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Romain Guy, Catherine Laredo, Elisabeta Vergu

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Statistical Inference for epidemic models approximated by diffusion processes

Romain GUY\textsuperscript{1,2}
Joint work with C. Larédo\textsuperscript{1,2} and E. Vergu\textsuperscript{1}

\textsuperscript{1} UR 341, MIA, INRA, Jouy-en-Josas
\textsuperscript{2} UMR 7599, LPMA, Université Paris Diderot

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Outline

Provide a framework for estimating key parameters of epidemics

1 Characteristics of the epidemic process
   - Constraints imposed by the observation of the epidemic process
   - Simple mechanistic models

2 Various mathematical approaches for epidemic spread
   - Natural approach: Markov jump process
   - First approximation by ODEs
   - Gaussian approximation of the Markov jump process
   - Diffusion approximation of the Markov jump process

3 Inference for discrete observations of diffusion or Gaussian processes with small diffusion coefficient
   - Contrast processes for fixed or large number of observations
   - Correction of a non asymptotic bias
   - Comparison of estimators on simulated epidemics

4 Epidemics incompletely observed: partially and integrated diffusion processes (Work in progress)
   - Back to epidemic data
   - Inference approach: Work in progress
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Characteristics of the epidemic process
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Epidemics incompletely observed: partially and integrated diffusion processes

Constraints imposed by the observation of the epidemic process
Simple mechanistic models

Incomplete Data

Different dynamics framework

Ex.: Influenza like illness cases (Sentinelles surveillance network)
One outbreak study

Recurrent outbreaks study

Imperfect data

- Incomplete observations
- Temporally aggregated
- Sampling & reporting error
- Unobserved cases

Main goal: key parameter estimation

- Basic reproduction number, $R_0$ (nb. of secondary cases generated by one primary case in an entirely susceptible population)
- Average infectious time period ($d$)
Define: Nb. of health states, possible transitions and associated rates. Notations

- \( N \): population size
- \( \lambda \): transmission rate
- \( \gamma \): recovery rate

\( S, I, R \): numbers of susceptible, infected, removed individuals

One of the simplest model: SIR

Closed population \( \Rightarrow N = S + I + R \)
Well-mixing population
\( \Rightarrow (S, I) \overset{\lambda SI/N}{\longrightarrow} (S-1, I+1) \)

Summary: coefficients \( \alpha_L \)

\( (S, I) \rightarrow (S - 1, I + 1) = (S, I) + (-1, 1) \) at rate \( \alpha_{(-1,1)}(S, I) = \lambda S \frac{I}{N} \)
and
\( (S, I) \rightarrow (S, I - 1) = (S, I) + (0, -1) \) at rate \( \alpha_{(0,-1)}(S, I) = \gamma I \)
Characteristics of the epidemic process
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Natural extensions of the SIR model

- Increase the number of health states: e.g. Exposed Class $\Rightarrow$ SEIR model
- Additional transitions: e.g. $(S, I) \rightarrow (S - 1, I)$ (vaccination)

Temporal dependence: SIRS with seasonality in transmission and demography

Key parameters: $R_{Moy}^0 = \frac{\lambda_0}{\gamma + \mu}$, $d = \frac{1}{\gamma}$

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

$\delta$: waning immunity rate (years)
$\mu$: demographic renewal rate (decades)
$\lambda(t) = \lambda_0(1 + \lambda_1\sin(2\pi \frac{t}{T_{per}}))$
$\lambda_1 = 0 \Rightarrow$ oscillations vanishes
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Markov jump process

\[ \alpha_{(-1,1)}(S, I) = \lambda S \frac{I}{N}, \quad \alpha_{(0,-1)}(S, I) = \gamma I \]

Notations:
\[ E = \{0, \ldots, N\}^d \]
\[ \forall L \in E^- = \{-N, \ldots, N\}^d, \text{ we define } \alpha_L(\cdot) : E \to [0, +\infty[ \]
We define \((Z_t)\) the Markov jump process on \(E\) with \(Q\)-matrix: \[ q_{X,Y} = \alpha_{Y-X}(X) \]
Assume \[ \alpha(X) = \sum_{L \in E^-} \alpha_L(X) < +\infty \Rightarrow \text{Sojourn time } \exp(\alpha(X)) \]

Easily simulated (using Gillespie algorithm)

3 realizations for \(N = 10000, \lambda = 0.5, \gamma = 1/3, (S_0, I_0) = (9990, 10)\)
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Interest of the deterministic approach

\[ \lambda(t) = \lambda_0(1 + \lambda_1 \sin(2\pi t / T_{\text{per}})) \]

SIRS ODE solution

\[
\begin{align*}
\frac{ds}{dt} &= \mu(1 - s) + \delta(1 - s - i) - \lambda(t)s \\
\frac{di}{dt} &= \lambda(t)s - (\mu + \gamma)i \\
\lambda(t) &= \lambda_0(1 + \lambda_1 \sin(2\pi t / T)) \\
(s(0), i(0)) &= \frac{Z_0}{N}
\end{align*}
\]

Diagrams showing trajectories of SIRS Markov process and ODE solution trajectories.

Some trajectories of the SIRS Markov proc.:

\( N = 10^5, R_0 = 1.5, d = 3, \frac{1}{\delta T_{\text{per}}} = 2, \frac{1}{\mu T_{\text{per}}} = 50 \)

Drawbacks of the Markov jump approach

- \( N = 10^7 \): more than \( 10^5 \) events in one week (MLE: observation of all the jumps required)
- Extinction probability non negligible

Link between the two approaches

As \( N \to +\infty \) we have \( \frac{Z_t}{N} \xrightarrow{N \to \infty} x(t) \), where \( x(t) \) is the deterministic solution of the ODE:

\[ \frac{dx(t)}{dt} = b(x(t)) \]

Function \( b \) is explicit
Beyond deterministic limit: Gaussian process

Additionnal assumption: smooth version of $\alpha_L, \beta_L$

We have $\alpha_L : E \to (0, +\infty)$ transition rate: $X \xleftarrow{\alpha_L(X)} X + l$

Assume $\beta_L : [0, 1]^d \to [0, +\infty]$ well define and regular:
$\forall x \in [0, 1]^d$, $\frac{1}{N} \alpha_L([Nx]) \xrightarrow{N \to \infty} \beta_L(x)$

SIR: $\alpha_{(-1,1)}(S, I) = \lambda S \frac{1}{N} \Rightarrow \beta_{(-1,1)}(x) = \lambda x_1 x_2$, $\alpha_{(0,1)}(S, I) = \gamma I \Rightarrow \beta_{(0,-1)}(x) = \gamma x_2$

Definition of function $b$ ($\frac{dx(t)}{dt} = b(x(t))$)

$$b(x) = \sum_{L \in E^{-}} L \beta_L(x), \text{SIR: } b((\lambda, \gamma), (s, i)) = \begin{pmatrix} -1 \\ 1 \end{pmatrix} \lambda si + \begin{pmatrix} 0 \\ 1 \end{pmatrix} \gamma i = \begin{pmatrix} -\lambda si \\ \lambda si + \gamma i \end{pmatrix}$$

ODE approximation: no longer dependance w.r.t. $N$

Asymptotic expansion w.r.t. $N$: Gaussian process

$$\sqrt{N} \left( \frac{Z}{N} - x(t) \right) \xrightarrow{N \to \infty} g(t) \text{ where } g(t) \text{ centered Gaussian process:}$$

$$dg(t) = \frac{\partial b}{\partial x}(x(t))g(t)dt + \sigma(x(t))dB_t, \text{ where } \sigma^T \sigma(x) = \Sigma(x) = \sum_{L \in E^{-}} L^T L \beta_L(x)$$

SIR: $\Sigma((\lambda, \gamma), (s, i)) = \lambda si \begin{pmatrix} -1 \\ 1 \end{pmatrix} (-1, 1) + \gamma i \begin{pmatrix} 0 \\ 1 \end{pmatrix} (0, 1) = \begin{pmatrix} \lambda si & -\lambda si \\ -\lambda si & \lambda si + \gamma i \end{pmatrix}$

Cholesky algorithm $\Rightarrow \sigma(x) = \begin{pmatrix} \sqrt{\lambda si} & 0 \\ \sqrt{-\lambda si} & \sqrt{\gamma i} \end{pmatrix}$
Renormalized version of the Markov jump process ($\tilde{Z}_t$):

$\tilde{Z}_t$ Markov jump process on $E$ with transition rates $q_{X,Y} = N\beta_{Y-X}(X)$

$\tilde{Z}_t = \frac{\tilde{Z}_t}{N}$ normalized process

Asymptotic development of the infinitesimal generator of $Z_t$ (Ethier & Kurtz (86))

Generator of $\tilde{Z}_t$: $A f(x) = \sum_{L \in E^-} NL\beta_L(x) (f(x + L) - f(x))$

⇒ Generator of $\tilde{Z}_t$: $\bar{A} f(x) = b(x) \cdot \nabla f(x) + \frac{1}{N} \sum_{i,j=1}^{d} \Sigma_{i,j}(x) \frac{\partial^2 f}{\partial x_i \partial x_j}(x) + O\left(\frac{1}{N^2}\right)$

Dropping negligible terms leads to the generator of a diffusion process:

$dX_t = b(X_t)dt + \frac{1}{\sqrt{N}} \sigma(X_t)dB_t$, where $b(x) = \sum_{L \in E^-} L\beta_L(x)$, $\Sigma(x) = \sum_{L \in E^-} L^t L\beta_L(x)$

Temporal dependence $\beta_L(t,x)$: generator approach no longer available

Decomposition of the diffusion process using Gaussian process ($\epsilon = \frac{1}{\sqrt{N}}$)

Taylor’s stochastic formula (Wentzell-Freidlin(79), Azencott (82))

Let $dX_t = b(X_t)dt + \epsilon \sigma(X_t)dB_t$, $X_0 = x_0$

Then, under regularity assumptions, $X_t = x(t) + \epsilon g(t) + O_P(\epsilon^2)$
Links between approximations

- $Z_t$ Markov jump process on $E$ with transition $q_{X,Y} = \alpha Y - X(X)$
- $\bar{Z}_t$ Markov jump process on $E/N$ with transition $q_{x,y} = N\beta \lfloor Nx \rfloor - \lfloor Ny \rfloor (x)$
- $\bar{Z}_t \sim x(t) + \frac{1}{\sqrt{N}}g(t)$ with $x(\cdot)$ the ODE solution and $g$ a Gaussian process
- $X_t: dX_t = b(x(t))dt + \frac{1}{\sqrt{N}}\sigma(x(t))dB_t$ diffusion with small diffusion coefficient

and $\mathbb{P}\{ \sup_{0 \leq t \leq T} \| \bar{Z}_t - X_t \| > CT \frac{\log(N)}{N} \} \xrightarrow{N \to \infty} 0$

- $X_t = x(t) + \frac{1}{\sqrt{N}}g(t) + O_P(\frac{1}{N})$

$\rightarrow$ Diffusion approximation
$\rightarrow$ Expansion in $N$ of the process
$\rightarrow$ Taylor's stochastic expansion

Important: All mathematical representations completely defined by $(\alpha_L)$
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Outline
Maximum likelihood estimation for the SIR Markov Jump process (Andersson & Britton (00))

- Observation of all jumps
- Analytic expression of the estimators for SIR model:
  \[ \hat{\lambda} = N \frac{S(0) - S(T)}{\int_0^T S(t)I(t)dt} \]
  \[ \hat{\gamma} = \frac{S(0) + I(0) - S(T) - I(T)}{\int_0^T I(t)dt} \]

- \[ \sqrt{N}(\hat{\theta}_{MLE} - \theta_0) \xrightarrow{N \to \infty} \mathcal{N}(0, I_b^{-1}(\theta_0)) \]
  where

\[ I_b^{-1}(\lambda_0, \gamma_0) = \begin{pmatrix}
  \frac{\lambda_0^2}{s(0) - s(T)} & 0 \\
  0 & \gamma_0^2 \\
  \frac{s(0) + I(0) - s(T) - I(T)}{s(0) + I(0) - s(T) - I(T)}
\end{pmatrix} \]

Maximum likelihood estimation for homoscedastic observations of the ODE

- \( n \) observations at \( n \) discrete times \( t_k \) of \( x_\theta(t_k) + \xi_k \), with \( \xi_k \sim \mathcal{N}(0, C_N(\theta_0)I_d) \)
- MLE=LSE
- \[ \sqrt{n}(\hat{\theta}_{LSE} - \theta_0) \xrightarrow{n \to \infty} \mathcal{N}(0, I_N(\theta_0)) \]
Specificities of the statistical framework

Model:
We define \( X_t: dX_t = b(\theta_1, X_t)dt + \epsilon \sigma(\theta_2, X_t)dB_t, X_0 = x_0 \in \mathbb{R}^d \)
⇒ separation of the parameters \( \theta_1, \theta_2 \) required (not estimated at the same rate)

Continuous observation of the diffusion on \([0, T]\) (Kutoyants (80))

\[
\text{MLE : } \epsilon^{-1} \left( \theta_1^{\text{MLE}} - \theta_1^0 \right) \rightarrow \mathcal{N} \left( 0, I_b(\theta_1^0, \theta_2^0)^{-1} \right)
\]

Existing discrete observation results : estimation of \( \theta_2 \) at rate \( \sqrt{n} \)

Observations:
We observe \( X_{t_k} \) for \( t_k = k\Delta, k \in \{0, \ldots, n\}, t_k \in [0, T] \) \((n\Delta = T)\), \( T \) is fixed

Two different asymptotics: \( \epsilon \rightarrow 0 \) & \( n (\Delta) \) is fixed // \( \epsilon \rightarrow 0 \) & \( n \rightarrow \infty \) \((\Delta \rightarrow 0)\)

Notation: \( \eta = (\theta_1, \theta_2) \)

SIR: \( \epsilon = \frac{1}{\sqrt{N}}, \theta_1 = \theta_2 = \theta = (\lambda, \gamma) \), and \( I_b(\theta_1^0, \theta_2^0) \) equals the Markov jump process Fisher Information matrix
**Main idea:** study of $g_\eta(t)$ (Multidimensionnal generalization of Genon-Catalot(90))

**Gaussian process:** $Y_t = x_{\theta_1}(t) + \epsilon g_\eta(t)$, n obs. at regular time intervals $t_k = k\Delta$, for $k = 1,..,n$.

**Definition:** Resolvent matrix of the linearized ODE system $\Phi_{\theta_1}$

Let $\Phi_{\theta_1}$ be the invertible matrix solution of

$$
\frac{d\Phi_{\theta_1}(t, t_0)}{dt} = \frac{\partial b}{\partial x}(x_{\theta_1}(t))\Phi_{\theta_1}(t, t_0), \quad \text{with } \Phi_{\theta_1}(t_0, t_0) = I_d.
$$

**Important property of $g_\eta$**

$$
g_\eta(t_k) = \Phi_{\theta_1}(t_k, t_{k-1})g_\eta(t_{k-1}) + \sqrt{\Delta} Z^\eta_k
$$

$(Z^\eta_k)_{k\in\{1,..,n\}}$ independent Gaussian vectors with covariance matrix $S^\eta_k$

$$
S^\eta_k = \frac{1}{\Delta} \int_{t_{k-1}}^{t_k} \Phi_{\theta_1}(t_k, s)\Sigma(\theta_2, x_{\theta_1}(s))\Phi_{\theta_1}^T(t_k, s)ds
$$

**Function of the observations**

Let $y \in C([0, T], \mathbb{R}^d)$

$$
N_k(\theta_1, y) = y(t_k) - x_{\theta_1}(t_k) - \Phi_{\theta_1}(t_k, t_{k-1})[y(t_{k-1}) - x_{\theta_1}(t_{k-1})] = \epsilon \sqrt{\Delta} Z^\eta_k
$$


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Back to the diffusion process: $dX_t = b(\theta_1, X_t)dt + \epsilon\sigma(\theta_2, X_t)dB_t$

$(Z^n_k)$ Gaussian family $\Rightarrow$ Likelihood tractable:

$$-L_{\Delta, \epsilon}(\eta) = \epsilon^2 \sum_{k=1}^n \log [\det (S^n_k)] + \frac{1}{\Delta} \sum_{k=1}^n tN_k(\theta_1, Y)(S^n_k)^{-1}N_k(\theta_1, Y)$$

$\hat{\theta}_2$ has good properties as $\epsilon \to 0$, only if $\Delta \to 0$ ($n \to +\infty$)

1. $n$ fixed, $\epsilon \to 0$: General case (low frequency contrast with $\theta_2$ unknown)

$$\bar{U}_{\epsilon}(\theta_1) = \frac{1}{\Delta} \sum_{k=1}^n tN_k(\theta_1, X)N_k(\theta_1, X) \Rightarrow \text{Associated MCE } \bar{\theta}_{1, \epsilon} = \arg\min_{\theta_1 \in \Theta} \bar{U}_{\epsilon}(\theta_1)$$

2. $n$ fixed, $\epsilon \to 0$: Case $\theta_2 = f(\theta_1)$ (low frequency contrast with information on $\theta_2$)

$$\tilde{U}_{\epsilon}(\theta_1) = \frac{1}{\Delta} \sum_{k=1}^n tN_k(\theta_1, X)(\tilde{S}_k^{\theta_1, f(\theta_1)})^{-1}N_k(\theta_1, X) \Rightarrow \tilde{\theta}_{1, \epsilon} = \arg\min_{\theta_1 \in \Theta} \tilde{U}_{\epsilon}(\theta_1)$$

3. $n \to \infty$, $\epsilon \to 0$ (high frequency contrast)

$$\bar{U}_{\Delta, \epsilon}(\theta_1, \theta_2) = \epsilon^2 \sum_{k=1}^n \log [\det (\Sigma(\theta_2, X_{t_k-1}))] + \frac{1}{\Delta} \sum_{k=1}^n tN_k(\theta_1, X)\Sigma^{-1}(\theta_2, X_{t_k-1})N_k(\theta_1, X)$$

$$\Rightarrow \bar{\theta}_{1, \epsilon, \Delta}, \bar{\theta}_{2, \epsilon, \Delta} = \arg\min_{\eta \in \Theta} \bar{U}_{\epsilon, \Delta}(\eta)$$
$N_k(\theta_1, y) = y(t_k) - x_{\theta_1}(t_k) - \Phi_{\theta_1}(t_k, t_{k-1}) \left[ y(t_{k-1}) - x_{\theta_1}(t_{k-1}) \right]$ 

$N = 1000, \ R_0 = 1.5, \ d = 3 \text{ days}, \ 1 \text{ obs/day}, \ T = 50 \text{ days}$

Figure: Diffusion (blue), $x_{\theta_1}(t)$ (green)
Zoom between $t = 5$ and $t = 6$

$$g_\eta(t_k) = \Phi_{\theta_1}(t_k; t_{k-1})g_\eta(t_{k-1}) + \sqrt{\Delta} Z^\eta_k$$
Zoom between $t = 5$ and $t = 6$

$$g_\eta(t_k) = \Phi_{\theta_1}(t_k, t_{k-1}) g_\eta(t_{k-1}) + \sqrt{\Delta Z_k^\eta}$$
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What kind of distance is minimized: comparison with Least square

**Figure:** Distance to the deterministic model

**Figure:** Comparison: $N_k(X, \theta_1)$ (blue) and $X_{t_k} - x_{\theta_1}(t_k)$ (green)
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Results about \( dX_t = b(\theta_1, X_t)dt + \epsilon \sigma(\theta_2, X_t)dB_t \)

Under classical regularity assumptions on \( b \) and \( \sigma \), we proved

\[
\begin{align*}
\text{n fixed, } \epsilon \to 0, \text{ low frequency contrast} \\
\text{Identifiability assumption: } \theta_1 \neq \theta'_1 \Rightarrow \{\exists k, \ 1 \leq k \leq n, \ x_{\theta_1}(t_k) \neq x_{\theta'_1}(t_k)\}.
\end{align*}
\]

1. General case (no information on \( \theta_2 \))

\[
\epsilon^{-1} \left( \bar{\theta}_1 - \theta_1^0 \right) \xrightarrow{\epsilon \to 0} \mathcal{N}(0, J_{\Delta}^{-1}(\theta_1^0, \theta_2^0))
\]

2. case \( \theta_2 = f(\theta_1) \) (with information on \( \theta_2 \))

\[
\epsilon^{-1} \left( \tilde{\theta}_1 - \theta_1^0 \right) \xrightarrow{\epsilon \to 0} \mathcal{N}(0, I_{\Delta}^{-1}(\theta_1^0, \theta_2^0))
\]

3. \( n \to \infty \) \( \epsilon \to 0 \): high frequency contrast

\[
\left( \begin{array}{c}
\epsilon^{-1} \left( \bar{\theta}_1, \Delta - \theta_1^0 \right) \\
\sqrt{n} \left( \bar{\theta}_2, \Delta - \theta_2^0 \right)
\end{array} \right) \xrightarrow{n \to \infty, \epsilon \to 0} \mathcal{N} \left( 0, \begin{pmatrix}
I_{\Delta}^{-1}(\theta_1^0, \theta_2^0) & 0 \\
0 & I_{\sigma}^{-1}(\theta_1^0, \theta_2^0)
\end{pmatrix} \right)
\]

Remarks

- Epidemics: \( \epsilon = \frac{1}{\sqrt{N}}, \theta = \theta_1 = \theta_2 \), then for contrast 3: \( I_b \) is the same as for the Markov jump process (all jumps observed)
- \( J_\Delta \) is not optimal, but \( l_\Delta \) is, in the sense that \( l_\Delta(\theta_1, \theta_2) \xrightarrow{\Delta \to 0} I_b(\theta_1, \theta_2) \)
Results on SIR for $N = 10000$, empirical mean estimators on 1000 runs and 95% theoretical CI ($R_0 = 1.2$, $d = 3$)

Figure: 0: MLE, 1: $\tilde{\theta}_1$ low frequency MCE (general case), 2: $\tilde{\theta}_1$ low frequency MCE ($\theta_1 = \theta_2$), 3: $\tilde{\theta}_1$, high frequency MCE

- Good results even for $N = 100$ (our methods seem more robust than MLE)
- Similar performance (w.r.t. MLE) on more sophisticated models
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### About $\hat{\theta}_1$ (Low frequency with information on $\theta_2$)

<table>
<thead>
<tr>
<th>$\theta_2$ unknown</th>
<th>With information on $\theta_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$1. \tilde{U}<em>\epsilon (\theta_1) = \frac{1}{\Delta} \sum</em>{k=1}^{n} t N_k(\theta_1, X) N_k(\theta_1, X)$</td>
<td>$2. \tilde{U}<em>\epsilon (\theta_1) = \frac{1}{\Delta} \sum</em>{k=1}^{n} t N_k(\theta_1, X) (\tilde{S}_k^{\theta_1})^{-1} N_k(\theta_1, X)$</td>
</tr>
</tbody>
</table>

**Figure:** Comparison between Data and ODE ($x_{\tilde{\theta}_1} (t)$)

**Figure:** Evolution of $\det \left( \Sigma^{-1}(\theta_0^1, x_{\theta_0^1}(t)) \right)$

Not good fit of the data

Too much weight on the boundaries
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About \( \hat{\theta}_1 \epsilon \) (Low frequency with information on \( \theta_2 \))

Comparing to high frequency contrast

\[
3. \tilde{U}_{\Delta, \epsilon}(\theta_1, \theta_2) = \epsilon^2 \sum_{k=1}^{n} \log [\det (\Sigma_k)] + \frac{1}{\Delta} \sum_{k=1}^{n} \epsilon^2 N_k(\theta_1) \Sigma_k^{-1} N_k(\theta_1)
\]

where
\[
\Sigma_k = \Sigma(\theta_2, X_{t_{k-1}})
\]

Corrected contrast with information on \( \theta_2 \)

\[
2'. \tilde{U}_{\epsilon}^{\text{cor}}(\alpha) = \epsilon^2 \sum_{k=1}^{n} \log [\det(\tilde{S}_{\theta_1}^k)] + \frac{1}{\Delta} \sum_{k=1}^{n} \epsilon^2 N_k(\theta_1) \left( \tilde{S}_{\theta_1}^k \right)^{-1} N_k(\theta_1)
\]

Figure: Previous results

Figure: Corrected results
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Different shapes of the confidence ellipsoids

SIR Model confidence ellipsoids for the corrected contrast

\( N = 1000, (R_0, d) = \{(1.5, 3), (1.5, 7), (5, 3), (5, 7)\} \)
Number of observations: \( n = 10 \) (blue), \( n = 1 \) obs/day \( \approx 40 \) d (green), \( n = 2000 \) (black), MLE CR (red) (Theoretical limit)
Bias of MLE ($N = 400; R_0 = 1.5; d = \{3, 7\}; (s_0, i_0) = (0.99, 0.01)$)

Too much variability

Figure: Trajectories for $d=3$

Need of an empiric threshold: 5% of infected

Estimation results ($d = 3$)

Other values of $d$ were investigated

Other thresholds: time of extinction, number max of infected

Results ($d = 7$, time of extinction)

Zoom on the red trajectory (see Figure)

$(R_0, d)_{MLE} = (0.8749, 2.9945)$

$(R_0, d)_{LSE} = (0.94, 2.5794)$

$(R_0, d)_{cont} = (1.01, 3.0973)$
Temporal dependence (SIRS): \( \lambda_1 \) difficult to estimate

**SIRS with constant immigration in I class**

\[
\lambda(t) = \lambda_0 (1 + \lambda_1 \sin(2\pi t / T))
\]

**Values**

- \( R_0 = 1.5; \ d = 3d; \ \frac{1}{\delta T_{per}} = 2y, \)
- \( \lambda_1 = \{0.05, 0.15\} \)
- Fixed: \( T_{per} = 365, \ \mu = 1/50 T_{per}, \ \zeta = \frac{10}{N}, \)
- \( N = 10^7, \) 1 obs/day(week) for 20 years

- Term for \( \lambda_1 \) in \( I_b(\theta_0) \) very small \( \Rightarrow N > 10^5 \) for satisfactory CI
- \( \lambda_1 \) bifurcation parameter for the ODE

- \( \lambda_1 = 0.05 \) (weak seasonality)
- \( \lambda_1 = 0.15 \) (stronger seasonality)

**Detailed results not shown**

Main idea: \( R_0, d, \delta \) well estimated

\( \lambda_1 \): biased (often estimated to 0)
Outline

1 Characteristics of the epidemic process
   - Constraints imposed by the observation of the epidemic process
   - Simple mechanistic models

2 Various mathematical approaches for epidemic spread
   - Natural approach: Markov jump process
   - First approximation by ODEs
   - Gaussian approximation of the Markov jump process
   - Diffusion approximation of the Markov jump process

3 Inference for discrete observations of diffusion or Gaussian processes with small diffusion coefficient
   - Contrast processes for fixed or large number of observations
   - Correction of a non asymptotic bias
   - Comparison of estimators on simulated epidemics

4 Epidemics incompletely observed: partially and integrated diffusion processes (Work in progress)
   - Back to epidemic data
   - Inference approach: Work in progress
Discrete observation of all the coordinates

- Confined studies
- Childhood diseases

SIR Model:

- Incidence at $t_2$: $\int_{t_1}^{t_2} \lambda S(t) \frac{I(t)}{N} dt$
- High frequency data $\approx \lambda S(t_2) \frac{I(t_2)}{N}$
- $d$ small: new infected $\approx$ new removed, $\int_{t_1}^{t_2} \gamma I(t) dt = R(t_2) - R(t_1)$

Diffusion perspectives

- Partial and discrete obs. of the diffusion process (Itô's formula)
- Partial and Integrated discrete obs.
Previous main idea not directly applicable:
No good properties for $n$ fixed, $\epsilon \to 0$. 
### Partially observed diffusion process: initial idea

Use that $\Phi_{\theta_1}(t + \Delta, t) \approx I_d$ as $\Delta \to 0$

Function of the observations: $l(t_k) - i(t_k) - l(t_{k-1}) + i(t_{k-1})$

### Integrated diffusion process

Integration of the relation: $g_\eta(t_k) = \Phi_{\theta_1}(t_k, t_{k-1}) g_\eta(t_{k-1}) + \sqrt{\Delta} Z_\eta$

$\Rightarrow$ link between $g$ and the integrated process: similar to Kalman filtering techniques