

## Lab session – Estimation of the reproduction number of COVID-19

### 1 Context, model and goals

From the very beginning of the COVID-19 pandemic National Health Authorities of all countries worldwide are monitoring the number of new infections each day, denoted by  $Z_t$  at day  $t$ . An example of such daily counts for five weeks in October and November 2022 in France is provided in Figure 1, as collected and made available by Johns Hopkins University<sup>1</sup>.

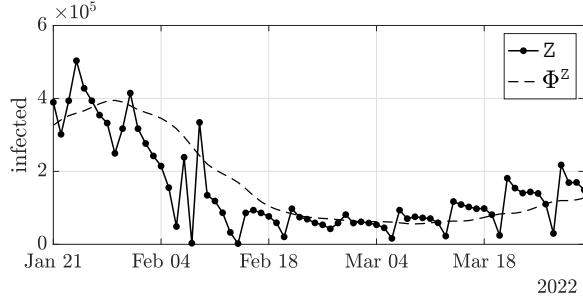


Figure 1: Daily new infection counts  $Z$  in France for 10 weeks.

- a. Load the MATLAB file `data_covid.mat` and plot the daily new infections  $Z$  with respect to days.

En MATLAB

```
load ('data_covid.mat')
plot (days ,Z)
```

En PYTHON

```
from scipy.io import loadmat
import matplotlib.pyplot as plt
data = loadmat ('data_covid.mat', squeeze_me = True)
plt.plot (Z)
```

Yet, the number of new infections itself is not informative enough about the dynamics of the pandemic. Thus, looking only at  $Z_t$  does not make it possible to detect an epidemic resurgence early enough, and therefore to react quickly enough to avoid a dramatic explosion in the number of infected people.

This is why we rapidly turn to the monitoring of the *standard reproduction number*,  $R_0$ , defined as the average number of secondary cases generated by a typical infected individual throughout its period of contagiousness [2, 3]. The reproduction number thus quantifies the intensity of the pandemic:

- when  $R_0 > 1$  the virus is spreading at exponential speed;
- when  $R_0 < 1$  the epidemic is vanishing;
- when  $R_0 = 1$  the epidemic is stable.

The standard definition of the reproduction number is relaxed into a time-dependent reproduction number  $R_t$  at day  $t$ , which is linked to the number of new infections by Cori's model [2]. In this epidemiological model the number of new infections at day  $t$  depends on the past daily counts  $Z_1, \dots, Z_{t-1}$  and follow a Poisson distribution

$$Z_t | Z_1, \dots, Z_{t-1} \sim \text{Poisson} (R_t \Phi_t^Z), \quad \text{with } \Phi_t^Z = \sum_{u=1}^{\tau_\Phi} \phi(u) Z_{t-u} \quad (1)$$

where  $\phi$  is the *serial interval function* associated to the pandemic, modeling the random delay between primary and secondary cases<sup>2</sup>.

<sup>1</sup><https://coronavirus.jhu.edu/map.html>

<sup>2</sup>For COVID-19 pandemic the serial interval function is modeled by a Gamma distribution with mean 6.6 days and standard deviation 3.5 days cropped at  $\tau_\Phi = 26$  days.

*Reminder 1* (Poisson distribution and likelihood). The Poisson distribution of parameter  $p \in \mathbb{R}_+$  is a probability distribution on nonnegative integers. A random variable  $Z$  follows a Poisson distribution if and only if

$$\forall k \in \mathbb{N}, \quad \mathbb{P}(Z = k|p) = e^{-p} \frac{p^k}{k!}.$$

Thus, given an observation  $\mathbf{Z} \in \mathbb{N}^T$  assumed to follow a Poisson model of parameter  $\mathbf{p}$ , the log-likelihood  $\ln \mathcal{L}(\mathbf{Z}|\mathbf{p})$  writes

$$\ln \left( e^{-p} \frac{p^Z}{Z!} \right) = -p + Z \ln(p) - \ln(Z!) \underset{Z \gg 1}{\simeq} -p + Z \ln(p) - Z \ln(Z) + Z = - \left( Z \ln \left( \frac{Z}{p} \right) + p - Z \right),$$

where the approximation  $\ln(Z!) \simeq Z \ln(Z) - Z$ , valid for  $Z \rightarrow \infty$ , can be derived from Stirling formula.

**Definition 1.** The Kullback-Leibler between a vector  $\mathbf{Z} \in \mathbb{R}^T$  and a vector  $\mathbf{p} \in \mathbb{R}^T$  is defined in a fully separable manner as

$$d_{KL}(\mathbf{Z}|\mathbf{p}) = \sum_{t=1}^T d_{KL}(Z_t|p_t), \text{ where } d_{KL}(Z_t|p_t) = \begin{cases} Z_t \ln \left( \frac{Z_t}{p_t} \right) + p_t - Z_t & \text{if } Z_t > 0, p_t > 0 \\ p_t & \text{if } Z_t = 0, p_t \geq 0 \\ \infty & \text{otherwise.} \end{cases}$$

If  $\mathbf{Z} \in \mathbb{N}^T$  is a vector of nonnegative integer observations, it quantifies the discrepancy between  $\mathbf{Z}$  and a vector of Poisson random variables of parameters  $\mathbf{p}$ .

Thus, the opposite log-likelihood associated to Cori's model (1) expresses in terms of the Kullback-Leibler divergence as

$$-\ln \mathcal{L}(\mathbf{Z}|\mathbf{R}) = d_{KL}(\mathbf{Z}|\mathbf{R} \odot \Phi^{\mathbf{Z}}) \tag{2}$$

where  $\mathbf{R} \odot \Phi^{\mathbf{Z}}$  denotes the component-wise vector product,  $(\mathbf{R} \odot \Phi^{\mathbf{Z}})_t = R_t \Phi_t^{\mathbf{Z}}$ .

- b. For  $Z_t$  fixed at  $Z_t \in \{0, 10, 250\}$  plot the function  $p_t \mapsto d_{KL}(Z_t|p_t)$ .
- c. Show that the function  $p_t \mapsto d_{KL}(Z_t|p_t)$  is convex and differentiable.
- d. Is the gradient of  $p_t \mapsto d_{KL}(Z_t|p_t)$  Lipschitzian? Justify your answer.

## 2 Estimation of the reproduction number

### 2.1 Maximum Likelihood Estimator

- a. Given fixed  $Z_t$  and  $\Phi_t^{\mathbf{Z}} = \sum_{u=1}^{\tau_{\Phi}} \phi(u) Z_{t-u}$ , compute the minimum and the minimizer of the function  $d_{KL} : R_t \mapsto d_{KL}(Z_t|R_t \Phi_t^{\mathbf{Z}})$ .
- b. Deduce the minimum and the minimizer  $\hat{\mathbf{R}}^{MLE}$  of the Kullback-Leibler divergence

$$D_{KL} : \begin{cases} \mathbb{R}^T & \rightarrow \mathbb{R} \\ \mathbf{R} & \mapsto \sum_{t=1}^T d_{KL}(Z_t|R_t \Phi_t^{\mathbf{Z}}).$$

This minimizer is denoted  $\hat{\mathbf{R}}^{MLE}$  because it is the *Maximum Likelihood Estimator* of  $\mathbf{R}$ .

Indeed, as stated in Equation (2), the Kullback-Leibler divergence is the opposite log-likelihood of the Poisson model, thus minimizing  $d_{KL}(\mathbf{Z}|\mathbf{R} \odot \Phi^{\mathbf{Z}})$  amounts to maximize the likelihood  $\mathcal{L}(\mathbf{Z}|\mathbf{R})$ .

- c. Compute numerically the Maximum Likelihood Estimate from the data  $\mathbf{Z}$ , named  $Z$  in the file `data_covid.mat`, and the global infectiousness  $\Phi^{\mathbf{Z}}$ , named `PhiZ` in `data_covid.mat`. Plot it and comment about its temporal behavior.
- d. Would you advocate the use of the Maximum Likelihood Estimator to monitor the COVID-19 pandemic? Explain why.

## 2.2 Penalized likelihood

In order to enforce some regularity on the temporal behavior of  $R_t$  we consider the penalized likelihood estimator

$$\widehat{\mathbf{R}} \in \operatorname{Argmin}_{\mathbf{R}} D_{\text{KL}}(\mathbf{Z} | \mathbf{R} \odot \Phi^{\mathbf{Z}}) + \lambda \|\mathbf{D}_2 \mathbf{R}\|_1, \quad (3)$$

where  $\mathbf{D}_2 : \mathbb{R}^T \rightarrow \mathbb{R}^{T-2}$  is the discrete Laplacian operator acting on  $\mathbb{R}^T$  as

$$\forall t \in \{1, 2, \dots, T-2\}, \quad (\mathbf{D}_2 \mathbf{R})_t = R_{t+2} - 2R_{t+1} + R_t.$$

The  $\ell_1$  penalization favors sparsity of the second order derivative of the estimate and thus  $\widehat{\mathbf{R}}$  is expected to be piecewise linear, with only a few days at which the slope of  $t \mapsto R_t$  is changing.

Because of the presence of the  $\ell_1$  norm in the objective function, (3) is a nonsmooth optimization problem. Thus one has to resort to proximal operators to solve it.

- a. Based on Question 1 d. explain why it is not possible to use the *forward-backward* algorithm.

To circumvent this limitation, we will use only proximity operators.

- b. For fixed  $Z_t$ , compute the proximity operator of  $p_t \mapsto d_{\text{KL}}(Z_t | p_t)$ .
- c. Given  $Z_t$  and  $\Phi_t^{\mathbf{Z}} = \sum_{u=1}^{\tau_{\Phi}} \phi(u) Z_{t-u}$ , deduce from 2 b. the expression of the proximity operator of  $R_t \mapsto d_{\text{KL}}(Z_t | R_t \Phi_t^{\mathbf{Z}})$ .
- d. Explain how to compute the proximity operator of

$$D_{\text{KL}} : \begin{cases} \mathbb{R}^T & \rightarrow \mathbb{R} \\ \mathbf{R} & \mapsto \sum_{t=1}^T d_{\text{KL}}(Z_t | R_t \Phi_t^{\mathbf{Z}}). \end{cases}$$

Because of the linear operator  $\mathbf{D}_2$  inside the  $\ell_1$  norm in (3), we do not have a closed-form expression of the proximity operator of the penalization  $\|\mathbf{D}_2 \mathbf{R}\|_1$  and hence it is necessary to use a *splitting* scheme. We will thus turn to the primal-dual algorithm proposed in [1]. To ensure convergence of **Algorithm 1**, the descent steps  $\tau > 0$  and  $\sigma > 0$  must be chosen so that  $\sigma\tau\|\mathbf{D}_2\|_{\text{op}}^2 < 1$ , where  $\|\mathbf{D}_2\|_{\text{op}}^2$  is the *operator norm* of  $\mathbf{D}_2$  defined as

$$\|\mathbf{D}_2\|_{\text{op}} = \sup_{\mathbf{R} \in \mathbb{R}^T, \mathbf{R} \neq \mathbf{0}} \frac{\|\mathbf{D}_2 \mathbf{R}\|}{\|\mathbf{R}\|}$$

To compute the operator norm of a matrix  $\mathbf{D}_2 \in \mathbb{R}^{T-2 \times T}$ , you can use the MATLAB function `norm(D2)` or the PYTHON function `numpy.linalg.norm(D2, ord = 2)`. A standard choice for the descent steps is  $\sigma = \tau = 0.99/\|\mathbf{D}_2\|_{\text{op}}$ . Feel free to explore other choices satisfying the convergence condition.

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**Algorithm 1** Primal-dual minimization of the penalized Kullback-Leibler (3) for the estimation of reproduction numbers.

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**Require:** Infection counts:  $\mathbf{Z} \in \mathbb{R}^T$  and  $\Phi^{\mathbf{Z}} \in \mathbb{R}^T$

Choose descent parameters:  $\tau, \sigma > 0$  such that  $\sigma\tau\|\mathbf{D}_2\|_{\text{op}}^2 < 1$

Max. iterations:  $k_{\max}$

**Initialization**  $\mathbf{R}^{[0]} = \mathbf{Z}/\Phi^{\mathbf{Z}}$

$\mathbf{Q}^{[0]} = \mathbf{D}_2 \mathbf{R}^{[0]}, \bar{\mathbf{R}}^{[0]} = \mathbf{R}^{[0]}$

**while**  $k < k_{\max}$  **do**

$$\begin{aligned} \mathbf{Q}^{[k+1]} &= \mathbf{Q}^{[k]} + \sigma \mathbf{D}_2 \bar{\mathbf{R}}^{[k]} - \sigma \operatorname{prox}_{\lambda\sigma^{-1}\|\cdot\|_1} \left( \sigma^{-1} \mathbf{Q}^{[k]} + \mathbf{D}_2 \bar{\mathbf{R}}^{[k]} \right) \\ \mathbf{R}^{[k+1]} &= \operatorname{prox}_{\tau D_{\text{KL}}(\mathbf{Z} \cdot \odot \Phi^{\mathbf{Z}})}(\mathbf{R}^{[k]} - \tau \mathbf{D}_2^* \mathbf{Q}^{[k+1]}) \\ \bar{\mathbf{R}}^{[k+1]} &= 2\mathbf{R}^{[k+1]} - \mathbf{R}^{[k]} \end{aligned}$$

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$k \leftarrow k + 1$   
**end while**

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- e. Compute the proximity operator of the  $\ell_1$  norm multiplied by a scalar  $\lambda\sigma^{-1}$ , that is of  $\lambda\sigma^{-1}\|\cdot\|_1 : \mathbf{Q} \in \mathbb{R}^N \mapsto \sum_{n=1}^N \lambda\sigma^{-1}|Q_n| \in \mathbb{R}$  and explain how to compute it in practice.

f. Construct the  $T - 2 \times T$  matrix of the discrete Laplacian  $\mathbf{D}_2$ .

g. Show that by setting  $\tilde{\mathbf{Z}} := \mathbf{Z}/\alpha$  for some  $\alpha > 0$ ,

$$D_{KL}(\tilde{\mathbf{Z}}|\mathbf{R}^{[k]} \odot \Phi^{\tilde{\mathbf{Z}}}) = \frac{1}{\alpha} D_{KL}(\mathbf{Z}|\mathbf{R}^{[k]} \odot \Phi^{\mathbf{Z}}). \quad (4)$$

Justify that running **Algorithm 1** with  $\mathbf{Z}$  and  $\Phi^{\mathbf{Z}}$  as input, with a given  $\lambda$  vs. with  $\tilde{\mathbf{Z}}$  and  $\Phi^{\tilde{\mathbf{Z}}}$  with  $\tilde{\lambda} := \lambda/\text{std}(\mathbf{Z})$  give the same reproduction number estimate  $\hat{\mathbf{R}}$ .

From now on, when running **Algorithm 1**, replace  $\mathbf{Z}$  by  $\mathbf{Z}/\text{std}(\mathbf{Z})$  and  $\Phi^{\mathbf{Z}}$  by  $\Phi^{\mathbf{Z}}/\text{std}(\mathbf{Z})$ . Take into account that this amounts to replace  $\lambda$  by  $\tilde{\lambda} := \lambda/\text{std}(\mathbf{Z})$ . This normalization of input data improve the numerical robustness of the algorithmic scheme: it is to be seen as a purely numerical trick.

h. Implement **Algorithm 1** and run it on the data  $\mathbf{Z}$ . Plot the estimated reproduction number  $\mathbf{R}$  and the evolution of the objective function

$$k \mapsto D_{KL}(\mathbf{Z}|\mathbf{R}^{[k]} \odot \Phi^{\mathbf{Z}}) + \lambda \|\mathbf{D}_2 \mathbf{R}^{[k]}\|_1 \quad (5)$$

along iterations to illustrate convergence of the scheme.

i. Run **Algorithm 1** for different values of the regularization parameter  $\tilde{\lambda}$  and comment on its influence on the estimated reproduction number  $\mathbf{R}$ . A possibility is to consider  $\tilde{\lambda} \in \{0.5, 3.5, 15, 50, 150, 250\}$ <sup>3</sup>.

## References

- [1] A. Chambolle and T. Pock. A first-order primal-dual algorithm for convex problems with applications to imaging. *Journal of Mathematical Imaging and Vision*, 40(1):120–145, 2011.
- [2] A. Cori, N. M. Ferguson, C. Fraser, and S. Cauchemez. A new framework and software to estimate time-varying reproduction numbers during epidemics. *American Journal of Epidemiology*, 178(9):1505–1512, 2013.
- [3] Q.-H. Liu, M. Ajelli, A. Aleta, S. Merler, Y. Moreno, and A. Vespignani. Measurability of the epidemic reproduction number in data-driven contact networks. *Proceedings of the National Academy of Sciences*, 115(50):12680–12685, 2018.

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<sup>3</sup>This correspond to non normalized regularization parameters  $\lambda \in \{0.5 \times \text{std}(\mathbf{Z}), 3.5 \times \text{std}(\mathbf{Z}), 15 \times \text{std}(\mathbf{Z}), 50 \times \text{std}(\mathbf{Z}), 150 \times \text{std}(\mathbf{Z}), 250 \times \text{std}(\mathbf{Z})\}$ .