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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

ANR MANEGE, Université Paris 13
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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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Inference for discrete observations of diffusion or Gaussian processes
Epidemics incompletely observed: partially and integrated diffusion process

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

Incomplete Data

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

Different dynamics framework
Ex.: Influenza like illness cases (Sentinelles surveillance network)

One outbreak study

Recurrent outbreaks study

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
\( \Rightarrow (S, I) \xrightarrow{\lambda SI/N} (S - 1, I + 1) \)

Key parameters: \( R_0 = \frac{\lambda}{\gamma}, d = \frac{1}{\gamma} \)

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 \( \alpha_{(0,-1)}(S, I) = \gamma I \)
• 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: $R_{0}^{Moy} = \frac{\lambda_0}{\gamma + \mu}$, $d = \frac{1}{\gamma}$

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

$$\frac{ds}{dt} = \mu(1-s) + \delta(1-s-i) - \lambda(t)s$$
$$\frac{di}{dt} = \lambda(t)s - (\mu + \gamma)i$$
$$\lambda(t) = \lambda_0(1 + \lambda_1 \sin(2\pi t / T))$$

(s(0), i(0)) = \frac{Z_0}{N}

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} \to 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: $X \overset{\alpha_L}{\to} X + 1$

Assume $\beta_L : [0, 1]^d \to [0, +\infty]$ well define and regular:

$\forall x \in [0, 1]^d, \frac{1}{N} \alpha_L([N x]) \xrightarrow{N \to \infty} \beta_L(x)$

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

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

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

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

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

Cholesky algorithm $\Rightarrow \sigma(x) = \begin{pmatrix} \sqrt{\frac{\lambda si}{\lambda si}} & 0 \\ -\sqrt{\frac{\lambda si}{\lambda si}} & \sqrt{\gamma i} \end{pmatrix}$
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Infinitesimal generator approach: diffusion approximation

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

\(\Rightarrow\) Generator of \(Z_t\): \(\tilde{A} f(x) = b(x). \nabla f(x) + \frac{1}{N} \sum_{i,j=1}^d \sum_{i,j=1}^d \partial^2 f \partial x_i \partial x_j(x) + O(\frac{1}{N^2})\)

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 \(b(x) = \sum_{L \in E^-} L\beta_L(x)\), \(\Sigma(x) = \sum_{L \in E^-} L^tL\beta_L(x)\)

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 \( q_{X,Y} = \alpha Y - X(X) \)
- \( \tilde{Z}_t \): Markov jump process on \( E/N \) with transition \( q_{x,y} = N\beta \lfloor Nx \rfloor - \lfloor Ny \rfloor (x) \)
- \( \tilde{Z}_t \sim x(t) + \frac{1}{\sqrt{N}} g(t) \) 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 \( \mathbb{P}\left\{ \sup_{0 \leq t \leq T} \| \tilde{Z}_t - X_t \| > C_T \frac{\log(N)}{N} \right\} \xrightarrow{N \to \infty} 0 \)

- \( X_t = x(t) + \frac{1}{\sqrt{N}} g(t) + \mathcal{O}_P\left( \frac{1}{N} \right) \)

\[ \rightarrow \text{Diffusion approximation} \]
\[ \rightarrow \text{Expansion in } N \text{ of the process} \]
\[ \rightarrow \text{Taylor’s stochastic expansion} \]

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

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

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

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

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
- \[
\sqrt{n} \left( \hat{\theta}_{LSE} - \theta_0 \right) \xrightarrow{n \to \infty} \mathcal{N}(0, I^N(\theta_0))
\]
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))

MLE: $\epsilon^{-1} (\theta_1^{MLE} - \theta_1^0) \rightarrow N(0, I_b(\theta_1^0, \theta_2^0)^{-1})$

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 $k = 1, \ldots, n$.

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

Let $\Phi_{\theta_1}$ be the invertible matrix solution of
\[
\frac{d\Phi_{\theta_1}}{dt}(t, t_0) = \frac{\partial b}{\partial x}(x_{\theta_1}(t))\Phi_{\theta_1}(t, t_0), \text{ with } \Phi_{\theta_1}(t_0, t_0) = I_d.
\]

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_k^\eta

(Z_k^\eta)_{k \in \{1, \ldots, n\}}$ independent Gaussian vectors with covariance matrix $S_k^\eta$

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

Function of the observations

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

$N_k(\theta_1, y) = y(t_k) - x_{\theta_1}(t_k) - \Phi_{\theta_1}(t_k, t_{k-1})[y(t_{k-1}) - x_{\theta_1}(t_{k-1})] (= \epsilon\sqrt{\Delta}Z_k^\eta)$
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 \( \theta_2 \))

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

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

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

\( \Rightarrow \check{\theta}_{1, \epsilon, \Delta}, \check{\theta}_{2, \epsilon, \Delta} = \arg\min_{\eta \in \Theta} \check{U}_{\epsilon, \Delta}(\eta) \)
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What kind of distance is minimized: comparison with Least squares

\[ N_k(\theta_1, y) = y(t_k) - x_{\theta_1}(t_k) - \Phi_{\theta_1}(t_k, t_{k-1}) [y(t_{k-1}) - x_{\theta_1}(t_{k-1})] \]

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

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

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

1. Joint work with C. Larédoo$^{1,2}$ and E. Vergu$^1$
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Zoom between $t = 5$ and $t = 6$

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

What kind of distance is minimized: comparison with Least squares

Romain GUY$^{1,2}$ Joint work with C. Larédol$^{1,2}$ and E. Vergu$^1$

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

For $n$ fixed, $\epsilon \to 0$, low frequency contrast

Identifiability assumption: $\theta_1 \neq \theta'_1 \Rightarrow \{\exists k, \quad 1 \leq k \leq n, \quad x_{\theta_1}(t_k) \neq x_{\theta'_1}(t_k)\}$.

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

$\epsilon^{-1} (\tilde{\theta}_1 - \theta_1^0) \xrightarrow{\epsilon \to 0} \mathcal{N}(0, J^{-1}_\Delta(\theta_1^0, \theta_2^0))$

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

$\epsilon^{-1} (\tilde{\theta}_1 - \theta_1^0) \xrightarrow{\epsilon \to 0} \mathcal{N}(0, I^{-1}_\Delta(\theta_1^0, \theta_2^0))$

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

$\left(\epsilon^{-1} (\tilde{\theta}_1, \Delta - \theta_1^0) \right) \xrightarrow{n \to \infty, \epsilon \to 0} \mathcal{N} \left(0, \begin{pmatrix} I^{-1}_b(\theta_1^0, \theta_2^0) & 0 \\ 0 & I^{-1}_\sigma(\theta_1^0, \theta_2^0) \end{pmatrix} \right)$

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 $I_\Delta$ is, in the sense that $I_\Delta(\theta_1, \theta_2) \xrightarrow{\Delta \to 0} I_b(\theta_1, \theta_2)$
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: $\tilde{\theta}_1, \Delta$ 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
### Characteristics of the epidemic process

- Various mathematical approaches for epidemic spread
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**Work in progress**

### Contrast processes for fixed or large number of observations

### Correction of a non asymptotic bias

### Comparison of estimators on simulated epidemics

#### 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>$1. \bar{U}<em>e (\theta_1) = \frac{1}{\Delta} \sum</em>{k=1}^{n} \bar{t} N_k(\theta_1, X) N_k(\theta_1, X)$</td>
<td></td>
</tr>
<tr>
<td>$2. \tilde{U}<em>e (\theta_1) = \frac{1}{\Delta} \sum</em>{k=1}^{n} \bar{t} N_k(\theta_1, X) (\tilde{S}_k^{\theta_1})^{-1} N_k(\theta_1, X)$</td>
<td></td>
</tr>
</tbody>
</table>

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

- Not good fit of the data

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

- Too much weight on the boundaries
Comparing to high frequency contrast

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

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

Corrected contrast with information on \( \theta_2 \)

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

*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), \( n = 1 \text{ obs/day} \approx 40 \text{ d.} \) (green), \( n = 2000 \) (black), MLE CR (red) (Theoretical limit)
Characteristics of the epidemic process
Various mathematical approaches for epidemic spread
Inference for discrete observations of diffusion or Gaussian processes
Epidemics incompletely observed: partially and integrated diffusion processes
Contrast processes for fixed or large number of observations
Correction of a non-asymptotic bias
Comparison of estimators on simulated epidemics

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 empirical 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
Incidence for SIR models

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, $\epsilon \to 0$. 
Characteristics of the epidemic process
Various mathematical approaches for epidemic spread
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Epidemics incompletely observed: partially and integrated diffusion

Partially observed diffusion process: initial idea

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

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

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

Integrated diffusion process

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

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