Modeling of Tumor Spheroids Growth

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Motivation

Example

Growth of Multicell Tumor Spheroids (MCTS)

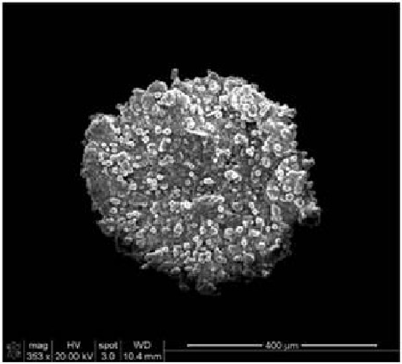


Figure from: Senavirathna et al., *Theranostics* 2013, Vol. 3, Issue 9 (687-691)

Motivation

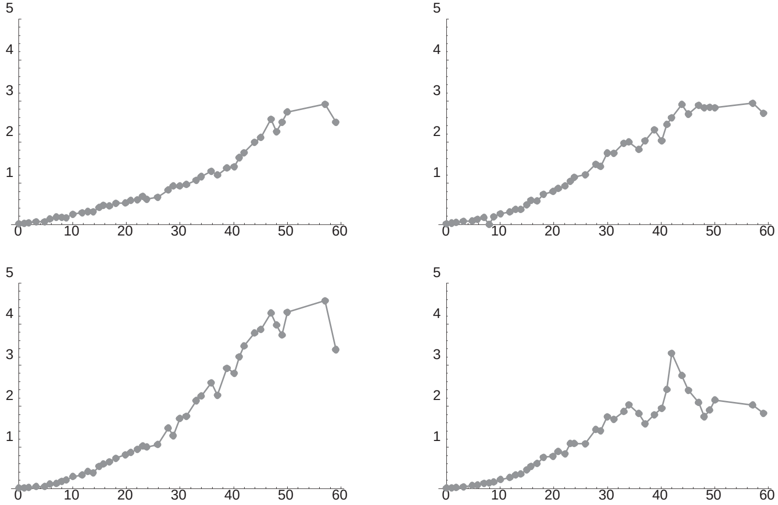
Data:

- 18 individual rat gliosarcoma spheorids
- grown separately *in vitro*, identical nutrient conditions
- volumes measured separately and daily for 59 days

M.H., J.P. Freyer, Z. Bajzer, and S. Vuk-Pavlović: A stochastic Gompertzian model for growth of MTS, *poster presentation*, First World Congress on Computational Medicine, Public Health and Biotechnology, 1994

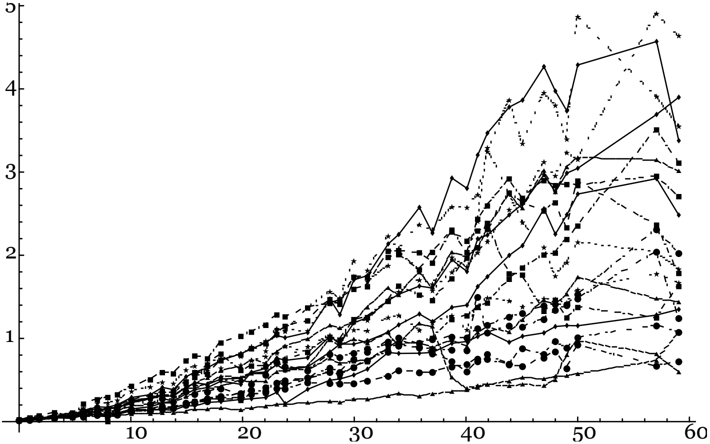
Motivation

Tumor spheroids growth data:



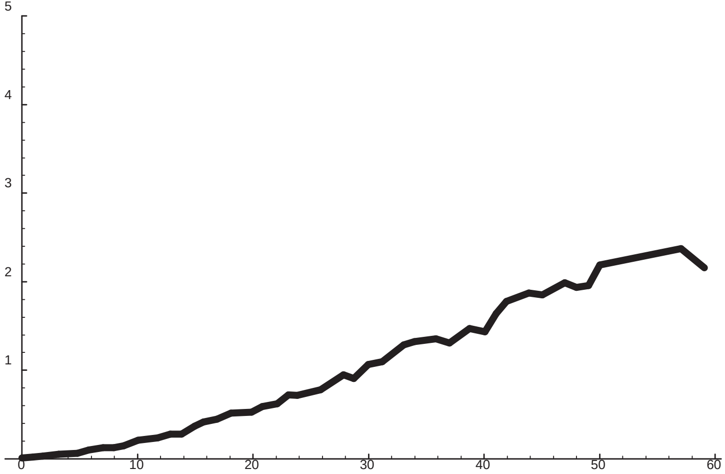
Motivation

All 18 tumor spheroids:



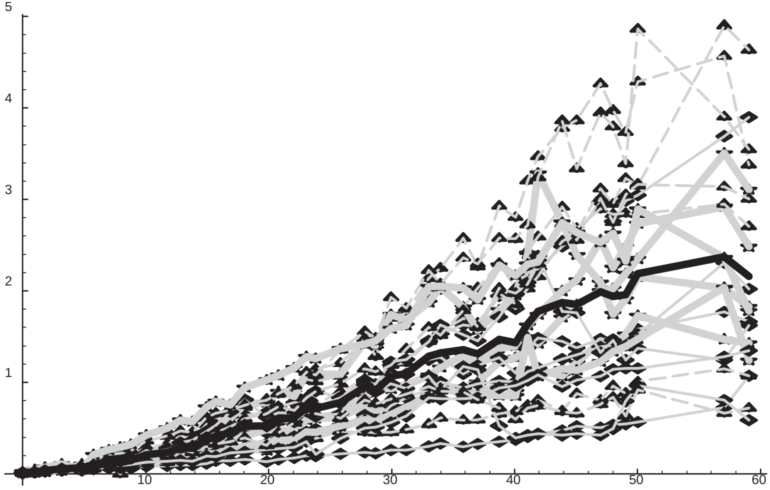
Motivation

Mean tumor spheroids volumes/time:



Motivation

All together:



Motivation

Modelling of MTS growth?

$\rightarrow$ diffusion processes

Diffusion models of tumor:

- Wette et al., *Math. Biosci.* 1974
- Hanson and Tier, *Math. Biosci.* 1982
- Aagaard-Hansen and Yeo, *J. Math. Biol.* 1984
- Holgate, *J. Theor. Biol.* 1989
- Ferrante et al., *Biometrics* 2000
- Albano and Giorno, *J. Theor. Biol.* 2006
- ...

Motivation

Generalized diffusion growth process X:

$$dX_t = (\alpha - \beta \mathrm{h}(\gamma, X_t))X_t\,dt + \sqrt{\sigma} X_t\,dW_t, \quad X_0 > 0$$

where

$$\mathrm{h}(\gamma, x) := \begin{cases} \frac{1}{\gamma}(x^\gamma - 1), & \gamma \neq 0 \\ \log x, & \gamma = 0 \end{cases}$$

Parameters:

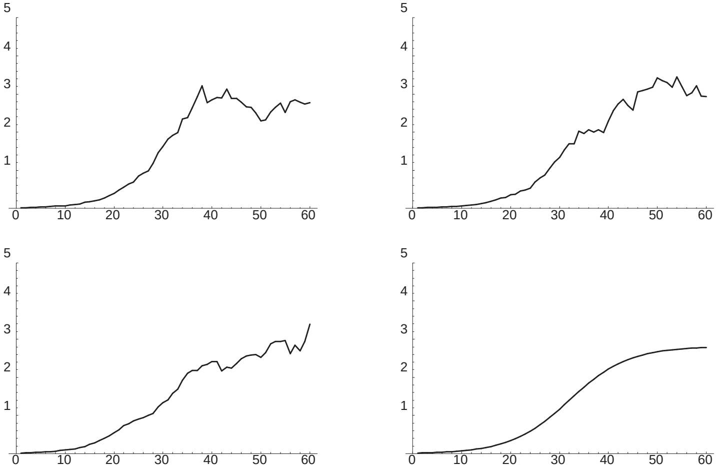
$$\alpha \in \mathrm{R},\ \beta > 0,\ \gamma > -1,\ \gamma\alpha + \beta > 0,\ \sigma > 0$$

$$\begin{aligned} \gamma > 0 &\quad \Rightarrow \quad \text{gen. logistic model} \\ \gamma = 0 &\quad \Rightarrow \quad \text{Gompertz model} \\ \gamma < 0 &\quad \Rightarrow \quad \text{gen. von Bertalanffy model} \end{aligned}$$

(Marušić et al., 1994, M.H., 1997)

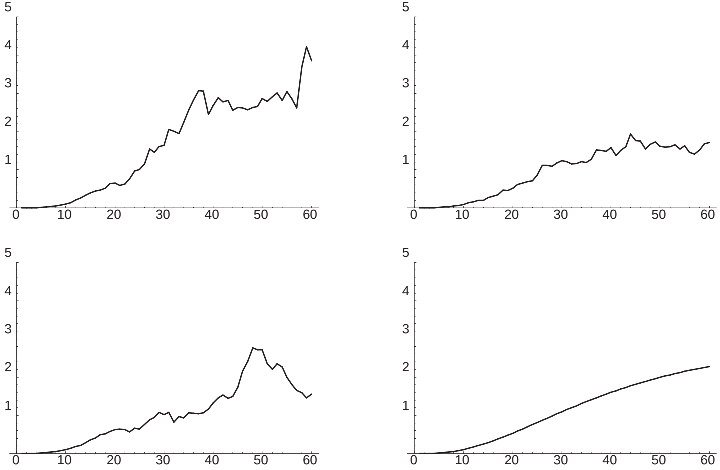
Motivation

Simulation of gen. logistic process:



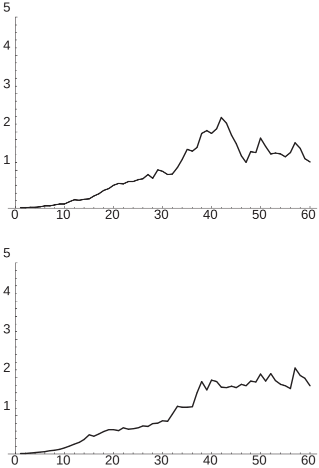
Motivation

Simulation of gen. von Bertalanffy process:



Motivation

Simulation of Gompertz process:



Motivation

Questions:

- Is the generalized model of growth an appropriate model of growth?
- How to estimate model parameters from discrete observation?
- What is the most appropriate model?
- ...

Generalized model of growth

Theorem (Existence and uniqueness of gen. growth process)

SDE of the general model of growth has strong, pathwise unique, continuous, and positive solution $X = (X_t, t \geq 0)$.

- strong: $X_t = F(W_s, s \leq t)$, $t \geq 0$
- continuous and positive: $(t \mapsto X_t(\omega)) \in C(\mathrm{R}_0^+, \mathrm{R}_+)$
- pathwise uniqueness: if X, Y are continuous solutions to the SDE and $X_0 = Y_0$ then

$$\mathrm{P}(\exists t > 0,\ X_t \neq Y_t) = 0$$

Generalized model of growth

Let $X = (X_t, t \geq 0)$ be a solution to the gen. growth model SDE.

Theorem

If $\gamma = 0$ *then* X *(Gompertz) is* recurrent *and* ergodic*, and its* stationary density *is*

$$f(x) = \frac{1}{\sigma x}\sqrt{\frac{\beta}{\pi}}\exp\left\{-\frac{\beta}{\sigma^2}\left(\log x - \frac{1}{\beta}\left(\alpha - \frac{\sigma^2}{2}\right)\right)^2\right\},\ x > 0.$$

Generalized model of growth

Theorem

If $\gamma(\alpha - \frac{\sigma^2}{2}) + \beta \geq 0$ *and* $\gamma \neq 0$ *then* X *is recurrent.*
If $\gamma(\alpha - \frac{\sigma^2}{2}) + \beta > 0$ *and* $\gamma \neq 0$ *then* X *is ergodic, and its stationary density is*

$$f(x) = \frac{|\gamma| \left(\frac{2\beta}{\sigma^2\gamma^2}\right)^{\frac{2}{\sigma^2\gamma^2}\left(\gamma\left(\alpha - \frac{\sigma^2}{2}\right)+\beta\right)}}{\Gamma\left(\frac{2}{\sigma^2\gamma^2}\left(\gamma\left(\alpha - \frac{\sigma^2}{2}\right)+\beta\right)\right)} \cdot x^{\frac{2}{\sigma^2}\left(\alpha - \sigma^2 + \frac{\beta}{\gamma}\right)} \cdot \exp\left\{-\frac{2\beta}{\sigma^2\gamma^2} x^{\gamma}\right\}, \quad x > 0.$$

Generalized model of growth

Theorem

If $\gamma(\alpha - \frac{\sigma^2}{2}) + \beta < 0$ *then*

$$\gamma > 0 \quad \Rightarrow \quad \lim_{t\to+\infty} X_t = 0 \text{ a.s.}$$
$$\gamma < 0 \quad \Rightarrow \quad \lim_{t\to+\infty} X_t = +\infty \text{ a.s.}$$

- recurrent (Markov process):

$$(\forall x \in S)(\forall B_x)\,\mathrm{P}(\exists t > 0,\ X_t \in B_x) = 1$$

- stationary density (distribution):

$$X_0 \sim \pi \ \Rightarrow\ (\forall t \geq 0)\,X_t \sim \pi$$

- ergodic (Markov process): X is recurrent, has stat. distrib. π, and

$$(\forall g \in L^1(\pi))\ \lim_{t\to+\infty} \frac{1}{t}\int_0^t g(X_s)\,ds = \int g\,d\pi = \mathrm{E}_\pi[g(X_0)]$$

Generalized model of growth

Definition

General diffusion process of growth *is a continuous solution of SDE:*

$$dX_t = (\alpha - \beta \mathrm{h}(\gamma, X_t))X_t\,dt + \sigma X_t\,dW_t, \quad X_0 > 0$$

with vector-parameters $\theta = (\alpha, \beta, \gamma, \sigma) \in \bar{\Theta}$,

$$\bar{\Theta} = \{(\alpha, \beta, \gamma, \sigma) \in \mathrm{R}^4 : \beta > 0,\ \sigma > 0,\ \gamma(\alpha - \frac{\sigma^2}{2}) + \beta > 0\}.$$

Generalized model of growth

Theorem (Stability of the model)

Let $(\theta_n = (\alpha_n, \beta_n, \gamma_n, \sigma_n),\ n \geq 0) \subseteq \bar{\Theta}$, *and* $X^{(n)} = (X_t^{(n)}, t \geq 0)$ *be s.t. for* $n \geq 0$*:*

$$dX_t^{(n)} = (\alpha_n - \beta_n \mathrm{h}(\gamma_n, X_t^{(n)}))X_t^{(n)}\, dt + \sigma_n X_t^{(n)}\, dW_t.$$

If $\lim_n \theta_n = \theta_0$ *and* $(\mathrm{P}) \lim_n X_0^{(n)} = X_0^{(0)}$ *then* $(ucp) \lim_n X^{(n)} = X^{(0)}$*, i.e.*

$$(\forall t > 0)\ (\mathrm{P}) \lim_{n\to\infty} \sup_{0 \leq s \leq t} |X_s^{(n)} - X_s^{(0)}| = 0.$$

Estimation of the parameters

Model: (SDE)

$$dX_t = \mu(X_t, \vartheta)\, dt + \sigma\, b(X_t)\, dW_t, \quad X_0 = x_0 > 0$$

Data:

$$X_{t_0}, X_{t_1}, \ldots, X_{t_n}$$

where

$$0 = t_0 < t_1 < \cdots < t_{n-1} < t_n = T$$

Drift parameter space: $\Theta \subset \mathrm{R}^d$ is open and convex set

$$\delta_{n,T} := \max_{1 \le i \le n}(t_i - t_{i-1})$$

$$\delta_{n,T} = \frac{T}{n} \text{ for equidistant sampling}$$

Estimation of the parameters

Maximum likelihood estimation of drift parameters

- requires transition density in closed form
- MLE is consistent, asymptotically normal and efficient

(Dacunha-Castelle and Florens-Zmirou, 1986)

Estimation of the parameters

Quasi-likelihood or Approximate maximum likelihood estimation of drift parameters

$\rightarrow$ based on approximation of transition density

$\rightarrow$ Approximate maximum likelihood estimator (AMLE)

- AMLE based on Euler-Ito approximation of integrals is consistent, asymptotically normal and efficient for equidistant sampling, when $T \rightarrow +\infty$, s.t. $T\delta_{n,T}^2 \rightarrow 0$ (Florens-Zmirou, 1989, Kessler, 1997)
- AMLE based on Hermite polynomial approx. of density converges to MLE when order of the expansion goes to $+\infty$ for equidistant sampling s.t. $n \rightarrow +\infty$ (Aït-Sahalia, 2002, 2008)

Estimation method

Quasi-likelihood based on Euler-Ito approximation of the integrals:

$$X_{t_{i+1}} - X_{t_i} \approx \mu(X_{t_i}, \vartheta)(t_{i+1} - t_i) + \sigma\, b(X_{t_i})(W_{t_{i+1}} - W_{t_i})$$

$\Rightarrow$ Criterion function:

$$\mathcal{L}_{n,T}(\vartheta, \sigma) := -\frac{1}{2} \sum_{i=0}^{n-1} \left(\frac{(\Delta_i X - \mu(X_{t_i}, \vartheta)\Delta_i t)^2}{\sigma^2 b^2(X_{t_i})\Delta_i t} + \log \sigma^2 \right)$$

where

$$\Delta_i X := X_{t_{i+1}} - X_{t_i}, \quad \Delta_i t := t_{i+1} - t_i$$

Estimation method

Criterion function (simplified):

$$\mathcal{L}_{n,T}(\vartheta,\sigma) = -\frac{1}{2\sigma^2}\sum_{i=0}^{n-1}\frac{(\Delta_i X)^2}{b^2(X_{t_i})\Delta_i t} - \frac{n}{2}\log\sigma^2 + \frac{1}{\sigma^2}\ell_{n,T}(\vartheta)$$

where

$$\ell_{n,T}(\vartheta) := \sum_{i=0}^{n-1}\frac{\mu(X_{t_i},\vartheta)}{b^2(X_{t_i})}\Delta_i X - \frac{1}{2}\sum_{i=0}^{n-1}\frac{\mu^2(X_{t_i},\vartheta)}{b^2(X_{t_i})}\Delta_i t$$

If $\Theta \subset \mathrm{R}^d$ is an open set then AMLE:

$$(\hat{\vartheta}_{n,T},\hat{\sigma}_{n,T}) = \operatorname*{Argmax}_{\vartheta\in\Theta,\sigma>0}\mathcal{L}_{n,T}(\vartheta,\sigma) \Rightarrow$$

$$D\mathcal{L}_{n,T}(\hat{\vartheta}_{n,T},\hat{\sigma}_{n,T}) = 0 \quad\Leftrightarrow\quad \begin{cases} D\ell_{n,T}(\hat{\vartheta}_{n,T}) = 0 \\ \hat{\sigma}^2_{n,T} = \frac{1}{n}\sum_{i=0}^{n-1}\frac{(\Delta_i X - \mu(X_{t_i},\hat{\vartheta}_{n,T})\Delta_i t)^2}{b^2(X_{t_i})\Delta_i t} \end{cases}$$

Estimation method

Log-likelihood based on continuous obs. $(X_t, 0 \le t \le T)$:

$$\ell_T(\vartheta) := \int_0^T \frac{\mu(X_t, \vartheta)}{b^2(X_t)}\, dX_t - \frac{1}{2}\int_0^T \frac{\mu^2(X_t, \vartheta)}{b^2(X_t)}\, dt$$

MLE based on continuous obs.:

$$\hat{\vartheta}_T = \underset{\vartheta \in \Theta}{\mathrm{Argmax}}\, \ell_T(\vartheta)$$

Notice:

$$\ell_{n,T}(\vartheta \,|\, X_{t_i}(\omega); 0 \le i \le n) \approx \ell_T(\vartheta \,|\, (X_t(\omega); 0 \le t \le T))$$

Estimation method

MLE based on continuous obs.:

- is consistent, asymptotically normal and efficient (Brown and Hewitt, 1975)

We proved that (M.H., 2017):

$$\hat{\vartheta}_{n,T} - \hat{\vartheta}_T = O_{\mathrm{P}}(\sqrt{\delta_{n,T}})$$

for equidistant sampling s.t. $T \to +\infty$, $\delta_{n,T} \to 0$
(in case of drift linear in ϑ: LeBreton, 1976)

$\Rightarrow$ AMLE is consistent, asymptotically normal and efficient for equidistant sampling s.t. $T \to +\infty$, $T\delta_{n,T} \to 0$.

Problem assumptions

(A1):

- For all $\vartheta \in \Theta$, $\sigma > 0$, there exists a strong solution (X, W) of the SDE on time interval $[0, +\infty\rangle$ with state space $E \subseteq \mathbb{R}$, an open interval.
- X is ergodic with stationary distribution π_ϑ on E, i.e.

$$(\forall f \in L^1(\pi_\vartheta)) \quad \lim_{T \to +\infty} \frac{1}{T} \int_0^T f(X_t)\, dt = \int_E f(x) \pi_\vartheta(dx)$$

Problem assumptions

(A2):

- For all $\vartheta \in \Theta$, $\mu(\cdot,\vartheta) \in C^2(E)$ and $b \in C^3(E)$.
- For all $x \in E$, $b(x) \neq 0$ and $\operatorname{sign} b = \text{const}$.
- For all $\vartheta \in \Theta$, $\mu(\cdot,\vartheta)b'/b, (b')^2, b''b \in L^{16}(\pi_\vartheta)$, $b^2 b''' \in L^8(\pi_\vartheta)$.
- There exists $c \in L^1(\pi_\vartheta)$ and $h_0 > 0$ s.t.

$$\sup_{0<h\leq h_0} \mathrm{E}_{(\vartheta,\sigma)} \exp\left(8 \int_0^h \left(2\frac{\mu(\cdot,\vartheta)b'}{b} + \sigma^2(b''b + 15b'^2)\right)(X_s)\, ds\right) \leq c(x_0)$$

Problem assumptions

(A3):

- Θ is a relative compact set in R^d.
- For each $0 \leq m \leq d+3$, $D_\vartheta^m \mu$, $\frac{\partial}{\partial x} D_\vartheta^m \mu$, $\frac{\partial^2}{\partial x^2} D_\vartheta^m \mu \in C(E \times \overline{\Theta})$.
- There exist $g_0, g_1, g_2 : E \to \mathrm{R}_+$ s.t. for all $\vartheta_0 \in \Theta$, $g_0 \in L^{32}(\pi_{\vartheta_0}) \cap C^1(E)$, $g_0' b \in L^{16}(\pi_{\vartheta_0})$, $g_1 \in L^{16}(\pi_{\vartheta_0}) \cap C(E)$, $g_2 \in L^8(\pi_{\vartheta_0}) \cap C(E)$.
- For all $x \in E$ and $0 \leq m \leq d+3$,

$$\begin{aligned} \sup_{\vartheta \in \overline{\Theta}} |D_\vartheta^m \mu(x, \cdot)/b(x)|_\infty &\leq g_0(x) \\ \sup_{\vartheta \in \overline{\Theta}} |\tfrac{\partial}{\partial x} D_\vartheta^m \mu(x, \cdot)|_\infty &\leq g_1(x) \\ \sup_{\vartheta \in \overline{\Theta}} |\tfrac{\partial^2}{\partial x^2} D_\vartheta^m \mu(x, \cdot) b(x)|_\infty &\leq g_2(x). \end{aligned}$$

Problem assumptions

(A4):
For all $\vartheta \in \Theta$,

$$(\forall \vartheta' \in \overline{\Theta})\ \vartheta' \neq \vartheta \Rightarrow \int_E \frac{(\mu(x,\vartheta) - \mu(x,\vartheta'))^2}{b^2(x)} \pi_\vartheta(dx) > 0.$$

(A5):
For all $\vartheta \in \Theta$, functions $\frac{\partial \mu}{\partial \vartheta_i}(\cdot, \vartheta)/b$, $1 \leq i \leq d$, are linearly independent in $L^2(\pi_\vartheta)$.

(A5) $\Rightarrow$

$$I(\vartheta_0) = \int_E \frac{1}{b^2(x)} (D_\vartheta^\tau \mu D_\vartheta \mu)(x, \vartheta_0)\, \pi_{\vartheta_0}(dx) > \mathbf{0}$$

Results

Theorem (MLE based on continuous obs.)

Let (A1-5) hold. Then there exists a $(\mathcal{F}_T^0, T > 0)$*-adapted process* $(\hat{\vartheta}_T, T > 0)$ *s.t. for every* $\theta_0 = (\vartheta_0, \sigma_0) \in \Theta \times \mathrm{R}_+$*:*

(i) P_{θ_0}*-a.s. there exists* $T_0 > 0$ *s.t. for all* $T \geq T_0$*:*
$\hat{\vartheta}_T \in \Theta$ *is the unique point of maximum of* ℓ_T *on* $\overline{\Theta}$*, and*
$\min_{|y|=1} y^\tau(-\frac{1}{T}D^2\ell_T(\hat{\vartheta}_T))y \geq \frac{1}{2}\min_{|y|=1} y^\tau I(\vartheta)y.$

(ii) $\lim_{T\to+\infty} \hat{\vartheta}_T = \vartheta_0$ P_{θ_0}*-a.s.*

(iii) $\sqrt{T}(\hat{\vartheta}_T - \vartheta_0) \xrightarrow{\mathcal{L}-\mathrm{P}_{\theta_0}} N(\mathbf{0}, \sigma_0^2 I(\vartheta_0)^{-1}).$

Results

Theorem (AMLE of drift parameters)

Let (A1-5) hold. Then there exists a process $(\hat{\vartheta}_{n,T}; n \geq 1, T > 0)$ *of* $\mathcal{F}_{n,T}$*-measurable random vectors* $\hat{\vartheta}_{n,T}$ *s.t. for all* $\theta_0 = (\vartheta_0, \sigma_0) \in \Theta \times \mathrm{R}_+$ *and* π_{ϑ_0}*-a.s. nonrandom initial conditions, and all equidistant samplings such that* $\delta_{n,T} = T/n \to 0$*:*

(i) $\lim_{n,T} \mathrm{P}_{\theta_0}(D\ell_{n,T}(\hat{\vartheta}_{n,T}) = \mathbf{0}) = 1.$

(ii) $(\mathrm{P}_{\theta_0}) \lim_{n,T}(\hat{\vartheta}_{n,T} - \hat{\vartheta}_T) = \mathbf{0},$

(iii) *If* $(\tilde{\vartheta}_{n,T}; n \geq 1, T > 0)$ *is a process in* Θ *that satisfies* $(i - ii)$ *then* $\lim_{n,T} \mathrm{P}_{\theta_0}(\tilde{\vartheta}_{n,T} = \hat{\vartheta}_{n,T}) = 1.$

(iv) $\hat{\vartheta}_{n,T} - \hat{\vartheta}_T = O_{\mathrm{P}_{\theta_0}}(\sqrt{\delta_{n,T}}), n \to +\infty, T \to +\infty$

(v) $(\mathrm{P}_{\theta_0}) \lim_{n,T} \hat{\vartheta}_{n,T} = \vartheta_0,$

(vi) *If in add.* $\lim_{n,T} T\delta_{n,T} = 0$ *then*

$$\sqrt{T}(\hat{\vartheta}_{T,n} - \vartheta_0) \xrightarrow{\mathcal{L}-\mathrm{P}_{\theta_0}} N(\mathbf{0}, \sigma_0^2 I(\vartheta_0)^{-1}), \ T \to +\infty, n \to +\infty.$$

Results

Corollary (AMLE of diff. coeff. parameter)

Let (A1-5) hold. Then for all $\theta_0 = (\vartheta_0, \sigma_0) \in \Theta \times \mathrm{R}_+$ *and* π_{ϑ_0}*-a.s. nonrandom initial conditions, and all equidistant samplings such that* $\delta_{n,T} = T/n \to 0$*:*

(i) $(\mathrm{P}_{\theta_0}) \lim_{n,T} \hat{\sigma}^2_{n,T} = \sigma_0^2$

(ii) *If in add.* $\lim_{n,T} T\delta_{n,T} = 0$ *then*

$$\sqrt{n}\frac{1}{\sigma_0^2\sqrt{2}}(\hat{\sigma}^2_{n,T} - \sigma_0^2) \xrightarrow{\mathcal{L}-\mathrm{P}_{\theta_0}} N(0,1), \ T \to +\infty, n \to +\infty.$$