

Approximation of epidemic models by diffusion processes and their statistical inferences

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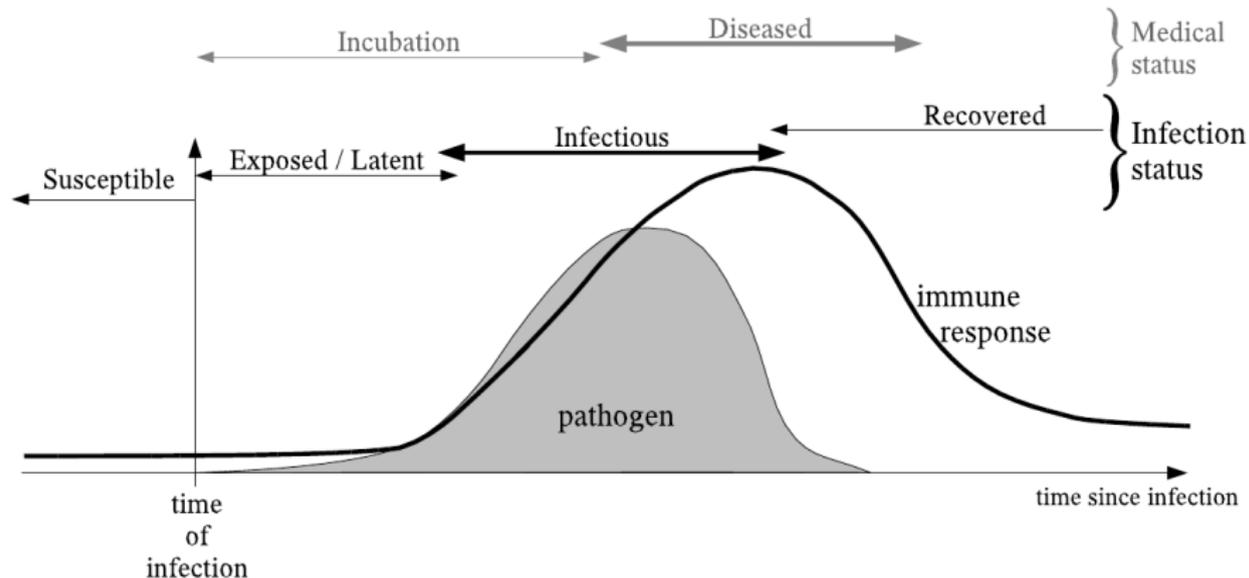
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Based on Guy^{1,2}, Larédo, Vergu¹ (JMB 2014)

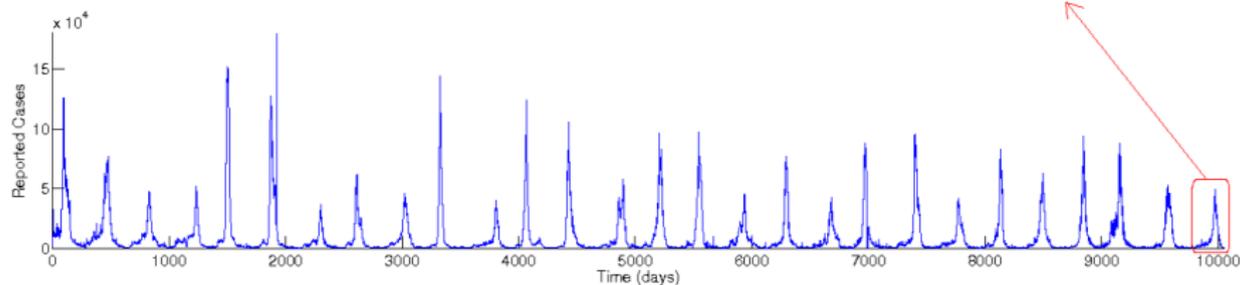
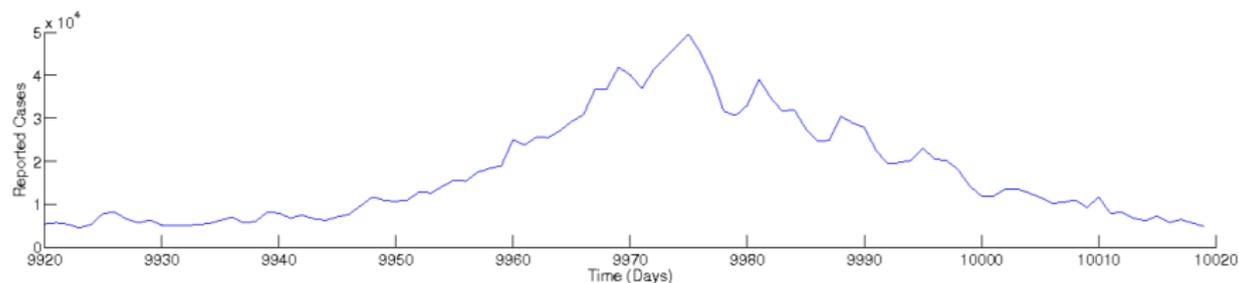
Context of infectious diseases (individual infection)



Modeling scheme for individual infection

- Compartmental models for describing the infection status :
(S) Susceptible; (E) Exposed/Latent ; (I) Infectious/Infected ; (R) Removed.
- Difficulty in detecting the infection status \Rightarrow systematically noisy data.

Various dynamics at the population scale: (epidemics with one outbreak or recurrent outbreaks)



Influenza like illness cases in France ("Sentinelles" surveillance network)

Main important issues (1)

Determine the key parameters of the epidemic dynamics

- Basic reproduction number R_0 (average nb of secondary cases by one primary case in an entirely susceptible population)
- Average infectious time period d
- Latency period, etc...

Based on the available data

- Exact times of infection beginning and ending are not observed.
- Data are collected at fixed times (daily, weekly .. data)
- Temporally aggregated data.
- Sampling and reporting errors
- Some disease stages cannot be observed.

Main important issues (2)

Provide a common framework for developing estimation methods as accurate as possible given the data available

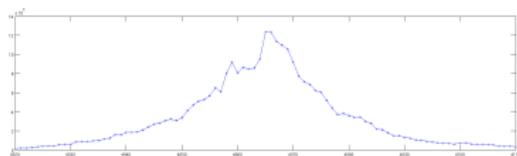
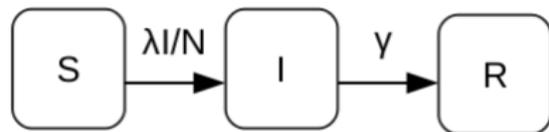
SEVERAL POSSIBLE WAYS TO OVERCOME THIS PROBLEM OF MISSING OR INCOMPLETE DATA

- 1 Develop algorithms to simulate the unobserved missing data.
- 2 Existence of lots of computer intensive methods in this domain.
- 3 Difficult to use for large populations.
- 4 Results are often unstable.

ANOTHER CHOICE HERE

- 1 Consider separately the model and the available data.
- 2 Study the properties of the observations derived from the model
- 3 Investigate inference based on these properties
- 4 Develop algorithms fast to implement in relation with the previous step

A simple mechanistic model for a single outbreak : *SIR*



S, I, R numbers of Susceptibles, Infected, Removed.

λ : transmission rate , γ : recovery rate.

Notations and assumptions:

- Closed population of size N ($\forall t, S(t) + I(t) + R(t) = N$).
- Homogeneous contacts in a well mixing population:
 $(S, I) \rightarrow (S - 1, I + 1)$ at rate $S \lambda \frac{I}{N}$
 $(S, I) \rightarrow (S, I - 1)$ at rate γI

Key parameters of this epidemic model

- Basic reproduction number $R_0 = \frac{\lambda}{\gamma}$.
- Average infectious period $d = \frac{1}{\gamma}$.

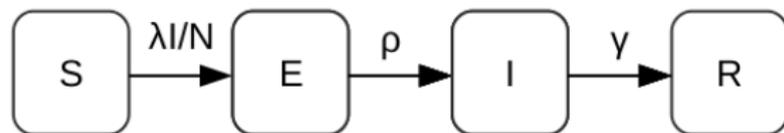
A minimal model for Ebola epidemics

- Explicit and detailed model in Legrand J., Grais R.F., Boelle P.Y. Valleron A.J. and Flahault A. (2007), *Epidemiology & Infection*
- Impossible to estimate parameters from available data.
- Due to identifiability problems.

A Minimal model for Ebola Transmission

Camacho et al. *PLoS Curr*, 2015;7.

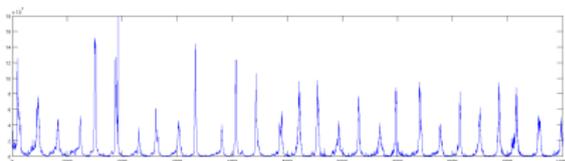
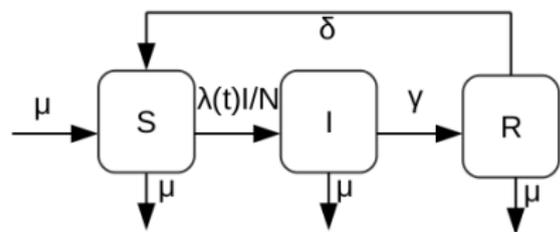
SEIR model with temporal transmission rate



- $(S, E, I) \rightarrow (S - 1, E + 1, I)$ at rate $S \lambda(t) \frac{I}{N}$,
- $(S, E, I) \rightarrow (S, E - 1, I + 1)$ at rate ρE
- $(S, E, I) \rightarrow (S, E, I - 1)$ at rate γI

A mechanistic model for recurrent epidemics

SIRS model with seasonal forcing (Keeling et Rohanni, 2011)



- δ : Immunity waning rate (per year) $^{-1}$,
- μ (Population renewal): birth rate and death rate (per decades) $^{-1}$
- $\lambda(t) = \lambda_0(1 + \lambda_1 \cos(2\pi \frac{t}{T_{per}}))$,
- λ_0 Baseline transition rate, λ_1 :intensity of the seasonal effect,
- T_{per} : period of the seasonal trend.

Important: $\lambda_1 = 0 \Rightarrow$ Damping out oscillations \Rightarrow need to have a temporal forcing

Appropriate model for recurrent epidemics in very large populations

Key parameters: $R_0 = \frac{\lambda_0}{\gamma + \mu}$, $d = \frac{1}{\gamma}$, Average waning period: $\frac{1}{\delta T_{per}}$

Recap on some mathematical approaches

Description

- p : number of health states (i.e. compartments).
- Depends on the model choice for describing the epidemic dynamics.
- *SIR* and *SIRS* models: $p = 3$.
- Adding a state "Exposed/latent" \Rightarrow *SEIR* model: $p = 4$.
- Addition of states where individuals have similar behaviour with respect to the pathogen: age, vaccination, structured populations).

Some classical mathematical models

- Pure jump Markovprocess with state space \mathbb{N}^P : $Z(t)$.
- Deterministic models satisfying an ODE on \mathbb{R}^P : $x(t)$.
- Gaussian Process with values in \mathbb{R}^P : $G(t)$.
- Diffusion process $X(t)$ satisfying a SDE on \mathbb{R}^P :

Links between these models?

Pure jump p - dimensional Markov process $Z(t)$

Simple and natural modelling of epidemics.

Notations

- Population size $N \Rightarrow Z(t) \in E = \{0, \dots, N\}^p$.
- Jumps of $Z(t)$: collection de functions $\alpha_\ell(\cdot) : E \rightarrow (0, +\infty)$, indexed by $\ell \in E^- = \{-N, \dots, N\}^p$
- For all $x \in E$, $0 < \sum_\ell \alpha_\ell(x) := \alpha(x) < \infty$.

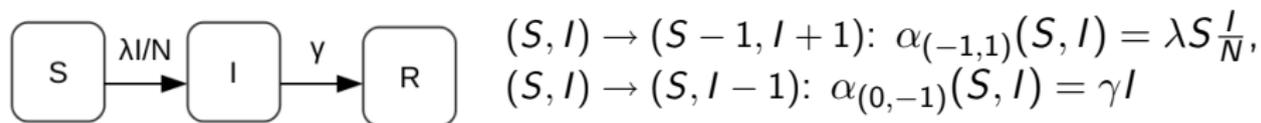
Pure jump Markov Process with state space de E : $Z(t)$

- \Rightarrow Transition rate from $x \rightarrow x + \ell$: $\alpha_\ell(x)$,
 - Q-matrix of $(Z(t))$: $Q = (q_{xy}, (x, y) \in E \times E)$
if $y \neq x$, $q_{xy} = \alpha_{y-x}(x)$, and $q_{xx} = -\alpha(x)$.
- ★ Each individual stays in state x with exponential holding time $\mathcal{E}(\alpha(x))$,
★ Then, it jumps to another state according to a Markov chain with transition kernel $\mathbb{P}(x \rightarrow x + \ell) = \frac{\alpha_\ell(x)}{\alpha(x)}$.

SIR, SEIR models in a closed population of size N

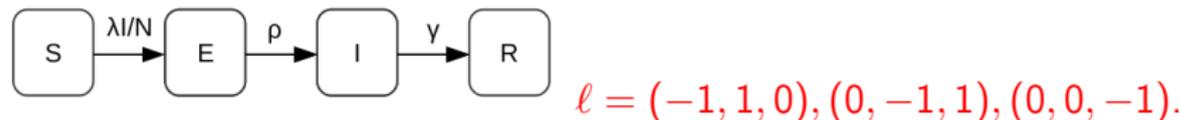
SIR epidemic model

$\forall t, S(t) + I(t) + R(t) = N \Rightarrow Z(t) = (S(t), I(t)) \in E = \{0, \dots, N\}^2$
and $\ell = (-1, 1), (0, -1)$



SEIR epidemic model: (Time-dependent process)

$Z(t) = (S(t), E(t), I(t)) \in E = \{0, \dots, N\}^3$.



$(S, E, I) \rightarrow (S - 1, E + 1, I): \alpha_{(-1,1,0)}(S, E, I) = \lambda(t) S \frac{I}{N}$,

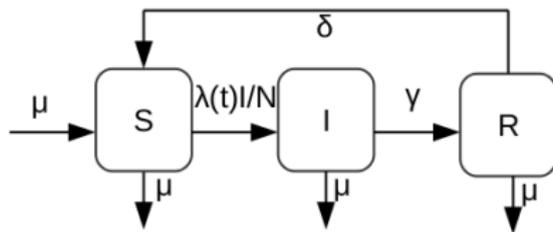
$(S, E, I) \rightarrow (S, E - 1, I + 1): \alpha_{(0,-1,1)}(S, E, I) = \rho I$,

$(S, E, I) \rightarrow (S, E, I - 1): \alpha_{(0,0,-1)}(S, E, I) = \gamma I$

SIRS model with seasonal forcing in a closed population

$\Rightarrow Z(t) = (S(t), I(t)) \in E = \{0, \dots, N\}^2$,

$\ell = (-1, 1), (0, -1), (1, 0), (-1, 0)$.



$(S, I) \rightarrow (S - 1, I + 1) : \alpha_{(-1,1)}(t; S, I) = \lambda(t)S \frac{I}{N}$,

$(S, I) \rightarrow (S, I - 1) : \alpha_{(0,-1)}(S, I) = (\gamma + \mu)I$,

$(S, I) \rightarrow (S + 1, I) : \alpha_{(1,0)}(S, I) = \mu N + \delta(N - S - I)$,

$(S, I) \rightarrow (S - 1, I) : \alpha_{(-1,0)}(S, I) = \mu S$.

$\lambda(t) = \lambda_0(1 + \lambda_1 \sin(2\pi \frac{t}{T_{per}})) \Rightarrow$ **Time-inhomogeneous Markov process.**

Remark: Simulations are easy with Gillespie's algorithm

Density dependent jump processes $Z(t)$ (1)

Extension of results Ethier et Kurz (2005) to time-dependent processes.

Notations

★ if $y = (y_1, \dots, y_p) \in \mathbb{R}^p$, $[y] = ([y_1], \dots, [y_p])$, with $[y_i]$ integer part of y_i .

Transposition of a vector y or a matrix M : ${}^t y$, ${}^t M$.

★ Gradient de $b(\cdot) \in C(\mathbb{R}^p, \mathbb{R}^p)$: $\nabla b(y) = (\frac{\partial b_i}{\partial y_j}(y))_{ij}$.

Framework

★ Constant population size $N \Rightarrow E = \{0, \dots, N\}^p$.

★ Collection $\alpha_\ell(\cdot) : E \rightarrow (0, \infty)$ with $\ell \in E^- = \{-N, \dots, N\}^p$.

★ Transition rates: $y \rightarrow y + \ell$: $\alpha_\ell(y) \Rightarrow q_{yz} = \alpha_{z-y}(y)$.

Normalization by the size N of $Z(t)$

- $Z_N(t) = \frac{Z(t)}{N} \Rightarrow$
- State space: $E_N = \{N^{-1}k, k \in E\}$;
- $Z_N(t)$ jump process on E_N with Q -matrix:
if $x, y \in E_N, y \neq x$, $q_{xy}^{(N)} = \alpha_{N(y-x)}(x)$.

Density dependent jump processes $Z(t):(2)$

Density dependent Process

Recall that the jumps ℓ of $Z(t)$ belong to $E^- = \{-N, \dots, N\}^p$.

Assumption (H):

(H1): $\forall (\ell, y) \in E^- \times [0, 1]$, $\frac{1}{N} \alpha_\ell([Ny]) \rightarrow \beta_\ell(y)$.

(H2): $\forall \ell, y \rightarrow \beta_\ell(y) \in C^2([0, 1]^p)$.

Definition of the key quantities $b(\cdot)$ and $\Sigma(\cdot)$

$$b(y) = \sum_{\ell} \ell \beta_\ell(y), \quad \Sigma(y) = \sum_{\ell} \ell^t \ell \beta_\ell(y).$$

These quantities are well defined since the number of jumps is finite.

Note that $b(y) = (b_k(y), 1 \leq k \leq p) \in \mathbb{R}^p$ and

$\Sigma(y) = (\Sigma_{kl}(y), 1 \leq k, l \leq p)$ is a p -dimensional matrix.

Approximations of $Z_N(\cdot)$

$$x(t) = x_0 + \int_0^t b(x(s)) ds.$$

$$\Phi(t, u) \text{ solution de } \frac{\partial \Phi}{\partial t}(t, u) = \nabla b(x(t))\Phi(t, u); \Phi(u, u) = I_p.$$

Convergence Theorem

Assume (H1),(H2), and that $Z_N(0) \rightarrow x_0$ as $N \rightarrow \infty$. Then,

★ $Z_N(\cdot)$ converges $x(\cdot)$ uniformly on $[0, T]$,

★ $\sqrt{N}(Z_N(t) - x(t))$ converges in distribution to $G(t)$,

★ $G(t)$ centered Gaussian process with

$$\text{Cov}(G(t), G(r)) = \int_0^{t \wedge r} \Phi(t, u) \Sigma(x(u)) {}^t\Phi(r, u) du.$$

Proof: Ethier & Kurtz (2005): $\alpha_I([Ny]) \equiv \beta_I(y)$; GLV (2014) for

(i) Jump rates $\alpha_I(\cdot)$ satisfying (H)

(ii) Time-dependent jump rates $\alpha_I(\mathbf{t}, x)$ with

$$\frac{1}{N} \alpha_I(\mathbf{t}, [Ny]) \rightarrow \beta_I(\mathbf{t}, y) \Rightarrow b(\mathbf{t}, y); \Sigma(\mathbf{t}, y)$$

(Proof based on general limit theorems (Jacod and Shiryaev)).

Diffusion approximation of $Z_N(t)$

Recap: $b(y) = \sum_{\ell} \ell \beta_{\ell}(y)$ and $\Sigma(y) := \sum_{\ell} \ell^t \ell \beta_{\ell}(y)$.

Let $f : \mathbb{R}^p \rightarrow \mathbb{R}$ a bounded measurable and \mathcal{A} the generator of $Z(t)$

- $\mathcal{A}(f)(y) = \sum_{\ell} \alpha_{\ell}(y)(f(y + \ell) - f(y))$
- $\Rightarrow \mathcal{A}_N(f)(y) = \sum_{\ell} \alpha_{\ell}(Ny)(f(y + \frac{\ell}{N}) - f(y))$

Euristically : Expanding the generator \mathcal{A}_N of $Z_N(\cdot) = \frac{Z(t)}{N}$.

$$\mathcal{A}_N(f)(y) = b(y)\nabla f(y) + \frac{1}{2N} \sum_{i,j=1}^p \Sigma_{ij}(y) \frac{\partial^2 f}{\partial y_i \partial y_j}(y) + o(1/N)$$
$$\Rightarrow \mathcal{A}_N(f)(y) = B_N(f)(y) + o(1/N).$$

Diffusion approximation of $Z_N(t)$: diffusion with generator B_N

$$dX_N(t) = b(X_N(t))dt + \frac{1}{\sqrt{N}}\sigma(X_N(t))dB(t),$$

$B(t)$: p -dimensional Brownian motion et $\sigma(\cdot)$ a square root of $\Sigma(\cdot)$
 $\sigma(y)^t \sigma(y) = \Sigma(y)$.

Small perturbations of Dynamical systems

Freidlin & Wentzell (1978) ; Azencott (1982)

$$\epsilon = 1/\sqrt{N} \Rightarrow X_N(t) = X_\epsilon(t)$$

Link between the CLT for $(Z_N(\cdot))$ and diffusion $(X_N(\cdot))$

Expanding $X_\epsilon(t)$ with respect to ϵ ,

- $X_\epsilon(t) = x(t) + \epsilon g(t) + \epsilon R_\epsilon(t)$,
- where $dg(t) = \nabla b(x(t))g(t)dt + \sigma(x(t))dB(t)$; $g(0) = 0$,
- $\sup_{t \leq T} \|\epsilon R_\epsilon(t)\| \rightarrow 0$ in probability as $\epsilon \rightarrow 0$.

Explicit solution of this stochastic differential equation

★ $g(t) = \int_0^t \Phi(t, s)\sigma(x(s))dB(s)$, where

★ $\Phi(t, u)$ s.t. $\frac{\partial \Phi}{\partial t}(t, u) = \nabla b(x(t))\Phi(t, u)$; $\Phi(u, u) = I_p$.

★ $g(\cdot)$: centered Gaussian process with same covariance matrix as $G(\cdot)$.

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TALK 3-Part1, CIMPA 2015

A primer on statistical inference for diffusion processes

This is mainly based on lectures on Statistics of diffusion processes of V. Genon-Catalot (MAP5, Université Paris-Descartes).

Continuous observation on a finite time interval $[0, T]$

On the probability space $(\Omega, \mathcal{F}, (\mathcal{F}_t, t \geq 0), \mathbb{P})$

$$d\xi_t = b(\theta_0; t, \xi_t)dt + \sigma(t, \xi_t)dW_t, \xi_0 = \eta$$

$\sigma(t, \xi_t)$ **identified** from this observation \Rightarrow

Assumption: $\sigma(t, \xi_t)$ known.

(B_t) : p - dimensional Brownian motion ,

η \mathcal{F}_0 -measurable ;

$\theta_0 \in \Theta$ compact subset of \mathbb{R}^k .

Aim: study of estimators of θ_0 depending on the observation

$(\xi_t, t \in [0, T])$.

Probability distribution of a continuous time process

- $C_T = \{x = (x(t)) : [0, T] \rightarrow \mathbb{R}^p \text{ continuous}\}$,
- \mathcal{C}_T : Borelian filtration associated with the uniform topology
- Coordinate function: $X_t : C_T \rightarrow \mathbb{R}^p$, $X_t(x) = x(t)$.
- (X_t) : canonical process \Rightarrow canonical filtration: $\mathcal{C}_t = \sigma(X_s, s \leq t)$.

Diffusion process (ξ_t) on $(\Omega, \mathcal{F}, \mathbb{P})$, $d\xi_t = b(t, \xi_t)dt + \sigma(t, \xi_t)dW_t$, $\xi_0 = \eta$.
 $\Rightarrow \forall \omega, t \rightarrow \xi_t(\omega)$ is continuous $[0, T] \Rightarrow \xi^T := (\xi_t(\omega), t \in [0, T]) \in C_T$.

Distribution of $(\xi_t, t \in [0, T])$ on (C_T, \mathcal{C}_T)

- $P_{b,\sigma}^T =$ probability distribution image of \mathbb{P} by the r.v. ξ^T .
- A_i borelian sets in \mathbb{R}^p , $A = \{x \in C_T, x(t_1) \in A_1, \dots, x(t_k) \in A_k\}$,
- $\mathbb{P}(\xi^T \in A) = P_{b,\sigma}^T(X_{t_1} \in A_1, \dots, X_{t_k} \in A_k)$.

Wiener measure W^T : distribution of $(B_t, t \in [0, T])$ on (C_T, \mathcal{C}_T) .

Likelihood for continuously observed diffusions on $[0, T]$

Consider the parametric model associated to the diffusion on \mathbb{R}

★ $d\xi_t = b(\theta_0; \xi_t)dt + \sigma(\xi_t)dB_t, \xi_0 = x_0.$

★ $\sigma(x), b(\theta, x)$ known; x_0 known; θ unknown $\Rightarrow \theta \in \Theta.$

★ P_θ^T : distribution on (C_T, \mathcal{C}_T) of $(\xi_t).$

★ P_0^T distribution of $\xi_t = x_0 + \int_0^t \sigma(\xi_s)dB_s$

Assumptions ensuring existence, uniqueness of solutions of the SDE+..

★ Additional assumptions

Theorem

For all θ , the distributions P_θ^T and P_0^T are equivalent and

$$\frac{dP_\theta^T}{dP_0^T}(X) = \exp\left[\int_0^T \frac{b(\theta, X_t)}{\sigma^2(X_t)} dX_t - \frac{1}{2} \int_0^T \frac{b^2(\theta, X_t)}{\sigma^2(X_t)} dt\right].$$

Above formula: stochastic integral w.r.t. the canonical process (X_t)

Under P_0^T , $\int_0^t \frac{dX_s}{\sigma^2(X_s)} ds$ is a standard Brownian motion,

Under P_θ^T , $\int_0^t \frac{dX_s - b(\theta, X_s)ds}{\sigma^2(X_s)}$ is a Brownian motion.

Comments and extensions

- Diffusions having distinct diffusion coefficients $\sigma(x)$, $\sigma'(x) \Rightarrow P_\sigma$ and $P_{\sigma'}$ are singular distributions on (C_T, C_T) .
- Diffusion having distinct starting point x_0, x'_0 have singular distributions.

(ξ_t) : time-dependent multidimensional diffusion process

- $b(\theta, x) \rightarrow b(\theta, t, x)$; $\sigma^2(x) \rightarrow \Sigma(t, x) = \sigma(t, x) {}^t\sigma(t, x)$.

(Karatzas & Shreve for conditions ensuring existence and uniqueness of solutions.

- On $(C_T = C([0, T], \mathbb{R}^p), C_T)$,

$$\begin{aligned} \frac{dP_\theta^T}{dP_0^T}(X) &= \exp\left(\int_0^T \Sigma^{-1}(t, X_t) b(\theta; t, X_t) dX_t \right. \\ &\quad \left. - \frac{1}{2} \int_0^T {}^t b(\theta; t, X_t) \Sigma^{-1}(t, X_t) b(\theta, t, X_t) dt\right). \end{aligned}$$

(Liptser & Shiryaev).

Maximum Likelihood Estimator

• Canonical statistical model: $(C_T, \mathcal{C}_T), (P_{\theta, \sigma}^T, \theta \in \Theta)$ ★ The likelihood function associated to the observation $(\xi_t = \xi_t^{\theta_0})$:

★ $\theta \rightarrow L_T(\theta)$, with

$$\star \ell_T(\theta) = \log L_T(\theta) = \int_0^T \frac{b(\theta, \xi_t)}{\sigma^2(\xi_t)} d\xi_t - \frac{1}{2} \int_0^T \frac{b^2(\theta, \xi_t)}{\sigma^2(\xi_t)} dt.$$

★ M.L.E. $\hat{\theta}_T$ s.t. $\ell_T(\hat{\theta}_T) = \sup\{\ell_T(\theta), \theta \in \Theta\}$.

Properties of the MLE as $T \rightarrow \infty$: no general theory.

Example : $d\xi_t = \theta_0 f(t) dt + \sigma(t) dB_t$; $\xi_0 = 0, f, \sigma(\cdot) > 0$.

$$\bullet \ell_T(\theta) = \theta \int_0^T \frac{f(s)}{\sigma^2(s)} d\xi_s - \frac{\theta^2}{2} \int_0^T \frac{f^2(s)}{\sigma^2(s)} ds \Rightarrow \hat{\theta}_T = \frac{\int_0^T \frac{f(s)}{\sigma^2(s)} d\xi_s}{\int_0^T \frac{f^2(s)}{\sigma^2(s)} ds}. \star \text{ Under } P_{\theta_0},$$

$$\hat{\theta}_T = \theta_0 + \frac{\int_0^T \frac{f(s)}{\sigma(s)} dB_s}{\int_0^T \frac{f^2(s)}{\sigma^2(s)} ds} \Rightarrow \hat{\theta}_T \sim \mathcal{N}(\theta_0, I_T^{-1}) \text{ with } I_T = \int_0^T \frac{f^2(s)}{\sigma^2(s)} ds.$$

Asymptotic behaviour as $T \rightarrow \infty$ depends on I_T .

★ $f(t) = 1, \sigma(t) = \sqrt{1+t^2} \rightarrow I_T = \text{Arctan} T \rightarrow \pi/2$: MLE not consistent.

Ergodic diffusion processes

Diffusion on \mathbb{R}^p :

$$d\xi_t = b(\theta, \xi_t)dt + \sigma(\xi_t)dB_t;$$

Assumptions:

- for $\theta \in \Theta$, (ξ_t) positive recurrent diffusion process.
- Stationary distribution on \mathbb{R}^p : $\lambda(\theta; x)dx$.

Continuous observation on $[0, T]$ with $T \rightarrow \infty$

Assumptions ensuring that the statistical model is regular
(Ibragimov Hasminskii)

MLE: Consistent estimator $\hat{\theta}_T$ of θ_0 ,

$$\sqrt{T}(\hat{\theta}_T - \theta_0) \rightarrow \mathcal{N}_k(0, I^{-1}(\theta_0))$$

$$I(\theta) = (I(\theta)_{i,j}, 1 \leq i, j \leq k),$$

$$I(\theta)_{i,j} = \int_{\mathbb{R}^p} \left(\frac{\partial b(\theta, x)}{\partial \theta_i} \right) \Sigma^{-1}(x) \frac{\partial b(\theta, x)}{\partial \theta_j} \lambda(\theta, x) dx$$

see Kutoyants (2004)

Discrete observations on a fixed time interval $[0, T]$

$$d\xi_t = b(t, \xi_t)dt + \sigma(\theta_0; t\xi_t)dB_t, \xi_0 = \eta$$

$b(t, x)$ known or unknown function, θ_0 unknown parameter to estimate.

Observations at times $t_i^n = iT/n, i = 0, \dots, n$.

Asymptotics: $T > 0$ fixed and $n \rightarrow \infty$

- (1) Only parameters in the diffusion coefficient can be estimated
- (2) No **consistent** estimators for parameters in the drift.
- (3) Estimation of $\theta_0 \Rightarrow$ Statistical model: Local Asymptotic Mixed Normal (Dohnal (JAP,1987), Genon-Catalot & Jacod (1993), Gobet (2001))
 $\hat{\theta}_n$ converges of θ_0 at rate \sqrt{n} ; $\sqrt{n}(\hat{\theta}_n - \theta_0)$: non Gaussian but Mixed variance Gaussian law.

Remark No explicit likelihood (unknown transition densities of ξ_t ; \Rightarrow No attempt to complete the sample path but use of contrast functions.

Discrete observations on $[0, T]$ with $T \rightarrow \infty$

(2) Discrete observations on $[0, T]$ with sampling interval Δ_n

$$d\xi_t = b(\alpha, t, \xi_t)dt + \sigma(\beta, t, \xi_t)dW_t, \xi_0 = \eta.$$

Observations: $(\xi_{t_i}, i = 1, \dots, n)$ with $t_i = i\Delta_n, T = n\Delta_n$.

Double asymptotics indexed as n (nb of observations) $\rightarrow \infty$

$\Delta_n \rightarrow 0$ and $T = n\Delta_n \rightarrow \infty$.

(3) Statistical model. Observations space: $((\mathbb{R}^p)^n, \mathcal{B}(\mathbb{R}^p)^n)$.

$P_{(\alpha, \beta)}^n$ distribution of the n -uple $\Rightarrow P_{(\alpha, \beta)}^n$ and $P_{(\alpha', \beta')}^n$ equivalent.

Likelihood: depends on the transitions of the Markov chain: untractable

Other approaches: Estimating functions, contrast functions...

- Parameters in the drift coefficient α estimated at rate $\sqrt{n\Delta_n}$.
- Parameters in the diffusion coefficient estimated at rate \sqrt{n} .

Diffusion processes with small diffusion coefficient

Model: Multidimensional diffusion process on \mathbb{R}^p

$$d\xi_t = b(\alpha, \xi_t)dt + \epsilon\sigma(\beta, \xi_t)dB_t, \xi_0 = x_0.$$

$P_{\alpha, \beta}^{\epsilon, T}$: distribution of $(\xi_t, 0 \leq t \leq T)$ on (C_T, C_T) .

Continuous observation on $[0, T]$

- $\beta \neq \beta' \Rightarrow P_{\alpha, \beta}^{\epsilon, T}$ and $P_{\alpha, \beta'}^{\epsilon, T}$ are singular
- $\Rightarrow \beta$ identified from the continuous observation $(\xi_t, 0 \leq t \leq T)$.
- $\beta = \beta_0$ or fixed $\sigma(\beta_0, x) = \sigma(x)$

Asymptotic framework: T fixed and $\epsilon \rightarrow 0$. (Kutoyants, 1980)

$$\star \ell_\epsilon(\alpha) = \frac{1}{\epsilon^2} \int_0^T \frac{b(\alpha, \xi_s)}{\sigma^2(\xi_s)} d\xi_s - \frac{1}{2\epsilon^2} \int_0^T \frac{b^2(\alpha, \xi_s)}{\sigma^2(\xi_s)} ds \Rightarrow \text{MLE } \hat{\alpha}_\epsilon$$

$$\star \epsilon^{-1} (\hat{\alpha}_\epsilon - \alpha_0) \rightarrow \mathcal{N}(0, I(\alpha_0)^{-1})$$

$$I(\alpha) = (I_{i,j}(\alpha))_{1 \leq i,j \leq k} = \int_0^T \frac{\partial b}{\partial \alpha_i}(\alpha, x(\alpha, s)) \Sigma^{-1}(x(\alpha, s)) \frac{\partial b}{\partial \alpha_j}(\alpha, x(\alpha, s))$$

$$\star x(\alpha, t) = x_0 + \int_0^t b(\alpha, x(\alpha, s)) ds \text{ and } \Sigma(x) = \sigma(x) {}^t \sigma(x).$$

Discrete observations on a fixed interval $[0, T]$

Diffusion process on \mathbb{R}^p

$$dX(t) = b(\alpha, X(t))dt + \epsilon\sigma(\beta, X(t))dB(t), X(0) = x_0.$$

Observations: $\{X(t_k), k = 0, \dots, n\}$ with $t_k = k\Delta$; $T = n\Delta$.

Two possible asymptotic frameworks

- ① $\epsilon \rightarrow 0$ and Δ fixed with $T = n\Delta \Rightarrow$ Fixed nb of observations n .
- ② $\epsilon \rightarrow 0$ and $\Delta = \Delta_n \rightarrow 0$ with $n\Delta_n = T$ simultaneously. $\Rightarrow n \rightarrow \infty$.

Results in framework (2)

- Different rates of convergence for parameters in the drift and in the diffusion coefficient (Gloter & Sorensen, 2009).
- Estimation of α at rate ϵ^{-1} , β at rate $\sqrt{n} = \Delta_n^{-1/2}$.

In practice difficult to assess which framework is more appropriate \Rightarrow

Distinction between parameters in the drift term α and in the diffusion term β necessary.

Approximation of epidemic models by diffusion processes and their statistical inferences

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Inference for discretely observed epidemic processes

Based on Guy, Laredo, Vergu (2014) Stoch. Proc. Appl.

Back to Epidemics in a close population of size N

Some characteristics of epidemic data

- $\epsilon = \frac{1}{\sqrt{N}}$ (small parameter present in the diffusion term).
- nb of observations n s.t. $n \ll N$ and $\Delta \geq 1$ (1 to 7 days).
- Framework (1) $\epsilon \rightarrow 0$, Δ fixed (n finite) more appropriate.
- Choice of a statistical framework:
- Depends more on the relative magnitudes of T, Δ, N than on their accurate values.
- Interest in studying estimation in both frameworks.
- **Data might change** \Rightarrow Asymptotic framework $\Delta = \Delta_n \rightarrow 0$ also appropriate:
- Available data can become more frequent.
- Study over a long time period for recurrent outbreaks.

Recap for the three epidemic models

- *SIR* diffusion approximation on \mathbb{R}^2 :

$$b_{\theta}(s, i) = \begin{pmatrix} -\lambda si \\ \lambda si - \gamma i \end{pmatrix} \text{ and } \sigma_{\theta}(s, i) = \begin{pmatrix} \sqrt{\lambda si} & 0 \\ -\sqrt{\lambda si} & \sqrt{\gamma i} \end{pmatrix}$$

- *SEIR* with temporal transmission rate : diffusion on \mathbb{R}^3

$$b_{\theta}(t; s, e, i) = \begin{pmatrix} -\lambda(t)si \\ \lambda(t)si - \rho e \\ \rho e - \gamma i \end{pmatrix} \text{ and } \sigma_{\theta}(t; x) = \begin{pmatrix} \sqrt{\lambda(t)si} & 0 & 0 \\ -\sqrt{\lambda(t)si} & \sqrt{\rho e} & 0 \\ 0 & -\sqrt{\rho e} & \sqrt{\gamma i} \end{pmatrix}$$

- *SIRS* model with seasonal forcing: $\lambda(t) = \lambda_0(1 + \lambda_1 \sin(2\pi \frac{t}{T_{per}}))$

$$b_{\theta}(t; s, i) = \begin{pmatrix} b_{\theta,1}(t; s, i) \\ b_{\theta,2}(t; s, i) \end{pmatrix} = \begin{pmatrix} -\lambda(t)si + \delta(1 - s - i) + \mu(1 - s) \\ \lambda(t)si - (\gamma + \mu)i \end{pmatrix}.$$

$$\Sigma = \begin{pmatrix} \lambda(t)si + \delta(1 - s - i) + \mu(1 + s) & -\lambda(t)si \\ -\lambda(t)si & \lambda(t)si + (\gamma + \mu)i \end{pmatrix}.$$

Discrete observations with fixed sampling interval Δ on $[0, T]$

$dX(t) = b(\alpha, X(t))dt + \epsilon\sigma(\beta, X(t))dB(t)$, $X(0) = x_0$: diffusion sur \mathbb{R}^p .

Observations: $X^n := (X(t_k); t_k = k\Delta, 0 \leq k \leq n)$ with $T = n\Delta$.

No time -dependence in the drift and diffusion terms; $X(0) = x_0$ known.

- $X(t)$ Markov process with transition probabilities :
 $p_t(x, y) = \mathbb{P}(X(t+s) = y / X(s) = x)$
- $\Rightarrow (X(t_k), k \geq 0)$ Markov chain with state space \mathbb{R}^p and transition kernel $Q_\Delta(x, dy) = p_\Delta(x, y)dy$
- These transition kernels depend on $b(\alpha, x)$ and $\epsilon\sigma(\cdot)$
- $\rightarrow p_\Delta(x, y) = p_{\Delta, \epsilon}(\alpha, \beta; x, y)$
- No analytic expression \Rightarrow untractable likelihood
- impossible to use in practice.

Discrete observations on a finite time interval

Use an estimation function (or contrast) derived from the Euler scheme:

Euler scheme associated with $(X(t))$

$$X(t_k) \simeq X(t_{k-1}) + \Delta b(X(t_{k-1})) + \epsilon \sqrt{\Delta} \sigma(X(t_{k-1})) \eta_k$$

with $(\eta_k) \sim \mathcal{N}(0, 1)$ i.i.d random variables.

\Rightarrow Markov chain model with explicit transition kernels

$$p_{\epsilon, \Delta}(\alpha, \beta; x, y) dy \sim \mathcal{N}(\Delta b(\alpha; x), \epsilon^2 \Delta \Sigma(\beta; x)).$$

Contrast process:

$$U_{\epsilon, \Delta}(\alpha, \beta; (X(t_k))) = \sum_{k=1}^n \log(\det(V_k(\beta))) + \frac{1}{\epsilon^2 \Delta} {}^t B_k(\alpha) V_k^{-1}(\beta) B_k(\alpha).$$

$$B_k(\alpha) = X(t_k) - X(t_{k-1}) - \Delta b(\alpha, X(t_{k-1})),$$

$$V_k(\beta) = \Sigma(\beta, X(t_{k-1})) = \sigma(\beta, X(t_{k-1})) {}^t \sigma(\beta, X(t_{k-1}))$$

Pb Δ fixed: The Euler scheme is not a good approximation of $(X(t))$.

Pb 2: $\Delta = \Delta_n \rightarrow 0$: ϵ and Δ_n are linked in this approach.

Choosing estimating functions

Other approach

- Use another approximation for the sample paths of $X(t)$
- Base the estimation method on this approximation.
- Theorem (Ventsell & Freidlin, 1997, Small perturbations of dynamical systems)

$$X_\epsilon(t) = x(\alpha; t) + \epsilon g(\alpha, \beta; t) + \epsilon R_\epsilon(t).$$

- ★ $x(\alpha; \cdot)$ satisfies $\frac{\partial x}{\partial t}(t) = b(\alpha; x(t))dt; x(0) = x_0$
- ★ $g(\alpha, \beta; t) = \int_0^t \Phi(\alpha; t, s) \sigma(\beta, x(\alpha; s)) dB(s):$
- ★ $\Phi(\alpha; t, u) : \frac{\partial \Phi}{\partial t}(t, u) = \nabla b(\alpha; x(\alpha; t)) \Phi(t, u); \Phi(u, u) = I_p.$
- ★ $\sup_{t \leq T} \|\epsilon R_\epsilon(t)\| \rightarrow 0$ in probability as $\epsilon \rightarrow 0,$
(Extension of Genon-Catalot (1990))

Estimation functions

We have that $X(t_k) \sim Y(t_k)$ with $Y(t) = x(\alpha; t) + \epsilon g(\alpha, \beta; t)$.

A noteworthy property of g

- $g(\alpha, \beta; t_k) = \Phi(\alpha; t_k, t_{k-1})g(\alpha, \beta; t_{k-1}) + \sqrt{\Delta} Z_k$
- $Z_k = \int_{t_{k-1}}^{t_k} \Phi(\alpha; t_k, s)\sigma(\beta; x(\alpha; s))dB(s)$
- $(Z_k, k = 1, \dots, n)$ independent \mathbb{R}^P Gaussian r.v. with covariance
- $S_k(\alpha, \beta) = \int_{t_{k-1}}^{t_k} \Phi(\alpha; t_k, s)\Sigma(\beta; x(\alpha; s)){}^t\Phi(\alpha; t_k, s)ds$

Define the function $\mathbb{R}^P \rightarrow \mathbb{R}^P$

$x \rightarrow B_k(\alpha; x) = x(\alpha; t_k) + \Phi(\alpha; t_k, t_{k-1})(x - x(\alpha, t_{k-1}))$.

$Z_k = \frac{1}{\epsilon\sqrt{\Delta}}(Y(t_k) - B_k(\alpha, Y(t_{k-1})))$.

$(Y(t_k), k \geq 0)$ Markov chain with explicit transition kernel

$$p_{\epsilon, \Delta}(\alpha, \beta; x, y)dy \sim \mathcal{N}_p(B_k(\alpha; x), \epsilon^2 \Delta S_k(\alpha, \beta)).$$

Parametric inference for fixed sampling interval

Asymptotic framework

$\epsilon \rightarrow 0$, and T, Δ fixed : \Rightarrow finite nb n of observations;

Only parameters in the drift can be consistently estimated

Ex: Brownian motion with drift: $dX(t) = \alpha dt + \epsilon \beta dB(t)$; $X(0) = 0$.

- $(X(t_k) - X(t_{k-1}), k = 1, \dots, n)$ i.i.d $\mathcal{N}(\alpha\Delta, \epsilon^2\beta^2\Delta)$.
- Explicit likelihood \rightarrow Explicit M.L.E.
- $\hat{\alpha}_\epsilon = \frac{X(T)}{T}$, $\hat{\beta}_\epsilon^2 = \frac{1}{\Delta\epsilon^2} \sum_{i=1}^n (U_k - \Delta\hat{\alpha}_\epsilon)^2$.
- Under $\mathbb{P}_{\alpha_0, \beta_0}^\epsilon$, $\hat{\alpha}_\epsilon = \alpha_0 + \epsilon\beta_0 \frac{B(T)}{T}$,
 $\hat{\beta}_\epsilon^2 = \beta_0^2 \left(\frac{1}{n} \sum_{i=1}^n U_k^2 - \frac{1}{n} \frac{B^2(T)}{T} \right)$ where (U_k) i.i.d. $\mathcal{N}(0, 1)$.
- $\hat{\alpha}_\epsilon \rightarrow \alpha_0$ and $\epsilon^{-1}(\hat{\alpha}_\epsilon - \alpha_0) \sim \mathcal{N}(0, \beta_0^2/T)$.
- $\hat{\beta}_\epsilon^2$ fixed random variable independent of ϵ ,
- $E_{\alpha_0, \beta_0}(\hat{\beta}_\epsilon^2) = \beta_0^2(1 - 1/n) \neq \beta_0^2$: biased estimator.

Inference for fixed sampling interval Δ

$dX(t) = b(\alpha, X(t))dt + \epsilon\sigma(\beta, X(t))dB(t)$, $X(0) = x_0$: diffusion on \mathbb{R}^p .

- Parameter β in $\sigma(\beta, x)$ cannot be consistently estimated.
- Only α in the drift term $b(\alpha, x)$ can be estimated.
- Diffusion approximations of epidemic models: $\beta = \alpha$.

Two-stage approach in framework (1)

Estimation of parameter α assuming β unknown.

Use of $\beta = \alpha$ to improve the estimator.

First step (General case):

Estimation of α : Approximate Conditional Least Squares

$$\tilde{U}_\epsilon(\alpha, \beta, X^{(n)}) =$$

$$\frac{1}{\epsilon^2 \Delta} \sum_{k=1}^n t(X(t_k) - B_k(\alpha; X(t_{k-1}))) (X(t_k) - B_k(\alpha; X(t_{k-1}))).$$

where $B_k(\alpha; x) = x(\alpha; t_k) + \Phi(\alpha; t_k, t_{k-1})(x - x(\alpha, t_{k-1}))$.

Diffusion approximation of epidemic models: $\beta = \alpha, \epsilon = \frac{1}{\sqrt{N}}$

$$S_k(\alpha, \beta) = \int_{t_{k-1}}^{t_k} \Phi(\alpha; t_k, s) \Sigma(\beta; x(\alpha; s)) {}^t \Phi(\alpha; t_k, s) ds$$

Contrast Process

$$U_{\epsilon, \Delta}(\alpha; X^{(n)}) = \frac{1}{2} \sum_{k=1}^n \log(\det(S_k(\alpha, \alpha))) + \\ \frac{1}{2\epsilon^2 \Delta} \sum_{k=1}^n {}^t (X(t_k) - B_k(\alpha; X(t_{k-1}))) S_k^{-1}(\alpha, \alpha) (X(t_k) - B_k(\alpha; X(t_{k-1}))).$$

$$\hat{\alpha}_\epsilon \text{ such that } U_{\epsilon, \Delta}(\hat{\alpha}_\epsilon, X^{(n)}) = \inf \{ U_{\epsilon, \Delta}(\alpha, X^{(n)}), \alpha \in \Theta \}.$$

Three conditions to check as $\epsilon \rightarrow 0$

(1) $\epsilon^2 U_{\epsilon, \Delta}(\alpha, \beta, X^{(n)}) \rightarrow K_\Delta(\alpha_0, \alpha) P_{\alpha_0}^\epsilon$ a.s. uniformly on Θ

$K(\alpha_0, \alpha)$ continuous deterministic + unique global minimum at α_0

(2) $\epsilon \nabla_\alpha U_{\epsilon, \Delta}(\alpha_0) \rightarrow \mathcal{N}(0, J_\Delta(\alpha_0))$ in distribution under $P_{\alpha_0}^\epsilon$

(3) There exists a non-singular matrix $I_\Delta(\alpha_0)$ such that

$$\lim_{\delta \rightarrow 0} \lim_{\epsilon \rightarrow 0} \sup \{ \| \epsilon^2 \nabla_\alpha^2 U_\epsilon(\alpha) - I_\Delta(\alpha_0) \|, \| \alpha - \alpha_0 \| \leq \delta \} = 0 P_{\alpha_0}^\epsilon \text{ a.s.}$$

Checking conditions (1)-(3)

Condition (1): ensures consistency of $\hat{\alpha}_\epsilon$

Assumption: $\alpha, \alpha' \in \Theta, \alpha \neq \alpha' \Rightarrow x(\alpha, t_k) \neq x(\alpha', t_k)$ for some k .

Condition (2): $\frac{1}{\epsilon\sqrt{\Delta}}(X(t_k) - B_k(\alpha_0, X(t_{k-1})))$: approximately Gaussian

$\Rightarrow \epsilon \nabla_\alpha U_{\epsilon, \Delta}(\alpha_0) \rightarrow \mathcal{N}(0, J_\Delta(\alpha_0))$ with

$J_\Delta(\alpha_0) = \Delta \sum_{i=1}^n {}^t D_k(\alpha_0) S_k(\alpha_0)^{-1} D_k(\alpha_0)$ where

$D_k(\alpha) = \frac{1}{\Delta} (\nabla_\alpha x(\alpha, t_k) - \Phi(\alpha; t_k, t_{k-1}) \nabla x(\alpha, t_{k-1}))$

Condition (3) $\epsilon^2 \nabla_\alpha^2 U_\epsilon(\alpha_0) \rightarrow I_\Delta(\alpha_0)$, with $I_\Delta(\alpha_0) = J_\Delta(\alpha_0)$.

Assumption: $J_\Delta(\alpha_0)$ non singular.

Result: $\epsilon^{-1}(\hat{\alpha}_\epsilon - \alpha_0) \rightarrow \mathcal{N}(0, I_\Delta^{-1}(\alpha_0))$

Remark: Approximate Conditional Least Squares

$J_\Delta(\alpha_0, \beta_0) = \Delta \sum_{i=1}^n {}^t D_k(\alpha_0) S_k(\alpha_0, \beta_0) D_k(\alpha_0);$

$I_\Delta(\alpha_0) = \Delta \sum_{i=1}^n {}^t D_k(\alpha_0) D_k(\alpha_0)$

$\epsilon^{-1}(\tilde{\alpha}_\epsilon - \alpha_0) \rightarrow \mathcal{N}(0, I_\Delta^{-1}(\alpha_0) J_\Delta(\alpha_0) I_\Delta^{-1}(\alpha_0))$

Inference for small sampling interval $\Delta = \Delta_n \rightarrow$

$dX(t) = b(\alpha; t, X(t))dt + \epsilon\sigma(\beta; t, X(t))dB(t)$, $X(0) = x_0$: diffusion on \mathbb{R}^p .

Asymptotics: $\epsilon \rightarrow 0$, $\Delta = \Delta_n \rightarrow 0$ with $T = n\Delta_n$ fixed;

$\Delta = T/n \Rightarrow$ Notation $(\epsilon, \Delta) = (\epsilon, n)$.

- $B_k(\alpha; x) = x(\alpha; t_k) + \Phi(\alpha; t_k, t_{k-1})(x - x(\alpha, t_{k-1}))$
- $S_k(\alpha, \beta) = \int_{t_{k-1}}^{t_k} \Phi(\alpha; t_k, s)\Sigma(\beta; s, x(\alpha; s)) {}^t\Phi(\alpha; t_k, s)ds$
- Since $\Delta_n \rightarrow 0$, $S_k(\alpha, \beta) \sim \Sigma(\beta, t_{k-1}, X_{t_{k-1}})$. $S_k^\theta \sim \Sigma(\beta, X_{t_{k-1}}) \Rightarrow$

$$U_{\epsilon, n}(\alpha, \beta; X^{(n)}) = \sum_{k=1}^n (\log(\det(\Sigma(\beta, X_{t_{k-1}})) + \frac{1}{\epsilon^2 \Delta} {}^t(X(t_k) - B_k(\alpha; X(t_{k-1})))\Sigma^{-1}(\beta; X(t_{k-1}))(X(t_k) - B_k(\alpha; X(t_{k-1}))).$$

Estimators: $(\hat{\alpha}_{\epsilon, n}, \hat{\beta}_{\epsilon, n})$ such that

$$U_{\epsilon, n}(\hat{\alpha}_{\epsilon, n}, \hat{\beta}_{\epsilon, n}; X^{(n)}) = \inf\{U_{\epsilon, n}(\alpha, \beta; X^{(n)})\}, (\alpha, \beta) \in \Theta\}$$

Checking additional conditions

- (a): $\epsilon^2 U_{\epsilon,n}(\alpha, \beta; X^{(n)}) \rightarrow K(\alpha_0, \alpha, \beta)$ a.s. under P_{α_0, β_0} as $\epsilon \rightarrow 0, n \rightarrow \infty$,
 $K(\cdot)$: Deterministic continuous, unique minimum at α_0 for all β
- (b) Uniform convergence of (a) for all β .
- (c) Uniform bound in P_{θ_0} -probability for $\epsilon^{-1}(\hat{\alpha}_{\epsilon,n} - \alpha_0)$.
- (d): Additional condition

$$I_b(\alpha, \beta) = \left(\int_0^T {}^t \frac{\partial b}{\partial \alpha_i}(\alpha; t, x(\alpha, t)) \Sigma^{-1}(\beta; t, x(\alpha, t)) \frac{\partial b}{\partial \alpha_j}(\alpha; t, x(\alpha, t)) dt \right)_{i,j}$$
$$I_\sigma(\alpha, \beta) = \left(\int_0^T \text{Tr} \left(\frac{\partial \Sigma}{\partial \beta_k} \Sigma^{-1} \right) \frac{\partial \Sigma}{\partial \beta_l}(\beta; t, x(\alpha, t)) dt \right)_{k,l}$$

Theorem

Under $P_{\alpha_0, \beta_0}^\epsilon$

$$\begin{pmatrix} \epsilon^{-1}(\hat{\alpha}_{\epsilon,n} - \alpha_0) \\ \sqrt{n}(\hat{\beta}_{\epsilon,n} - \beta_0) \end{pmatrix} \xrightarrow{n \rightarrow \infty, \epsilon \rightarrow 0} \mathcal{N} \left(0, \begin{pmatrix} I_b^{-1}(\alpha_0, \beta^0) & 0 \\ 0 & I_\sigma^{-1}(\alpha_0, \beta_0) \end{pmatrix} \right)$$

Additional conditions

The function K is equal to

$$K(\alpha_0, \alpha, \beta) = \int_0^T \Gamma(\alpha_0, \alpha; t) \Sigma^{-1}(\beta, x(\alpha_0, t)) \Gamma(\alpha_0, \alpha; t) dt$$

with

$$\Gamma(\alpha_0, \alpha; t) = b(\alpha_0; t, x(\alpha_0, t)) - b(\alpha; t, x(\alpha, t)) - \nabla_x b(\alpha; t, x(\alpha, t))(x(\alpha_0, t) - x(\alpha, t)).$$

Additional condition on U :

Let $V(\alpha_0, \beta_0, \beta)(t) = \Sigma^{-1}(\beta, t, x(\alpha_0, t)) \Sigma(\beta_0, t, x(\alpha_0, t))$

$$K'(\alpha_0, \beta_0, \beta) = \frac{1}{T} \int_0^T \text{Tr}(V((\alpha_0, \beta_0, \beta)(t))) dt - \frac{1}{T} \int_0^T \log \det V(\alpha_0, \beta_0, \beta)(t) dt - p.$$
$$\left| \frac{1}{n} (U_{\epsilon, n}(\hat{\alpha}_{\epsilon, n}, \beta) - U_{\epsilon, n}(\hat{\alpha}_{\epsilon, n}, \beta_0)) - K'(\alpha_0, \beta_0, \beta) \right| \rightarrow 0 \text{ uniformly w.r.t. } \beta.$$

Approximation of epidemic models by diffusion processes and their statistical inferences

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Assessment of estimators on simulated and real data set

Based on Guy, Laredo, Vergu, JMB, 2015 and JSFDS (2016)

Simulation study

Assessment of the inference method

- Simulation of epidemics with jump Markov processes
- *SIR* epidemic model simulated with Gillespie's algorithm (1977)
- *SIRS* with time-dependent transmission rate and demography simulated with the τ -leap method (Cao,2005)

Accuracy of estimators

- According to the population size N
- Number of observations n
- Parameter values ruling the epidemic

Simulation scheme

- Choose an epidemic scenario: mechanistic model, population size, parameters
- Perform 1000 simulations of the **Pure jump Markov Process** associated with this scenario.

Reference

- Compute the M.L.E of the Jump Process assuming that **all the jumps are observed**
- Compute the Fisher information I_{PJM} of the Pure Jump Model.
- **Reference:** this MLE together with the associated confidence interval.

Remark: $I_{PJM} = I_b$, Fisher information of continuous observation of the diffusion.

Computation of estimators for each simulation

- Choose a sampling interval Δ and keep only the observations of the simulation at times $i\Delta$ (with realistic values of $\Delta \geq 1$).
- Compute our estimators on these discrete data (Point estimators)
- Compute the theoretical confidence intervals (CI_{th}) based on our inference method

Joining all the 1000 simulations results

- Compute the empirical confidence intervals (CI_{emp}) based on the 1000 simulations;
- Compute the average point estimators.

Remark: Only non extinct trajectories are kept;

Criterion: Final epidemic size larger than $5\%S_0$; \Rightarrow Possible bias?

SIR model

Basic reproduction number: $R_0 = \frac{\lambda}{\gamma}$

Average infectious duration: $d = \frac{1}{\gamma}$

Schéma de simulation:

| Parameter | Description | Values |
|-----------|---------------------------|------------------------|
| R_0 | basic reproduction number | 1.5, 3 |
| d | infectious period | 3, 7 days |
| $T^{(1)}$ | final time of observation | 20, 40, 45, 100 days |
| N | population size | 400, 1000, 10000 |
| n | number of observations | 5, 10, 20, 40, 45, 100 |

Table: Range of parameters for the *SIR* model defined in Section ???. ⁽¹⁾: T is chosen as the time point where the corresponding deterministic trajectory passes below the threshold of $1/100$.

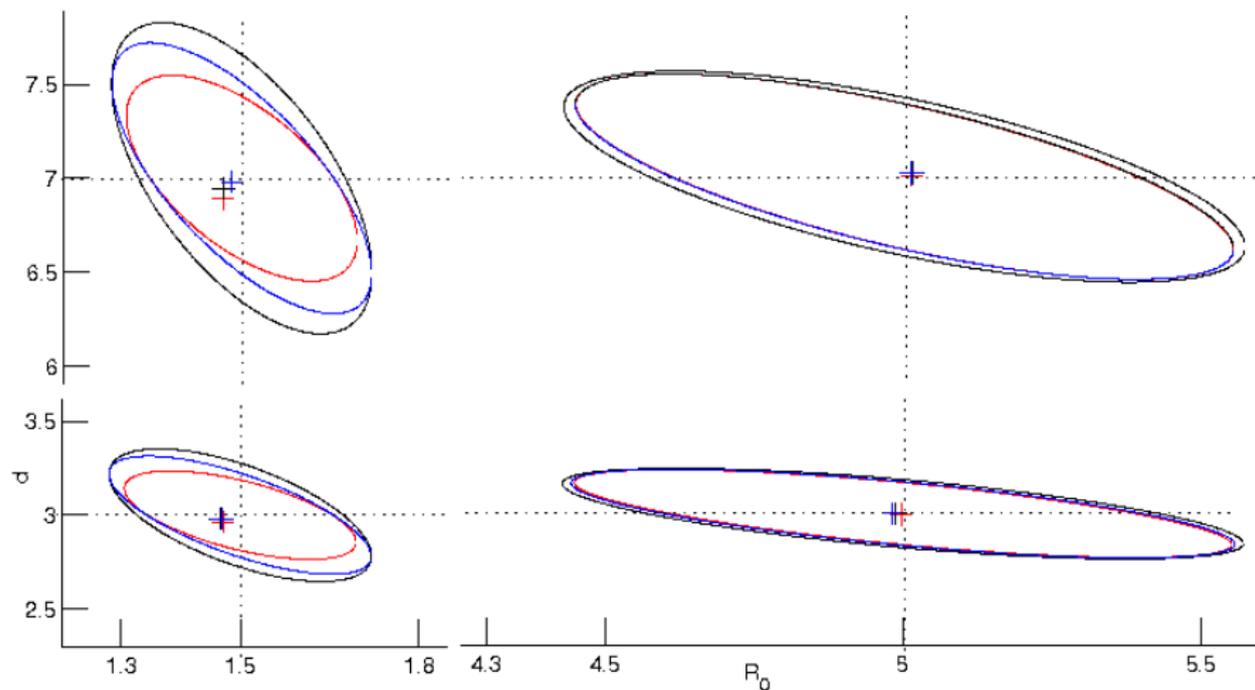
Observations of all the jumps \rightarrow MLE and theoretical confidence interval CI_{th} ; for $\Delta = 1$, Contrast estimator and CI_{th} , $\Delta = T/10$

SIR theoretical confidence ellipsoids and estimators

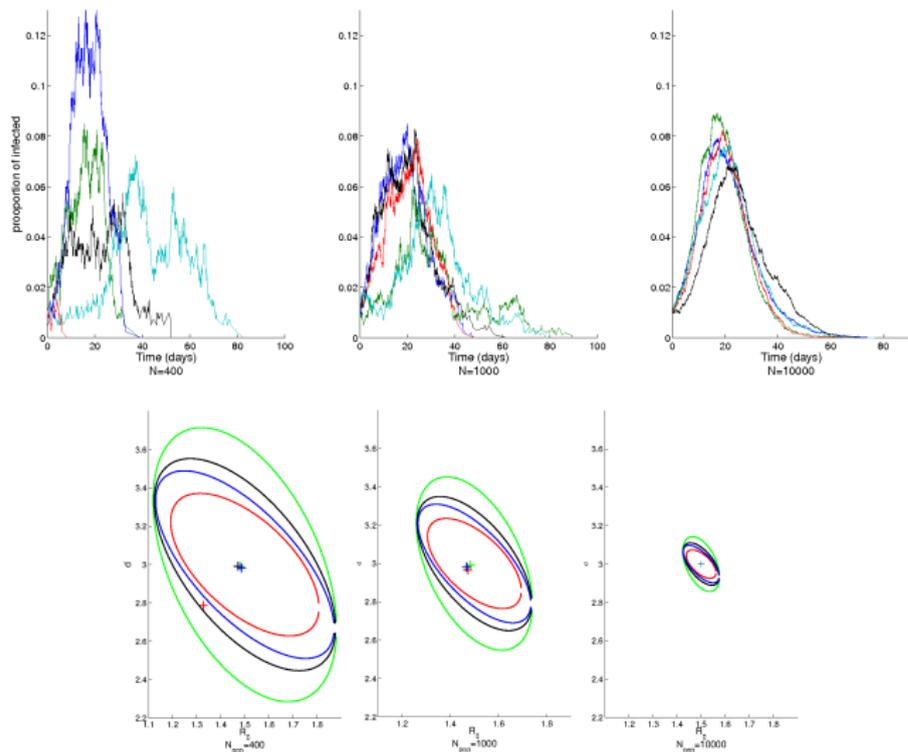
Population size $N = 1000$; $R_0 = 1.5, 5$, $d = 3, 7$. Complete

Obs.; $\Delta = 1, \Delta = T/10$

Average point estimator based on the 1000 simulations for (MLE et $\hat{\alpha}_{\epsilon, n}$)



Good results when varying the population size in the *SIR*



$R_0 = 1.5$; $d = 3$ (days); $T = 50$ (days); $\Delta = 1; 5; 10$ (days) and
 $N = 4 \cdot 10^2; 10^3; 10^4$

Results for small R_0 and large R_0

Results for a population size $N = 1000$, and various nb of obs. n

- Correlation between parameters: increases with d , decreases with R_0 ,
- Empirical CI: allways very tight \Rightarrow not shown,
- Theoretical confidence intervals CI_{PJM} and CI_{th} for various samplings: very close
- No loss in estimation accuracy for $n = 40$ (1 obs/day) for large R_0 .

Results when varying N

- Width of CI decreases with N ; correlation not impacted.
- Given N , confidence ellipsoids are still very close, even for small n .
- $N = 400$ MLE biased while CE is OK.
- Very noisy sample paths.
- MLE optimal for "typical" realizations of the jump process.

SIRS model with seasonal forcing

Time-dependent transmission rate (Keeling and Rohani, 2011)

To avoid extinction, immigration flow η added $S \rightarrow I$: $\frac{\lambda(t)}{N}S(I + N\eta)$.

★ μ : demography parameter; δ :immunity waning; $\gamma(= 1/d)$ recovery rate;

★ $\lambda(t) = \lambda_0(1 + \lambda_1 \sin(2\pi t/T_{per})) \Rightarrow$ New parameter $R := \frac{\lambda_0}{\gamma}$.

★ $b(\theta; t, x) = \begin{pmatrix} -\lambda(t)s(i + \eta) + \delta(1 - s - i) + \mu(1 - s) \\ \lambda(t)s(i + \eta) - (\gamma + \mu)i \end{pmatrix}$.

ODE: dynamical system with bifurcation according to λ_1

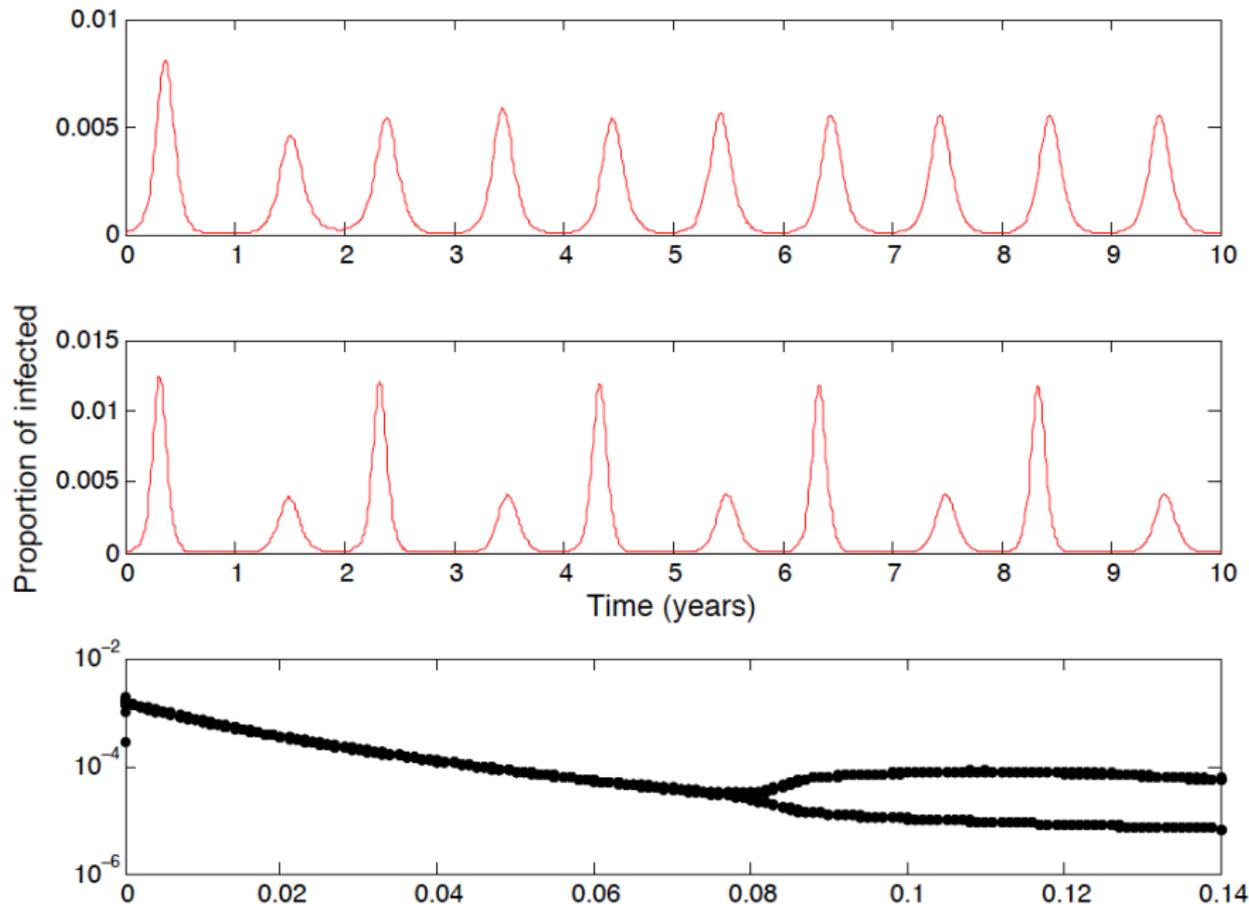
★ ODE: $\frac{dx}{dt} = b(\theta; t, x)$.

★ Before bifurcation: annual oscillations with constant amplitude.

★ After bifurcation: Biennial oscillations with unequal amplitudes.

★ Bifurcation diagram w.r.t. λ_1 .

Dynamics of the ODE



Parameter values chosen in the previous figure

- $N = 10^7$; $T_{per} = 365$, $\mu = 1/(50 T_{per})$, $\eta = 10^{-6}$,
- $\lambda_0 = 0.5$, $\gamma = 1/3 \Rightarrow R_0 = 1.5$, $d = 3$; $\delta = 1/(2 \times 365)$,
- $(s_0, i_0) = (0.7, 10^{-4})$.
- Top panel: $\lambda_1 = 0.1$; middle panel: $\lambda_1 = 0.1$.
- Bottom panel: bifurcation diagram w.r.t. λ_1 .

Choice of plausible values for modeling influenza seasonal outbreaks

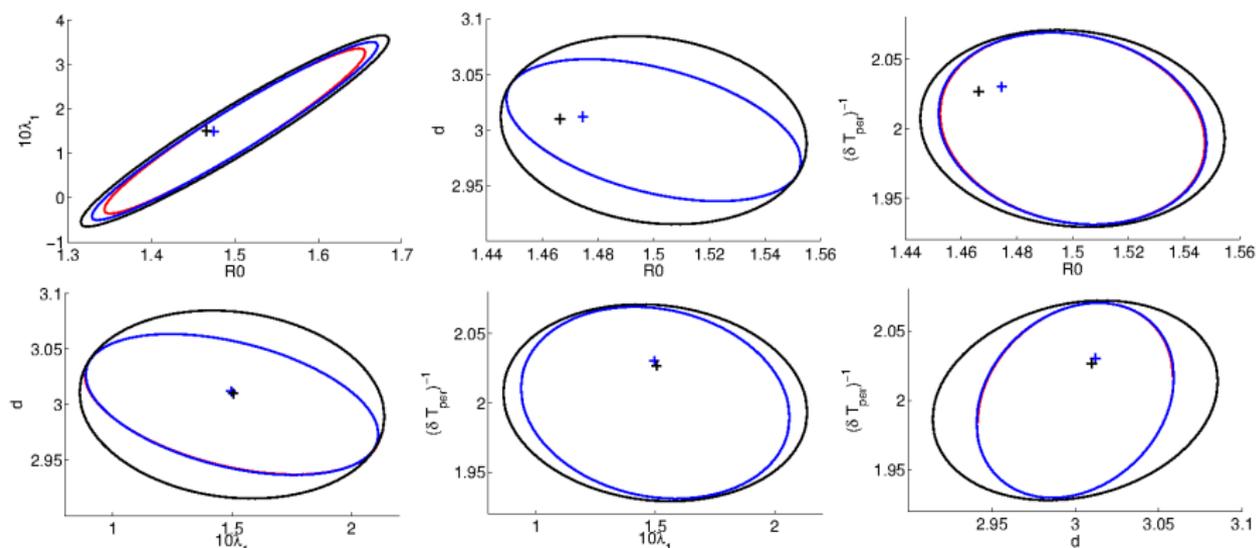
- ★ Large population size: $N = 10^7$ to ensure
 - > Sufficiently large "signal over noise" ratio.
 - > Sufficient pool of S and I after each outbreak.
- ★ $\mu = 1/50 \text{ years}^{-1}$; $T_{per} = 365$ (days), $\eta = 10^{-6}$
- ★ $R_0 = 1.5$, $d = 3$, $\delta = 2 \Rightarrow$ bifurcation for $\lambda_1 = 0.07$;
- ★ $\lambda_1 = 0.05$ and $\lambda_1 = 0.15$ (before and after bifurcation)

Numerically, these 2 scenarios have the characteristics of influenza seasonal outbreaks.

Simulation study: 1000 simulations of these 2 scenarios

- **Known parameters:** μ, T_{per}, η .
- **Unknown parameters:** R, d, λ_1, δ .
- Estimation of these parameters on each simulation.
- Results displayed with different projections of the 4-dimensional theoretical ellipsoid.

Estimation results and confidence ellipsoids for the *SIRS*



$R = 1.5$; $d = 3$; $\lambda_1 = 0.15$, $\delta = 2$ (days), $T = 20$ (years), $N = 10^7$.

Observations on $[0, T]$: **Complete (MLE)**, $\Delta = 1$, $\Delta = 7$ (days).

Average point estimator and theoretical confidence ellipsoids.

Results for the *SIRS*

- Almost no correlation between parameters, except R_0 and λ_1
- Good accuracy of estimation for all parameters.
- Disposing one obs/day \rightarrow accuracy identical to corresponding complete obs. of the epidemic process.
- One obs/per week \rightarrow still reasonably accurate estimations