t\geq 0}, P)$ be a stochastic basis on which is defined the Gompertz diffusion process $\{X_t\}_{t\geq 0}$ satisfying the Itô stochastic dierential equation

$$dX_t = (\alpha X_t - \beta X_t \ln X_t)dt + \sigma X_t dW_t, t \geq 0, X_0 = x_0 \qquad (1:1)$$

Where $\{W_t\}_{t\geq 0}$ is a standard Brownian motion with the filtration $\{F_t\}_{t\geq 0}$ and $\alpha > 0$; $\beta > 0$; $\sigma > 0$ are the unknown parameters to be estimated on the basis of discrete observations of the process $\{X_t\}$ at times $0 = t_0 < t_1 < .... t_n = T$ with $t_i - t_{i-1} = \frac{T}{n}$, $i = 1,2....,n$. We assume equi-spaced sampling for simplicity. We assume two types of high frequency data: 1) $T \to \infty, n \to \infty, \frac{T}{\sqrt{n}} \to 0$ 2) $T \to \infty, n \to \infty, \frac{T}{n^{2/3}} \to 0$

Here X_t is the tumor volume which is measured at discrete time, α is the intrinsic growth rate of the tumor, β is the tumor growth acceleration factor, and σ is the diffusion coefficient. Other parameters are the plateau of the model $X_\infty = \exp\exp\left(\frac{\alpha}{\beta}\right)$ tumor growth decay, and the first time the growth curve of the model reaches X_∞. We assume that the growth deceleration factor β does not change, while the variability of environmental conditions induces fluctuations in the intrinsic growth rate (mitosis rate) α. In finance literature, this model is known as Black-Karasinski model which is a geometric mean reverting Vasicek model used for modeling term structure of interest rates which preserves positivity of the interest rates.

Let the continuous realization be $\{X_t, 0 \leq t \leq T\}$ denoted by x_0^T. Denote $\Theta := (\alpha, \beta, \sigma)$. Let P_θ^T be the measure generated on the space (C_T, B_T) of continuous functions on [0,T] with the associated Borel σ algebra B_T generated under the supremum norm by the process X_0^T and let P_0^T be the standard Wiener measure. It is well known that when θ is the true value of the parameter P_θ^T is absolutely continuous with respect to P_0^T and the Radon-Nikodym derivative (likelihood) of P_0^T with respect to P_0^T based on the data X_0^T is given by

$$L_T(\theta) := \frac{dP_\theta^T}{dP_0^T}(X_0^T) = \exp\{\frac{1}{\sigma^2}\int_0^T (\propto -\beta\, In X_t)\, X_t^{-1} dX_t - \frac{1}{2\sigma^2}\int_0^T (\alpha - \beta In X_t)^2 dt\} \quad (1{:}2)$$

Consider the log-likelihood function, which is given by

$$l_T(\theta) := \frac{dP_\theta^T}{dP_0^T}(X_0^T) = \frac{1}{\sigma^2}\{\int_0^T (\propto -\beta\, In X_t)\, X_t^{-1} dX_t - \frac{1}{2}\int_0^T (\alpha - \beta In X_t)^2 dt\} \quad (1{:}3)$$

A solution of the estimating equation $\gamma^T(\theta) = 0$ provides the conditional maximum likelihood estimators (MLEs)

$$\bar{a}_T := \frac{1}{T}\left\{\int_0^T X_t^{-1} dX_t - \hat{\beta}_T \int_0^T In X_t dt\right\} \quad (1{:}4)$$

$$\hat{\beta}_T := \frac{\left(\int_0^T X_t^{-1} dX_t\right)\left(\int_0^T In X_t dt\right) - T\left(\int_0^T X_t^{-1} In X_t dX_t\right)}{\int_0^T In^2 X_t dX_t - \left(\int_0^T In X_t dX_t\right)^2} \quad (1{:}5)$$

$$\hat{\sigma}^2 := \frac{\sum_{i=1}^n (X_{ti} - X_{t-i})^2}{\sum_{i=1}^n X_{ti-1}^2 (t_i - t_{i-1})} \quad (1{:}6)$$

As an alternative to maximum likelihood method and to obtain robust estimators with higher efficiency we use contrast functions. Suppose α and σ are known, for simplicity let $i = \frac{1}{2}$, σ=1, 1; x0=1 and our aim is to estimate the tumor growth acceleration parameter β. Using Itô formula, the score function can be written as

$$\gamma T(\beta) := -\frac{1}{2} In^2 X_T - \int_0^T (\beta In^2 X_t - \frac{1}{2}) dt \quad (1{:}7)$$

Using a contrast function which is related to the negative derivative of the log-likelihood function, we consider the estimating function,

$$M_T(\beta) := \int_0^T (\beta In^2 X_t - \frac{1}{2}) dt \quad (1{:}8)$$

Then the minimum contrast estimate (MCE) of β which is the solution of $M_T(\beta) = 0$ is given by

$$\beta_T := \frac{T}{2}\{\int_0^T In^2 X_t dt\}^{-1} =: \frac{T}{2I_T} \quad (1{:}9)$$

Where $I_T = \int_0^T In^2 X_t dt$ Hence $M_T(\beta) = \beta l_T - \frac{T}{2}$. Sometimes we will denote this by just M_T. We find several discrete approximations of the MCE. Define a weighted approximation of I_T:

$$K_{n,T} := \{\sum_{i=1}^n \omega_{t_i} In^2 X_{t_{i-1}} + \sum_{i=1}^n (1 - \omega_{t_i}) In^2 X_{t_i}\} \quad (1{:}10)$$

Where $w_{ti} \geq 0$ is a weight function. Denote the forward and backward approximations of I_T:

$$I_{n,T} := \frac{T}{n}\sum_{i=1}^n In^2 X_{t_{i-1}} \quad (1{:}11)$$

$$J_{n,T} := \frac{T}{n}\sum_{i=1}^n In^2 X_{t_i} \quad (1{:}12)$$

General weighted AMCE is defined as

$$\hat{\beta}_{n,T} := \{\frac{2}{T} K_{n,T}\}^{-1} \quad (1{:}13)$$

With $w_{t_i} = 1$ in (1.10), we obtain the forward AMCE as

$$\hat{\beta}_{n,T,F} := \{\frac{2}{T} I_{n,T}\}^{-1} \quad (1{:}14)$$

With = 0 in (1.10), we obtain the backward AMCE as

$$\tilde{\beta}_{n,T,B} := \{\frac{2}{T} J_{n,T}\}^{-1} \quad (1{:}15)$$

With w_(t_i)=0.5 in (1.10), the simple symmetric AMCE is defined as

$$\hat{\beta}_{n,T,S} := \{\frac{1}{T}|I_{n,T} + J_{n,T}|\}^{-1} = \{\frac{2}{T}\sum_{i=2}^n In^2 X_{t_{i-1}} + 0.5(ln^2 X_{t0} + In^2 X_{tn})\}^{-1} \quad (1{:}16)$$

Define the weighted symmetric estimators: With the weight function

$$\omega_{t_i} = \begin{cases} 0 : i = 1 \\ \frac{i-1}{n} = i : 1,2,3,\ldots,n \\ 1 : i = n+1 \end{cases}$$

the weighted symmetric AMCE is defined as $\bar{\beta}_{n,T,\omega} := \{\frac{2}{T}\sum_{i=2}^n In^2 X_{t_{i-1}} + \frac{1}{n}\sum_{i=1}^n In^2 X_{t_{i-1}}\}^{-1}$ Note that estimator (1.16) is analogous to the trapezoidal rule in numerical analysis. One can instead use the midpoint rule to define another estimator $\hat{\beta}_{n,T,A} := \{\frac{2}{T}\sum_{i=1}^n In^2 (\frac{X_{t_{i-1}} + X_{t_i}}{2})\}^{-1}$. One can further use the Simpson's rule to define another estimator where the denominator is a convex combination of the trapezoidal and midpoint estimators,

$$\tilde{\beta}_{n,T,N} := \{\frac{1}{3T}\sum_{i=1}^n \{In^2 X_{t_{i-1}} + 4In^2\left(\frac{X_{t_{i-1}} + X_{t_i}}{2}\right) + In^2 X_{t_i}\}\}^{-1}.$$

The AMCE has several good properties. The AMCE is simpler to calculate, in the sense that it does not involve simulation of a stochastic integral unlike AMLE. Hence AMCE is a more practical estimator. This is robust since M-estimator is reduced to the AMCE. The AMCE is efficient, Tanaka [5]. Tanaka [5] calculated the asymptotic relative efficiency of the minimum contrast estimator with respect to least squares estimator (LSE) and showed that MCE is asymptotically efficient while LSE is inefficient. We study the distributional properties of the AMCE. We obtain the rate of weak convergence to normal distribution of the AMCE using different normings. We also obtain stochastic bound on the difference of the AMCE and its continuous counterpart MCE when T is fixed. We need the following lemmas from Bishwal [6] to prove our main results.

Lemma 1.1 Let X, Y and Z be any three random variables on a probability space (Ω,F,P) with P(Z>0)=1. Then, for any ε>0, we have

$$\sup_{x \in R} |P\{X + Y \leq x\} - \Phi(x)| \leq \sup_{x \in R} |P\{X \leq x\} - \Phi(x)| + P(|Y| > \epsilon) + \epsilon$$

$$\sup_{x \in R} |P\{\frac{X}{Y} \leq x\} - \Phi(x)| \leq \sup_{x \in R} |P\{X \leq x\} - \Phi(x)| + P\{|Z - 1| > \epsilon\} + \epsilon$$

Lemma 1.2 Let Q_n, R_n, Q and R be random variables on the same probability space (Ω,F,P) with $P(R_n > 0) = 1$ and $P(R_n > 0) = 1$. Suppose $|Q_n - Q| = O_p(\delta_{1n})$ and $|R_n - R| = O_p(\delta_{2n})$ where

$$\delta_{1n}, \delta_{2n} \to 0\, n \to \infty \quad \left|\frac{Q_n}{R_n} \frac{Q}{R}\right| = O_p\left(\max \max(\delta_{1n}, \delta_{2n})\right)$$

Distributional Properties of Estimators

Let $\emptyset(.)$ denote the standard normal distribution function. Throughout the paper C denotes a generic constant (perhaps depending on β, but not on anything else). Since $\ln X_t$ is an Ornstein-Uhlenbeck process, we can use the following lemmas from Bishwal [6] in the sequel.

Lemma 2.1 For every $\delta > 0, P\left\{\left|\frac{2\beta}{T} I_T - I\right| \geq \delta\right\} \leq CT^{-1}\delta^{-2}$

Lemma 2.2 $Sup_{x \in R}\left|P\{(\frac{2\beta}{T})^{1/2} M_T \leq x\} - \emptyset(x)\right| \leq CT^{-1/2}$

Lemma 2.3 (a) $E\left|I_{n,T} - I_T\right|^2 = O\left(\frac{T^4}{n^2}\right)$, (b) $E\left|\frac{I_{n,T} - J_{n,T}}{2} - I_T\right|^2 = O\left(\frac{T^4}{n^2}\right)$

The following theorem gives the bound on the error of approximation of the distributions of the AMCE to normal distribution. Note that part (a) uses parameter dependent non-random norming. While this is useful for testing hypotheses about β, it may not necessarily give a confidence interval. The normings in parts (b) and (c) are sample dependent which can be used for obtaining a confidence interval. Following theorem shows that asymptotic normality of the AMCE needs the design condition $T \to \infty$ and $\frac{T}{\sqrt{n}} \to 0$.

Theorem 2.1

Denote $b_{n,T} := O(\max(T^{-1/2}(\log\log T)^{1/2}, (\frac{T^4}{n^2})(\log\log T)^{-1}))$

(a) $Sup_{x \in R}\left|P\left\{\left(\frac{T}{2\beta}\right)^{1/2}(\tilde{\beta}_{n,T,F} - \beta) \leq x\right\} - \emptyset(x)\right| = O(b_{n,T})$

(b) $Sup_{x \in R}\left|P\left\{I_{n,T}^{1/2}(\tilde{\beta}_{n,T,F} - \beta) \leq x\right\} - \emptyset(x)\right| = O(b_{n,T})$

(c) $Sup_{x \in R}\left|P\left\{\left(\frac{T}{2\tilde{\beta}_{n,T,F}}\right)^{1/2}(\tilde{\beta}_{n,T,F} - \beta) \leq x\right\} - \emptyset(x)\right| = O(b_{n,T})$

Proof: (a) Observe that $\left(\frac{T}{2\beta}\right)^{1/2}(\tilde{\beta}_T - \beta) = -\frac{\left(\frac{2\beta}{T}\right)^{1/2} M_T}{\left(\frac{2\beta}{T}\right)^{1/2} I_T}$ (2.1)

Thus, we have I Hence

$$\left(\frac{T}{2\beta}\right)^{1/2}(\tilde{\beta}_{n,T,F} - \beta) = \frac{\left(\frac{T}{2\beta}\right)^{1/2} M_T + \beta\left(\frac{T}{2\beta}\right)^{1/2}(I_T - I_{n,T})}{I_{n,T}} = \frac{\left(\frac{2\beta}{T}\right)^{1/2} M_T + \beta\left(\frac{2\beta}{T}\right)^{1/2}(I_T - I_{n,T})}{\left(\frac{2\beta}{T}\right) I_{n,T}}$$

(2.2)

Further,

$$P\left\{\left|\left(\frac{2\beta}{T}\right)(I_{n,T} - 1)\right| > \in\right\} = \left\{\left|\left(\frac{2\beta}{T}\right)(I_{n,T} - I_T + I_T) - 1\right| > \in\right\}$$

$$\leq P\left\{\left|\left(\frac{2\beta}{T}\right)(I_T - 1)\right| > \frac{\in}{2}\right\} + P\left(\frac{2\beta}{T}\right)\left|I_{n,T} - I_T\right| > \frac{\in}{2}$$

$$\leq C_{\exp}\left(-\frac{T\beta}{16}\delta^2\right) + \frac{16\beta^2}{T^2}\frac{\left|I_{n,T} - I_T\right|^2}{\delta^2} \leq C_{\exp}\left(-\frac{T\beta}{16}\delta^2\right) + C\frac{T^2/n^2}{\in^2} \quad (2.3)$$

Next, observe that

$$Sup_{x \in R}\left|P\left\{\left(\frac{T}{2\beta}\right)^{1/2}(\tilde{\beta}_{n,T,F} - \beta) \leq x\right\} - \emptyset(x)\right|$$

$$= Sup_{x \in R}\left|P\left\{\frac{\left(\frac{2\beta}{T}\right)^{1/2} M_T + \left(\frac{2\beta}{T}\right)^{1/2}(I_T - I_{n,T})}{\left(\frac{2\beta}{T}\right)I_{n,T}} \leq x\right\} - \emptyset(x)\right|$$

$$\leq Sup_{x \in R}\left|P\left\{\left(\frac{2\beta}{T}\right)^{1/2} M_T \leq x\right\} - \emptyset(x)\right| + P\left\{\left|\beta\left(\frac{2\beta}{T}\right)^{1/2}(I_{n,T} - I_T)\right| > \in\right\} + P\left\{\left|\beta\left(\frac{2\beta}{T}\right)^{1/2}(I_{n,T} - 1)\right| > \in\right\} + 2\in$$

$$\leq CT^{-1/2} + \beta^2\frac{\left(\frac{2\beta}{T}\right)E\left|I_{n,T} - I_T\right|^2}{\delta^2} + C_{\exp}\left(-\frac{T\beta}{4}\delta^2\right) + C\frac{T^2}{n^2\in^2} + 2\in \quad (2.4)$$

(the bound for the 3rd term in the right hand side of (2.4) is obtained from (2.3))

$$\leq CT^{-1/2} + C\frac{T^2}{n^2\in^2} + C_{\exp}\left(-\frac{T\beta}{4}\delta^2\right) + C\frac{T^2}{n^2\in^2} + \in$$

(by Lemma 2.3(a)).

Choosing $\delta = CT^{-1/2}(\log T)^{1/2}$, the terms in the right hand side of (2.5) are of the order $O(\max(T^{-1/2}(\log T)^{1/2}, (\frac{T^2}{n^2})(\log T)^{-1}))$

(b) From (2.1), we have $I_{n,T}^{1/2}(\tilde{\beta}_{n,T,F} - \beta) = \frac{M_T + \beta(I_T - I_{n,T})}{I_{n,T}^{1/2}}$. Then,

$$Sup_{x \in R}\left|P\{I_{n,T}^{1/2}(\tilde{\beta}_{n,T,F} - \beta) \leq x\} - \emptyset(x)\right| = Sup_{x \in R}\left|P\left\{\frac{M_T}{I_{n,T}^{1/2}} + \beta\frac{I_T - I_{n,T}}{I_{n,T}^{1/2}} \leq x\right\} - \emptyset(x)\right|$$

$$\leq Sup_{x \in R}\left|P\left\{\frac{M_T}{I_{n,T}^{1/2}} \leq x\right\} - \emptyset(x)\right| + P\left\{\left|\beta\frac{I_T - I_{n,T}}{I_{n,T}^{1/2}}\right| > \in\right\} + \in =: U_1 + U_2 + \in \quad (2.6)$$

We have from (2.3),

$$U_1 \leq CT^{-1/2} + C_{\exp}\left(-\frac{T\beta}{16}\in^2\right) + C\frac{T^2}{n^2\delta^2} + \in \quad (2.7)$$

Further,

$$U_2 = P\left\{\beta\left|\frac{I_T - I_{n,T}}{I_{n,T}^{1/2}}\right| > \in\right\} = P\left\{\beta\frac{\left(\frac{2\beta}{T}\right)^{1/2}(I_{n,T} - I_T)}{\left(\frac{2\beta}{T}\right)^{1/2} I_{n,T}^{1/2}} > \in\right\}$$

$$\leq P\left\{\left(\frac{2\beta}{T}\right)^{1/2}\left|(I_{n,T} - I_T)\right| > \delta\right\} + P\left\{\left|\left(\frac{2\beta}{T}\right)^{1/2} I_{n,T}^{1/2} - 1\right| > \delta_1\right\}$$

(Where $\delta = \epsilon - C\epsilon^2$ $and\,\delta_1 = \dfrac{\delta - \delta}{\delta} > 0$)

$$\leq \left(\frac{2\beta}{T}\right)\frac{E|I_{n,T}-I_T|^2}{\delta^2} + P\left\{\left|\left(\frac{2\beta}{T}\right)I_{n,T}-1\right| > \delta_1\right\}$$

$$\leq C\,\frac{T^3}{n^2\delta^2} + C_{exp}\left(-\frac{T\beta}{16}\delta_1^2\right) + C\,\frac{T^2}{n^2\delta_1^2} \qquad (2.8)$$

Here, the bound for the first term in the right hand side of (2.7) comes from Lemma 2.2(c) and that for the second term is obtained from (2.3) [2]. Now, using the bounds (2.7) and (2.8) in (2.6) with $\delta = CT^{-1/2}(logT)^{1/2}$, we obtain that the terms in (2.6) are of the order

$$O(\max(T^{-1/2}(logT)^{1/2},(\frac{T^2}{n^2})(logT)^{-1}))$$

(c) Let $G_T := \left\{\left|\tilde{\beta}_{n,T,F}-\beta\right| \leq d_T\right\}$, $d_T := CT^{-1/2}(logT)^{1/2}$. On the set G_T, expanding $(2|\tilde{\beta}_{n,T,F}|)^{1/2}$, we obtain

$$(2\beta_{n,T,F})^{-1/2} = (2\beta)^{1/2}[1-\frac{\beta-\tilde{\beta}_{n,T,F}}{\beta}]^{-1/2} = (2\beta)^{1/2}\left[1+\frac{\beta-\tilde{\beta}_{n,T,F}}{\beta}\right] + O(d_T^2)$$

Then

$$Sup_{x\in R}\left|P\left\{\left(\frac{T}{2\tilde{\beta}_{n,T,F}}\right)^{1/2}(\tilde{\beta}_{n,T,F}-\beta)\leq x\right\}-\varnothing(x)\right| \leq Sup_{x\in R}\left\{\left(\frac{T}{2\tilde{\beta}_{n,T,F}}\right)^{1/2}\left(\tilde{\beta}_{n,T,F}-\beta\right)\leq x, G_T\right\} + P(G_T^c)$$

Further,

$$P\left(G_T^c\right) = P\left\{\left|\tilde{\beta}_{n,T,F}-\beta\right| > CT^{-1/2}(\log\log T)^{1/2}\right\}$$

$$= P\left\{\left(\frac{T}{2\beta}\right)^{1/2}\left|\tilde{\beta}_{n,T,F}-\beta\right| > C(\log\log T)^{1/2}(2\beta)^{-1/2}\right\}$$

$$\leq C_{\max}\left(T^{-1/2}(\log\log T)^{1/2},\frac{T^3}{n^2}(\log\log T)^{-1}\right) + 2(1-\varnothing((\log\log T)^{1/2})(2\beta)^{-1/2})$$

$$\leq C_{\max}(T^{-1/2}(\log\log T)^{1/2},\frac{T^3}{n^2}(\log\log T)^{-1})$$

On the set $G_T, \left|(\frac{\tilde{\beta}_{n,T,F}}{\beta})^{1/2}-1\right| \leq CT^{-1/2}(logT)^{1/2}$. Hence, upon choosing $\delta = CT^{-1/2}(logT)^{1/2}$, C large, using Lemma 1.1(b)) and Theorem 2.1(a)), we obtain

$$\left|P\left\{\left(\frac{T}{2\tilde{\beta}_{n,T,F}}\right)^{1/2}\left(\tilde{\beta}_{n,T,F}-\beta\right)\leq x, G_T\right\}-\varnothing(x)\right|$$

$$\leq P\left\{\left(\frac{T}{2\beta}\right)^{1/2}\left|\tilde{\beta}_{n,T,F}-\beta\leq x, G_T\right| + P\left\{\left|\left(\frac{\tilde{\beta}_{n,T,F}}{\beta}\right)^{1/2}-1\right| < \epsilon, G_T\right\} + \epsilon\right.$$

$$\leq C_{\max}(T^{-1/2}(\log\log T)^{1/2},\frac{T^4}{n^2}(\log\log T)^{-1})$$

In the following theorem, we improve the bound on the error of normal approximation using a mixture of random and non-random normings. Thus asymptotic normality of the AMCEs need $T \to \infty$ and $\frac{T}{n^{2/3}} \to 0$ which are sharper than the bound in Theorem 2.1.

Theorem 2.2

$$Sup_{x\in R}\left|P\left\{I_{n,T}\left(\frac{2\beta}{T}\right)^{1/2}\left(\tilde{\beta}_{n,T,F}-\beta\right)\leq x\right\}-\varnothing(x)\right| = O(\max(T^{-1/2},(\frac{T^3}{n^2})^{1/3}))$$.

Proof: From (2.2), we have

$$I_{n,T}\left(\frac{2\beta}{T}\right)^{1/2}\left(\tilde{\beta}_{n,T,F}-\beta\right) = \left(\frac{2\beta}{T}\right)^{1/2}M_T + \beta\left(\frac{2\beta}{T}\right)^{1/2}\left(I_T-I_{n,T}\right)$$.

Hence, by Lemma 2.1-2.3

$$Sup_{x\in R}\left|P\left\{I_{n,T}\left(\frac{2\beta}{T}\right)^{1/2}\left(\tilde{\beta}_{n,T,F}-\beta\right)\leq x\right\}-\varnothing(x)\right|$$

$$= Sup_{x\in R}\left|P\left\{\left(\frac{2\beta}{T}\right)^{1/2}M_T+\beta\left(\frac{2\beta}{T}\right)^{1/2}(I_T-I_{n,T})\leq x\right\}-\varnothing(x)\right|$$

$$\leq Sup_{x\in R}\left|P\left\{\left(\frac{2\beta}{T}\right)^{1/2}M_T\leq x\right\}-\varnothing(x)\right| + P\left\{\left|\beta\left(\frac{2\beta}{T}\right)^{1/2}\left(I_T-I_{n,T}\right)\right| > \epsilon\right\} + \epsilon$$

$$\leq CT^{-1/2} + C\frac{E|I_T-I_{n,T}|^2}{T\epsilon^2} + \epsilon \leq CT^{-1/2} + C\frac{T^2}{n^2\delta^2} + \epsilon$$

Choosing $\epsilon = (\frac{T^3}{n^2})^{1/3}$, the theorem follows.

The following theorem gives stochastic bound on the error of approximation of the continuous MCE by AMCEs.

Theorem 2.3

(a) $\left|\tilde{\beta}_{n,T,F}-\tilde{\beta}_T\right| = O_P(\frac{T}{n})^{1/2}$, (b) $\left|\tilde{\beta}_{n,T,S}-\tilde{\beta}_T\right| = O_P(\frac{T^2}{n^2})^{1/2}$.

Proof: From (1.9) and (1.14), we have $\tilde{\beta}_T = \frac{T}{2I_T}$, $\tilde{\beta}_{n,T,F} = \frac{T}{2I_{n,T}}$. Hence, applying Lemma 1.2 with the aid of Lemma 2.3(a) and noting that $\left|\frac{I_{n,T}}{T}\right| = O_P(1)$ and $\left|\frac{I_T}{T}\right| = O_P(1)$ the part (a) of theorem follows. From (1.9) and (1.16), we have $\tilde{\beta}_T = \frac{T}{2I_T}$, $\tilde{\beta}_{n,T,S} = \frac{T}{I_{n,T}+J_{n,T}}$. Applying Lemma 1.2 with the aid of Lemma 2.3(b) and noting that $\left|\frac{J_{n,T}}{T}\right| = O_P(1)$ and $\left|\frac{I_T}{T}\right| = O_P(1)$ the part (b) of theorem follows.

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