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

Oswaldo Gressani [a], Jacco Wallinga [b,c], Christian Althaus [d], Niel Hens [a,e], Christel Faes [a]

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[a] Interuniversity Institute for Biostatistics and statistical Bioinformatics (I-BioStat), Data Science Institute, Hasselt University, Belgium.
[b] Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, The Netherlands.
[c] Department of Biomedical Data Sciences, Leiden University Medical Centre, Leiden, The Netherlands.
[d] Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland.
[e] Centre for Health Economics Research and Modelling Infectious Diseases, Vaxinfectio, University of Antwerp, Belgium.

What is EpiLPS?

- **Epi**demiological modelling (tool) with **L**aplacian-**P**-**S**plines.
- 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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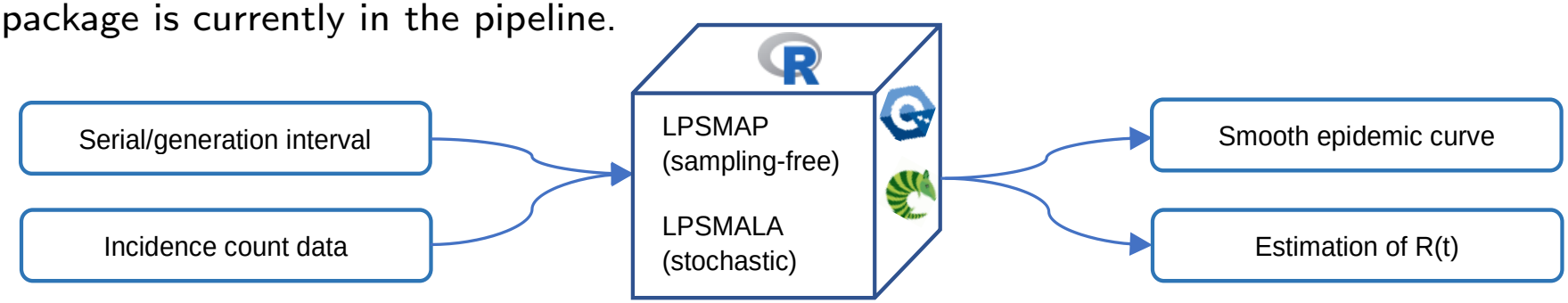
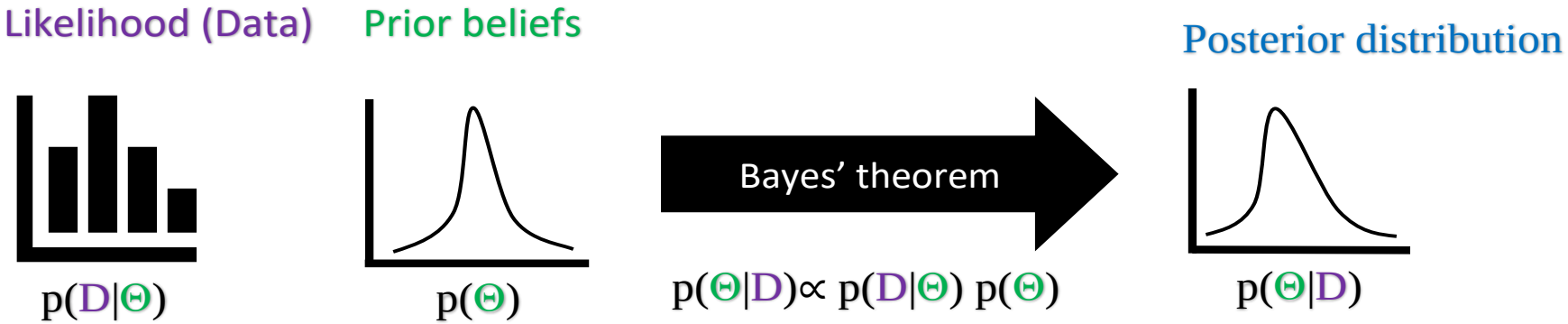
- Revisit model of Azmon et al. (2013)
- Will Laplace approximations do the job?



Bayes' theorem and the Laplace approximation in a nutshell

- Laplace approx. $\rightarrow$ key for making EpiLPS lightning fast, but what is it really?



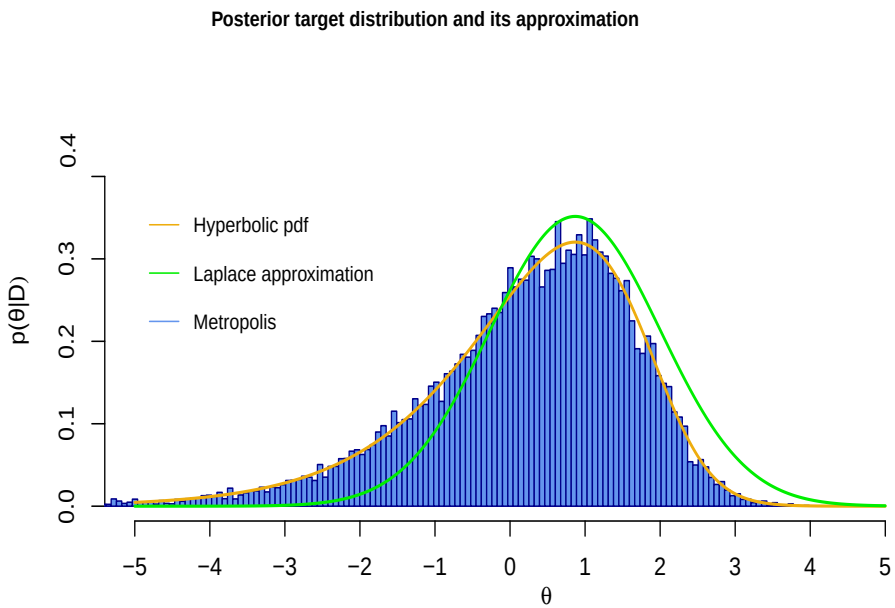
- Laplace approx.: simplify $p(\theta|\mathcal{D})$ but retain crucial features.
- Taylor expansion of $g(\theta) := \log p(\theta|\mathcal{D})$ around modal value $\hat{\theta}$:

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

- Apply exponential function on both sides:

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

- Ex: Hyperbolic distribution.



- Let $\{y_t, t = 1, \ldots, T\}$ 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):

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

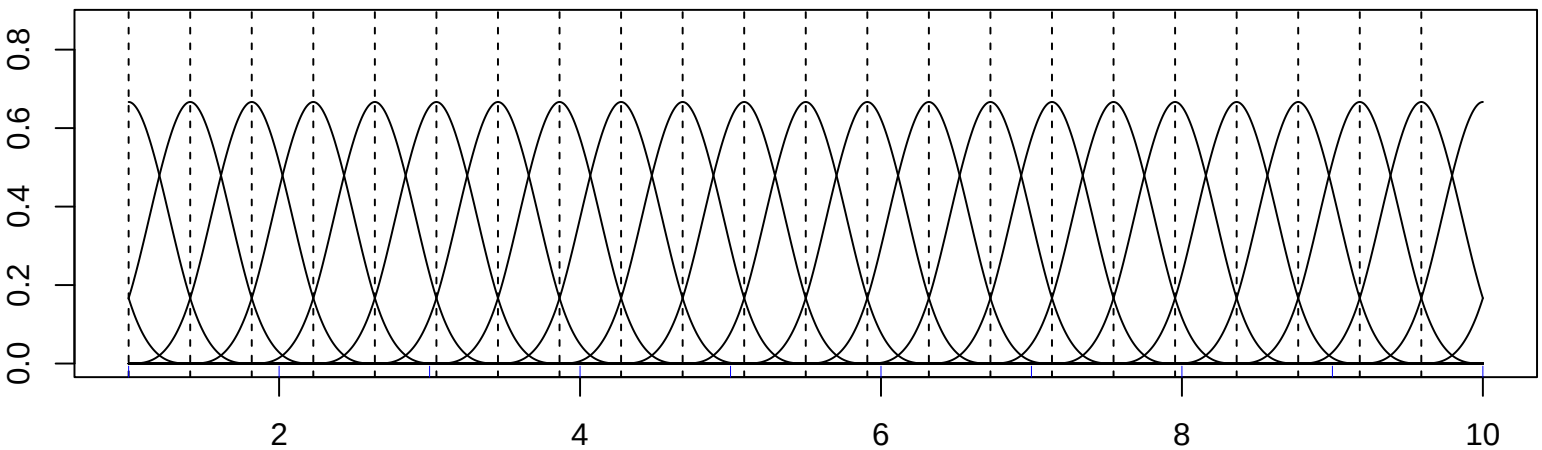
- Following Eilers and Marx (1996), we model $\mathbb{E}(y_t) = \mu(t)$ by means of cubic B-splines with amplitudes θ_k:

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

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

- 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 λ and ρ have to be specified.

- The Bayesian model formulation underlying EpiLPS is as follows:

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

- We fix $\phi = 2$, $a_\delta = b_\delta = 10$ and a proper (uninformative) prior on ρ 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 $\boldsymbol{\theta}$ and $\boldsymbol{\eta} = (\lambda, \rho)^\top$.
- Gaussian prior $\boldsymbol{\theta}|\boldsymbol{\eta} \sim \mathcal{N}$ (LGM). Main goal is to approximate the joint posterior:

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

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

$$p(\boldsymbol{\theta}|\boldsymbol{\eta}, \mathcal{D}) \to \widetilde{p}_G(\boldsymbol{\theta}|\boldsymbol{\eta}, \mathcal{D}).$$

  2. Approximation of the hyperparameter vector:

$$p(\boldsymbol{\eta}|\mathcal{D}) = \frac{p(\boldsymbol{\theta}, \boldsymbol{\eta}|\mathcal{D})}{p(\boldsymbol{\theta}|\boldsymbol{\eta}, \mathcal{D})} \to \widetilde{p}(\boldsymbol{\eta}|\mathcal{D}) = \left.\frac{p(\boldsymbol{\theta}, \boldsymbol{\eta}|\mathcal{D})}{\widetilde{p}_G(\boldsymbol{\theta}|\boldsymbol{\eta}, \mathcal{D})}\right|_{\boldsymbol{\theta}=\widehat{\boldsymbol{\theta}}(\boldsymbol{\eta})}.$$

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

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

The renewal equation "plug-in" estimator

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

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

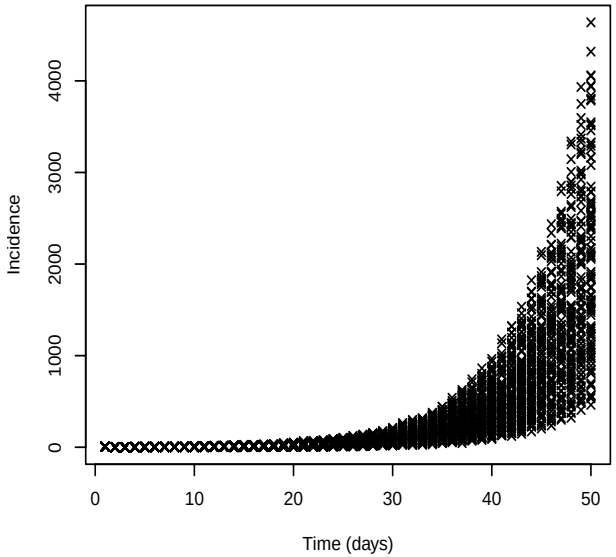
- Replace y_t by $\widehat{\mu}(t) = \exp\left(\widehat{\boldsymbol{\theta}}^\top b(t)\right)$ and write in compact notation:

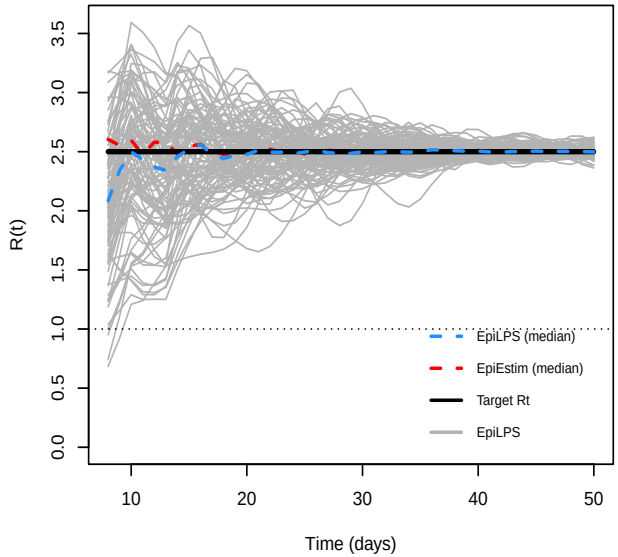
$$\begin{aligned} \widehat{R}(t) \quad = \quad & \exp\left(\widehat{\boldsymbol{\theta}}^\top b(t)\right) \Bigg\{ \mathbb{I}(t = 1) + \left(\sum_{s=1}^{t-1} \varphi_s \exp\left(\widehat{\boldsymbol{\theta}}^\top b(t-s)\right) \right)^{-1} \mathbb{I}(2 \leq t \leq k) \\ & + \left(\sum_{s=1}^{k} \varphi_s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

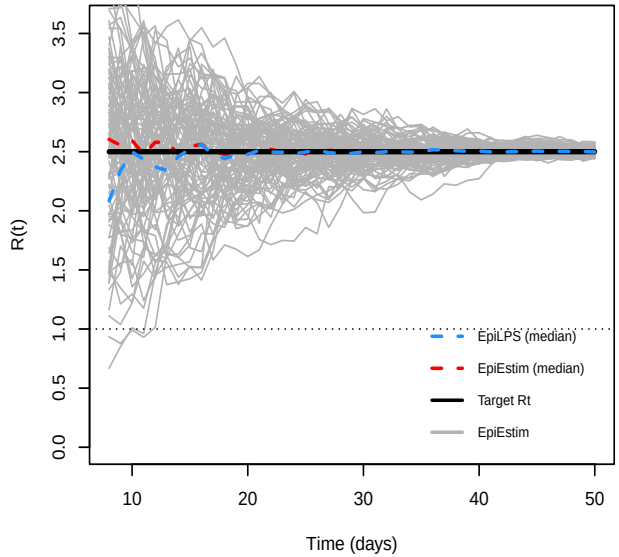
Validation of LPSMAP via simulations

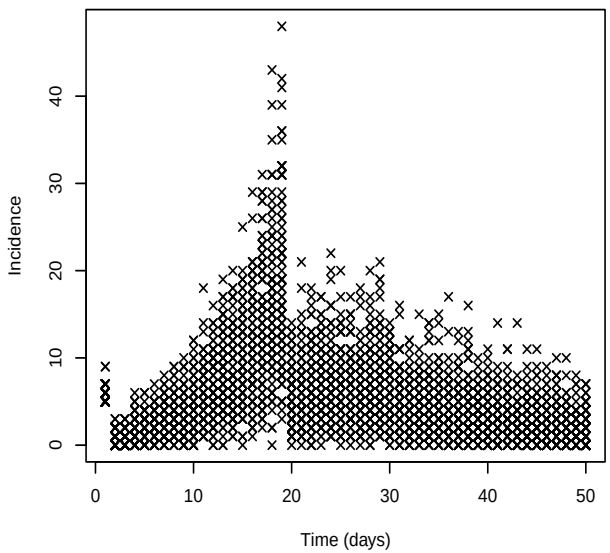
- Consider an epidemic of $T = 50$ days.
- Data generating process based on Poisson counts and the renewal equation $\rightarrow$ repeat $S = 100$ times.
- Compare with *estimate_R()* routine of **EpiEstim** package Cori et al. (2013).
- For **EpiEstim**, we need to specify a sliding window, (here 7 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 $R(t)$.

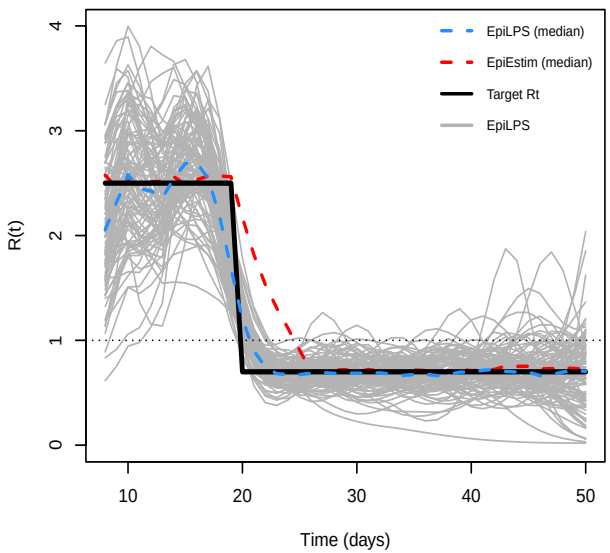
Scenarios 1 and 2

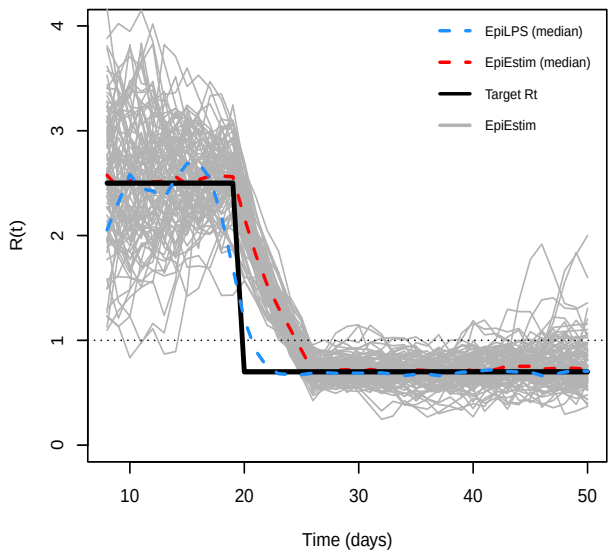




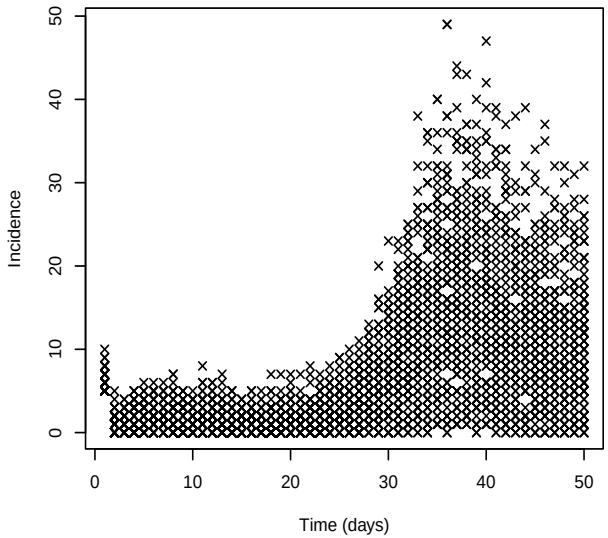


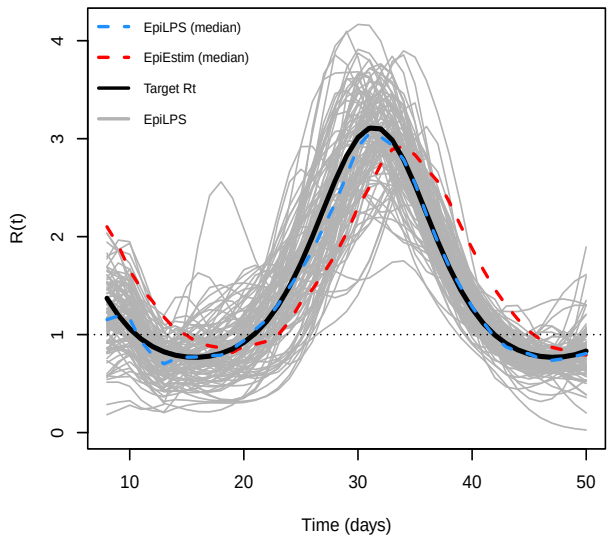


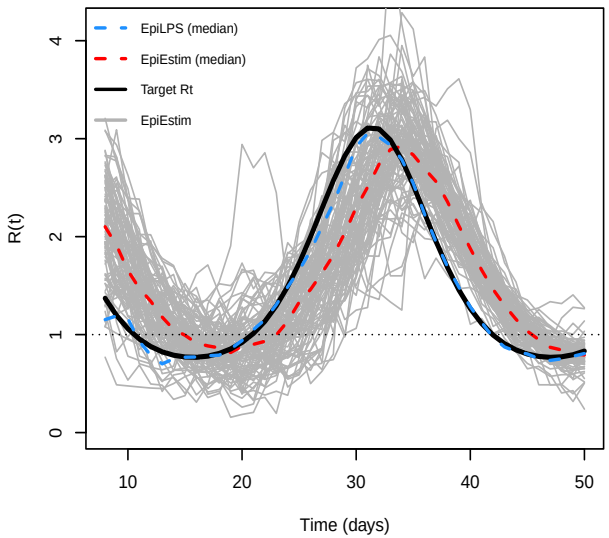


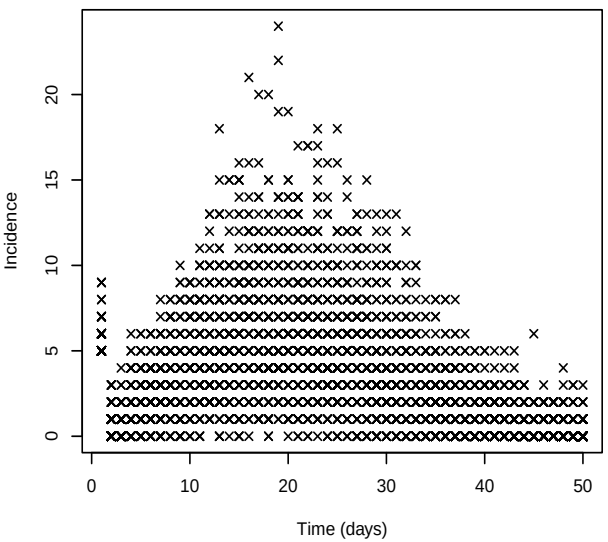


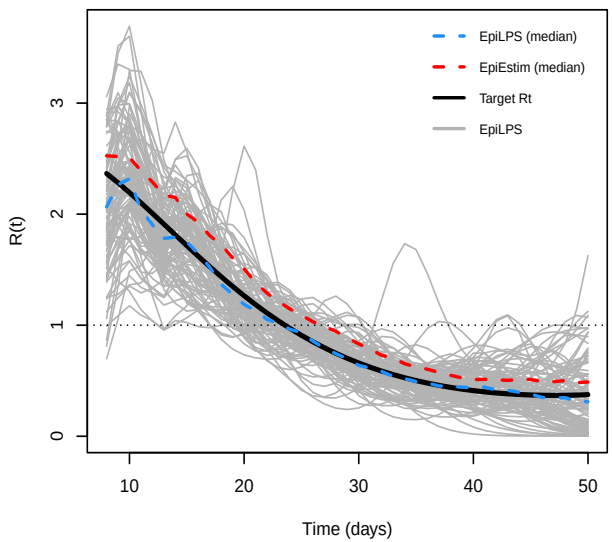
Scenarios 3 and 4

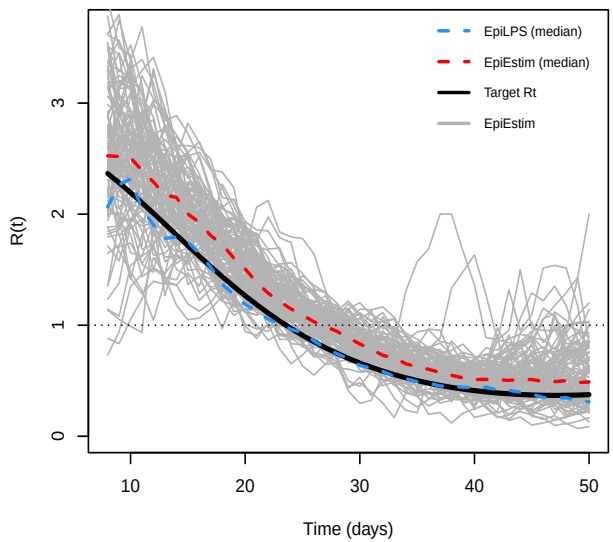








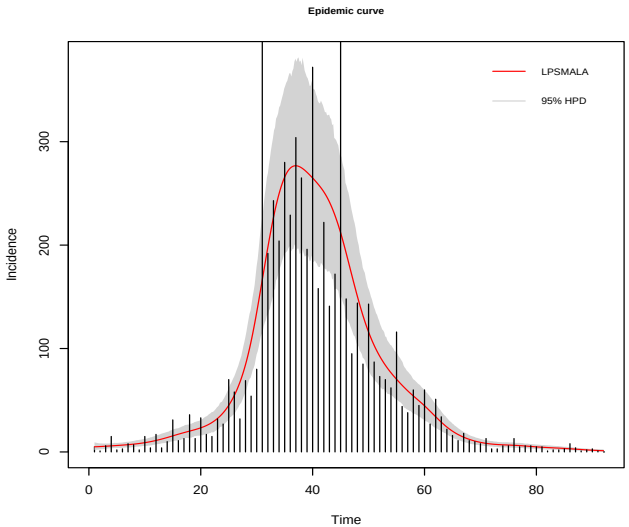


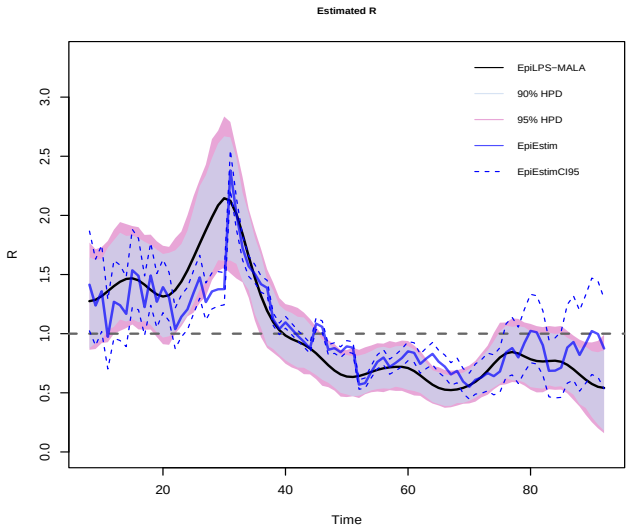


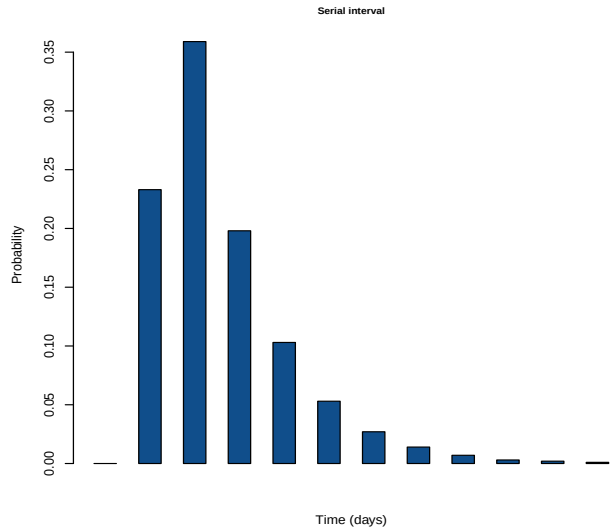
Real data applications with LPSMALA

We revisited historical outbreaks analyzed in Cori et al. (2013) with LPSMALA.

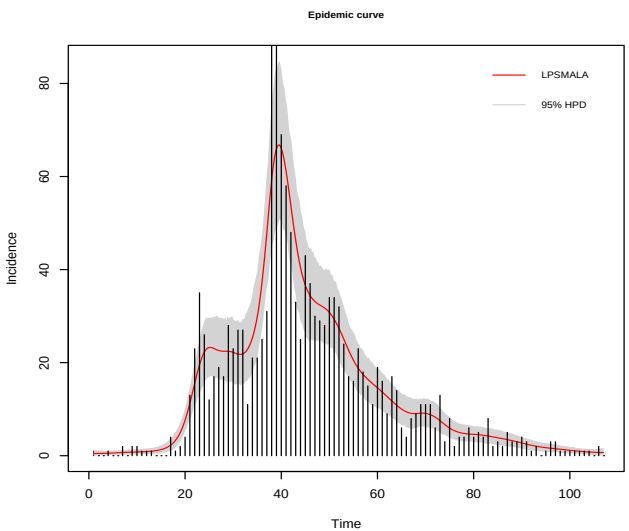
- Influenza pandemic in Baltimore (1918)

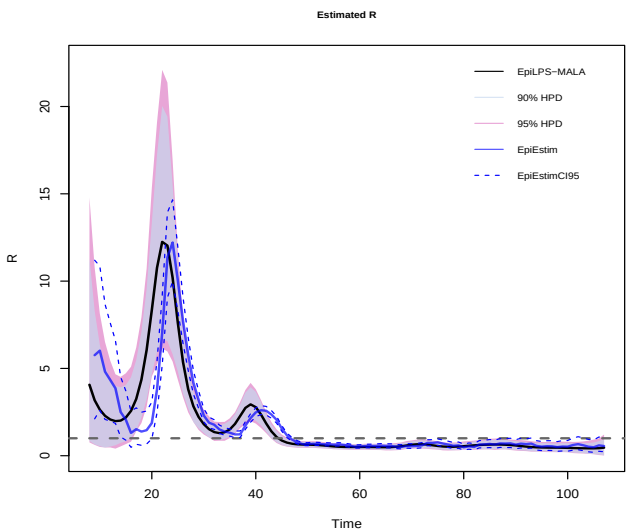


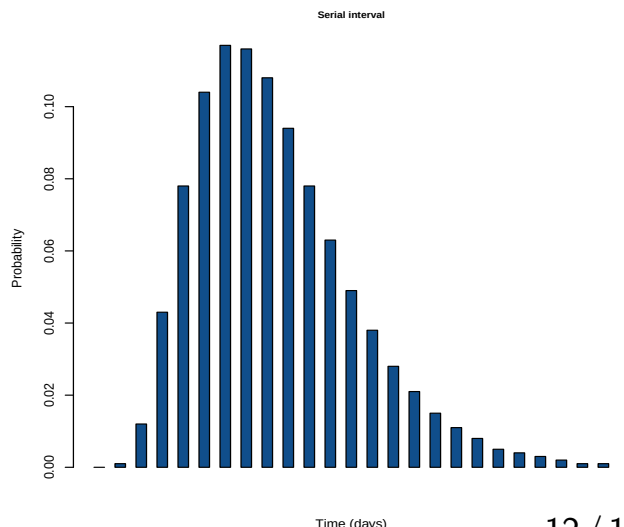




- SARS epidemic in Hong Kong (2003)







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?).

Concluding remarks and take home message

- 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 conjuction 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 $R(t)$.

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