Probabilistic, mean-field and transport PDE models of Covid-19 epidemics, with variable contact rates and user mobility

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1st part: done jointly with the following physicians of the SAMU of AP-HP and applied mathematicians from INRIA and École polytechnique: Stéphane Gaubert, Xavier Allamigeon, Marin Boyet, Baptiste Colin, Théotime Grohens, Laurent Massoulié, David P. Parsons, Frédéric Adnete, Érick Chanzy, Laurent Goix, Frédéric Lapostolle, Éric Lecarpentier, Christophe Leroy, Thomas Loeb, Jean-Sébastien Marx, Caroline Télion, Laurent Tréluyer, and Pierre Carli.
2nd part: done jointly with Luca Ganassali, Stéphane Gaubert, and Laurent Massoulié.

How it started

- Since 2014, Collaboration of part of the team (Stéphane Gaubert, Xavier Allamigeon) with the direction de programme of Plate Forme d'Appels d'Urgence (PFAU), at Préfecture de Police (BSPP and DSAP), analysis / dimensioning of the new two-level organization answering calls to 17, 18 and 112 in a unified manner. With the help of Polytechnique students.
- Since Jan. 2019, "Étude d'interopérabilité" between PFAU and the SAMU Centers 15 of the Paris area, followed by a collaboration with SAMU 75, 92, 93 and 94, of AP-HP, on the dimensioning of these centers.
- From 13/03/20: Crisis dimensioning of the emergency call centers ("Centre 15") – "Services d'aide médicale urgente" (SAMU) – of the central Paris Area (SAMU 75, 92, 93 and 94).

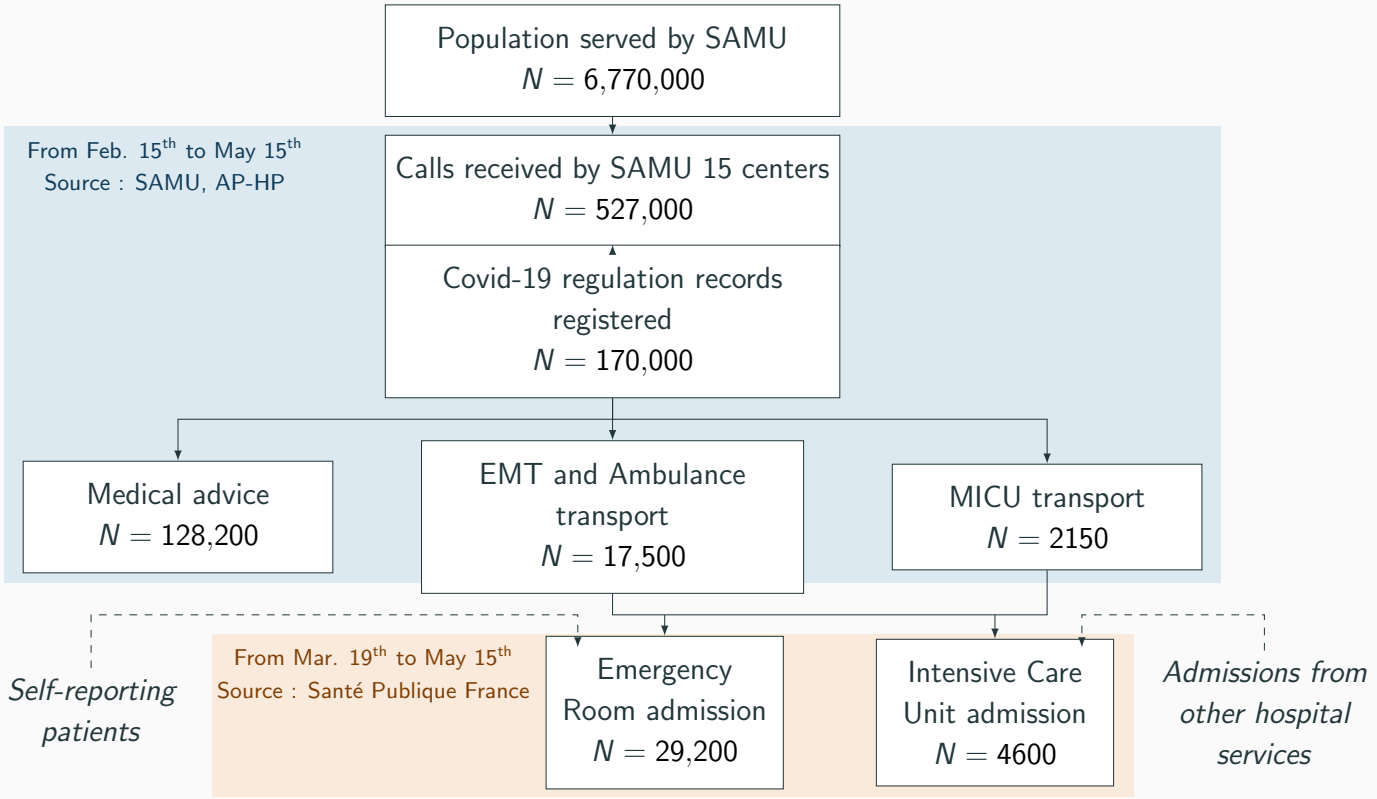
Crisis work from 13/03 to June, 2020:

- Dimensioning of the SAMU 75, 92, 93 and 94.
- Construction of early epidemic indicators, based on the analysis of SAMU patient records ("dossiers de régulation médicale")
- Used to provide predictions with confidence regions.
- Building block of a cartography of the epidemic.
- SFR, Orange, Enedis provided aggregated data allowing to take into account the influence of mobility in the analysis of the epidemics.

Scientific work:

- Analytic results: L_1 approximation, Perron-Frobenius theory, ideas of tropical geometry.
- Understanding the evolution of the epidemic in the Paris area.
- Branching processes models and simulations in order to estimate the parameters.

Indicators of the epidemic evolution based on SAMU patient records



Flowchart: from calls to Center 15 to admission in hospital units during the begining of the Covid-19 crisis. The numbers are summed over the departments 75, 92, 93 and 94 of the Paris area.

Classification of calls, Centre 15

Since January 20th 2020 all calls and patient records with a suspicion of Covid-19 were flagged in the information system of each Center-15 and a daily automated activity report was produced.

In order to develop a mathematical analysis of the evolution of the epidemic, we classified the calls tagged as Covid-19 in three categories, according to the decision taken:

1: calls resulting in the dispatch of a Mobile Intensive Care Unit;

2: calls resulting in the dispatch of an ambulance staffed with Emergency Medical Technicians (EMT), including: Croix Rouge, Ordre de Malte, BSPP (Paris firemen, only calls to number 15, not 17-112-18, are counted), private ambulances ...

3: calls resulting in no dispatch decision. Such calls correspond to different forms of medical advice (recommendation to consult a GP, specific instructions to the patient, etc.).

Epidemic observables – SAMU

All numbers apply only to Covid-19 calls.

- $Y_{\mathrm{MICU}}(t)$, number of MICU (SMUR) dispatches
- $Y_{\mathrm{EMT}}(t)$, number of dispatches of EMT (ambulances)
- $Y_{\mathrm{adv}}(t)$, number of calls without vehicle dispatch.

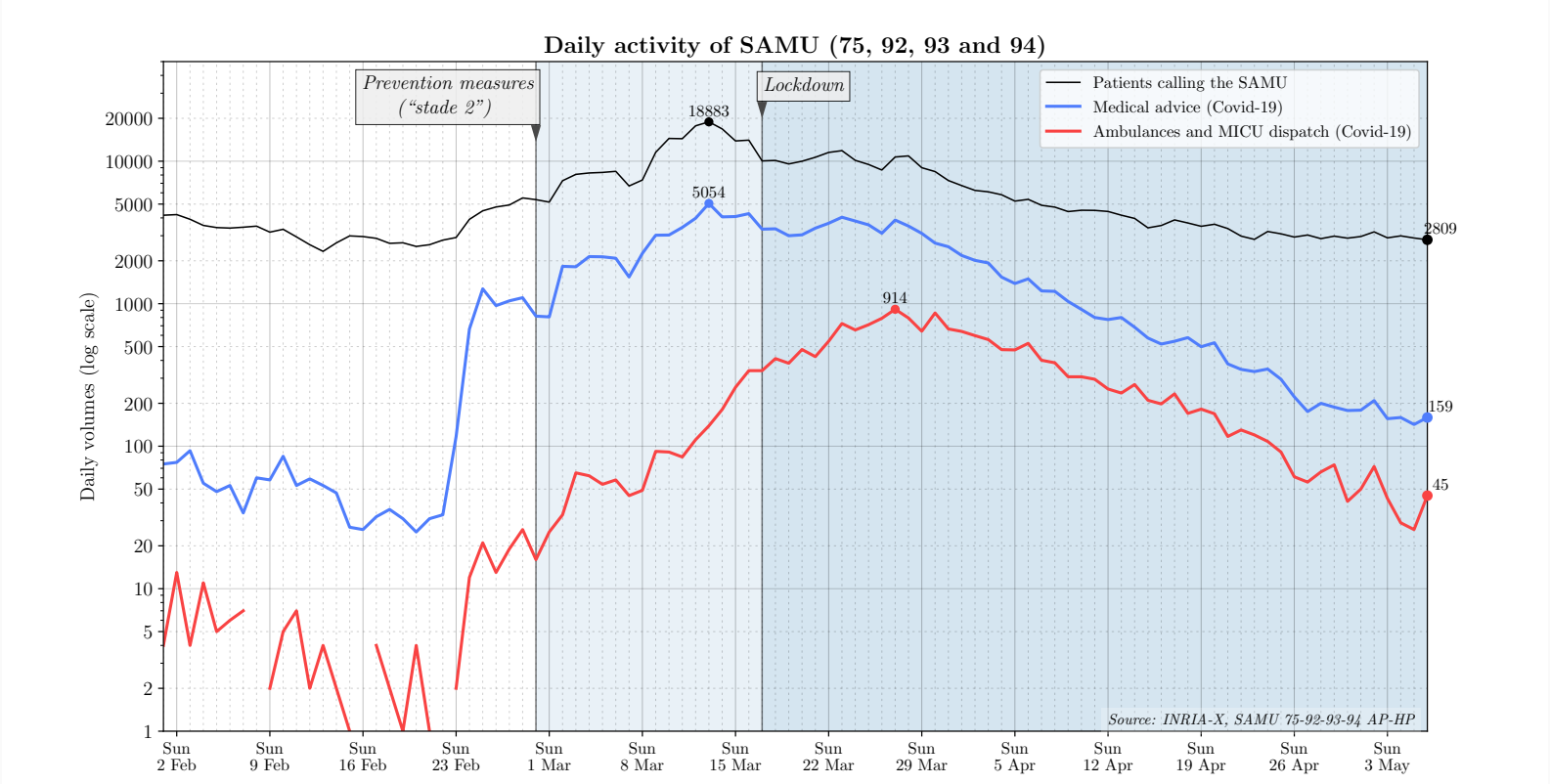
The term *observables* contrasts with $C(t)$, the actual number of *new contaminations on day* t, which cannot be measured.

Observables are *delayed*:

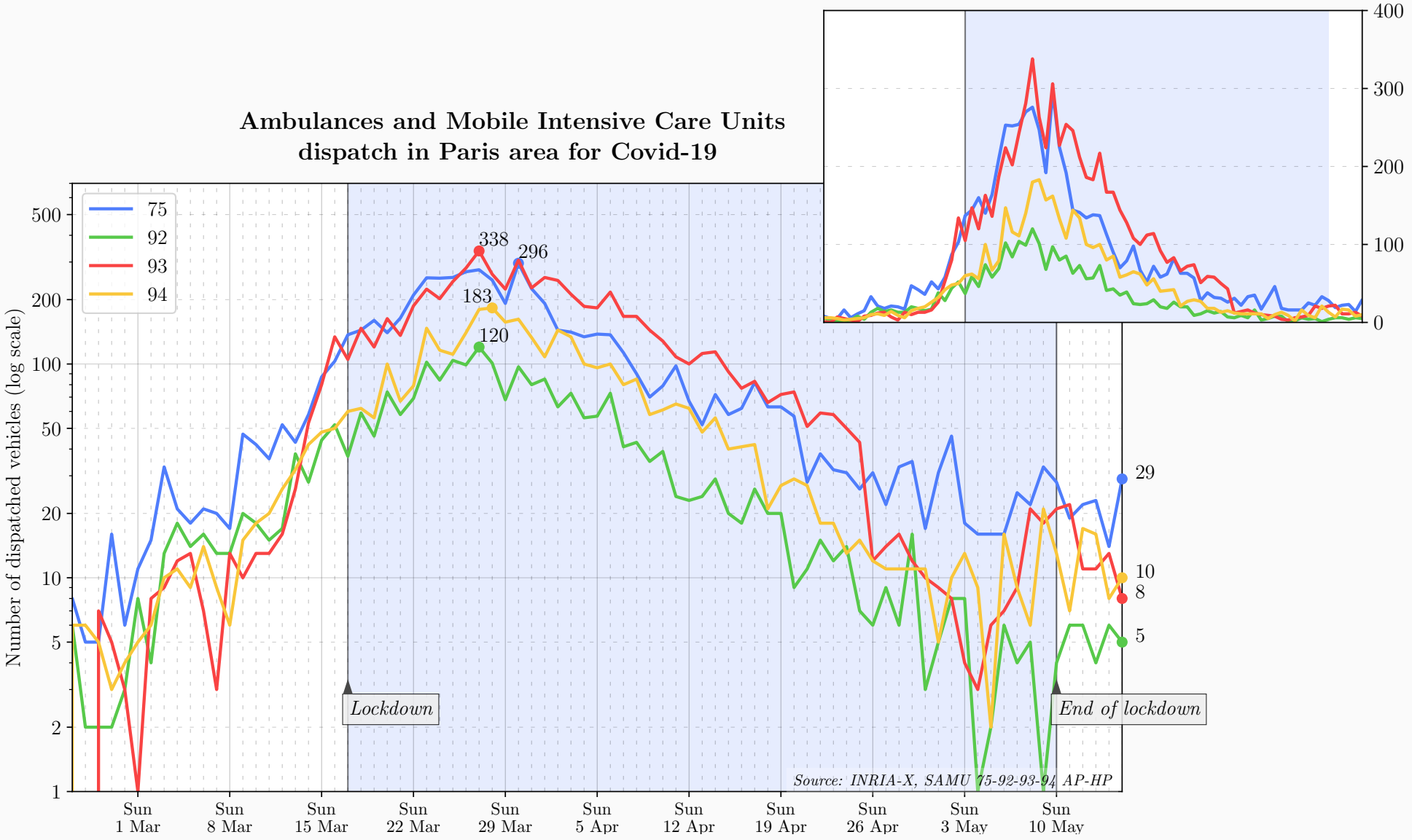
$$Y_{\mathrm{MICU}}(t) = \pi_{\mathrm{MICU}}\, C(t - \tau_{\mathrm{MICU}})$$

$\pi_{\mathrm{MICU}} =$ proportion of patients who will need a MICU dispatch, and τ_{MICU} delay between contamination and severe aggravation.

There are other relevant (non-SAMU) epidemic observables, e.g., home visits of GP (SOS médecins), ICU admissions, and deceases, with different proportions and delays.



Number of patients calling Center-15, of MICU and ambulances dispatch for Covid-19 suspicion in the Paris area (departments 75, 92, 93 and 94)


Ambulances and Mobile Intensive Care Units
dispatch in Paris area for Covid-19
Number of dispatched vehicles (log scale)
75
92
93
94
338
296
183
120
29
10
8
5
Lockdown
End of lockdown
Source: INRIA-X, SAMU 75-92-93-94 AP-HP
Sun 1 Mar
Sun 8 Mar
Sun 15 Mar
Sun 22 Mar
Sun 29 Mar
Sun 5 Apr
Sun 12 Apr
Sun 19 Apr
Sun 26 Apr
Sun 3 May
Sun 10 May

Models of COVID-19 epidemics

Models of COVID-19 epidemics

- SEIR ODE
- Multi-compartment transport PDE model
- Discrete time mean-field model
- Multi-type Branching process model

SEIR ODE

Four compartments: "susceptible" (S), "exposed" but not yet infectious (E), "infectious" (I), and finally, "removed" from the contamination chain (R), either by recovery or death.

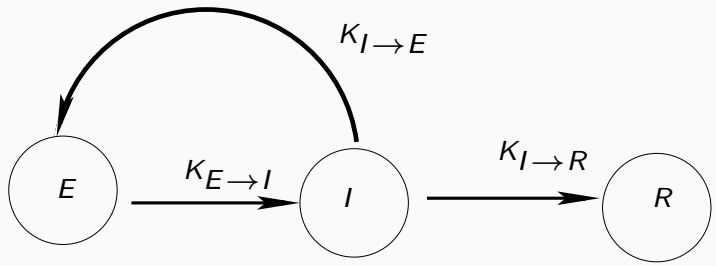
$$\dot{S} = -\frac{S}{N} K_{I\to E} I \ ,$$

$$\dot{E} = \frac{S}{N} K_{I\to E} I - K_{E\to I} E \ ,$$

$$\dot{I} = K_{E\to I} E - K_{I\to R} I \ ,$$

$$\dot{R} = K_{I\to R} I \ ,$$

$N = S + E + I + R$ total population (invariant) .



A refinement of the SEIR model splits the S and E compartments in sub-compartments corresponding to different age classes. It includes a contact matrix, providing differentiated age-dependent infectiosity rates (e.g., Crepey et al.).

Another refinement includes additional compartments, representing, for instance, patients at hospital (e.g., Colizza et al.).

Covid-19 is characterized by significant delays

ODE SEIR models assume exponential distribution times in compartments. In particular, the transitions $S \to E$ and $E \to I$ can be arbitrarily fast, with positive probability.

This leads to a potentially coarse approximation in the case of Covid-19.

- The median incubation period of Covid-19 is estimated of 5.1 days, with a 95% confidence interval of 4.5-5.8, and 95% of patients in the range [2.2, 11.5] (Lauer et al., Annals. Int. Med. 2020)
- Compare with a median incubation time of 1.4 days for toxigenic Cholera (Azman et al, J. Infect., 2013) or with an interval of 36 hours between infection by pneumonic plague and first symptoms in Brown Norway rats, with rapid deaths, 2-4 days after infection (Anderson et al., Am. J. Path., 2009).

Multi-compartment transport PDE model

Each compartment $\tau \in \{E, I\}$ is decomposed in ages: $n_\tau(x,t)$ is the density of the number of individuals which are in compartment τ for x time units before time t, then $\tau(t) = \int_0^\infty n_\tau(x,t)\,\mathrm{d}x$.

$$\frac{\mathrm{d}S}{\mathrm{d}t} = -\frac{S(t)}{N(t)} \int_0^\infty K_{I\to E}(x,t) n_I(x,t)\,\mathrm{d}x \ ,$$

$$n_E(0,t) = \frac{S(t)}{N(t)} \int_0^\infty K_{I\to E}(x,t) n_I(x,t)\,\mathrm{d}x \ ,$$

$$\frac{\partial n_E}{\partial t}(x,t) + \frac{\partial n_E}{\partial x}(x,t) + K_{E\to I}(x,t) n_E(x,t) = 0\,, \quad \text{for } x > 0 \ ,$$

$$n_I(0,t) = \int_0^\infty K_{E\to I}(x,t) n_E(x,t)\,\mathrm{d}x \ ,$$

$$\frac{\partial n_I}{\partial t}(x,t) + \frac{\partial n_I}{\partial x}(x,t) + K_{I\to R}(x,t) n_I(x,t) = 0\,, \quad \text{for } x > 0 \ ,$$

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \int_0^\infty K_{I\to R}(x,t) n_I(x,t)\,\mathrm{d}x \ .$$

Initial condition at time 0, $S(0)$, $n_E(\cdot,0)$, $n_I(\cdot,0)$ and $R(0)$ is given.

$K_{I\to E}$, $K_{E\to I}$ and $K_{I\to R}$ are given *nonnegative* functions.

Linearized PDE system

For epidemics in their early stages, the majority of the population is susceptible, $S(t)/N(t) \simeq 1$, and so, we are reduced to the following linear system:

$$
\begin{aligned}
n_E(0,t) &= \int_0^\infty K_{I\to E}(x,t) n_I(x,t)\,\mathrm{d}x \ , \\
\frac{\partial n_E}{\partial t}(x,t) &+ \frac{\partial n_E}{\partial x}(x,t) + K_{E\to I}(x,t) n_E(x,t) = 0 \,, \quad \text{for } x > 0 \ , \\
n_I(0,t) &= \int_0^\infty K_{E\to I}(x,t) n_E(x,t)\,\mathrm{d}x \ , \\
\frac{\partial n_I}{\partial t}(x,t) &+ \frac{\partial n_I}{\partial x}(x,t) + K_{I\to R}(x,t) n_I(x,t) = 0 \,, \quad \text{for } x > 0 \ , \\
\frac{\mathrm{d}R}{\mathrm{d}t} &= \int_0^\infty K_{I\to R}(x,t) n_I(x,t)\,\mathrm{d}x \ .
\end{aligned}
$$

Initial condition at time 0, $S(0)$, $n_E(\cdot,0)$, $n_I(\cdot,0)$ and $R(0)$ is given.

$K_{I\to E}$, $K_{E\to I}$ and $K_{I\to R}$ are given *nonnegative* functions.

This is a multi-compartment version of the model introduced by Kermack and McKendrick (1927), to analyze the Plague epidemy of Dec. 1905 – July 1906 in Mumbai.

Von Forster studied a similar model.

Recent work: Perthame's monography, Mischler, Lepoutre, ...

When the functions $K_{I\to E}, K_{E\to I}$ and $K_{I\to R}$ are constant, S, E, I, R satisfy the SEIR ODE.

When $K_{E\to I}$ and $K_{I\to R}$ are constant, and $K_{I\to E}$ only depend on time, this is a time dependent SEIR ODE, see (Chen, Lu, Chang, Liu, 2020) for a time dependent SIR model.

When the epidemic does not change (no mutation), we can assume:

- The rates $K_{E\to I}(x,t) = K_{E\to I}(x) \geqslant 0$ and $K_{I\to R}(x,t) = K_{I\to R}(x) \geqslant 0$ are measurable functions of x, independent of time.
- The rate $K_{I\to E}$ has the product form

$$K_{I\to E}(x,t) = \mu(t)\psi(x) \ .$$

- $\psi \geqslant 0$ is a fixed measurable function of x, not *a.e.* zero (infectiosity rate).
- $\mu(t) > 0$ represents the control of the epidemic by sanitary measures (social distancing, wearing masks, closing schools, lockdown, etc.).
- Bounded ages in compartments: there is a maximal "age" x_E^* of an individual in the exposed state: the essential support of $K_{E\to I}$ is included in $[0, x_E^*]$;
- Similarly, there is a maximal "age" x_I^* of an individual in the infectious state: the essential support of $K_{I\to R}$ is included in $[0, x_I^*]$.
- Bounded rates: the functions $K_{E\to I}$ on $[0, x_E^*]$, and ψ and $K_{I\to R}$, on $[0, x_I^*]$, are bounded.
- The point x_I^* is the maximum of the essential support of the function ψ.

Note that if $\psi(x) = 0$ for $x \in (x_I^* - \epsilon, x_I^*)$, individuals in the I compartment older than $x_I^* - \epsilon$ will not participate any to the contamination chain, breaking the interpretation of R as the number of *all* the removed individuals.

Multi-compartment transport PDE model with bounded ages

$$
\begin{aligned}
n_E(0,t) &= \int_0^{x_I^*} \mu(t)\psi(x) n_I(x,t)\,\mathrm{d}x\,,\\
\frac{\partial n_E}{\partial t}(x,t) + \frac{\partial n_E}{\partial x}(x,t) &+ K_{E\to I}(x) n_E(x,t) = 0\,, \quad \text{for } 0 < x < x_E^*\,,\\
n_I(0,t) &= \int_0^{x_E^*} K_{E\to I}(x) n_E(x,t)\,\mathrm{d}x + n_E(x_E^*,t)\,,\\
\frac{\partial n_I}{\partial t}(x,t) + \frac{\partial n_I}{\partial x}(x,t) &+ K_{I\to R}(x) n_I(x,t) = 0\,, \quad \text{for } 0 < x < x_I^*\,,\\
\frac{\mathrm{d}R}{\mathrm{d}t}(t) &= \int_0^{x_I^*} K_{I\to R}(x) n_I(x,t)\mathrm{d}x + n_I(x_I^*,t)\ .
\end{aligned}
$$

Order preserving PDE

Systems of PDE of this nature have been studied by Michel, Mischler and Perthame. Arguing as in Perthame's monography:

- Unique solution in the distribution sense $n := (n_E, n_I)$ with $n_E \in \mathcal{C}(\mathbb{R}_{\geqslant 0}, L^1([0, x_E^*]))$ and $n_I \in \mathcal{C}(\mathbb{R}_{\geqslant 0}, L^1([0, x_I^*]))$.
- Time evolution linear operators $(T_{s,t})_{t \geqslant s \geqslant 0}$, $t \geqslant s$, acting on the space $L^1([0, x_E^*]) \times L^1([0, x_I^*])$, mapping $n(\cdot, s) := (n_E(\cdot, s), n_I(\cdot, s))$ to $n(\cdot, t) := (n_E(\cdot, t), n_I(\cdot, t))$.
- The operator $T_{s,t}$ are order preserving:

$$(n_c^1(x, s) \leqslant n_c^2(x, s),\ \forall x \geqslant 0, \forall c \in \{E, I\}) \\ \Longrightarrow\ (n_c^1(x, t) \leqslant n_c^2(x, t),\ \forall x \geqslant 0, \forall c \in \{E, I\})$$

Perron-Frobenius Eigenproblem for Transport PDE

Proposition

Suppose the control $\mu(t)$ is constant and positive. Then $T_{s,t} = S_{t-s}$ and

1. There exists $\lambda \in \mathbb{R}$, and $\bar{n} := (\bar{n}_I, \bar{n}_E)$, where the functions $\bar{n}_E : [0, x_E^*] \to \mathbb{R}_+$ and $\bar{n}_I : [0, x_I^*] \to \mathbb{R}_+$ are continuous and positive, such that

$$n(x,t) = e^{\lambda t}\bar{n}(x)$$

   is solution of the linear PDE system.
2. λ and $\bar{n}$ are solution of a stationary PDE system: the *Perron-Frobenius eigenproblem*.
3. $\bar{n} := (\bar{n}_I(\cdot), \bar{n}_E(\cdot))$ is a nonnegative eigenvector, and λ is an eigenvalue.
4. The eigenvalue λ is unique, and the eigenvector $\bar{n}$ satisfying the latter conditions is unique up to a multiplicative constant.

Proof as in Perthame's monography (semiexplicit formula for the eigenvector in terms of characteristics).

Universality of the log-rate of epidemic observables

An epidemic observable will be of the form

$$Y_\kappa(t) = \varphi(n(\cdot, t)) := \int_0^{x_I^*} n_I(x, t)\, \mathrm{d}\kappa(x) \ , \tag{1}$$

where $\mathrm{d}\kappa(x)$ is a nonnegative nonzero Borel measure.

Proposition

Suppose that for some $T > 0$, there exist positive constants α, β such that $\alpha\bar{n} \leqslant n(\cdot, T) \leqslant \beta\bar{n}$. Then, for all epidemic observables of the form (1), the map $t \mapsto \log Y_\kappa(t) - \lambda t$ is bounded. A fortiori,

$$\lim_{t\to\infty} \frac{1}{t} \log Y_\kappa(t) = \lambda \ .$$

Hilbert's projective metric

- Consider the Hilbert's projective metric d_H on the positive cone of $L^1([0, x_E^*]) \times L^1([0, x_I^*])$:

$$d_H(v, w) = \log \inf \left\{ \frac{\beta}{\alpha} : \alpha, \beta > 0,\ \alpha v \leqslant w \leqslant \beta v \right\} .$$

- The semigroup operators S_t are nonexpansive for the Hilbert's projective metric.
- Let $w = (w_E, w_I) \in L^1([0, x_E^*]) \times L^1([0, x_I^*])$, be such that

$$\alpha \bar{n} \leqslant w \leqslant \beta \bar{n}$$

for some $\alpha, \beta > 0$. Then,

$$\alpha \exp(\lambda t) \bar{n} \leqslant S_t w \leqslant \beta \exp(\lambda t) \bar{n}, \qquad \text{for all } t \geqslant 0 .$$

Discrete time mean-field model

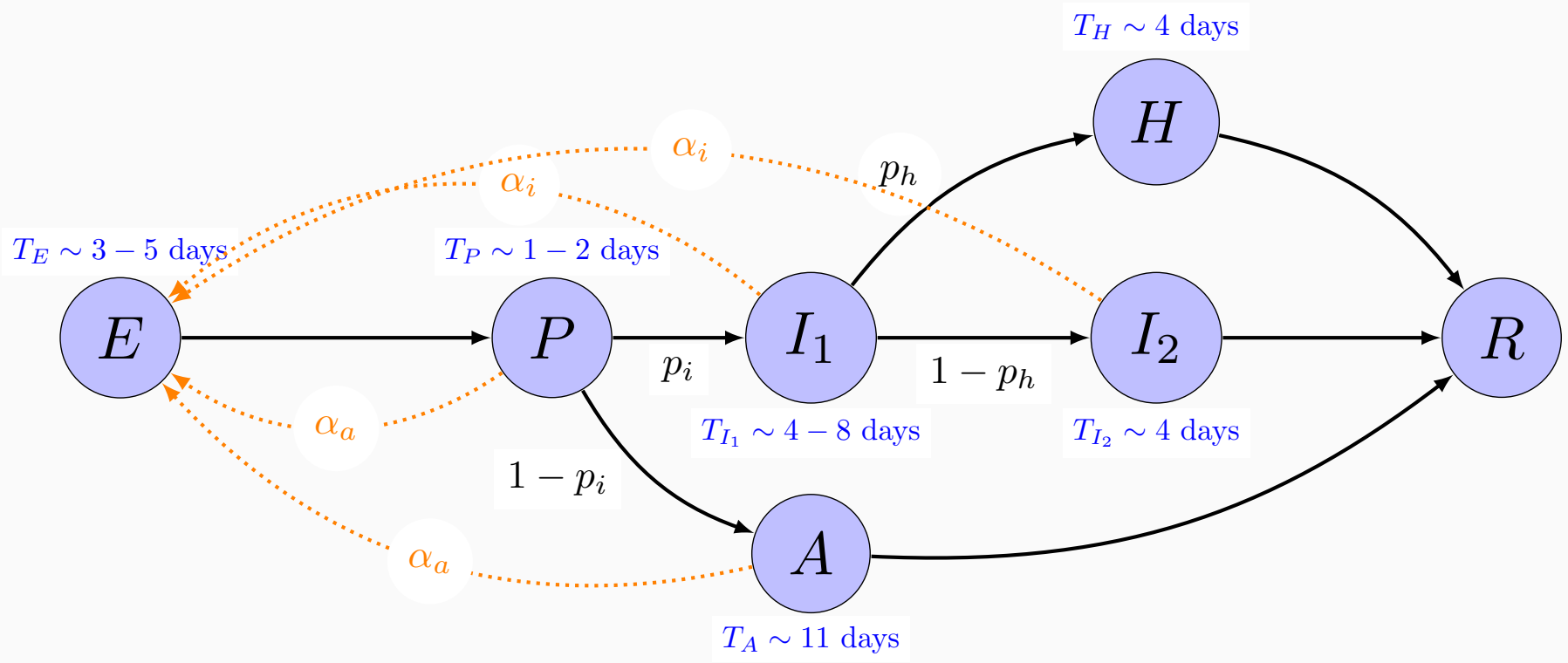
Discrete time versions of the PDE systems lead to systems of equations of the form

$$x(t+1) = Mx(t)$$

where

- discrete time t may correspond to days, hours,...
- $x(t)$ is a finite dimensional state vector, representing the mean number of individuals at time t in each compartment and age in the compartment.
- M is an irreducible, nonnegative matrix.
- An observable $y(t)$ is for instance one coordinate of $x(t)$.

In (M.A, Ganassali, Gaubert, Massoulié, 2020), we considered more compartments:



where the compartments are: E is for *exposed*; P for *prodromic*; A for *infectious asymptomatic*; I_1 for *phase 1 infectious symptomatic*; H for *hospitalized*; I_2 for (non-hospitalized) *phase 2 infectious symptomatic*; and R for *removed* from the contamination chain.

For each compartment $\tau \in \{E, P, I_1, I_2, A, H\}$

- $p_\tau(d)$ is the probability that phase τ lasts d days;
- $r_\tau(d)$ is the probability that phase τ will end on the following day, given that it has lasted d days. So $r_\tau(d) = \frac{p_\tau(d)}{\sum_{\delta \geqslant d} p_\tau(\delta)}$ if $\sum_{\delta=1}^{d} p_\tau(\delta) > 0$.

Using available statistics, we take

- $p_E(d) = 1/3$ for $d \in \{3, 4, 5\}$ and $p_E(d) = 0$ otherwise,
- $p_P(1) = p_P(2) = 1/2$ and $p_P(d) = 0$ otherwise,
- $p_{I_1}(d) = 1/3$ for $d \in \{5, 6, 7\}$ and $p_{I_1}(d) = 0$ otherwise,
- $p_{I_2}(d) = 1$ for $d = 4$ and $p_{I_2}(d) = 0$ otherwise,
- $p_A(d) = 1$ for $d = 11$ and $p_A(d) = 0$ otherwise.
- $p_i = 0.7$ for the probability that previously exposed individual becomes symptomatic at end of incubation.
- $p_h = 0.05$ for the probability that previously phase 1 infectious individual develops aggravated form at end of phase 1.

To simplify the model, one may also assume that all contact rates are equal: $\alpha_a = \alpha_i = \alpha$.

For each compartment $\tau \in \{E, P, I_1, I_2, A, H\}$, $x_{\tau,d}$ is the mean number of individuals in phase τ, having spent d days in this phase.

x is the vector of all the possible $x_{\tau,d}$ (except for $\tau = H$, for which we consider only one age $d = 1$).

The matrix M is determined by the dynamics $x(t+1) = Mx(t)$ with:

$$
\begin{aligned}
x_{\tau,d+1}(t+1) &= x_{\tau,d}(t)(1 - r_\tau(d)), \quad \forall \tau \in \{E, P, I_1, I_2, A\}\,,\ 1 \leqslant d \leqslant h-1,\\
x_{E,1}(t+1) &= \sum_{\delta>0} \left[\alpha_i(x_{I_1,\delta} + x_{I_2,\delta})(t) + \alpha_a(x_{A,\delta} + x_{P,\delta})(t)\right],\\
x_{P,1}(t+1) &= \sum_{\delta>0} x_{E,\delta}(t) r_E(\delta),\\
x_{I_1,1}(t+1) &= p_i \sum_{\delta>0} x_{P,\delta}(t) r_P(\delta),\\
x_{A,1}(t+1) &= (1-p_i) \sum_{\delta>0} x_{P,\delta}(t) r_P(\delta),\\
x_{I_2,1}(t+1) &= (1-p_h) \sum_{\delta>0} x_{I_1,\delta}(t) r_{I_1}(\delta),\\
x_H(t+1) &= p_h \sum_{\delta>0} x_{I_1,\delta}(t) r_{I_1}(\delta).
\end{aligned}
$$

An epidemic observable is $x_H(t)$.

Multi-type Branching process model

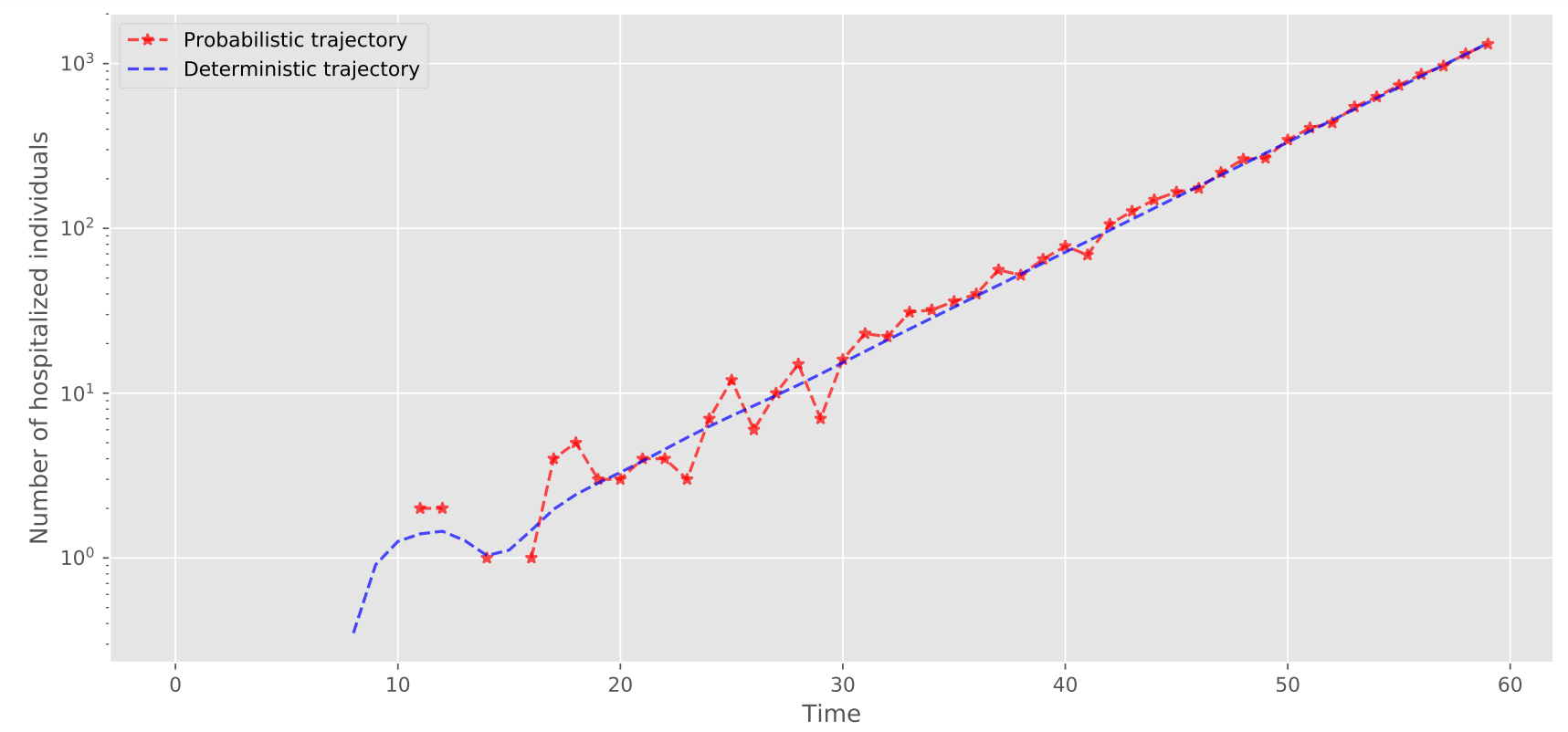
Let $X(t) = (X_{\tau,d}(t))$ be the random number of individuals in each compartment τ and age d at time t. Assume that, conditioning to $X(t)$, we have

$$
\begin{aligned}
X_{\tau,d+1}(t+1) &\sim \mathcal{B}\left(X_{\tau,d}(t), 1 - r_\tau(d)\right), \quad \forall \tau \in \{E, P, I_1, I_2, A\}, \ 1 \leqslant d \leqslant h, \\
X_{E,1}(t+1) &\sim \mathcal{P}\left(\sum_{\delta>0} \left[\alpha_i (X_{I_1,\delta} + X_{I_2,\delta})(t) + \alpha_a (X_{A,\delta} + X_{P,\delta})(t)\right]\right), \\
X_{P,1}(t+1) &= \sum_{\delta>0} \left[X_{E,\delta}(t) - X_{E,\delta+1}(t+1)\right], \\
X_{I_1,1}(t+1) &\sim \mathcal{B}\left(\sum_{\delta>0} \left[X_{P,\delta}(t) - X_{P,\delta+1}(t+1)\right], p_i\right), \\
X_{A,1}(t+1) &= \sum_{\delta>0} \left[X_{P,\delta}(t) - X_{P,\delta+1}(t+1)\right] - X_{I_1,1}(t+1), \\
X_{I_2,1}(t+1) &\sim \mathcal{B}\left(\sum_{\delta>0} [X_{I_1,\delta}(t) - X_{I_1,\delta+1}(t+1)], 1 - p_h\right), \\
X_H(t+1) &= \sum_{\delta>0} \left[X_{I_1,\delta}(t) - X_{I_1,\delta+1}(t+1)\right] - X_{I_2,1}(t+1).
\end{aligned}
$$

This is a multi-type branching process, corresponding to the mean-field model in which the number of newly exposed individuals follows a Poisson distribution.

When, $\rho(M) > 1$, Kesten and Stigum proved that there is a random variable Z such that for large t, the state $X(t)$ renormalized by $\rho(M)^{-t}$ converges to Zu, where u is the Perron eigenvector of M.

The probabilistic model may be relevant when infected populations are not so large, or in sub-critical cases ($\rho(M) \leqslant 1$).



Newly hospitalized individuals ($X_H(t)$), during 60 days, with $p_i = 0.7$, $p_h = 0.05$, $\alpha_i = 0.4$, $\alpha_a = 0.3$, initialized with 200 individuals entering in E.

Piecewise linear approximation of the logarithm of epidemic observables

Modeling different stages of sanitary policies

- Assume that the rates μ (PDE model) or α (discrete time model) depend on time, due to sanitary measures.
- Assume that they are piecewise constants. Let $t_0 := 0 < t_1 < \cdots < t_{m-1}$ be the commutation instants. Convention: $t_m := +\infty$.
- m semigroups $S^i = (S^i_t)_{t \geqslant 0}$, for $i = 1, \ldots, m$, acting on $(V, \leqslant)$, a partially ordered Banach space (e.g., $V = L^1([0, x^*_E]) \times L^1([0, x^*_I])$ for the PDE or $V = \mathbb{R}^n$ for the discrete time model), representing the evolution of the population, in each of the phases of sanitary policy.
- State at time $t \in [t_j, t_{j+1})$:

$$v_t := S^{j+1}_{t-t_j} \circ S^j_{t_j - t_{j-1}} \circ \cdots \circ S^1_{t_1 - t_0}(v_0) \ .$$

- Assume that $(S^i_t)_{t \geqslant 0}$ are linear, bounded and order preserving.
- Consider observables that are nonnegative linear forms of the state and take their logarithm:

$$Y_t := \varphi(v_t) \quad y_t = \log(Y_t) \ ,$$

where $\varphi \in V'$ takes nonnegative values on $V_{\geqslant 0}$.

Piecewise linear approximation of the log of observables

Theorem

Suppose that the each semigroup S^i is order preserving and has an eigenvector $u^i \geqslant 0$, with eigenvalue λ^i, $S^i_t u^i = \exp(\lambda^i t) u^i, \quad \forall t \geqslant 0$.

Suppose in addition that the initial condition v_0 and the eigenvectors $u^1, \dots, u^m$ are such that

$$\Delta = d_H(v_0, u^1) + d_H(u^1, u^2) + \cdots + d_H(u^{m-1}, u^m) < +\infty \ ,$$

where d_H is the Hilbert's projective metric on $V_{\geqslant 0}$. (For instance they are all positive in the positive orthant, when $V = \mathbb{R}^n$.)

Then, there exists a constant γ such that the piecewise linear map $t \mapsto y_t^{\mathrm{trop}}$ defined, for $t \in [t_j, t_{j+1})$, by

$$y_t^{\mathrm{trop}} := \lambda_{j+1}(t - t_j) + \lambda_j(t_j - t_{j-1}) + \cdots + \lambda_1(t_1 - t_0) + \gamma \ ,$$

satisfies

$$|y_t - y_t^{\mathrm{trop}}| \leqslant \frac{\Delta}{2}, \qquad \forall t \geqslant 0 \ .$$

Best piecewise linear approximation

Given an epidemiologic observable $Y(t)$, approximate $\log Y(t)$ by a function

$$\mathcal{L}(t) := \min_{1 \leqslant j \leqslant \nu} (\lambda_j t + c_j)\,,$$

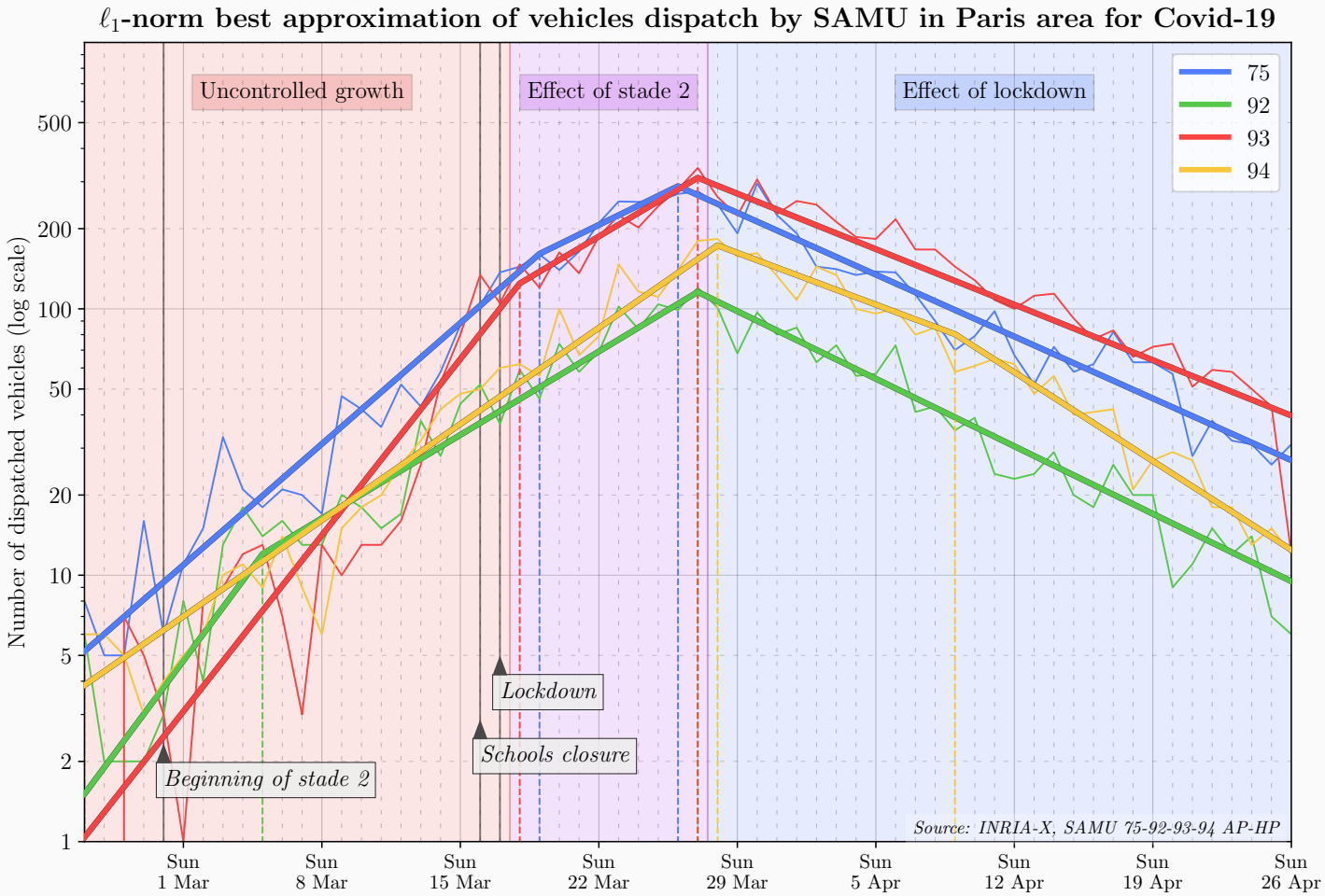
where ν is the number of phases with constant sanitary policy during the considered time period.

Minimize the ℓ_1 loss function

$$\sum_{t \in \mathcal{T}} |\mathcal{L}(t) - \log Y(t)|$$

Non-smooth & nonconvex problem. We initially used Nelder-Mead's derivative free algorithm, with an initial condition obtained by epidemiologic considerations. We use now a dynamic programming algorithm developed by Ayoub Foussoul $\rightarrow$ certified global optimum, up to a fixed precision of ϵ.

The effect of the successive sanitary measures



		Feb. 28th– Mar. 15th	Mar. 15th– Mar. 29th	Mar. 29th– April 24th
Doubling time (L2 log-regression)	75	5.9 d	9.8 d	-9.4 d
	92	4.9 d	10.6 d	-8.3 d
	93	4.2 d	8.5 d	-10.2 d
	94	4.6 d	6.9 d	-7.7 d

Understanding the evolution of the epidemic in the Paris area

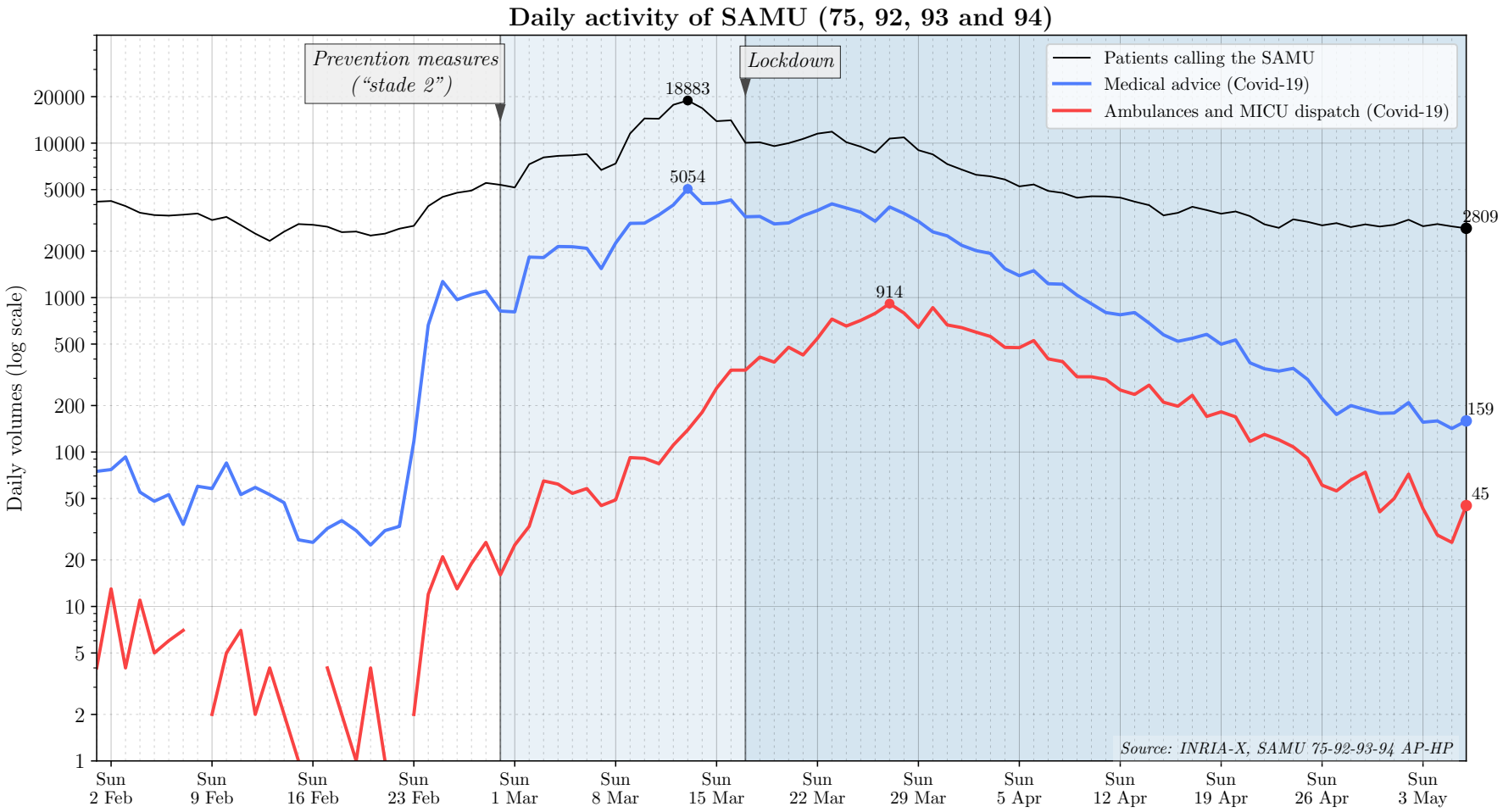
In the Paris area, between February and May 2020. We may distinguish the following phases of sanitary measures:

- Initial development of the epidemic, no general sanitary measures in the Paris area, until Feb 29th, first day of so-called "stade 2".
- Stade 2 (stage 2) measures: general instructions of social distancing given to the population (e.g., not shaking hands), ban on large gatherings. Moreover, some large companies created crisis committees, and decided to take more restrictive measures than the ones required by the authorities, including for instance banning meetings with more of 10 people, and banning business travels. Restrictive measures in companies were deployed gradually during the work week from March 2nd to March 6th.
- School closure on March 16th.
- Lockdown on March 17th. The lockdown ended on May 11th, throughout the country.

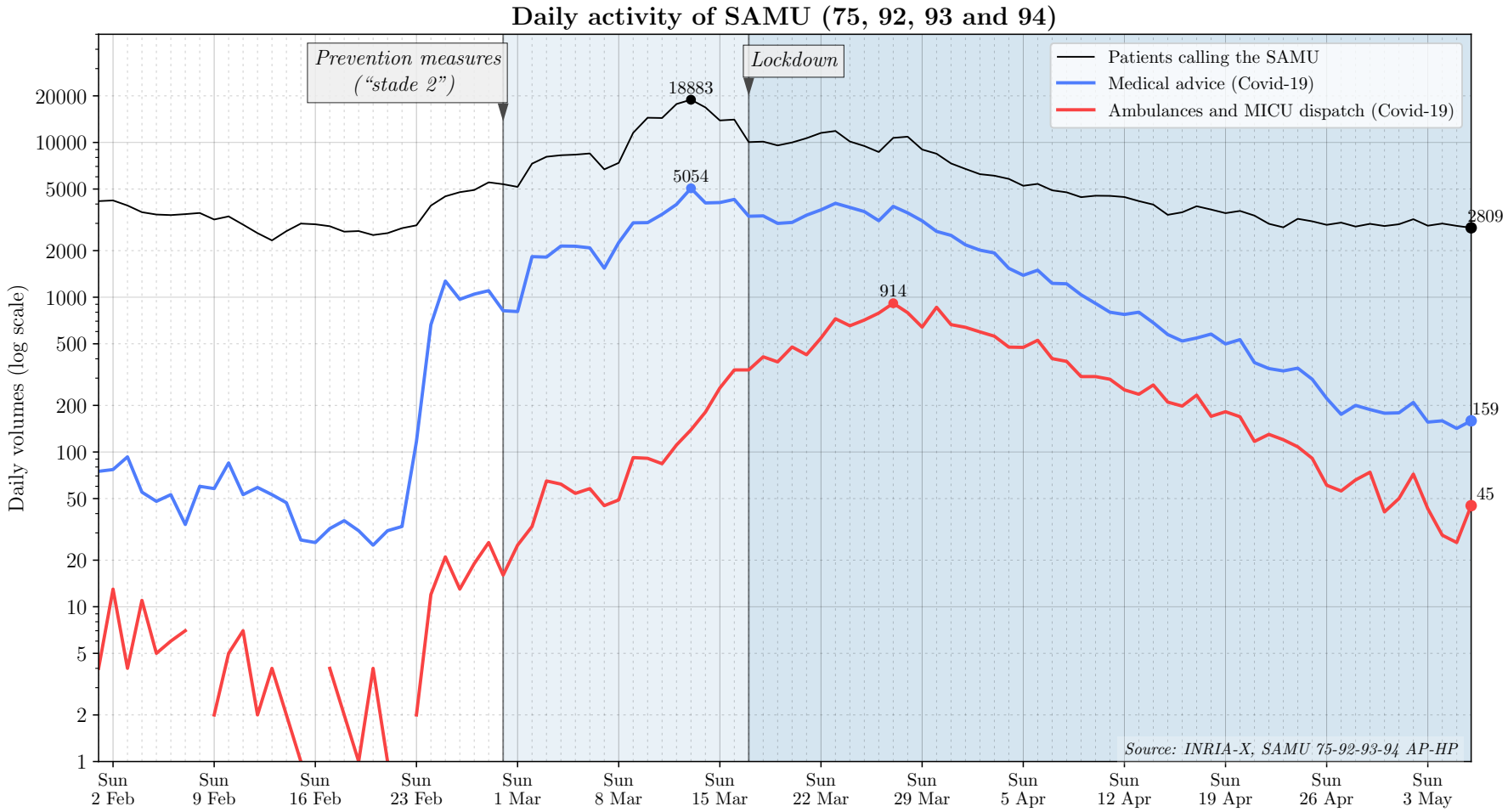
We will interpret the variations in the slope in the piecewise linear approximation of the logarithm of the number of ambulances and MICU dispatched, as the effect of sanitary measures.

Estimation of the delay between a sanitary measure and its impact on ambulance dispatch

- The latest breakpoint of the piecewise linear approximation of the 75 curve (in blue) arises on March 26^{th}, to be compared with March 30^{th} in the 93 (red curve). The dates of breakpoints in the 92 and 94 are intermediate.
- Given the first strong measure (closing of schools) was taken on March 16^{th}, we may evaluate the delay between a sanitary measure and its effect on the ambulances and MICU dispatch to be between 10 and 14 days. This corresponds to a delay between contamination and occurrence of severe symptoms.

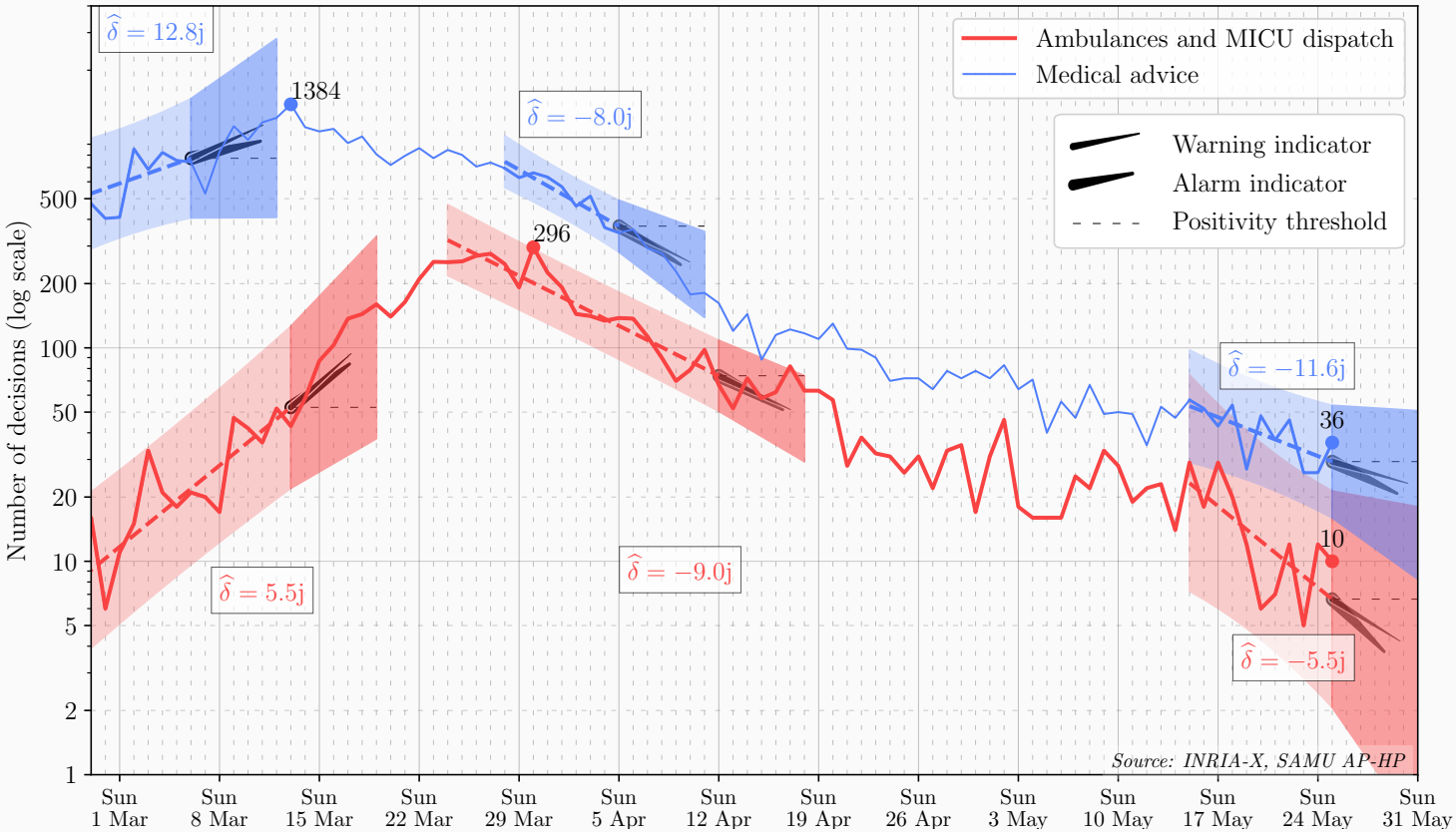


The peak of the number of calls for medical advice, on 13/03 is not consistent with epidemiological modeling. It seems rather to be caused by the presidential address. The peak for justified medical advice should occur 5-8 days (delay of appearance of first symptoms) after the peak of contaminations, expected to be immediately before 16/03.



The simulatenous jump of the advice and ambulance dispatch curves around Feb. 23 is the sign of a transport of epidemic. Possible sources: North of Italy (end of school vacation) and Semaine Évangélique macro-cluster in Mulhouse.

Construction of statistical indicators of epidemic resurgence based on emergency calls



Short term predictor for SAMU 75, with confidence regions and warning and alarms indicators. Think needle: warning = 25% probability of positive doubling time, alarm = 75% probability of positive doubling time. Uses log-regression L_2.

Parameter estimation of the probabilistic model

Parameter estimation of the probabilistic model

- Consider the population of Paris (Department 75).
- Consider the observable $Y(t) = X_H(t)$ (number of new hospitalizations) given by the noisy public data provided by SurSaUD syndromic surveillance system.
- Consider the multi-type branching process with all parameters fixed as before, except $\alpha = \alpha_i = \alpha_a$, which depend on time and is piecewise constant, with 3 pieces corresponding to phases of successive sanitary measures from Feb. 8, to May 5, 2020:
  - between day 0 (February 8th) and day t_2, $\alpha(t) = \alpha_1$.
  - between day t_2 and day t_3, $\alpha(t) = \alpha_2$.
  - between day t_3 and day T (May 5th), $\alpha(t) = \alpha_3$.
- Then, the model depend on the six parameters $(X_E(0), \alpha_1, t_2, \alpha_2, t_3, \alpha_3)$, where $X_E(0)$ is the initial total number of exposed individuals. (It is then divided into the variables $X_{E,d}(0)$ according to distribution p_E.)
- We sample random independent trajectories of the multi-type branching process.

- We minimize the L^1 loss function:

$$\mathcal{L}\left(X_E(0), \alpha_1, t_2, \alpha_2, t_3, \alpha_3\right) := \mathbb{E}_{X_E(0)}\left[\frac{1}{T}\sum_{t=0}^{T}\left|X_H(t) - Y(t)\right|\right],$$

- or the L^1-log loss function:

$$\widetilde{\mathcal{L}}\left(X_E(0), \alpha_1, t_2, \alpha_2, t_3, \alpha_3\right) := \mathbb{E}_{X_E(0)}\left[\frac{1}{T}\sum_{t=0}^{T}\left|\log X_H(t) - \log Y(t)\right|\right].$$

- Prediction for one week: from $T+1$ (May 6th) to T_{pred} (May 12th).
- The performance is evaluated by the mean L^1 norm :

$$\mathcal{L}_{\mathrm{pred}} := \mathbb{E}_{\mathrm{fit}}\left[\frac{1}{T_{\mathrm{pred}} - T}\sum_{t=T+1}^{T_{\mathrm{pred}}}\left|X_H(t) - Y(t)\right|\right],$$

  where the probability $\mathbb{P}_{\mathrm{fit}}$ is defined for inferred parameters $(\hat{X}_E(0), \hat{\alpha}_1, \hat{t}_2, \hat{\alpha}_2, \hat{t}_3, \hat{\alpha}_3)$.

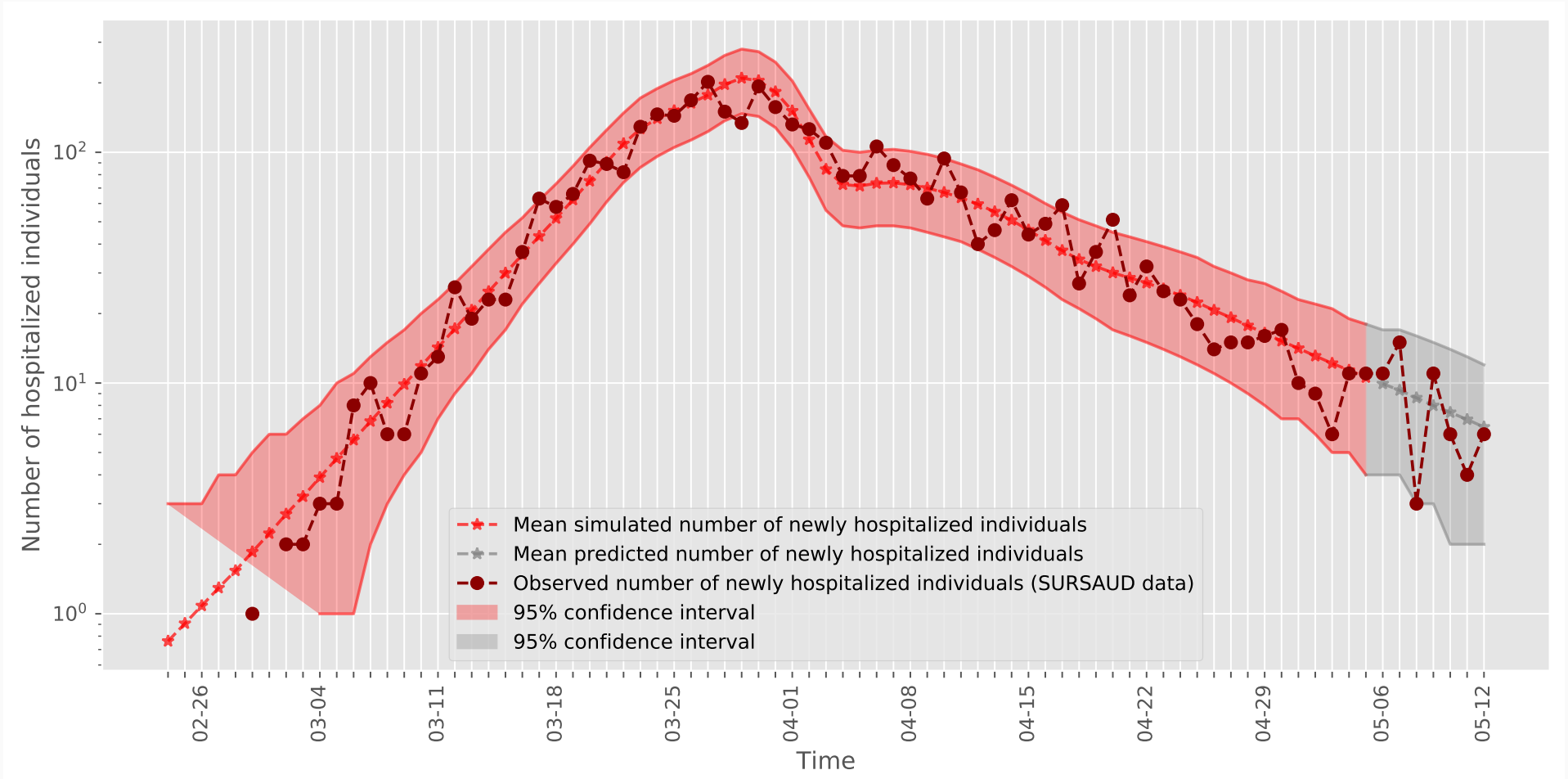
Approximate values of inferred parameters

Loss function	$\hat{X}_E(0)$	$\hat{\alpha}_1$	$\hat{t}_2$	$\hat{\alpha}_2$	$\hat{t}_3$	$\hat{\alpha}_3$
L^1	59	0.360	03-15	0.215	03-20	0.042
L^1-log	18	0.455	03-15	0.265	03-20	0.040

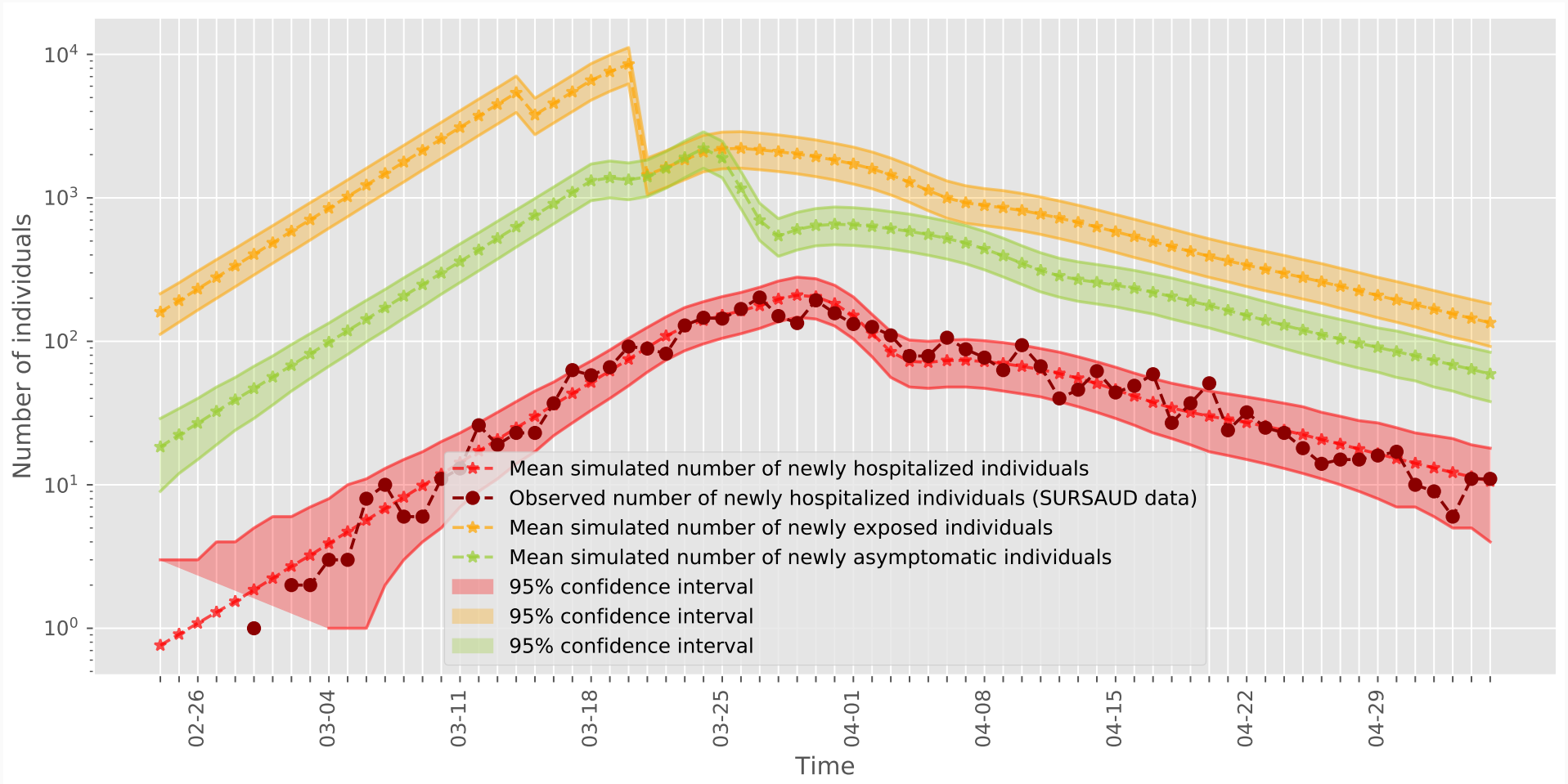
Loss function	Fitting error	Prediction error
L^1	11.1195 ± 0.0232	4.0093 ± 0.0185
L^1-log	0.29904 ± 0.00062	3.7201 ± 0.0125

Errors with 95% confidence interval obtained by Monte Carlo simulations.

Best fitting with log-L^1 cost function



With hidden trajectories



Models with mobility

Models with user mobility

- Assume that the daily outflows $f(t)$ are known and are normalized so as to have zero mean and standard deviation 1.
- The contact rate $\alpha(t)$ is now mobility-dependent:

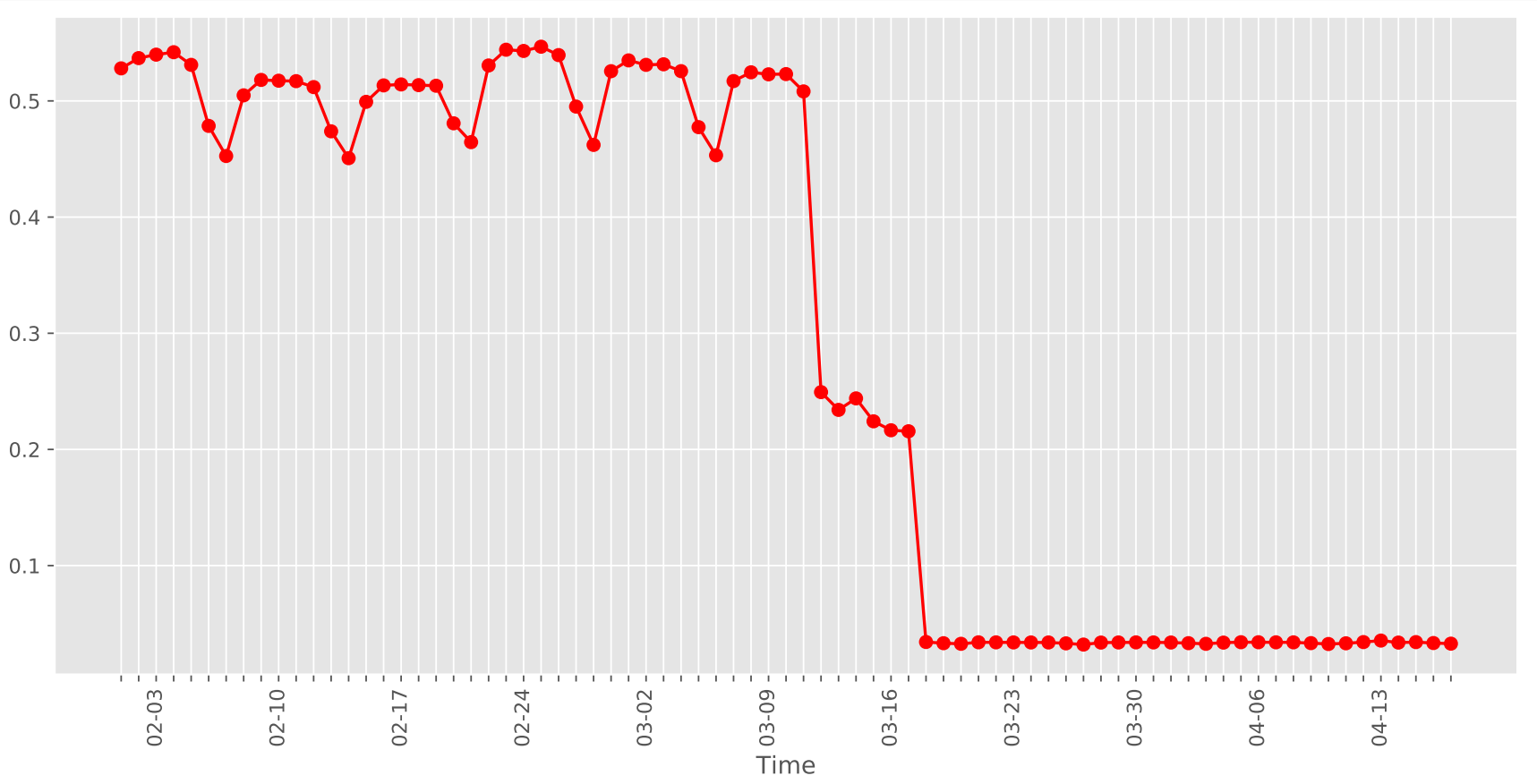
$$\alpha(t) = F\left(\phi(t), f(t)\right).$$

  where $\phi(t)$ is a discrete phase, e.g. $\phi(t) \in \{1, 2, 3\}$ as before.
- F can be taken as a logistic function in the variable $f(t)$ or as an affine function:

$$\alpha(t) = \alpha_{\phi(t)}\left(1 + \gamma f(t)\right).$$

- where $\alpha_{\phi(t)}$ is the value of α when the commuting flow is at its equilibrium, and $\gamma \geqslant 0$ is a parameter.

Evolution of the mobility-dependent contact rates for Paris, when the observables $f(t)$ are obtained from SFR mobile operator data, with parameters $\alpha_1 = 0.45$, $\alpha_2 = 0.3$, $\alpha_3 = 0.05$, and $\gamma = 0.15$:



The shape of the contact rates reflects the discrete phases, together with weekly periodicity patterns. Contact rates are lower on Saturdays and Sundays, when daily commuting trips are less numerous.

Models with routing mobility

- Refined compartments: Subdivise the global population into cohorts $c \in \mathcal{C}$. For instance $c = (r, a)$, where r is for geographical region, and a is for age range.
- $\mathcal{N}_c(t)$ is the size of cohort c at time t.
- Each cohort $c \in \mathcal{C}$ may have its own biological parameters $\theta_c = (r_\tau, p_i, p_h, \alpha)$.
- Routing mobility:

$$\mathcal{N}_c(t+1) = \sum_{c' \in \mathcal{C}} R_{c',c}(t)\mathcal{N}_{c'}(t) + \mathcal{E}_c(t+1) \quad \text{with} \sum_{c \in \mathcal{C}} R_{c',c}(t) \leqslant 1 \ .$$

- Contacts between sub-populations: $n_{c,c'}(t)$= the average number of individuals from cohort c' that a typical individual from cohort c will encounter.
- Assume $\mathcal{N}_c(t) n_{c,c'}(t) = \mathcal{N}_{c'}(t) n_{c',c}(t)$.
- If $q_{c,c'}$ is the probability of infection of an individual in c' by an individual in c, given that they are in contact:

$$\alpha_{c,c'}(t) := q_{c,c'} n_{c,c'}(t).$$

The mean-field model is decomposed into two steps:

1) evolution and infection of individuals similar to the case of one cohort:

$$
\begin{aligned}
y^c_{\tau,d+1}(t) &= x^c_{\tau,d}(t)(1 - r_\tau(d)), \quad \forall \tau \in \{E, P, I_1, I_2, A\}\,, \\
y^c_{E,1}(t) &= \sum_{c' \in \mathcal{C}} \alpha_{c',c}(t) \sum_{\delta > 0} \left[(x^{c'}_{I_1,\delta} + x^{c'}_{I_2,\delta})(t) + (x^{c'}_{A,\delta} + x^{c'}_{P,\delta})(t) \right], \\
y^c_{P,1}(t) &= \sum_{\delta > 0} x^c_{E,\delta}(t) r_E(\delta), \\
y^c_{I_1,1}(t) &= p_i \sum_{\delta > 0} x^c_{P,\delta}(t) r_P(\delta), \\
y^c_{A,1}(t) &= (1 - p_i) \sum_{\delta > 0} x^c_{P,\delta}(t) r_P(\delta), \\
y^c_{I_2,1}(t) &= (1 - p_h) \sum_{\delta > 0} x^c_{I_1,\delta}(t) r_{I_1}(\delta), \\
y^c_H(t) &= p_h \sum_{\delta > 0} x^c_{I_1,\delta}(t) r_{I_1}(\delta).
\end{aligned}
$$

2) routing mobility between cohorts:

$$
x^c(t+1) = \sum_{c'} R_{c',c}(t) y^c(t) \ .
$$

Estimation of parameters

- The parameters $R_{c,c'}$ and $n_{c,c'}$ should be estimated using mobility data.
- For instance, if $c = (r, r', a)$, where r is the usual address of individuals and r' the place where they spent the previous night, and if we observe $\mathcal{N}_c(t)$, and, for all pair of regions (r_1, r_2), the quantities:

$$\Delta_{r_1,r_2,a}(t) := \sum_{r,r'} \mathcal{N}_{(r,r_1,a)}(t) R_{(r,r_1,a),(r',r_2,a)}(t),$$

  that is the flow of people of age range a who slept on night before t in r_1 and slept on the following night in r_2. (The usual address of these individuals is however assumed unknown.)
- On can estimate the unobserved quantities $R_{c,c'}(t)$ as the solution of

$$\begin{aligned} \max_{R_{c,c'} \geqslant 0} \quad & \sum_{c,c'} R_{c,c'} \ln\left(\frac{1}{R_{c,c'}}\right) \\ \text{subject to} \quad & \forall c', \sum_{c} R_{c',c} \leqslant 1 \\ & \forall (r_1, r_2), \sum_{r,r'} \mathcal{N}_{r,r_1,a}(t) R_{(r,r_1,a),(r',r_2,a)} = \Delta_{r_1,r_2,a}(t). \end{aligned}$$

Contact tracing

Contact tracing

- Motivation: control of the epidemics via case isolation.
- Contact tracing allows to focus tests on such contacts.
- One can modify the multi-type branching process to include contact tracing and case isolation. See also (A. Lambert,2020).
- Fixed tracing probability $p_t > 0$ that the contact between an infectious individual and another individual that became infected is being recorded.
- Consider a multi-type branching process where user types τ encode the succession of future phases ϕ that an individual will visit over the coming days, e.g. $j = (E, E, P, I_1, H)$, together with the number of days d until the corresponding individual will be positively tested.
- On can consider that an indicidual in H is necessarily tested, or that there is a random testing.
- Once an individual is tested positive, it is isolated (removed) and its traced contacts are subsequently tested positive on the following day, and subsequently isolated, and so on.

- A possible model is to replace the children $\tau = (j, d)$ of $\tau' = (j', d')$ by $(\tilde{j}, \tilde{d})$ such that

$$\tilde{d} = \begin{cases} d_1 & \text{with probability } 1 - p_t, \\ \min(d_1, d' + 1) & \text{with probability } p_t. \end{cases}$$

  and $\tilde{j}$ has length $\tilde{d}$, where d_1 has same distribution as d.
- This modify the matrix M of the mean-field version of the multi-type branching process.
- Then, testing is efficient if $\rho(M) < 1$.

Conclusion

- EMS receive early signals of the epidemic evolution. Exponential blowup retrospectively visible in the Paris area from the end of February, using the extractions of patient records made during the crisis.
- Spatially differentiated evolution, e.g., more intense epidemy in the 93 (shorter doubling time) than in 75 or 92, probably caused by social factors (dependence on public transport, jobs involvings more contamination risks, bigger size of household).
- Models of COVID-19 epidemics using PDE, discrete time mean-field or branching processes.
- Approximations by piecewise affine logarithm of observables.
- Short-term predictions on EMS and Paris hospitalization data.
- User mobility can be included to improve estimation of parameters.
- Possible models with routing mobility.
- Possible models with contact tracing and case isolation.

Preprints and articles corresponding to this talk

1. Stéphane Gaubert, Marianne Akian, Xavier Allamigeon, Marin Boyet, Baptiste Colin, Théotime Grohens, Laurent Massoulié, David P. Parsons, Frédéric Adnet, Erick Chanzy, Laurent Goix, Frédéric Lapostolle, Eric Lecarpentier, Christophe Leroy, Thomas Loeb, Jean-Sébastien Marx, Caroline Télion, Laurent Tréluyer and Pierre Carli, *Understanding and monitoring the evolution of the Covid-19 epidemic from medical emergency calls: the example of the Paris area*, C. R. Math. Acad. Sci. Paris, **358(7)**, 843–875, 2020.
2. M. Akian, L. Ganassali, S. Gaubert, L. Massoulié. *Probabilistic and mean-field model of covid-19 epidemics with user mobility and contact tracing*, arXiv 2009.05304, 2020.

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