

# The EpiLPS project: a new Bayesian tool for estimating the time-varying reproduction number

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28th Annual Meeting of the Royal Statistical Society of Belgium  
October 22, 2021

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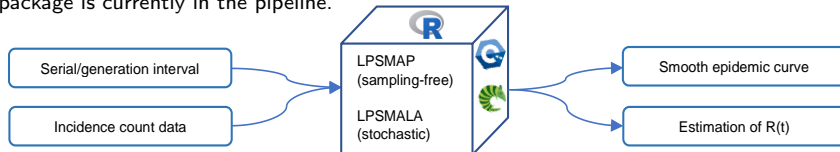
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## What is EpiLPS?

- ▶ **Epidemiological modelling (tool) with Laplacian-P-Splines.**
- ▶ Reproduction number  $R(t)$ : key metric to assess disease dynamics.
- ▶ A novel methodology for fast and flexible (approximate) Bayesian inference of  $R(t)$ .
  - \* Laplace approximations  $\Rightarrow$  computationally very attractive.
  - \* P-splines  $\Rightarrow$  flexible modeling framework with smooth estimates of the epidemic curve and  $R(t)$ .
- ▶ A set of (efficient) routines with intuitive functional calls for the end user.
- ▶ R package is currently in the pipeline.



## What motivated EpiLPS?

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**An approximate Bayesian approach for estimation of the reproduction number under misreported epidemic data**

Oswaldo Gressani, Christel Faes, Niel Hens  
doi: <https://doi.org/10.1101/2021.05.19.21257438>

*This article is a preprint and has not been peer-reviewed [what does this mean?].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.*

Abstract

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- ▶ Revisit model of [Azmon et al. \(2013\)](#)
- ▶ Will Laplace approximations do the job?

# Bayes' theorem and the Laplace approximation in a nutshell

- ▶ Laplace approx. → key for making EpiLPS lightning fast, but what is it really?

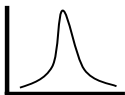
Likelihood (Data)

Prior beliefs

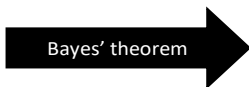
Posterior distribution



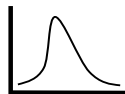
$p(\mathbf{D}|\Theta)$



$p(\Theta)$



Bayes' theorem  
 $p(\Theta|\mathbf{D}) \propto p(\mathbf{D}|\Theta) p(\Theta)$



$p(\Theta|\mathbf{D})$

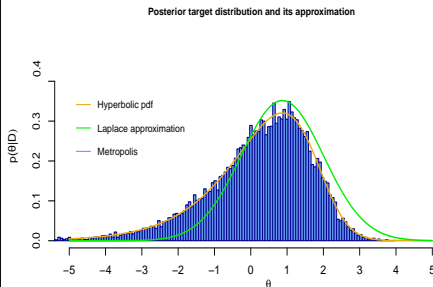
- ▶ Laplace approx.: simplify  $p(\theta|\mathcal{D})$  but retain crucial features.
- ▶ Taylor expansion of  $g(\theta) := \log p(\theta|\mathcal{D})$  around modal value  $\hat{\theta}$ :

$$g(\theta) \approx g(\hat{\theta}) + \frac{1}{2} g''(\hat{\theta})(\theta - \hat{\theta})^2.$$

- ▶ Apply exponential function on both sides:

$$\begin{aligned} \tilde{p}_G(\theta|\mathcal{D}) &\propto \exp\left(-\frac{1}{2}(-g''(\hat{\theta}))(\theta - \hat{\theta})^2\right) \\ \Rightarrow \mathcal{N}(\hat{\theta}, (-g''(\hat{\theta}))^{-1}). \end{aligned}$$

- ▶ Ex: Hyperbolic distribution.



# The “Epi” part: smoothing incidence count data

- ▶ Let  $\{y_t, t = 1, \dots, T\}$  be a time series of incidence counts.
- ▶ Negative Binomial model for  $y_t$ , i.e.  $y_t \sim \text{NegBin}(\mu(t), \rho)$  following the parameterization of [Piegorsch \(1990\)](#):

$$p(y_t | \mu(t), \rho) = \frac{\Gamma(y_t + \rho)}{\Gamma(y_t + 1)\Gamma(\rho)} \left( \frac{\mu(t)}{\mu(t) + \rho} \right)^{y_t} \left( \frac{\rho}{\rho + \mu(t)} \right)^\rho, \quad \mu(t) > 0, \quad \rho > 0.$$

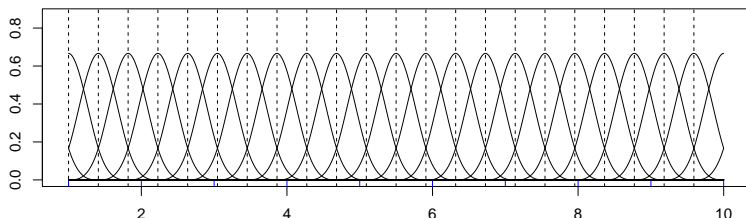
- ▶ Following [Eilers and Marx \(1996\)](#), we model  $\mathbb{E}(y_t) = \mu(t)$  by means of cubic B-splines with amplitudes  $\theta_k$ :

$$\log(\mu(t)) = \sum_{k=1}^K \theta_k b_k(t) = \boldsymbol{\theta}^\top \mathbf{b}(t).$$

- ▶ Idea of P-splines: Fix  $K$  large enough and counterbalance the flexibility by introducing a roughness penalty on adjacent B-spline coefficients:  $\lambda \boldsymbol{\theta}^\top \mathbf{P} \boldsymbol{\theta}$ .
- ▶  $\mathbf{P}$  is a penalty matrix and  $\lambda > 0$  is the roughness penalty parameter to be maximized *a posteriori*  $\rightarrow$  **LPSMAP**.

- ▶ B-spline basis defined on  $\mathcal{T} = [r_l, T]$ , where  $r_l$  is typically the first day of the epidemic (i.e.  $r_l = 1$ ). In the **blapsr** package:

```
> lb <- 1    # Lower bound
> ub <- 10   # Upper bound
> xdom <- seq(lb,ub)
> Bsmat <- cubicbs(xdom, lb, ub, 25)
> plot(Bsmat) # Plot the basis
```



- ▶ In the Bayesian version [Lang and Brezger \(2004\)](#), the vector of B-spline coefficients is random  $\Rightarrow$  Gaussian prior (based on random-walks).
- ▶ Also, priors on hyperparameters  $\lambda$  and  $\rho$  have to be specified.

- ▶ The Bayesian model formulation underlying EpiLPS is as follows:

$$\begin{aligned}y_t | \mu(t), \rho &\sim \text{NegBin}(\mu(t), \rho), \\ \log(\mu(t)) &= \boldsymbol{\theta}^\top \mathbf{b}(t), \\ \boldsymbol{\theta} | \lambda &\sim \mathcal{N}_{\dim(\boldsymbol{\theta})}(0, \mathbf{Q}_\lambda^{-1}), \\ \lambda | \delta &\sim \mathcal{G}(\phi/2, (\phi\delta)/2), \\ \delta &\sim \mathcal{G}(a_\delta, b_\delta), \\ \rho &\sim \mathcal{G}(a_\rho, b_\rho).\end{aligned}$$

- ▶ We fix  $\phi = 2$ ,  $a_\delta = b_\delta = 10$  and a proper (uninformative) prior on  $\rho$  with  $a_\rho = b_\rho = 10^{-4}$ .
- ▶ Denote by  $\boldsymbol{\eta} := (\lambda, \rho)^\top$ , the vector of model hyperparameters (to be optimized).
- ▶ Laplace approximations are used to approximate the posterior of  $\boldsymbol{\theta}$  in three steps.

# The “mechanics” of Laplacian-P-splines in 3 steps

- ▶ Objective: come up with approximated posteriors for  $\theta$  and  $\eta = (\lambda, \rho)^\top$ .
- ▶ Gaussian prior  $\theta|\eta \sim \mathcal{N}$  (LGM). Main goal is to approximate the joint posterior:

$$\begin{aligned} p(\theta|\mathcal{D}) &= \int p(\theta, \eta|\mathcal{D}) d\eta \\ &= \int p(\theta|\eta, \mathcal{D}) p(\eta|\mathcal{D}) d\eta. \end{aligned}$$

- ▶ In the philosophy of Tierney and Kadane (1986) and Rue et al. (2009):
  1. Laplace approximation to the conditional posterior:

$$p(\theta|\eta, \mathcal{D}) \rightarrow \tilde{p}_G(\theta|\eta, \mathcal{D}).$$

2. Approximation of the hyperparameter vector:

$$p(\eta|\mathcal{D}) = \frac{p(\theta, \eta|\mathcal{D})}{p(\theta|\eta, \mathcal{D})} \rightarrow \tilde{p}(\eta|\mathcal{D}) = \frac{p(\theta, \eta|\mathcal{D})}{\tilde{p}_G(\theta|\eta, \mathcal{D})} \bigg|_{\theta=\hat{\theta}(\eta)}.$$

3. Approximation at the MAP for  $\eta$  (but other possibilities exist):

$$\tilde{p}(\theta|\mathcal{D}) = \mathcal{N}_{\dim(\theta)}(\theta^*(\eta^*), \Sigma^*(\eta^*)).$$

# The renewal equation “plug-in” estimator

- ▶ Remember what we have so far:  $\tilde{p}(\theta|\mathcal{D}) = \mathcal{N}_{\dim(\theta)}(\theta^*(\eta^*), \Sigma^*(\eta^*))$ .
- ▶ Denote by  $\varphi = \{\varphi_1, \dots, \varphi_k\}$  the serial interval distribution and let  $\hat{\theta} := \theta^*(\eta^*)$ .
- ▶ Start with the renewal equation:  $y_t = \sum_s R(t) \varphi_s y_{t-s}$  and write it as:

$$R(t) = \begin{cases} y_t & ; \text{for } t = 1, \\ y_t \left( \sum_{s=1}^{t-1} \varphi_s y_{t-s} \right)^{-1} & ; \text{for } 2 \leq t \leq k, \\ y_t \left( \sum_{s=1}^k \varphi_s y_{t-s} \right)^{-1} & ; \text{for } k < t \leq T. \end{cases}$$

- ▶ Replace  $y_t$  by  $\hat{\mu}(t) = \exp(\hat{\theta}^\top b(t))$  and write in compact notation:

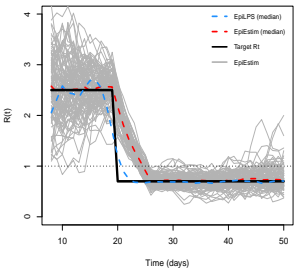
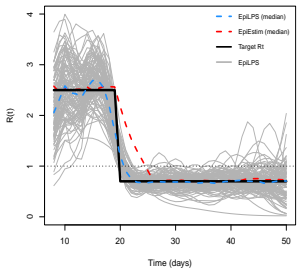
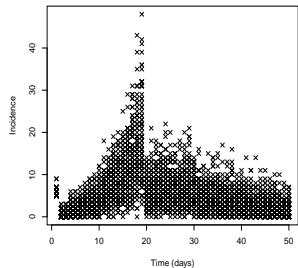
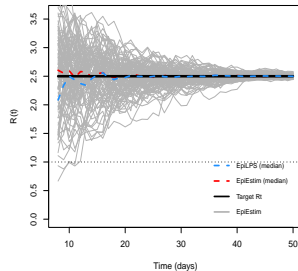
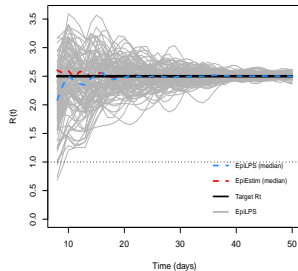
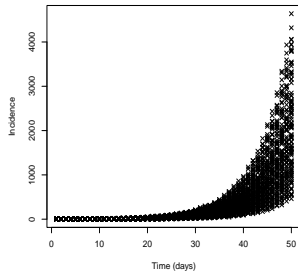
$$\begin{aligned} \hat{R}(t) = & \exp(\hat{\theta}^\top b(t)) \left\{ \mathbb{I}(t=1) + \left( \sum_{s=1}^{t-1} \varphi_s \exp(\hat{\theta}^\top b(t-s)) \right)^{-1} \mathbb{I}(2 \leq t \leq k) \right. \\ & \left. + \left( \sum_{s=1}^k \varphi_s \exp(\hat{\theta}^\top b(t-s)) \right)^{-1} \mathbb{I}(k < t \leq T) \right\}. \end{aligned}$$



- ▶ Consider an epidemic of  $T = 50$  days.
- ▶ Data generating process based on Poisson counts and the renewal equation  $\rightarrow$  repeat  $S = 100$  times.
- ▶ Compare with *estimate\_R()* routine of **EpiEstim** package [Cori et al. \(2013\)](#).
- ▶ For **EpiEstim**, we need to specify a sliding window, (here 7 days).
- ▶ Four different scenarios:
  - ▶ Scenario 1: constant  $R(t)$ .
  - ▶ Scenario 2: assess impact of intervention, step function for  $R(t)$ .
  - ▶ Scenario 3: curved  $R(t)$ .
  - ▶ Scenario 4: decaying  $R(t)$ .

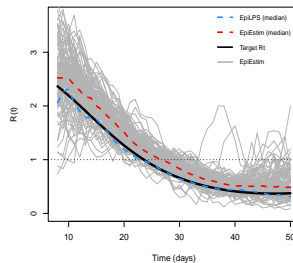
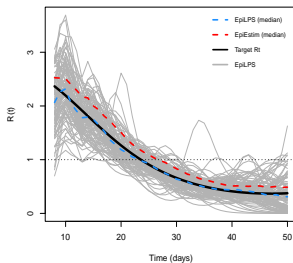
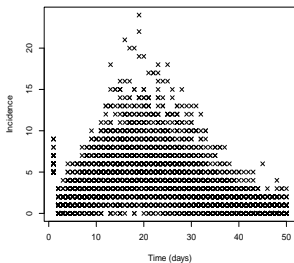
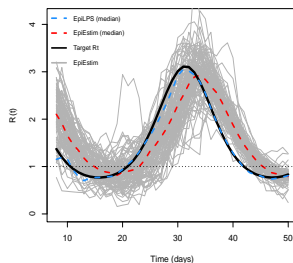
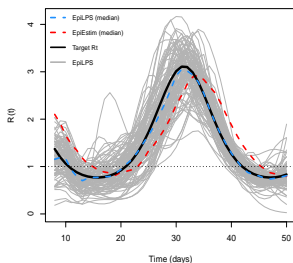
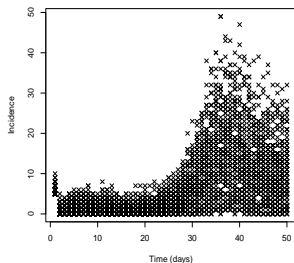
# Scenarios 1 and 2

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# Scenarios 3 and 4

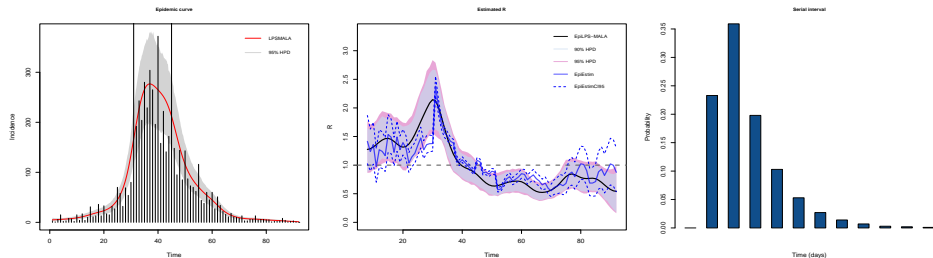
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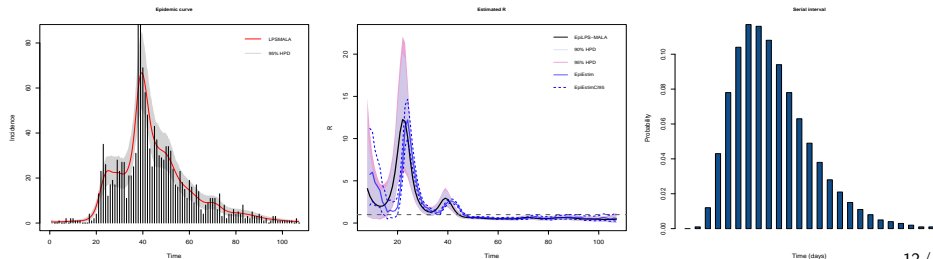
# Real data applications with LPSMALA

We revisited historical outbreaks analyzed in [Cori et al. \(2013\)](#) with LPSMALA.

## ► Influenza pandemic in Baltimore (1918)



## ► SARS epidemic in Hong Kong (2003)



Main methodological differences between EpiLPS and EpiEstim:

- ▶ EpiLPS extracts a signal from the epidemic curve (smoothed version of mean incidence counts) and injects it into the renewal equation. Priors imposed on overdispersion parameter and smoothing parameter.
- ▶ EpiEstim imposes a (conjugate) Gamma prior on  $R(t)$ , so that *a posteriori*  $R(t)$  is also Gamma distributed. In [Cori et al. \(2013\)](#), they assume a Gamma prior with mean 5 and standard deviation 5.
- ▶ In EpiLPS, we show that *a posteriori*  $R(t)$  has a log-normal distribution.
- ▶ EpiEstim uses a Poisson distribution to model transmissions, while EpiLPS uses a Negative Binomial model (accounts for overdispersion).
- ▶ In EpiLPS no need to choose a time window, simply estimate  $R(t)$  over the whole time interval of interest. EpiEstim requires a specification of a time window as an input (what is the optimal sliding window?).

- ▶ EpiLPS is a novel methodology for fast and flexible approximate Bayesian inference of the epidemic curve and the time-varying reproduction number  $R(t)$ .
- ▶ The computational efficiency is mainly due to Laplace approximations and its associated routine coded in C++ and integrated via Rcpp.
- ▶ The Bayesian P-splines framework allows to get smooth estimates of the epidemic curve and the latter information is used in conjunction with the epidemic renewal equation to provide a smooth estimate of  $R(t)$ .
- ▶ Credible intervals of  $R(t)$  can be efficiently computed via the delta method.
- ▶ EpiLPS provides both a sampling-free approach (LPSMAP) and a fully stochastic approach based on Langevin diffusions (LPSMALA) to estimate  $R(t)$ .

**Acknowledgments:** This project is funded by the European Union's Research and Innovation Action under the H2020 work programme, EpiPose (grant number 101003688).



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