Approximation of epidemic models by diffusion processes and their statistical inferences

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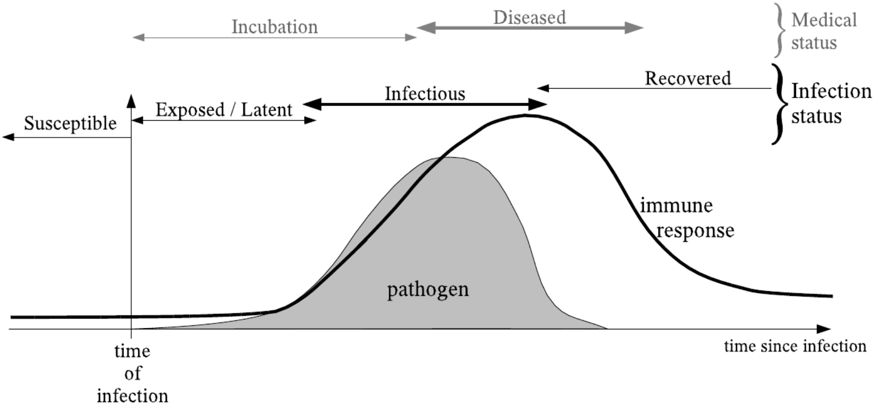
TAlK 2

Based on Guy[1,2], Larédo, Vergu[1] (JMB 2014)

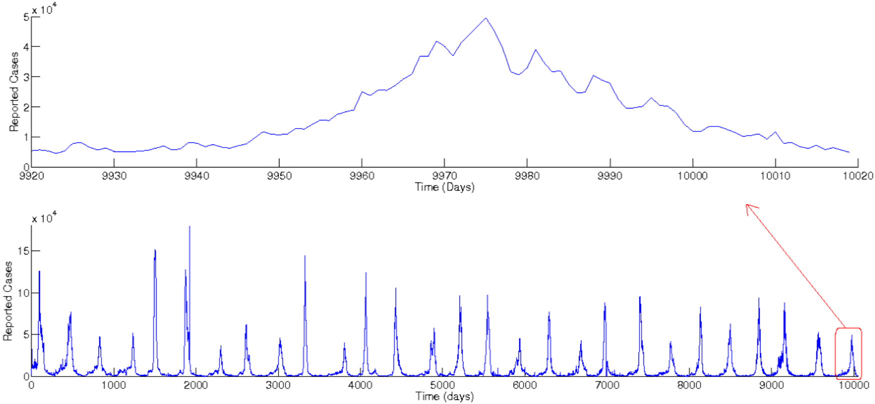
Context of infectious diseases (individual infection)



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 ⇒ systematically noisy data.

Various dynamics at the ppopulation 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 developping estimation methods as accurate as possible given the data available

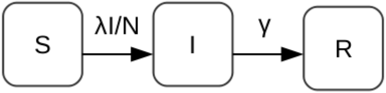
SEVERAL POSSIBLE WAYS TO OVERCOME THIS PROBLEM OF MISSING OR INCOMPLETE DATA

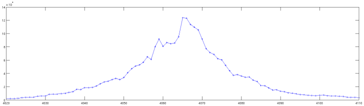
1. Develop algorithms to simulate the unobserved missing data.
2. Existence of lots of computer intensive methods in this domain.
3. Difficult to use for large populations.
4. Results are often unstable.

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:
  $(S, I) \to (S-1, I+1)$ at rate $S\ \lambda\ \frac{I}{N}$
  $(S, I) \to (S, I-1)$ at rate $\gamma\ I$

Key parameters of this epidemic model

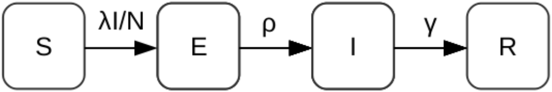
- Basic reproduction number $R_0 = \frac{\lambda}{\gamma}$.
- Average infectious period $d = \frac{1}{\gamma}$.

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.

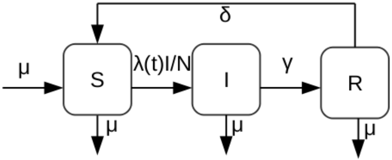
***SEIR* model with temporal transmission rate**

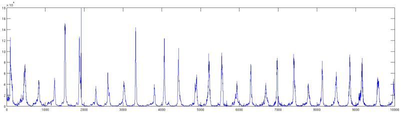


- $(S, E, I) \rightarrow (S-1, E+1, I)$ at rate $S\ \lambda(t)\frac{I}{N}$,
- $(S, E, I) \rightarrow (S, E-1, I+1)$ at rate $\rho\ E$
- $(S, E, I) \rightarrow (S, E, I-1)$ at rate $\gamma\ I$

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

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

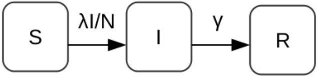
- $\Rightarrow$ Transition rate from $x \to x + \ell$: $\alpha_\ell(x)$,
- Q-matrix of $(Z(t))$: $Q = (q_{xy}, (x, y) \in E \times E)$
  if $y \neq x$, $q_{xy} = \alpha_{y-x}(x)$, and $q_{xx} = -\alpha(x)$.

$\star$ Each individual stays in state x with exponential holding time $\mathcal{E}(\alpha(x))$,
$\star$ Then, it jumps to another state according to a Markov chain with transition kernel $\mathbb{P}(x \to x + \ell) = \frac{\alpha_\ell(x)}{\alpha(x)}$.

SIR, *SEIR* models in a closed population of size N

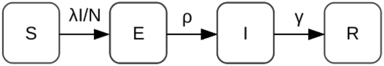
SIR epidemic model

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



$(S,I)\to(S-1,I+1)$: $\alpha_{(-1,1)}(S,I)=\lambda S\frac{I}{N}$,
$(S,I)\to(S,I-1)$: $\alpha_{(0,-1)}(S,I)=\gamma I$

SEIR epidemic model:(Time-dependent process)
$Z(t)=(S(t),E(t),I(t)) \ \in E=\{0,\dots,N\}^3$.

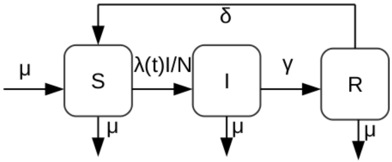


$\ell=(-1,1,0),(0,-1,1),(0,0,-1)$.

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

SIRS model with seasonal forcing in a closed population

$\Rightarrow Z(t) = (S(t), I(t)) \in E = \{0, \ldots, N\}^2$,
$\ell = (-1,1), (0,-1), (1,0), (-1,0)$.



$(S, I) \to (S-1, I+1) : \alpha_{(-1,1)}(t; S, I) = \lambda(t) S \frac{I}{N}$,
$(S, I) \to (S, I-1) : \alpha_{(0,-1)}(S, I) = (\gamma + \mu) I$,
$(S, I) \to (S+1, I) : \alpha_{(1,0)}(S, I) = \mu N + \delta(N - S - I)$,
$(S, I) \to (S-1, I) : \alpha_{(-1,0)}(S, I) = \mu S$.
$\lambda(t) = \lambda_0 (1 + \lambda_1 sin(2\pi \frac{t}{T_{per}})) \Rightarrow$ 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

$\star$ if $y = (y_1, \ldots, y_p) \in \mathbb{R}^p, [y] = ([y_1], \ldots, [y_p])$, with $[y_i]$ integer part of y_i.
Transposition of a vector y or a matrix M: ${}^t y$, ${}^t M$.
$\star$ Gradient de $b(.) \in C(\mathbb{R}^p, \mathbb{R}^p)$: $\nabla b(y) = (\frac{\partial b_i}{\partial y_j}(y))_{ij}$.

Framework

$\star$ Constant population size $N \Rightarrow E = \{0, .., N\}^p$.
$\star$ Collection $\alpha_\ell(\cdot) : E \rightarrow (0, \infty)$ with $\ell \in E^- = \{-N, .., N\}^p$.
$\star$ 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 $E^- = \{-N, .., N\}^p$.

Assumption (H):
(H1): $\forall(\ell, y) \in E^- \times [0,1],\ \frac{1}{N}\alpha_\ell([Ny]) \to \beta_\ell(y)$.
(H2): $\forall \ell,\ \ y \to \beta_\ell(y) \in C^2([0,1]^p)$.

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

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

These quantities are wel 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 $Z_N(.)$

$x(t) = x_0 + \int_0^t b(x(s))ds.$
$\Phi(t,u)$ 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 $Z_N(0) \to x_0$ as $N \to \infty$.Then,
$\star$ $Z_N(.)$ converges $x(.)$ uniformly on $[0,T]$,
$\star$ $\sqrt{N}(Z_N(t) - x(t))$ converges in distribution to $G(t)$,
$\star$ $G(t)$ centered Gaussian process with
$Cov(G(t), G(r)) = \int_0^{t \wedge r} \Phi(t,u)\Sigma(x(u))\,{}^t\Phi(r,u)du.$

Proof: Ethier & Kurz (2005): $\alpha_l([Ny]) \equiv \beta_l(y)$; GLV (2014) for
(i) Jump rates $\alpha_l(.)$ satisfying (H)
(ii) Time-dependent jump rates $\alpha_l(t,x)$ with
$\frac{1}{N}\alpha_l(t,[Ny]) \to \beta_l(t,y) \Rightarrow b(t,y); \Sigma(t,y)$
(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 $f : \mathbb{R}^p \to \mathbb{R}$ 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 $Z_N(.) = \frac{Z(t)}{N}$.
$\mathcal{A}_N(f)(y) = b(y)\nabla f(y) + \frac{1}{2N} \sum_{i,j=1}^p \Sigma_{ij}(y) \frac{\partial^2 f}{\partial y_i \partial y_j}(y) + o(1/N)$
$\Rightarrow \mathcal{A}_N(f)(y) = B_N(f)(y) + o(1/N)$.

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-dimensionnal Brownian motion et $\sigma(.)$ a square root of Σ ()
$\sigma(y)\, {}^t\sigma(y) = \Sigma(y)$.

Small pertubations of Dynamical systems

Freidlin & Wentzell (1978) ; Azencott (1982)

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

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

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

- $X_\epsilon(t) = x(t) + \epsilon g(t) + \epsilon R_\epsilon(t)$,
- where $dg(t) = \nabla b(x(t))g(t)dt + \sigma(x(t))dB(t)$; $g(0) = 0$,
- $sup_{t \leq T} \parallel \epsilon R_\epsilon(t) \parallel \rightarrow 0$ 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. $\frac{\partial \Phi}{\partial t}(t,u) = \nabla b(x(t))\Phi(t,u)$; $\Phi(u,u) = I_p$.

⋆ $g(.)$: centered Gaussian process with same covariance matrix as $G(.)$.

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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

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

Diffusion process (ξ_t) on $(\Omega, \mathcal{F}, \mathbb{P})$, $d\xi_t = b(t, \xi_t)dt + \sigma(t, \xi_t)dW_t, \xi_0 = \eta$.
$\Rightarrow \forall \omega, t \to \xi_t(\omega)$ 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 $(C_T, \mathcal{C}_T)$

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

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 $\mathbb{R}$

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

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

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

$\star$ 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+..

$\star$ Additional asssumptions

Theorem

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

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

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 $(C_T, \mathcal{C}_T)$.
• Diffusion having distinct starting point x_0, x_0' have singular distributions.

(ξ_t): time-dependent multidimensional diffusion process
• $b(\theta, x) \to b(\theta, t, x)$; $\sigma^2(x) \to \Sigma(t, x) = \sigma(t, x)\, {}^t\sigma(t, x)$.
(Karatzas & Shreve for conditions ensuring existence and uniqueness of solutions.
• On $(C_T = C([0, T], \mathbb{R}^p), \mathcal{C}_T)$,

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

(Liptser & Shiryaev).

Maximum Likelihood Estimator

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

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

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

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

• $\ell_T(\theta) = \theta \int_0^T \frac{f(s)}{\sigma^2(s)} d\xi_s - \frac{\theta^2}{2}\int_0^T \frac{f^2(s)}{\sigma^2(s)} ds \Rightarrow \hat{\theta}_T = \frac{\int_0^T \frac{f(s)}{\sigma^2(s)} d\xi_s}{\int_0^T \frac{f^2(s)}{\sigma^2(s)} ds}$. $\star$ Under P_{θ_0},

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

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

$\star$ $f(t) = 1, \sigma(t) = \sqrt{(1+t^2)} \rightarrow I_T = Arctan T \rightarrow \pi/2$: 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 $T \to \infty$

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

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

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

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

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

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 $t_i^n = iT/n, i = 0, \ldots n$.
Asymptotics: $T > 0$ fixed and $n \to \infty$

(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 $T \to \infty$

(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) $\to \infty$
$\Delta_n \to 0$ and $T = n\Delta_n \to \infty$.

(3) Statistical model. Observations space: $((\mathbb{R}^p)^n, \mathcal{B}(\mathbb{R}^p)^n))$.
$P^n_{(\alpha,\beta)}$ distribution of the n-uple $\Rightarrow P^n_{(\alpha,\beta)}$ and $P^n_{(\alpha',\beta')}$ 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 $\mathbb{R}^p$

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

$P^{\epsilon,T}_{\alpha,\beta}$: distribution of $(\xi_t, 0 \leq t \leq T)$ on $(C_T, \mathcal{C}_T)$.

Continuous observation on $[0, T]$

- $\beta \neq \beta' \Rightarrow P^{\epsilon,T}_{\alpha,\beta}$ and $P^{\epsilon,T}_{\alpha,\beta'}$ 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)

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

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

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

$\star\ x(\alpha, t) = x_0 + \int_0^t b(\alpha, x(\alpha, s))ds$ 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: $\{X(t_k), k = 0, \ldots, n\}$ with $t_k = k\Delta$; $T = n\Delta$.

Two possible asymptotic frameworks

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

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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December 6, 2015

TALK 3-Part 2, CIMPA 2015
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. $n << N$ and $\Delta \geq 1$ (1 to 7 days).
- Framework (1) $\epsilon \to 0$, 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 $\Delta = \Delta_n \to 0$ 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 $\mathbb{R}^3$

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

- *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 $\epsilon\sigma(.)$
- $\rightarrow p_\Delta(x, y) = p_{\Delta,\epsilon}(\alpha, \beta; x, y)$
- 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:

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

$B_k(\alpha) = X(t_k) - X(t_{k-1}) - \Delta b(\alpha, X(t_{k-1})),$
$V_k(\beta) = \Sigma(\beta, X(t_{k-1})) = \sigma(\beta, X(t_{k-1}))\,{}^t\sigma(\beta, X(t_{k-1}))$
Pb Δ fixed: The Euler scheme is not a good approximation of $(X(t))$.
Pb 2:$\Delta = \Delta_n \to 0$: 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,19??, Small pertubations of dynamical systems)

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

$\star$ $x(\alpha; .)$ satisfies $\frac{\partial x}{\partial t}(t) = b(\alpha; x(t))dt; x(0) = x_0$
$\star$ $g(\alpha, \beta; t) = \int_0^t \Phi(\alpha; t, s)\sigma(\beta, x(\alpha; s))dB(s)$:
$\star$ $\Phi(\alpha; t, u)$: $\frac{\partial \Phi}{\partial t}(t, u) = \nabla b(\alpha; x(\alpha; t))\Phi(t, u)$; $\Phi(u, u) = I_p$.
$\star$ $sup_{t \leq T} \parallel \epsilon R_\epsilon(t) \parallel \rightarrow 0$ 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

- $g(\alpha, \beta; t_k) = \Phi(\alpha; t_k, t_{k-1}) g(\alpha, \beta; t_{k-1}) + \sqrt{\Delta}\, Z_k$
- $Z_k = \int_{t_{k-1}}^{t_k} \Phi(\alpha; t_k, s) \sigma(\beta; x(\alpha; s)) dB(s)$
- $(Z_k, k = 1, \ldots, n)$ 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 $\mathbb{R}^p \longrightarrow \mathbb{R}^p$

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

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

$(Y(t_k), k \geq 0)$ 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

$\epsilon \to 0$, 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.
- $\hat{\alpha}_\epsilon = \frac{X(T)}{T})$, $\hat{\beta}^2_\epsilon = \frac{1}{\Delta\epsilon^2}\sum_{i=1}^n (U_k - \Delta\hat{\alpha}_\epsilon)^2$.
- Under $\mathbb{P}^\epsilon_{\alpha_0,\beta_0}$, $\hat{\alpha}_\epsilon = \alpha_0 + \epsilon\beta_0\frac{B(T)}{T}$,
  $\hat{\beta}^2_\epsilon = \beta_0^2(\frac{1}{n}\sum_{i=1}^n U_k^2 - \frac{1}{n}\frac{B^2(T)}{T})$ where (U_k) i.i.d. $\mathcal{N}(0, 1)$.
- $\hat{\alpha}_\epsilon \to \alpha_0$ and $\epsilon^{-1}(\hat{\alpha}_\epsilon - \alpha_0) \sim \mathcal{N}(0, \beta_0^2/T)$.
- $\hat{\beta}^2_\epsilon$ fixed random variable independent of ϵ,
- $E_{\alpha_0,\beta_0}(\hat{\beta}^2_\epsilon) = \beta_0^2(1 - 1/n) \neq \beta_0^2$: 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 $\epsilon \to 0$

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

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

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

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

$lim_{\delta\to 0} lim_{\epsilon\to 0} sup\{\| \epsilon^2\nabla^2_\alpha U_\epsilon(\alpha) - I_\Delta(\alpha_0) \|, \| \alpha - \alpha_0 \| \leq \delta\} = 0$ $P^\epsilon_{\alpha_0}$ 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
$\Rightarrow \epsilon \nabla_\alpha U_{\epsilon,\Delta}(\alpha_0) \to \mathcal{N}(0, J_\Delta(\alpha_0))$ with
$J_\Delta(\alpha_0) = \Delta \sum_{i=1}^{n} {}^tD_k(\alpha_0) S_k(\alpha_0)^{-1} D_k(\alpha_0)$ 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) $\epsilon^2 \nabla_\alpha^2 U_\epsilon(\alpha_0) \to I_\Delta(\alpha_0)$, with $I_\Delta(\alpha_0) = J_\Delta(\alpha_0)$.
Assumption: $J_\Delta(\alpha_0)$ non singular.

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

Remark: Approximate Conditional Least Squares
$J_\Delta(\alpha_0, \beta_0) = \Delta \sum_{i=1}^{n} {}^tD_k(\alpha_0) S_k(\alpha_0), \beta_0) D_k(\alpha_0)$;
$I_\Delta(\alpha_0) = \Delta \sum_{i=1}^{n} {}^tD_k(\alpha_0) D_k(\alpha_0)$
$\epsilon^{-1}(\tilde{\alpha}_\epsilon - \alpha_0) \to \mathcal{N}(0, I_\Delta^{-1}(\alpha_0) J_\Delta(\alpha_0) I_\Delta^{-1}(\alpha_0))$

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

$dX(t) = b(\alpha; t, X(t))dt + \epsilon\sigma(\beta; t, X(t))dB(t), X(0) = x_0$: diffusion on $\mathbb{R}^p$.
Asymptotics: $\epsilon \to 0$, $\Delta = \Delta_n \to 0$ 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 $\Delta_n \to 0, S_k(\alpha, \beta) \sim \Sigma(\beta, t_{k-1}, X_{t_{k-1}})$. $S_k^\theta \sim \Sigma(\beta, X_{t_{k-1}}) \Rightarrow$

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

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): $\epsilon^2 U_{\epsilon,n}(\alpha,\beta;X^{(n)}) \to K(\alpha_0,\alpha,\beta)$ a.s. under P_{α_0,β_0} as $\epsilon \to 0, n \to \infty$,
$K(.)$: 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

$$I_b(\alpha,\beta) = \left(\int_0^T {}^t\frac{\partial b}{\partial \alpha_i}(\alpha;t,x(\alpha,t))\Sigma^{-1}(\beta;t,x(\alpha,t))\frac{\partial b}{\partial \alpha_j}(\alpha;t,x(\alpha,t))dt \right)_{i,j}$$

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

Theorem

Under $P^{\epsilon}_{\alpha_0,\beta_0}$

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

Additional conditions

The function K is equal to
$K(\alpha_0, \alpha, \beta) = \int_0^T {}^t\Gamma(\alpha_0, \alpha; t)\Sigma^{-1}(\beta, x(\alpha_0, t))\Gamma(\alpha_0, \alpha; t)dt$ 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 $V(\alpha_0, \beta_0, \beta)(t) = \Sigma^{-1}(\beta, t, x(\alpha_0, t))\Sigma(\beta_0, tx(\alpha_0, t))$ $K'(\alpha_0, \beta_0, \beta) =$
$\frac{1}{T} \int_0^T Tr(V((\alpha_0, \beta_0, \beta)(t)))dt - \frac{1}{T} \int_0^T logdetV(\alpha_0, \beta_0, \beta)(t))dt - p$.
$|\frac{1}{n}(U_{\epsilon,n}(\hat{\alpha}_{\epsilon,n}, \beta) - U_{\epsilon,n}(\hat{\alpha}_{\epsilon,n}, \beta_0)) - K'(\alpha_0, \beta_0, \beta))| \rightarrow 0$ uniformly w.r.t. β.

Approximation of epidemic models by diffusion processes and their statistical inferences

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December 6, 2015

TALK 4, CIMPA 2015
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 Gillepsie'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
- Parmeter 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 $5\% S0$; $\Rightarrow$ 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

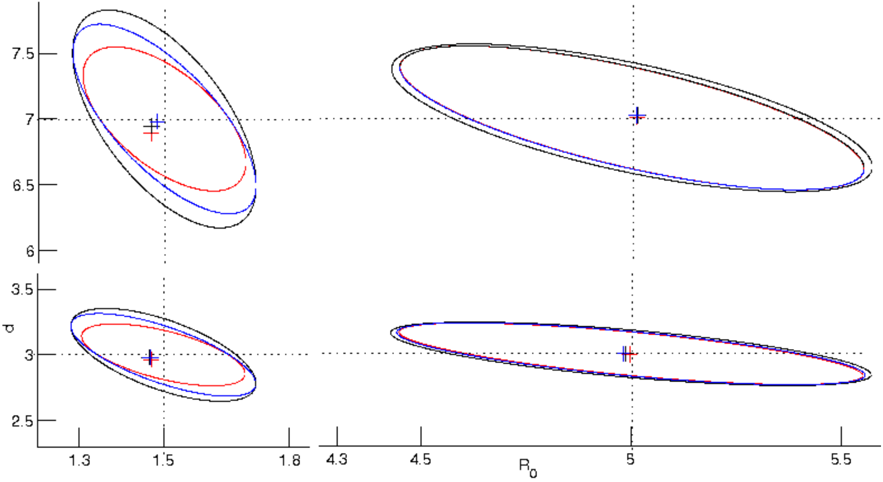
Table: Range of parameters for the *SIR* model defined in Section **??**. $^{(1)}$: T is chosen as the time point where the corresponding deterministic trajectory passes below the threshold of $1/100$.

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

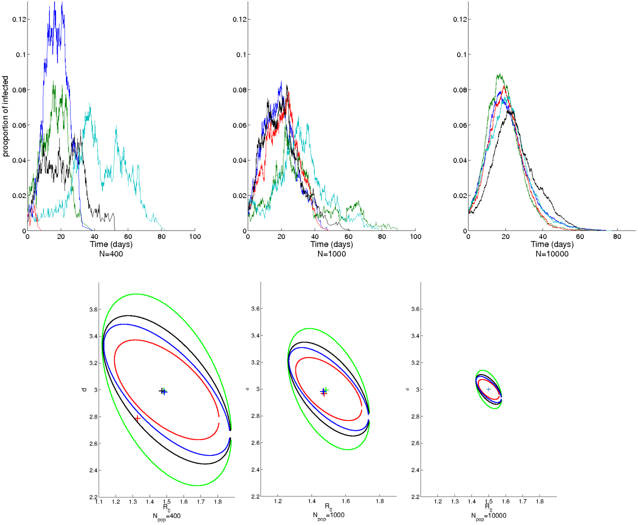
SIR theoretical confidence ellipsoids and estimators

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 $N = 4.10^2; 10^3; 10^4$

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)

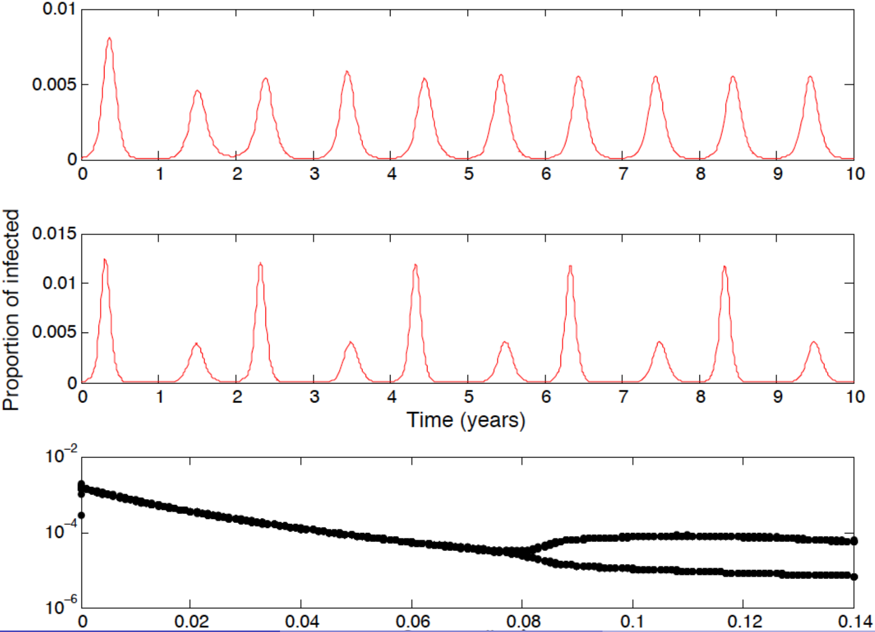
To avoid extinction, immigration flow η added $S \rightarrow I$: $\frac{\lambda(t)}{N} S(I + N\eta)$.

$\star$ μ: demography parameter; δ:immunity waning; $\gamma(= 1/d)$ recovery rate;
$\star$ $\lambda(t) = \lambda_0(1 + \lambda_1 sin(2\pi t/T_{per})) \Rightarrow$ New parameter $R := \frac{\lambda_0}{\gamma}$.
$\star$ $b(\theta; t, x) = \begin{pmatrix} -\lambda(t)s(i+\eta) + \delta(1-s-i) + \mu(1-s) \\ \lambda(t)s(i+\eta) - (\gamma+\mu)i \end{pmatrix}$.

ODE: dynamical system with bifurcation according to λ_1

$\star$ ODE:$\frac{dx}{dt} = b(\theta; t, x)$.
$\star$ Before bifurcation: annual oscillations with constant amplitude.
$\star$ After bifurcation: Biennial oscillations with unequal amplitudes.
$\star$ 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

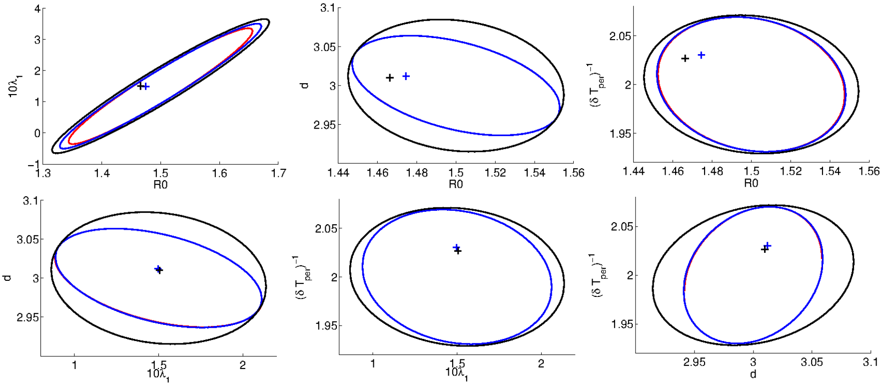
⋆ Large population size: $N = 10^7$ to ensure
—> Sufficiently large "signal over noise" ratio.
—> Sufficient pool of S and I after each outbreak.
⋆ $\mu = 1/50$ years^{-1}; $T_{per} = 365$ (days), $\eta = 10^{-6}$
⋆ $R0 = 1.5$, $d = 3$, $\delta = 2 \Rightarrow$ bifurcation for $\lambda_1 = 0.07$;
⋆ $\lambda_1 = 0.05$ 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 parametres, except R_0 and λ_1
• Good accuracy of estimation for all parameters.
• Disposing one obs/day $\rightarrow$ accuracy identical to corresponding complet obs. of the epidemic process.
• One obs/per week $\rightarrow$ still reasonably accurate estimations