# Nonparametric comparison of epidemic time trends: the case of COVID-19

Marina Khismatullina Michael Vogt April 2, 2021 University of Connecticut

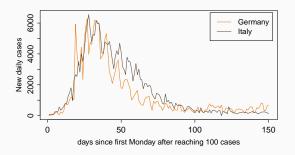
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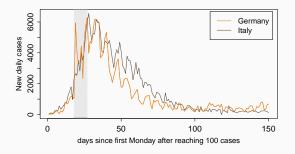
# Introduction

# Aim of the paper

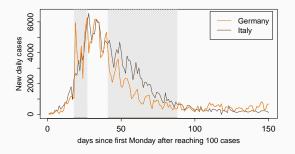
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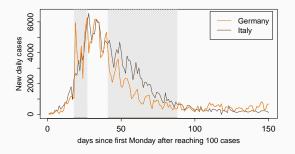


# Aim of the paper



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To develop new inference methods that allow to *identify* and *locate* differences between epidemic time trends.



**Research question:** Out of many given intervals, how to find those where the trends are significantly different?

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Finding systematic differences between trends = basis for further research

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#### Is it limited to COVID-19?

No! Our method = general method for comparing nonparametric trends

⇒ new statistical test for equality of nonparametric trend curves.

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In applications the variance can be larger than the mean  $\Rightarrow$  quasi-Poisson models.

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#### where

- $\lambda_i$  are unknown trend functions on [0, 1];
- $\sigma$  is the overdispersion parameter;
- η<sub>it</sub> are error terms that are independent across i and t and have zero mean and unit variance.

**Testing procedure** 

Let  $\mathcal{F}:=\{\mathcal{I}_k\subseteq [0,1]:1\leq k\leq K\}$  be a family of rescaled time intervals on [0,1], and for each triplet (i,j,k) consider the null hypothesis that the functions  $\lambda_i$  and  $\lambda_j$  are equal on an interval  $\mathcal{I}_k$ 

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$$H_0^{(ijk)}: \quad \lambda_i(w) = \lambda_j(w) \text{ for all } w \in \mathcal{I}_k$$

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We want to test  $H_0^{(ijk)}$  simultaneously for all pairs of countries i and j and all intervals  $\mathcal{I}_k$  in the family  $\mathcal{F}$  and we want to control the familywise error rate (FWER) at level  $\alpha$ 

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$$\mathsf{FWER}(lpha) = \mathrm{P}\Big(\exists (i,j,k) : \mathsf{we} \ \mathsf{wrongly} \ \mathsf{reject} \ \mathcal{H}_0^{(ijk)}\Big)$$

For a given interval  $\mathcal{I}_k$  and a pair of time series i and j we calculate

$$\hat{s}_{ijk} = rac{1}{Th_k} \sum_{t=1}^T \mathbb{1}\Big(rac{t}{T} \in \mathcal{I}_k\Big) (X_{it} - X_{jt}),$$

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$$\begin{split} \hat{s}_{ijk} &= \frac{1}{Th_k} \sum_{t=1}^{T} 1 \left( \frac{t}{T} \in \mathcal{I}_k \right) \left( \lambda_i \left( \frac{t}{T} \right) - \lambda_j \left( \frac{t}{T} \right) \right) \\ &+ \frac{\sigma}{Th_k} \sum_{t=1}^{T} 1 \left( \frac{t}{T} \in \mathcal{I}_k \right) \left( \sqrt{\lambda_i \left( \frac{t}{T} \right)} \eta_{it} - \sqrt{\lambda_j \left( \frac{t}{T} \right)} \eta_{jt} \right) \\ &= \frac{1}{Th_k} \sum_{t=1}^{T} 1 \left( \frac{t}{T} \in \mathcal{I}_k \right) \left( \lambda_i \left( \frac{t}{T} \right) - \lambda_j \left( \frac{t}{T} \right) \right) + o_P(1) \end{split}$$

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#### Test statistic, part 2

Under certain assumptions,

$$\operatorname{Var}(\hat{s}_{ijk}) = \frac{\sigma^2}{T^2 h_k^2} \sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right) \left\{\lambda_i\left(\frac{t}{T}\right) + \lambda_j\left(\frac{t}{T}\right)\right\}$$

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In order to normalize the variance of the statistic  $\hat{s}_{ijk}$ , we scale it by an estimator of its variance:

$$\widehat{\mathrm{Var}(\widehat{s}_{ijk})} = rac{\widehat{\sigma}^2}{T^2 h_k^2} \sum_{t=1}^T \mathbb{1}\Big(rac{t}{T} \in \mathcal{I}_k\Big)(X_{it} + X_{jt}),$$

with  $\hat{\sigma}^2$  being an appropriate estimator of  $\sigma^2$ . Details

#### Test statistic, part 3

Test statistic for the hypothesis  $H_0^{(ijk)}$  is defined as

$$\widehat{\psi}_{ijk} := \frac{\widehat{s}_{ijk}}{\sqrt{\widehat{\mathrm{Var}}(\widehat{s}_{ijk})}} = \frac{\sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right)(X_{it} - X_{jt})}{\widehat{\sigma}\left\{\sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right)(X_{it} + X_{jt})\right\}^{1/2}}$$

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- More modern approach:  $c_{ijk}(\alpha)$  depend on the length  $h_k$  of the time interval (Dümbgen and Spokoiny (2001)):

$$c_{ijk}(\alpha) = c(\alpha, h_k) := b_k + q(\alpha)/a_k,$$

where  $a_k$  and  $b_k$  are scale-dependent constants and  $q(\alpha)$  is chosen such that we control FWER. Details

We want to control FWER.

$$\mathsf{FWER}(\alpha) = \mathrm{P}\Big(\exists (i,j,k) \in \mathcal{M}_0 : |\widehat{\psi}_{ijk}| > c_{ijk}(\alpha)\Big)$$

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We want to control FWER. Let  $\mathcal{M}_0 := \left\{ (i,j,k) | H_0^{(ijk)} \text{ is true} \right\}$ , then

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Hence, we choose  $q(\alpha)$  as the  $(1-\alpha)$ -quantile of the statistic

$$\hat{\Psi}_T = \max_{(i,j,k)} a_k (|\hat{\psi}_{ijk}^0| - b_k),$$

where  $\hat{\psi}^0_{iik}$  is equal to  $\hat{\psi}_{ijk}$  under the null.

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which can be approximated by a Gaussian version of the test statistic:

$$\phi_{ijk} = \frac{1}{\sqrt{2Th_k}} \sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_k\right) (Z_{it} - Z_{jt}),$$

where  $Z_{it}$  are independent standard normal random variables.

1. Consider the Gaussian test statistic

$$\Phi_T = \max_{(i,j,k)} a_k (|\phi_{ijk}| - b_k),$$

where  $a_k$  and  $b_k$  are scale-dependent constants and  $\phi_{ijk}$  are weighted averages of the differences of standard normal random variables.

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#### Test procedure

For the given significance level  $\alpha \in (0,1)$  and for each (i,j,k), reject  $H_0^{(ijk)}$  if  $|\widehat{\psi}_{ijk}| > c_{\text{Gauss}}(\alpha,h_k)$ .

Theoretical properties

 ${\cal C}1$  The functions  $\lambda_i$  are uniformly Lipschitz continuous:

$$|\lambda_i(u)-\lambda_i(v)|\leq L|u-v| \text{ for all } u,v\in[0,1].$$

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 for all  $u, v \in [0, 1]$ .

C2 
$$0 < \lambda_{\min} \le \lambda_i(w) \le \lambda_{\max} < \infty$$
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- C2  $0 < \lambda_{\min} \le \lambda_i(w) \le \lambda_{\max} < \infty$  for all  $w \in [0,1]$  and all i.
- C3  $\eta_{it}$  are independent both across i and t.
- $\mathcal{C}4$   $\mathbb{E}[\eta_{it}] = 0$ ,  $\mathbb{E}[\eta_{it}^2] = 1$  and  $\mathbb{E}[|\eta_{it}|^{\theta}] \leq C_{\theta} < \infty$  for some  $\theta > 4$ .

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- C6  $p := \{\#(i, j, k)\} = O(T^{(\theta/2)(1-b)-(1+\delta)})$  for some small  $\delta > 0$ .

# Theoretical properties

#### **Proposition**

Let  $\mathcal{M}_0$  be the set of triplets (i, j, k) for which  $H_0^{(ijk)}$  holds true. Then under C1 - C6, it holds that

$$P\Big( orall (i,j,k) \in \mathcal{M}_0 : |\hat{\psi}_{ijk}| \leq c_{\mathsf{Gauss}}(lpha,h_k) \Big) \geq 1 - lpha + o(1)$$

# Theoretical properties

#### **Proposition**

Let  $\mathcal{M}_0$  be the set of triplets (i, j, k) for which  $H_0^{(ijk)}$  holds true. Then under  $\mathcal{C}1-\mathcal{C}6$ , it holds that

$$P\Big( orall (i,j,k) \in \mathcal{M}_0 : |\hat{\psi}_{ijk}| \le c_{\mathsf{Gauss}}(\alpha,h_k) \Big) \ge 1 - \alpha + o(1)$$

#### **Proposition**

Consider a sequence of functions  $\lambda_i = \lambda_{i,T}$ ,  $\lambda_j = \lambda_{j,T}$  such that

$$\exists \mathcal{I}_k : \lambda_i(w) - \lambda_j(w) \ge c_T \sqrt{\log T/(Th_k)} \ \forall w \in \mathcal{I}_k, \tag{1}$$

and  $c_T \to \infty$  faster than  $\frac{\sqrt{\log T} \sqrt{\log \log T}}{\log \log \log T}$ . Let  $\mathcal{M}_1$  be the set of triplets (i,j,k) for which (1) holds true. Then under  $\mathcal{C}1-\mathcal{C}6$ , it holds that

$$P\Big(orall (i,j,k)\in\mathcal{M}_1:|\hat{\psi}_{ijk}|>c_{\mathsf{Gauss}}(lpha,h_k)\Big)=1-o(1)$$

# Application

# **Graphical representation**

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Plot the results of pairwise comparison  $\mathcal{F}_{\text{reject}}(i,j)$ :

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#### Minimal intervals

An interval  $\mathcal{I}_k \in \mathcal{F}_{\mathsf{reject}}(i,j)$  is called **minimal** if there is no other interval  $\mathcal{I}_{k'} \in \mathcal{F}_{\mathsf{reject}}(i,j)$  with  $\mathcal{I}_{k'} \subset \mathcal{I}_k$ .

The set of minimal intervals is denoted  $\mathcal{F}_{\text{reject}}^{\min}(i,j)$ .

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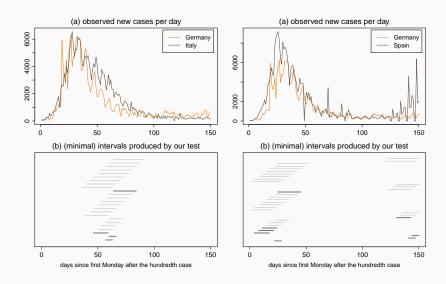
We can make similar confidence statements about minimal intervals:

$$P\Big(\forall (i,j,k) \in \mathcal{M}_0 : \mathcal{I}_k \notin \mathcal{F}^{\sf min}_{\sf reject}(i,j)\Big) \geq 1 - \alpha + o(1)$$

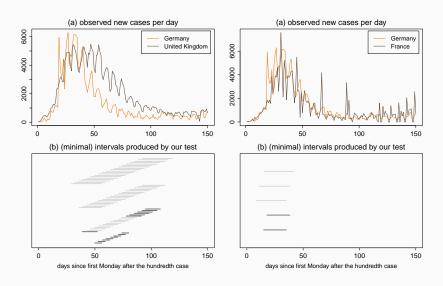
## **Application setting**

- Five countries: Germany, Italy, Spain, France and the UK.
- T = 150 days.
- The data is aligned by weekdays: first Monday after reaching 100 cases as t = 1.
- Lengths of time intervals 7, 14, 21, 28 days. The intervals start at days 1, 8, 15, ... and 4, 11, 19, ...
- $\alpha = 0.05$ .
- 5000 Monte Carlo simulation runs to produce critical values.

## **Application results**



## Application results, part 2



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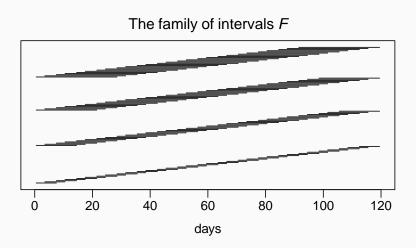
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#### Further possible extensions:

- introduce scaling factor in the trend function, that will allow to adjust for the size of the country (population, density, testing regimes, etc.);
- include dependence in the error terms;
- cluster the countries based on the trends they exhibit.

# Thank you!

# Family of time intervals



#### Simulation results for the size of the test

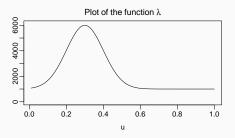


Table 1: Size of the multiscale test

	n=5 significance level $lpha$			$\mathit{n} = 10$ significance level $\alpha$			n=50 significance level $lpha$		
	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1
T = 100	0.011	0.047	0.093	0.010	0.044	0.087	0.008	0.037	0.075
T = 250	0.009	0.047	0.091	0.009	0.046	0.087	0.008	0.035	0.069
T = 500	0.010	0.044	0.083	0.008	0.048	0.093	0.007	0.035	0.077

## Simulation results for the power of the test

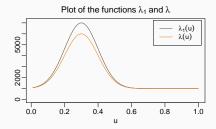


Table 2: Power of the multiscale test for scenario A

	$n=5$ significance level $\alpha$			$\mathit{n} = 10$ significance level $\alpha$			n = 50		
							significance level $\alpha$		
	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1
T = 100	0.335	0.518	0.597	0.306	0.474	0.545	0.212	0.352	0.418
T = 250	0.615	0.790	0.836	0.580	0.764	0.800	0.470	0.648	0.705
T = 500	0.736	0.905	0.917	0.738	0.884	0.890	0.636	0.799	0.830

## Simulation results for the power of the test

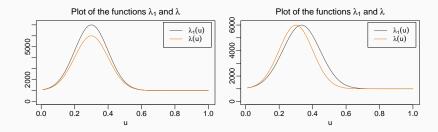


Table 3: Power of the multiscale test for scenario B

	n = 5			n = 10			n = 50		
	significance level $\alpha$			significance level $\alpha$			significance level $\alpha$		
	0.01	0.05	0.1	0.01	0.05	0.1	0.01	0.05	0.1
T = 100	0.824	0.910	0.903	0.812	0.893	0.890	0.738	0.847	0.857
T = 250	0.991	0.972	0.941	0.991	0.960	0.920	0.991	0.965	0.933
T = 500	0.997	0.973	0.949	0.995	0.961	0.923	0.996	0.969	0.932

We estimate the overdispersion paramter  $\sigma^2$  by

$$\hat{\sigma}^2 = \frac{1}{n} \sum_{i=1}^n \hat{\sigma}_i^2 \text{ and } \hat{\sigma}_i^2 = \frac{\sum_{t=2}^T (X_{it} - X_{it-1})^2}{2 \sum_{t=1}^T X_{it}}$$

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We assume that  $\lambda_i$  is Lipschitz continuous. Then

$$X_{it} - X_{it-1} = \sigma \sqrt{\lambda_i \left(\frac{t}{T}\right) (\eta_{it} - \eta_{it-1}) + r_{it}},$$

where  $|r_{it}| \leq C(1+|\eta_{it-1}|)/T$  with a sufficiently large C.

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$$\frac{1}{T}\sum_{t=2}^{T}(X_{it}-X_{it-1})^2=2\sigma^2\left\{\frac{1}{T}\sum_{t=2}^{T}\lambda_i(t/T)\right\}+o_p(1)$$

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Together with

$$\frac{1}{T}\sum_{t=1}^{T}X_{it} = \frac{1}{T}\sum_{t=1}^{T}\lambda_{i}(t/T) + o_{p}(1),$$

we get that  $\hat{\sigma}_i^2 = \sigma^2 + o_p(1)$  for any i and thus  $\hat{\sigma}^2 = \sigma^2 + o_p(1)$ .

#### **Notation**

In order to proceed with the proof, we will need the following notation:

$$\begin{split} \hat{\psi}_{ijk,T} &= \frac{\sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right) (X_{it} - X_{jt})}{\hat{\sigma}\left\{\sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right) (X_{it} + X_{jt})\right\}^{1/2}} \\ \hat{\psi}_{ijk,T}^{0} &= \frac{\sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right) \sigma \overline{\lambda}_{ij}^{1/2} \left(\frac{t}{T}\right) (\eta_{it} - \eta_{jt})}{\hat{\sigma}\left\{\sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right) (X_{it} + X_{jt})\right\}^{1/2}} \quad \hat{\Psi}_{T}^{0} &= \max_{(i,j,k)} a_{k} (|\hat{\psi}_{ijk,T}^{0}| - b_{k}) \\ \hat{\psi}_{ijk,T}^{0} &= \frac{1}{\sqrt{2Th_{k}}} \sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right) (\eta_{it} - \eta_{jt}) \qquad \Psi_{T} &= \max_{(i,j,k)} a_{k} (|\hat{\psi}_{ijk,T}^{0}| - b_{k}) \\ \hat{\phi}_{ijk,T} &= \frac{1}{\sqrt{2Th_{k}}} \sum_{t=1}^{T} 1\left(\frac{t}{T} \in \mathcal{I}_{k}\right) (Z_{it} - Z_{jt}) \qquad \Phi_{T} &= \max_{(i,j,k)} a_{k} (|\hat{\phi}_{ijk,T}| - b_{k}) \end{split}$$

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$$\sup_{q \in \mathsf{R}} \left| \mathsf{P} \big( \Psi_{\mathcal{T}} \leq q \big) - \mathsf{P} \big( \Phi_{\mathcal{T}} \leq q \big) \right| = o(1)$$

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4. It can be shown that  $P(\Phi_T \leq q_{Gauss}(\alpha)) = 1 - \alpha$ . From this and (2), it immediately follows that

$$P(\hat{\Psi}_{\mathcal{T}}^0 \leq q_{\mathsf{Gauss}}(\alpha)) = 1 - \alpha + o(1),$$

which in turn implies the desired statement.

## Idea behind $a_k$ and $b_k$

Dümbgen and Spokoiny (2001): the critical values  $c_{ijk}(\alpha)$  depend on the scale of the testing problem, i.e. the length  $h_k$  of the time interval.

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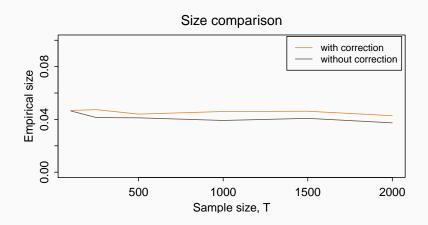
Specifically,

$$c_{ijk}(\alpha) = c(\alpha, h_k) := b_k + q(\alpha)/a_k,$$

where  $a_k = \{\log(e/h_k)\}^{1/2}/\log\log(e^e/h_k)$  and  $b_k = \sqrt{2\log(1/h_k)}$  are scale-dependent constants and  $q(\alpha)$  is chosen such that we control FWFR.

## Idea behind $a_k$ and $b_k$ , part 2

This choice of scale-dependent constants helps us balance the significance of hypotheses between the time intervals of different lengths  $h_k$ :





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$$\Phi^{\mathrm{uncor}} = \max_{(i,j,k)} |\phi_{ijk}|$$

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Then we can rewrite the uncorrected test statistic as

$$\Phi^{\text{uncor}} = \max_{\substack{i,j \\ 1 \le m \le 1/h_l}} \max_{\substack{1 \le l \le L, \\ 1 \le m \le 1/h_l}} \left| \frac{1}{\sqrt{2Th_l}} \sum_{t=1}^{T} 1\left(\frac{t}{T} \in [(m-1)h_l, mh_l]\right) (Z_{it} - Z_{jt}) \right|$$

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 $\Rightarrow$  max<sub>m</sub>... =  $\sqrt{2\log(1/h_l)} + o_P(1) \to \infty$  as  $h \to 0$  and the stochastic behavior of  $\Phi^{\text{uncor}}$  is dominated by the elements with small bandwidths  $h_l$ . Go back