A stochastic SIR model with contact-tracing

Conference "R_0 and related concepts: methods and illustrations"

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Agenda for today

- The HIV/AIDS epidemic in Cuba

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- Accounting for the impact of the contact-tracing system

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- Open questions

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1. Individuals identified as **infected** are asked to name persons with whom they have had possibly infectious contacts
2. On the basis of the information provided, try to find those persons in order to propose them a medical exam and a cure in case of infection

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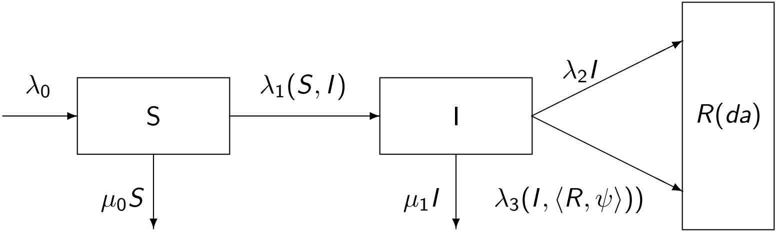
- The sizes of the strates evolve through

$E = 0$ Recruitment of a susceptible
$E = 1$ Death/emigration of a susceptible
$E = 2$ Infection
$E = 3$ "Spontaneous" detection
$E = 4$ Detection by contact-tracing
$E = 5$ Death/emigration of an infective

- May be complexified: time-varying infectivity, socio-demographic features, *etc.*
- Propose a macroscopic model, interpretable at a microscopic level

SIR model



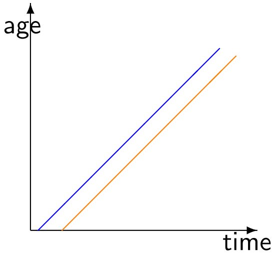
$$\begin{aligned}\lambda_1(S, I) =& \lambda_1 SI, \quad \text{(mass action principle)}\\ =& \lambda_1 SI/(I+S) \quad \text{or} \quad \lambda_1 I, \quad \text{(frequency dependence)}\end{aligned}$$

$$\begin{aligned}\lambda_3(I, \langle R, \psi \rangle) =& \lambda_3 I \langle R, \psi \rangle\\ =& \lambda_3 I \langle R, \psi \rangle / (I + \langle R, \psi \rangle) \quad \text{or} \quad \lambda_3 \langle R, \psi \rangle.\end{aligned}$$

Age-structured component

$R_t(da)$ is a point measure: $R_t(da) = \sum_{i=1}^{N_t} \delta_{a_i(t)}$

Detected individuals age with speed 1 and contribute to the search of infectious people with rate $\psi(a)$.



Examples of ψ:

$$\psi(a) = C_1 e^{-C_2 a}, \quad \text{or} \quad \psi(a) = \text{Gamma density function}$$

Notation:

$$\langle R_t, \psi \rangle = \int_{\mathbb{R}_+} \psi(a) R_t(da) = \sum_{i=1}^{N_t} \psi(a_i(t)).$$

Stochastic differential equation

Following Fournier and Méléard (2004), it is possible to describe $(S_t, I_t, R_t(da))$ as the solution of a SDE driven by a Poisson point measure.

$$
\begin{aligned}
S_t =& S_0 + \int_{v=0}^{t} \int_{u=0}^{\infty} \left(\mathbf{1}_{0\le u\le \lambda_0} - \mathbf{1}_{\lambda_0 < u \le \lambda_0 + \mu_0 S_{v-} + \lambda_1(S_{v-}, I_{v-})}\right) Q^S(dv, du) \\
I_t =& I_0 + \int_{v=0}^{t} \int_{u=0}^{\infty} \mathbf{1}_{\lambda_0 < u \le \lambda_0 + \lambda_1(I_{v-}, S_{v-})} Q^S(dv, du) \\
& - \int_{v=0}^{t} \int_{u=0}^{\infty} \mathbf{1}_{0 \le u \le (\mu_1 + \lambda_2) I_{v-} + \lambda_3(I_{v-}, \langle R_{v-}, \psi\rangle)} Q^I(dv, du) \\
\langle R_t, f\rangle =& \int_{v=0}^{t} \int_{u=0}^{\infty} f(0) \mathbf{1}_{0 \le u \le \lambda_2 I_{v-} + \lambda_3(I_{v-}, \langle R_{v-}, \psi\rangle)} Q^I(dv, du) \\
& + \int_{v=0}^{t} \int_{a=0}^{\infty} \partial_a f(a) R_v(da) dv,
\end{aligned}
$$

Large population renormalization

- $(s_t^{(n)}, i_t^{(n)}, r_t^{(n)}(da))_{t\ge 0} = (\frac{1}{n} S_t^{(n)}, \frac{1}{n} I_t^{(n)}, \frac{1}{n} R_t^{(n)}(da))_{t\ge 0}$.
- We assume that the $(\frac{1}{n} S_0^{(n)}, \frac{1}{n} I_0^{(n)})$ converges in probability to a deterministic couple $(s_0, i_0) \in \mathbb{R}_+^{*2}$.

PDE approximation

Under sufficient moment condition for the sequence $(\frac{1}{n}S_0^{(n)}, \frac{1}{n}I_0^{(n)})$, the process $(s_t^{(n)}, i_t^{(n)}, r_t^{(n)}(da))_{t\in\mathbb{R}_+} = (\frac{1}{n}S_t^{(n)}, \frac{1}{n}I_t^{(n)}, \frac{1}{n}R_t^{(n)}(da))_{t\in\mathbb{R}_+}$ converges in $\mathbb{D}(\mathbb{R}_+, \mathbb{R}_+^2 \times \mathcal{M}_F(\mathbb{R}_+))$ to the weak solution of the following PDE:

$$\begin{aligned}
\frac{ds_t}{dt} =& \lambda_0 - \mu_0 s_t + \lambda_1(s_t, i_t) \\
\frac{di_t}{dt} =& \lambda_1(s_t, i_t) - (\mu_1 + \lambda_2) i_t - \lambda_3\left(i_t, \int_{\mathbb{R}_+} \psi(a)\rho_t(a)da\right) \\
\frac{\partial \rho_t}{\partial t}(a) =& -\partial_a \rho_t(a) \\
\rho_t(0) =& \lambda_2 i_t + \lambda_3\left(i_t, \int_{\mathbb{R}_+} \psi(a)\rho_t(a)da\right).
\end{aligned}$$

We have a Central Limit Theorem for this convergence.

Simulations

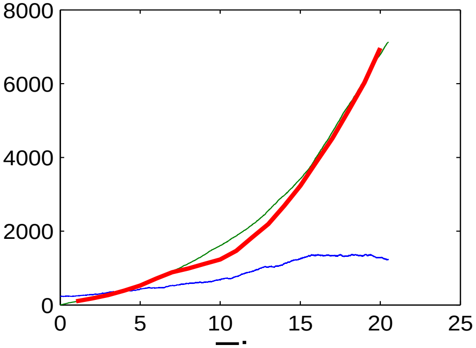


Figure: *Green: simulated cumulated number of detected individuals. Blue: simulated cumulated number of infectious individuals. Red: Observed cumulated number of detected individuals.*

Maximum likelihood estimation

Aim: estimation of λ_2 and $\lambda_3(S, I)$

Complete likelihood

$$\mathcal{L}_T^{(n)}(\theta) = e^{nT - \int_{u=0}^{T} (n\lambda_0 + \mu_0 n s_u^{(n)} + n\lambda_1(s_u^{(n)}, i_u^{(n)}) + (\mu_1 n + \lambda_2(\theta) n) i_u^{(n)} + n\lambda_3(i_u^{(n)}, \langle r_u^{(n)}, \psi\rangle, \theta)) du} \times \prod_{k=1}^{K_T^{(n)}} L_\theta(E_k, (s_{T_k}^{(n)}, i_{T_k}^{(n)}, r_{T_k}^{(n)}(da))),$$

where: $L_\theta(E, (s, i, r(da))) = \lambda_0^{\mathbf{1}_{\{E=0\}}} (\mu_0 s)^{\mathbf{1}_{\{E=1\}}} \lambda_1(s, i)^{\mathbf{1}_{\{E=2\}}} (\lambda_2(\theta) i)^{\mathbf{1}_{\{E=3\}}} \lambda_3(i, \langle r, \psi\rangle, \theta)^{\mathbf{1}_{\{E=4\}}} (\mu_1 i)^{\mathbf{1}_{\{E=5\}}}.$

Maximum likelihood estimator
$\hat{\theta}_n = \arg\max_{\theta \in \Theta} \log \mathcal{L}_T^{(n)}(\theta) = \arg\max_{\theta \in \Theta} l_T^{(n)}(\theta).$

Limit theorems for the MLE

For all $T > 0$ and any $(\theta^*, \theta) \in \Theta^2$, as $n \to \infty$, we have the following convergence in $\mathbb{P}_{\theta^*}$-probability,

$$\frac{1}{n}\{l_T^{(n)}(\theta^*) - l_T^{(n)}(\theta)\} \to K(\theta, \theta^*),$$

$$\text{where: } K(\theta,\theta^*) = \int_{t=0}^{T} \lambda_2(\theta^*) i_t^* \Phi\left(\frac{\lambda_2(\theta^*)}{\lambda_2(\theta)}\right) dt + \int_{t=0}^{T} \lambda_3(i_t^*, \langle r_t^*, \phi\rangle, \theta^*) \Phi\left(\frac{\lambda_3(i_t^*, \langle r_t^*, \phi\rangle, \theta^*)}{\lambda_3(i_t^*, \langle r_t^*, \phi\rangle, \theta)}\right) dt,$$

where $\Phi(x) = \log(x) + 1/x - 1$ and where $(s^*, i^*, r^*(da))$ is the solution of the PDE system with rate functions associated with θ^*.

Law of large numbers: Under identifiability and regularity assumptions, if the parameter space Θ is compact, the MLE is consistent:

$$\lim_{n\to\infty} \hat{\theta}_n = \theta^*, \text{ in } \mathbb{P}_{\theta^*} - \text{probability}.$$

Asymptotic normality: Under the proper regularity assumptions:

$$\sqrt{n}(\hat{\theta}_n - \theta^*) \Rightarrow \mathcal{N}(0, \mathcal{I}_{\theta^*}^{-1}), \text{ as } n \to \infty.$$

where the *Fisher information matrix* is given by:

$$\mathcal{I}_\theta = -\int_{u=0}^{T} \Big\{ \mathcal{H}_\theta \lambda_2(\theta) i_u^* \left(\frac{\lambda_2(\theta^*)}{\lambda_2(\theta)} - 1 \right) - \nabla_\theta \lambda_2(\theta) \cdot^t \nabla_\theta \lambda_2(\theta) \frac{\lambda_2(\theta^*) i_u^*}{\lambda_2(\theta)^2}$$
$$+ \mathcal{H}_\theta \lambda_3(i_u^*, \langle r_u^*, \psi \rangle, \theta) \left(\frac{\lambda_3(i_u^*, \langle r_u^*, \psi \rangle, \theta^*)}{\lambda_3(i_u^*, \langle r_u^*, \psi \rangle, \theta)} - 1 \right)$$
$$- \nabla_\theta \lambda_3(i_u^*, \langle r_u^*, \psi \rangle, \theta) \cdot^t \nabla_\theta \lambda_3(i_u^*, \langle r_u^*, \psi \rangle, \theta) \frac{\lambda_3(i_u^*, \langle r_u^*, \psi \rangle, \theta^*)}{\lambda_3(i_u^*, \langle r_u^*, \psi \rangle, \theta)^2} \Big\} du.$$

where$\mathcal{H}_\theta g$ denotes the hessian matrix of any twice differentiable function $\theta \in \Theta \mapsto g(\theta)$.

Examples

$$
\begin{aligned}
\text{Model (A):} \quad \lambda_3(i, \langle r, \psi \rangle) &= \lambda_3 \langle r, \psi \rangle, \\
\text{Model (B):} \quad \lambda_3(i, \langle r, \psi \rangle) &= \lambda_3 \frac{\langle r, \psi \rangle i}{\langle r, \psi \rangle + i}, \\
\text{Model (C):} \quad \lambda_3(i, \langle r, \psi \rangle) &= \lambda_3 \langle r, \psi \rangle i.
\end{aligned}
$$

Here $\theta = (\lambda_2, \lambda_3) \in \Theta \subset \mathbb{R}_+^{*2}$, and the true parameter is denoted $\theta^* = (\lambda_2^*, \lambda_3^*)$.

$$
\widehat{\lambda}_2^{(n)} = \frac{\text{number of detections by random screening}}{n \int_{v=0}^{T} i_v^{(n)} dv},
$$

Model (A):

$$
\widehat{\lambda}_3^{(n,A)} = \frac{\text{number of detections by contact tracing}}{n \int_0^T \langle r_v^{(n)}, \psi \rangle dv}.
$$

Model (B):

$$
\widehat{\lambda}_3^{(n,B)} = \frac{\text{number of detections by contact tracing}}{n \int_0^T \frac{i_v^{(n)} \langle r_v^{(n)}, \psi \rangle}{(i_v^{(n)} + \langle r_v^{(n)}, \psi \rangle)} dv}
$$

Model (C):

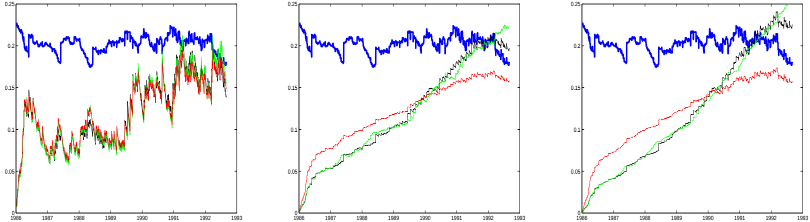
$$
\widehat{\lambda}_3^{(n,C)} = \frac{\text{number of detections by contact tracing}}{n \int_0^T i_v^{(n)} \langle r_v^{(n)}, \psi \rangle dv}.
$$

Results

$\psi(a) = e^{-ca}$

model	parameter	estimated value	asymptotic std	log-likelihood
	λ_2	$9.57\,10^{-4}$	$4.34\,10^{-5}$	
		$c = 10^{-2}$		
(A)	λ_3	$3.90\,10^{-3}$	$2.30\,10^{-4}$	-2115
(B)	λ_3	$4.50\,10^{-3}$	$2.67\,10^{-4}$	-2119
(C)	λ_3	$1.85\,10^{-5}$	$1.09\,10^{-6}$	-2117
		$c = 10^{-3}$		
(A)	λ_3	$6.56\,10^{-4}$	$3.87\,10^{-5}$	-2138
(B)	λ_3	$1.30\,10^{-3}$	$7.72\,10^{-5}$	-2143
(C)	λ_3	$3.11\,10^{-6}$	$1.83\,10^{-7}$	-2140
		$c = 3\,10^{-4}$		
(A)	λ_3	$4.37\,10^{-4}$	$2.58\,10^{-5}$	-2144
(B)	λ_3	$1.10\,10^{-3}$	$6.54\,10^{-5}$	-2146
(C)	λ_3	$2.07\,10^{-6}$	$1.22\,10^{-7}$	-2147

Table: *Estimated parameters and asymptotic standard deviations.*



Evolution of the instantaneous detection rates $t \mapsto \widehat{\lambda}_2^{(n)} i_t^{(n)}$ (in thick blue line) and $t \mapsto \widehat{\lambda}_3^{(n)}(i_t^{(n)}, \langle r_t^{(n)}, \psi\rangle)$ (in green (resp. red and black) line for Model (A) (resp. (B) and (C))). Left: $c = 10^{-2}$, middle: $c = 10^{-3}$, right: $c = 3\,10^{-4}$

Open questions

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- Why does the I class is getting older?
- Use the noisy information at the individual level
  Form networks based on incompletely observed random graphs