Monitoring the temporal and spatio-temporal dynamics of the effective reproduction number from mortality data

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With :
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Part I: Estimating R_t from mortality data, a simple formula

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Towards unified and real-time analyses of outbreaks at country-level during pandemics

Samuel Soubeyrand [a], Jacques Demongeot [b], Lionel Roques [a]

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https://doi.org/10.1016/j.onehlt.2020.100187

Samuel Soubeyrand

Jacques Demongeot

Main ideas

- SIRD model with constant parameters over moving window $(t-\tau, t)$
- Work with daily mortality data (cumulated value $\hat{D}_t$)

$$\begin{cases} S'(s) = -\dfrac{\alpha_s}{N} S\, I \\ I'(s) = \dfrac{\alpha_s}{N} S\, I - (\beta+\gamma)\, I \\ R'(s) = \beta\, I \\ D'(s) = \gamma\, I \end{cases} \xrightarrow{5\cdot 10^{-4} \approx \gamma \ll \beta \approx 0.1} I'(s) = \beta\, I(s) \left(\frac{\alpha_s\, S}{\beta\, N} - 1 \right)$$

$\mathcal{R}_s = \alpha_s S(s)/(\beta\, N)$ is constant $(= \mathcal{R}_t)$ for $s \in (t-\tau, t)$

$$\begin{cases} I'(s) = \beta\, I(s)\, (\mathcal{R}_t - 1) \\ D'(s) = \gamma\, I \end{cases}$$

$$D(s) = D(t-\tau) + \gamma\, I(t-\tau) \int_{t-\tau}^{s} e^{\beta\, u\, (\mathcal{R}_t - 1)}\, du$$

$D(t-\tau) = \hat{D}_{t-\tau}$ and $D(t) = \hat{D}_t$

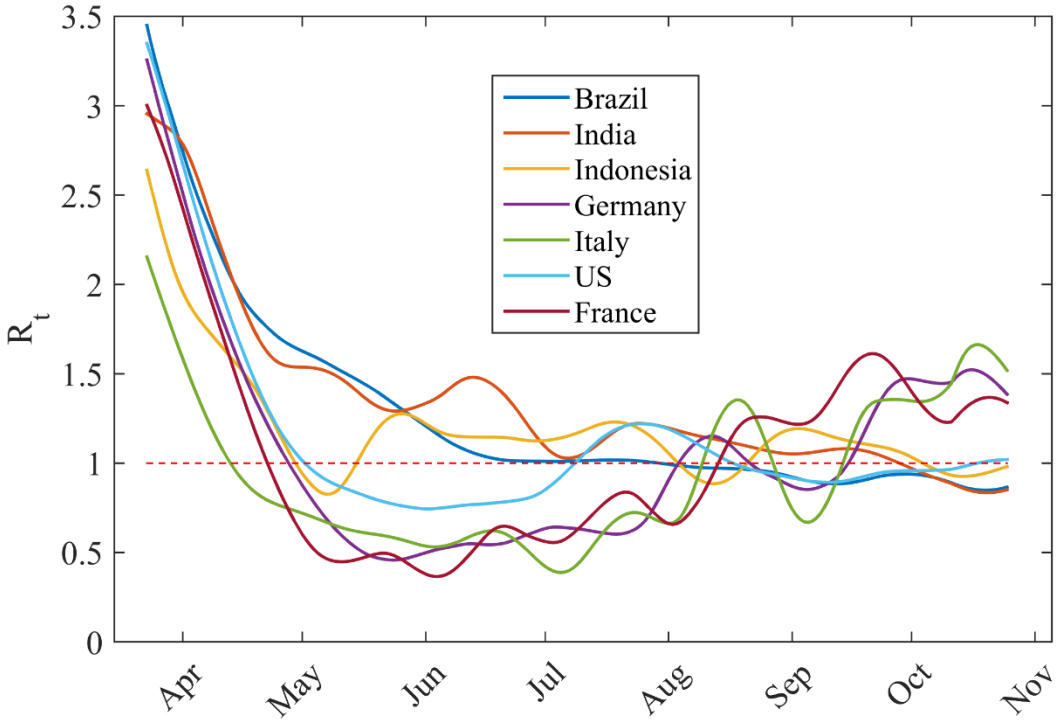
$$D(s) = \hat{D}_{t-\tau} + (\hat{D}_t - \hat{D}_{t-\tau}) \frac{e^{\beta\, (R_t - 1)\, (s - (t-\tau))} - 1}{e^{\beta\, \tau\, (R_t - 1)} - 1}, \text{ for all } s \in (t-\tau, t).$$

$\rightarrow$ $D(s)$ does not depend on the mortality rate γ and on $I(t-\tau)$

$$D(s) = \hat{D}_{t-\tau} + (\hat{D}_t - \hat{D}_{t-\tau}) \frac{e^{\beta\,(R_t - 1)\,(s-(t-\tau))} - 1}{e^{\beta\,\tau\,(R_t-1)} - 1}, \text{ for all } s \in (t-\tau, t).$$

For each t, $\mathcal{R}_t$ is computed with a standard (mean square) fitting procedure, over *smoothed* mortality data.

Example with $\tau = 28$:



Data: JHU CSSE, 27 October 2020

$$D(s) = \hat{D}_{t-\tau} + (\hat{D}_t - \hat{D}_{t-\tau}) \frac{e^{\beta\,(R_t - 1)\,(s-(t-\tau))} - 1}{e^{\beta\,\tau\,(R_t-1)} - 1}, \text{ for all } s \in (t-\tau, t).$$

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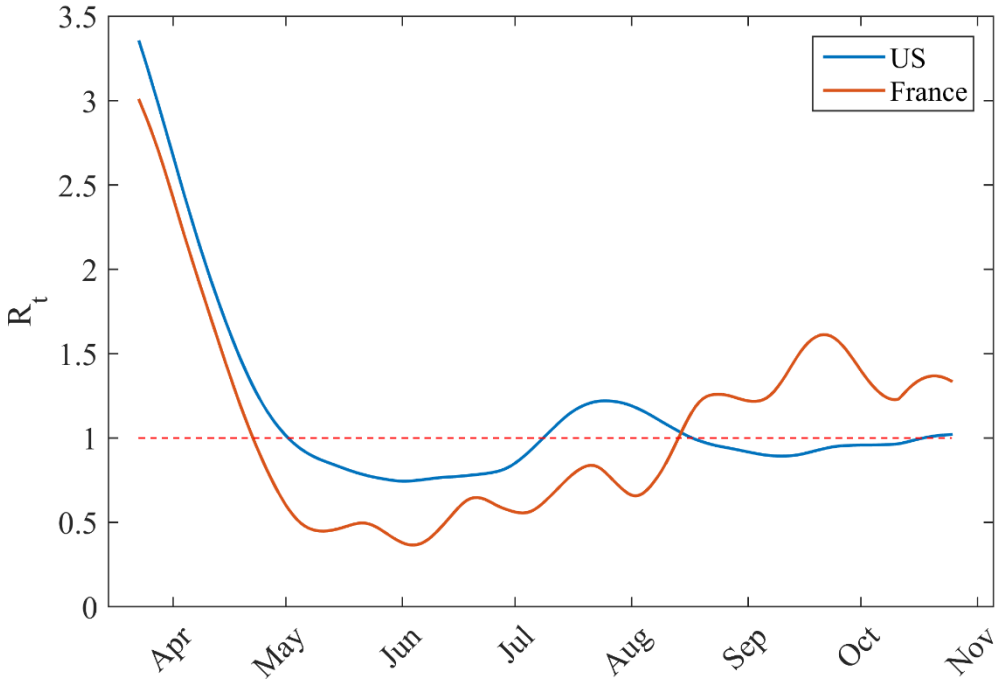

Data: JHU CSSE, 27 October 2020

October 27: $\mathcal{R}_t(\text{France}) \approx 1.3$ vs $\mathcal{R}_t(\text{US}) \approx 1.0$

$$PFR := \frac{number\ of\ deaths}{total\ population}$$

October 27: $PFR(\text{France}) = 51/100\,000$ vs $PFR(\text{US}) = 69/100\,000$

$$\rightarrow PFR(\text{US}) \approx 1.3 \times PFR(\text{France})$$

Higher immunity rate in the US explains the lower $\mathcal{R}_t$?

Part II: Spatio-temporal dynamics of COVID-19 in France

local effects vs global factors

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A parsimonious model for spatial transmission and heterogeneity in the COVID-19 propagation

Lionel Roques, Olivier Bonnefon, Virgile Baudrot, Samuel Soubeyrand, Henri Berestycki

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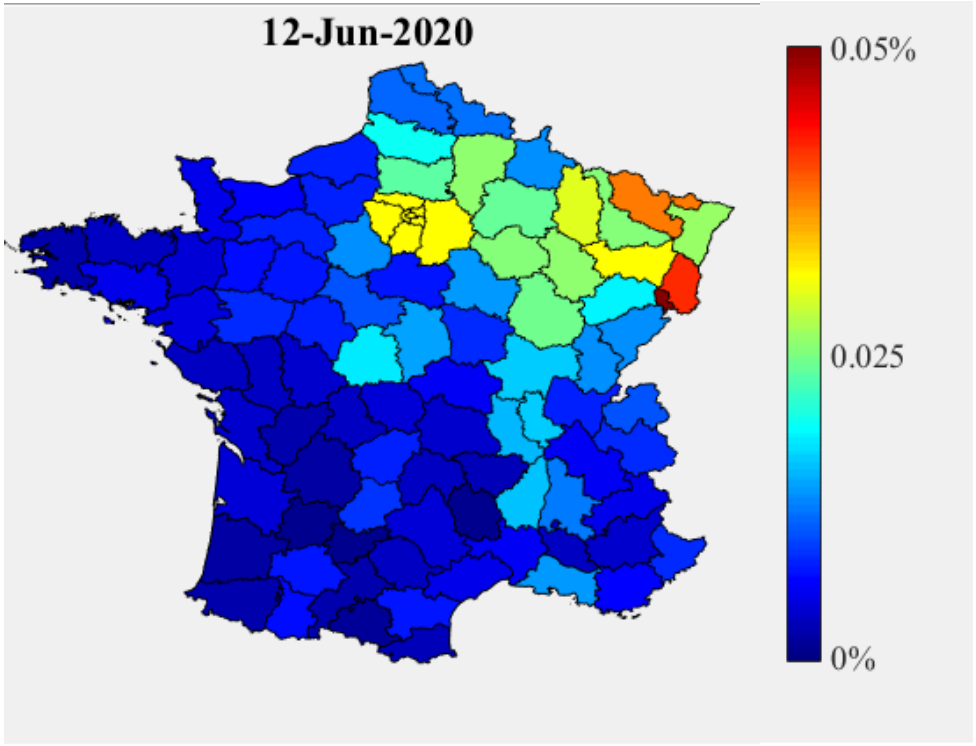
This article is a preprint and has not been certified by peer review [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

January 24, 2020: 1st reported cases in France. Some cases already present in December 2019 (Retrospective PCR tests, [Deslandes et al. 2020]).

In June, the spatial pattern of the disease spread seems to have kept track of the first introductions

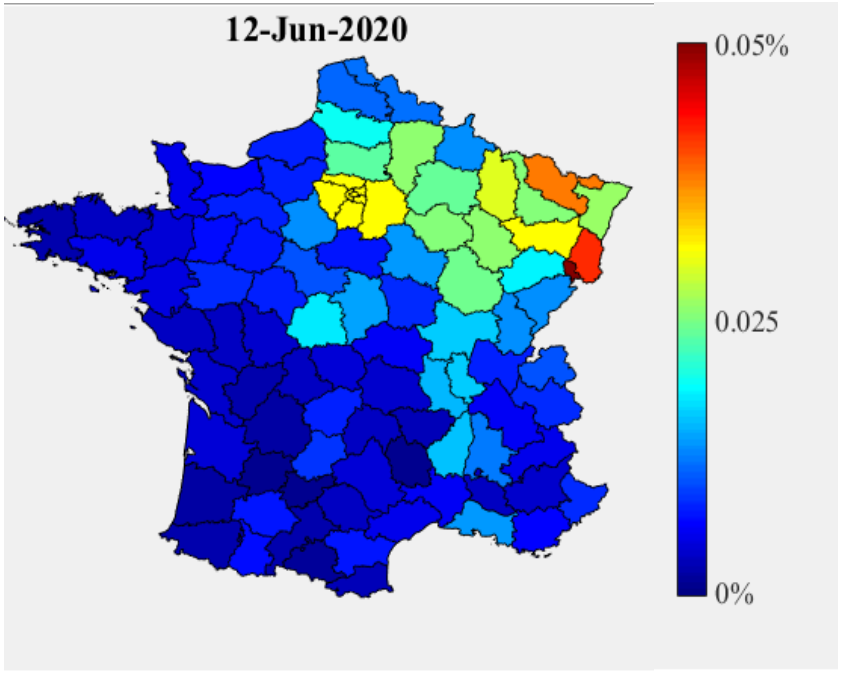
Local PFR at county scale



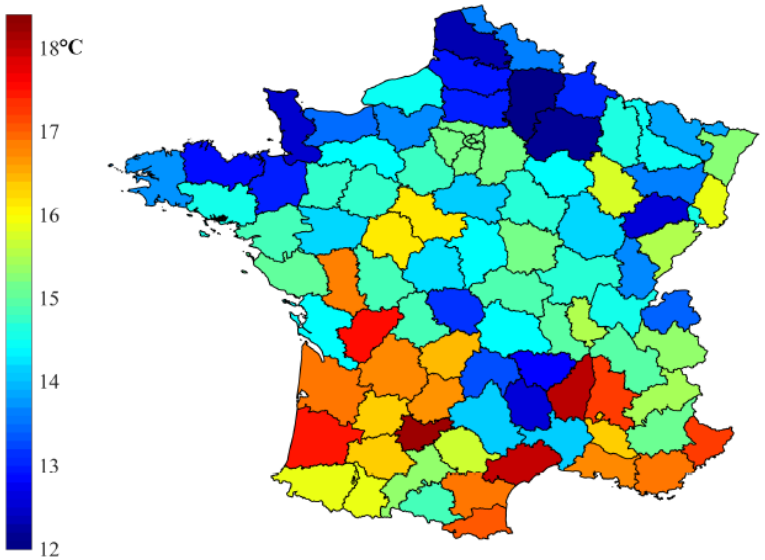
$$PFR := \frac{number\ of\ deaths}{total\ population}$$

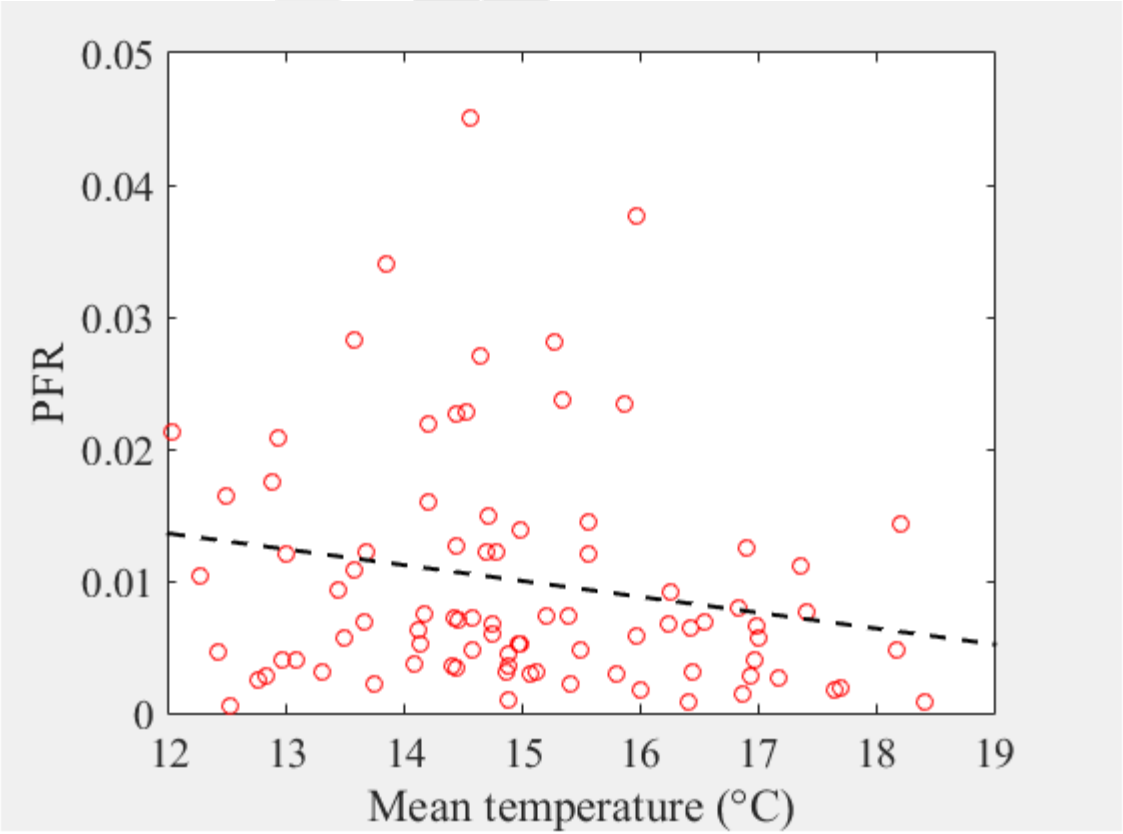
This spatial pattern may also be correlated with covariates such as climate [Demongeot et al. 2020]

PFR



Mean temperature (30 March -11 June)





Pearson correlation coefficient: -0.21.

Is this pattern the consequence of the heterogeneity of spatial covariates?

Does it simply reflect the initial heterogeneity?

Data

Mainland France (excluding Corsica island) = 94 counties called 'départements'.

Daily number of hospital deaths excluding nursing homes at the county scale are available from Santé Publique France

Models

Model $\mathcal{M}_0$: Standard mean field SIRD model at country scale

$$\begin{cases} S'(t) = -\dfrac{\alpha(t)}{N}\, S\, I, \\ I'(t) = \dfrac{\alpha(t)}{N}\, S\, I - (\beta + \gamma)\, I, \\ R'(t) = \beta\, I, \\ D'(t) = \gamma\, I, \end{cases}$$

- $\alpha(t)$: the contact rate (to be estimated)
- $1/\beta$ is the mean time until an infectious becomes recovered: 10 days

  $\rightarrow$ Median period of viral shedding: 20 days

  $\rightarrow$ infectiousness tends to decay before the end of this period: starts from 2.5 days before symptom onset and declines within 7 days of illness onset.
- γ: hospital death rate of the infectious. The IFR corresponds to the fraction of the infected who die, that is: $\gamma/(\gamma + \beta)$. Thus, a value of 0.5% [Roques et al, 2020, Salje et al, 2020] for the IFR implies a value $\gamma = 5 \cdot 10^{-4}$.

Model $\mathcal{M}_1$: SIRD model at the 'département' scale with globally constant contact rate and no spatial transmission. The model $\mathcal{M}_0$ is applied at the scale of each département k, leading to compartments S_k, I_k, R_k, D_k, with N replaced by N_k, the total population in the département k.

In this approach, the contact rate $\alpha(t)$ is assumed to be the same in all of the départements.

Model $\mathcal{M}_2$: SIRD model at the 'département' scale with spatially heterogeneous contact rate and no spatial transmission.

The model $\mathcal{M}_1$ is extended by assuming that the contact rate $\alpha_k(t)$ depends on the considered département.

Model $\mathcal{M}_3$: Département scale model with globally constant contact rate and spatial transmission [Kendall, 1956]. The model $\mathcal{M}_1$ is extended to take into account disease transmission events between the départements:

$$\begin{cases} S_k'(t) = -\dfrac{\rho(t)}{N_k}\, S_k \displaystyle\sum_{j=1}^{n_d} w_{j,k}\, I_j, \\ I_k'(t) = \dfrac{\rho(t)}{N_k}\, S_k \displaystyle\sum_{j=1}^{n_d} w_{j,k}\, I_j - (\beta+\gamma)\, I_k, \\ R_k'(t) = \beta\, I_k, \\ D_k'(t) = \gamma\, I_k. \end{cases}$$

- Implicitly assumes that infectious individuals may transmit the disease to susceptible individuals in other départements, but eventually return to their département of origin.
- Power law decay with the distance: $w_{j,k} = \frac{1}{1+(\mathrm{dist}(j,k)/d_0)^\delta}$, with $\mathrm{dist}(j,k)$ the geographic distance (in km) between the centroids of départements j and k
- Supported by analysis of the short-time dispersal of bank notes in the US [Brockmann et al, 2006]
- Standard choice in infectious disease modelling [e.g., Merler and Ajelli 2009, for influenza]

Summary of the models

	Heterog. initial data	Heterog. contact rate	Intercounty transmission	Nb. parameters
$\mathcal{M}_0$	no	no	no	n_t
$\mathcal{M}_1$	yes	no	no	n_t
$\mathcal{M}_2$	yes	yes	no	$n_d \times n_t$
$\mathcal{M}_3$	yes	no	yes	$n_t + 2$

Table 1: Main characteristics of the four models. The quantity $n_t = 74$ corresponds to the number of days of the observation period and $n_d = 87$ corresponds to the number of administrative units.

Observation model. $\overline{D}_k(t)$: expected cumulative number of deaths given by the model, in département k. Daily number of new observed deaths $\hat{\mu}_{k,t}$ in département k:

$$\hat{\mu}_{k,t} \sim \text{Poisson}(\overline{D}_k(t) - \overline{D}_k(t-1)).$$

With the mean-field model $\mathcal{M}_0$, $\overline{D}_k(t) = D(t)\, N_k/N$.

Real-time monitoring of the parameters and data assimilation procedure.

-Smooth out the effect of small variations in the data

-Avoid identifiability/computational issues due to the large number of parameters, while keeping the temporal dependence of the parameters

$\rightarrow$ we fit auxiliary problems with time-constant parameters over moving windows $(t-\tau/2, t+\tau/2)$:

$$\begin{cases} \tilde{S}_k'(s) = -\dfrac{\tilde{\alpha}}{N_k}\,\tilde{S}_k\,\tilde{I}_k, \\ \tilde{I}_k'(s) = \dfrac{\tilde{\alpha}}{N_k}\,\tilde{S}_k\,\tilde{I}_k - (\beta+\gamma)\,\tilde{I}_k, \quad \text{for } s \in (t-\tau/2, t+\tau/2), \qquad (\tilde{\mathcal{M}}_{1,t}) \\ \tilde{R}_k'(s) = \beta\,\tilde{I}_k, \\ \tilde{D}_k'(s) = \gamma\,\tilde{I}_k, \end{cases}$$

Initial conditions at the date $t-\tau/2$ are computed iteratively from the solution of the model $\mathcal{M}_i$.

The parameters of the models $\tilde{\mathcal{M}}_i$ are estimated with a maximum likelihood procedure

Inference procedure: maximum likelihood estimation over $(t-\tau/2, t+\tau/2)$ for each t.

Probability of the observations $\hat{\mu}_k$, given the model:

$$f_{\overline{D}_k,\hat{\mu}_k}(s) := \frac{(\overline{D}_k(s) - \overline{D}_k(s-1))^{\hat{\mu}_{k,s}}}{\hat{\mu}_{k,s}!}\, e^{-(\overline{D}_k(s)-\overline{D}_k(s-1))}.$$

Models $\tilde{\mathcal{M}}_{0,t}$, $\tilde{\mathcal{M}}_{1,t}$: $\mathcal{L}(\tilde{\alpha}_t) = \prod_{k=1}^{n_d} \prod_{s=t-\tau/2}^{t+\tau/2} f_{\overline{D}_k,\hat{\mu}_k}(s)$.

MLE $\tilde{\alpha}_t^*$, we set $\alpha(t) = \tilde{\alpha}_t^*$ in models $\mathcal{M}_0,\ \mathcal{M}_1$.

Model $\tilde{\mathcal{M}}_{2,t}$, esimated parameters $\tilde{\alpha}_k$ (independently in each département).

$$\mathcal{L}_k(\tilde{\alpha}_k) = \prod_{s=t-\tau/2}^{t+\tau/2} f_{\overline{D}_k,\hat{\mu}_k}(s).$$

MLE $\tilde{\alpha}_{k,t}^*$, we set $\alpha_k(t) = \tilde{\alpha}_{k,t}^*$

Model $\mathcal{M}_3$, use the estimate obtained with model $\mathcal{M}_1$ with $\rho(t) = C\,\alpha(t)$. Estimate 3 parameters:

C, the proximity scale d_0 and the exponent δ (ML estimation).

Results: model fit

	Heterog. initial data	Heterog. contact rate	Intercounty transmission	Nb. parameters
$\mathcal{M}_0$	no	no	no	n_t
$\mathcal{M}_1$	yes	no	no	n_t
$\mathcal{M}_2$	yes	yes	no	$n_d \times n_t$
$\mathcal{M}_3$	yes	no	yes	$n_t + 2$

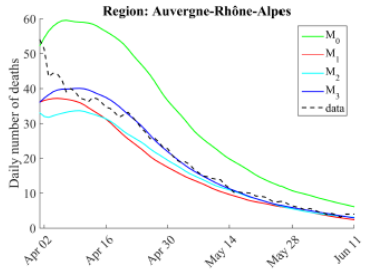
Table 1: Main characteristics of the four models. The quantity $n_t = 74$ corresponds to the number of days of the observation period and $n_d = 87$ corresponds to the number of administrative units.

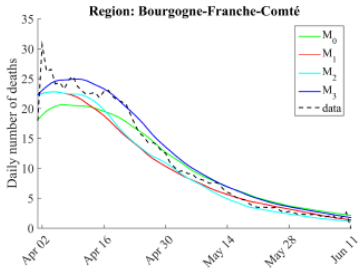
Model	AIC	BIC	Log-likelihood	ΔAIC
$\mathcal{M}_0$	$2.68 \cdot 10^4$	$2.73 \cdot 10^4$	$-13.4 \cdot 10^3$	$-9.57 \cdot 10^3$
$\mathcal{M}_1$	$1.74 \cdot 10^4$	$1.79 \cdot 10^4$	$-8.62 \cdot 10^3$	-220
$\mathcal{M}_2$	$2.97 \cdot 10^4$	$7.36 \cdot 10^4$	$-8.41 \cdot 10^3$	$-1.25 \cdot 10^4$
$\mathcal{M}_3$	$1.72 \cdot 10^4$	$1.77 \cdot 10^4$	$-8.52 \cdot 10^3$	0

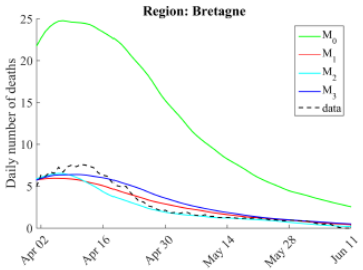
Table 2: Log-likelihood, AIC and BIC values for the four models. The last column ΔAIC corresponds to the difference with the AIC value of the best model (here $\mathcal{M}_3$).

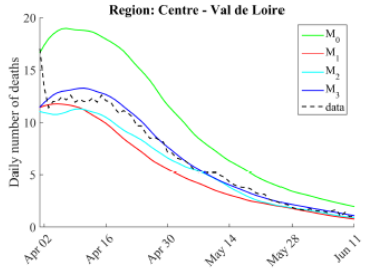
Statisticians often argue that AIC chooses the best predictive model, and BIC attempts to select the 'true' process that generated the data.

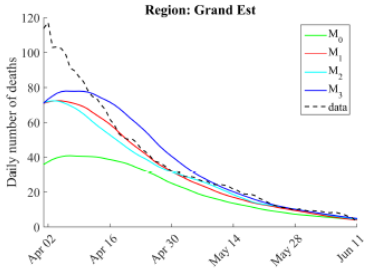
Results: model fit, regional scale

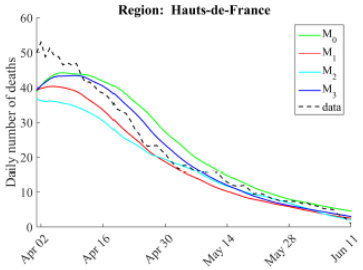


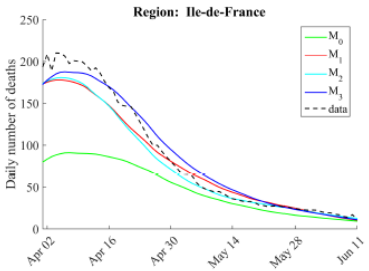


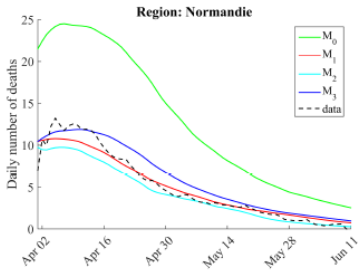


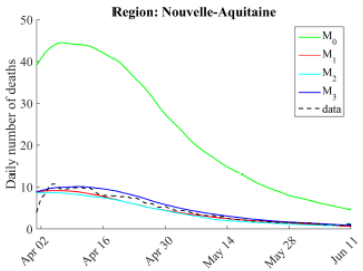


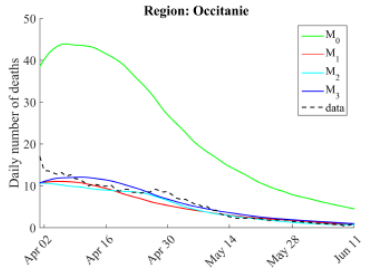


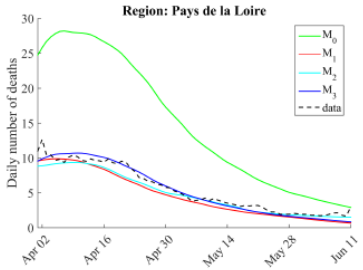


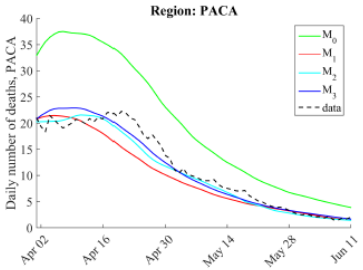












Results: model fit, parameter values

For model $\mathcal{M}_3$,
MLE: $C = 0.87$, $d_0 = 2.16$ km and $\delta = 1.85$

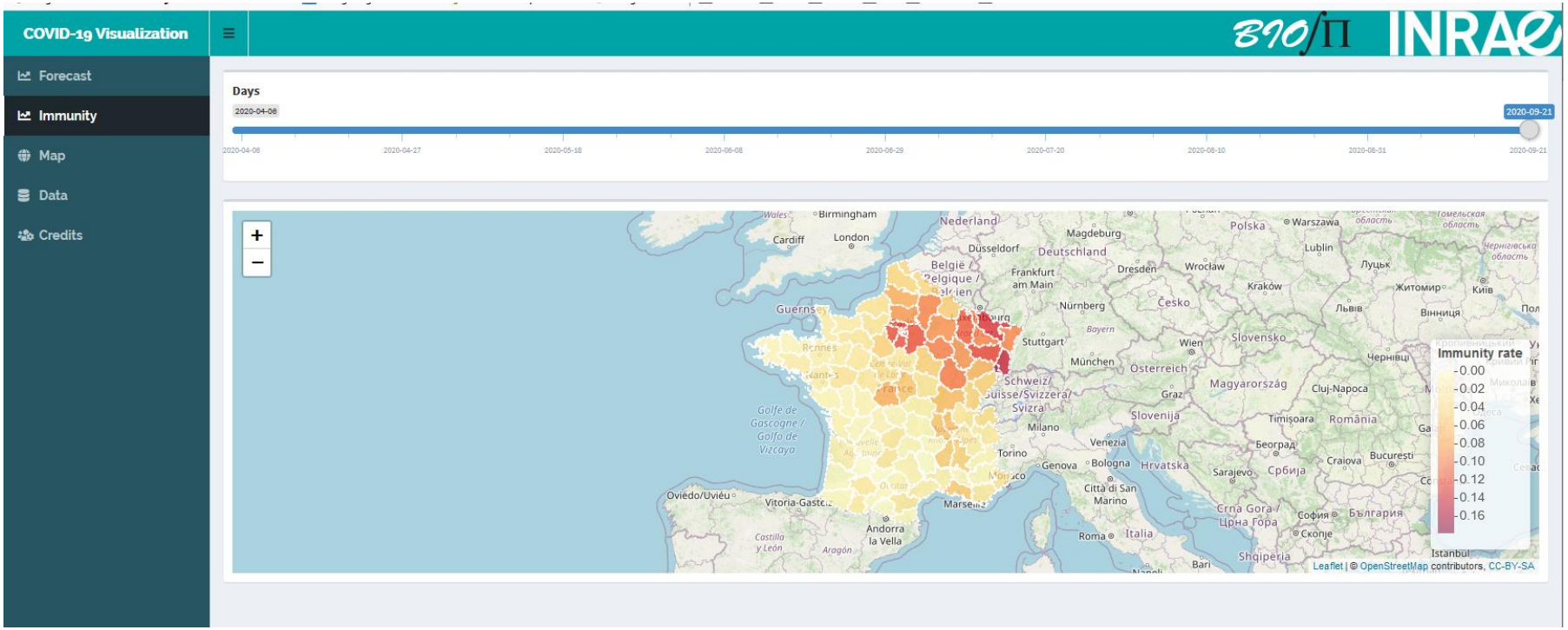
- nearly quadratic decay of the weights with the distance
- non-local contagion plays a secondary role compared to within-county contagion: the minimum distance between two counties is 36 km $\rightarrow$ weight 5.5/1000, to be compared with the weight 1 for within-county contagion.
- C is significantly smaller than 1 thus non-local contagion term plays an important role on the spreading of the epidemic.

Byproduct of the estimation of the parameter $\alpha(t)$ (resp. $\alpha_k(t)$) of model $\mathcal{M}_1$ effective reproduction number in each département, which is given by the formula:

$$\mathcal{R}_t^k = \frac{\alpha(t)}{\beta+\gamma}\frac{S_k(t)}{N_k},$$

Other byproduct: immunity rate R_k/N_k (model $\mathcal{M}_3$)

http://covid19-forecast.biosp.org/



Results: limiting movement vs limiting the probability of transmission per contact

We start from the state of the epidemic at June 11.
During 10 days, with model $\mathcal{M}_3$:

- 'local' contact rate $\rho(t) \approx 0.05 \rightarrow \rho(t) = 0.1$ $(\times 2)$
- $d_0 \approx 2$ km $\rightarrow d_0 = 20$ km $(\times 10)$

We test four strategies (during 30 days):

- Strategy 1: no restriction. $\rho(t) = 0.11$ and $d_0 = 20$ km;
- Strategy 2: restriction on intercounty movement. $\rho(t) = 0.11$, $d_0 = 2.16$ km, corresponding
- Strategy 3: reduction of the contact rate within each département. $\rho(t) = 0.05$ and $d_0 = 20$ km;
- Strategy 4: reduction of the contact rate and restriction on intercounty movement: $\rho(t) = 0.05$ and $d_0 = 2.16$ km.

We test four strategies:

- Strategy 1: no restriction.
- Strategy 2: restriction on intercounty movement.
- Strategy 3: reduction of the contact rate within each département.
- Strategy 4: reduction of the contact rate and restriction on intercounty movement

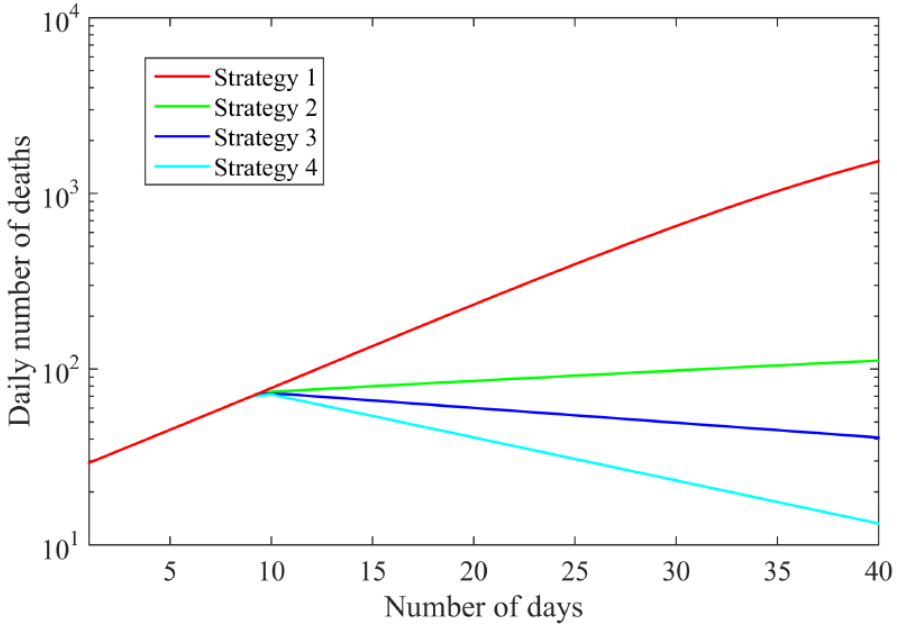


Figure 4: Daily number of deaths due to a new outbreak in logarithmic scale; comparison between four management strategies. The number of deaths is computed over the whole country.

Final number of deaths and $\mathcal{R}_t$ over the whole country estimated by fitting $I(t)$ with an exponential function ($I'(t) = (\beta + \gamma)I(\mathcal{R}_t - 1)$).

- Strategy 1: no restriction. 17 271 deaths and $\mathcal{R}_t \approx 2$.
- Strategy 2: restriction on intercounty movement. 81% decrease in the cumulative number of deaths (3 281 deaths) and $\mathcal{R}_t \approx 1.2$;
- Strategy 3: reduction of the contact rate within each département. 88% decrease (strategy 3, 2 139 deaths) and $\mathcal{R}_t \approx 0.8$;
- Strategy 4: reduction of the contact rate and restriction on intercounty movement. 91% decrease (1 503 deaths) and $\mathcal{R}_t \approx 0.4$.

To be compared with the 3 232 deaths during the last 30 days.

Conclusions

- Once the epidemic is established, the effect of global processes such as **restriction policies and sanitary measures overwhelms the effect of local factors.**

  $\rightarrow$ France is a geographically middle size centralised country

- Initial conditions and spatial diffusion are the main drivers of the spatial pattern of the COVID-19 epidemic

  $\rightarrow$ Covariates might play a major role in the emergence of the disease, but our work focuses on the disease dynamics after the emergence.

- Herd immunity (without masks) $1 - 1/\mathcal{R}_0 \approx 70\%$ of the population has been infected. Most impacted dépatements: the immunity rate is 16%, whereas it is less than 1% in less affected counties.

- Model $\mathcal{M}_3$ much more parsimonious than fully heterogeneous model $\mathcal{M}_2$

  $\rightarrow$ better suited to isolating key features of the epidemiological dynamics.

Thank you!