

Simultaneous statistical inference for epidemic trends: the case of COVID-19

Marina Khismatullina Michael Vogt

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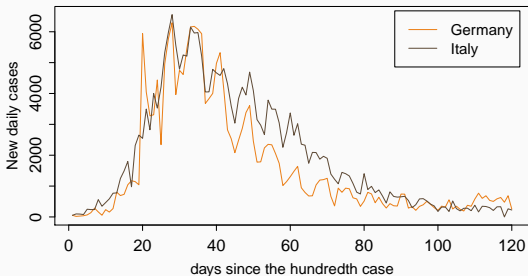
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Introduction

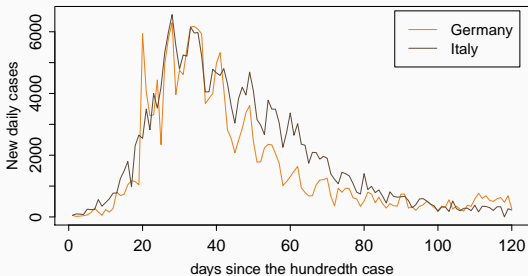
Motivation

Research question: How do outbreak patterns of COVID-19 compare across countries?



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Aim of the paper

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

Comparison of deterministic trends:

- Park et al. (2009), Degras et al. (2012), Zhang et al. (2012), Hidalgo and Lee (2014), Chen and Wu (2019).

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Studies of COVID-19:

- SIR models: Yang et al. (2020), Wu et al. (2020), De Brouwer et al. (2020).
- Time series analysis: Gu et al. (2020), Li and Linton (2020).
- Dong et al. (2020).

Model

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Since $\lambda_i(t/T) = \mathbb{E}[X_{it}] = \text{Var}(X_{it})$, we can rewrite X_{it} as

$$X_{it} = \lambda_i\left(\frac{t}{T}\right) + u_{it} \quad \text{with} \quad u_{it} = \sqrt{\lambda_i\left(\frac{t}{T}\right)} \eta_{it}$$

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

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- λ_i are unknown trend functions on $[0, 1]$;
- σ is the overdispersion parameter;
- η_{it} are error terms that are independent across i and t and have zero mean and unit variance.

Testing

Testing problem

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 let $H_0^{(ijk)}$ be the hypothesis that the functions λ_i and λ_j are equal on an interval \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 α .

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Let \mathcal{M}_0 be the set of triplets (i, j, k) for which $H_0^{(ijk)}$ holds true. Then, FWER is

$$\text{FWER}(\alpha) = \mathbb{P}\left(\exists (i, j, k) \in \mathcal{M}_0 : \text{we reject } H_0^{(ijk)}\right)$$

Test statistic

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

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

where h_k is the length of \mathcal{I}_k .

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where h_k is the length of \mathcal{I}_k . $\hat{s}_{ijk,T}$ estimates the average distance between λ_i and λ_j on \mathcal{I}_k . Under certain assumptions,

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

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

$$\widehat{\text{Var}}(\hat{s}_{ijk,T}) = \frac{\hat{\sigma}^2}{T^2 h_k^2} \sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right) (X_{it} + X_{jt}),$$

with $\hat{\sigma}^2$ being an appropriate estimator of σ^2 . [Details](#)

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

$$\hat{\psi}_{ijk,T} = \frac{\sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right)(X_{it} - X_{jt})}{\hat{\sigma}\left\{\sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right)(X_{it} + X_{jt})\right\}^{1/2}}$$

Test statistic, part 2

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

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Under certain conditions and under the null, $\hat{\psi}_{ijk,T}$ can be approximated by a Gaussian version of the test statistic:

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

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

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In our context:

$$c_{ijk,T}(\alpha) = c_T(\alpha, h_k) := b_k + q_T(\alpha)/a_k,$$

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 $q_T(\alpha)$ is chosen such that we control FWER.

Critical values, part 2

We want to control FWER:

$$\begin{aligned}\text{FWER}(\alpha) &= \mathbb{P}\left(\exists(i, j, k) \in \mathcal{M}_0 : |\hat{\psi}_{ijk, T}| > c_{ijk, T}(\alpha)\right) \\ &= 1 - \mathbb{P}\left(\forall(i, j, k) \in \mathcal{M}_0 : |\hat{\psi}_{ijk, T}| \leq c_{ijk, T}(\alpha)\right) \\ &= 1 - \mathbb{P}\left(\forall(i, j, k) \in \mathcal{M}_0 : a_k(|\hat{\psi}_{ijk, T}| - b_k) \leq q_T(\alpha)\right) \\ &= 1 - \mathbb{P}\left(\max_{(i, j, k) \in \mathcal{M}_0} a_k(|\hat{\psi}_{ijk, T}| - b_k) \leq q_T(\alpha)\right) \\ &\leq \alpha\end{aligned}$$

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

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

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

Test procedure

1. Consider the Gaussian test statistic

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

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

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$$c_{T,\text{Gauss}}(\alpha, h_k) = b_k + q_{T,\text{Gauss}}(\alpha)/a_k$$

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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 $|\hat{\psi}_{ijk,T}| > c_{T,\text{Gauss}}(\alpha, h_k)$.

Theoretical properties

$\mathcal{C}1$ The functions λ_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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$\mathcal{C4}$ $\mathbb{E}[\eta_{it}] = 0$, $\mathbb{E}[\eta_{it}^2] = 1$ and $\mathbb{E}[|\eta_{it}|^\theta] \leq C_\theta < \infty$ for some $\theta > 4$.

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$\mathcal{C}5$ $h_{\max} = o(1/\log T)$ and $h_{\min} \geq CT^{-b}$ for some $b \in (0, 1)$.

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C5 $h_{\max} = o(1/\log T)$ and $h_{\min} \geq CT^{-b}$ for some $b \in (0, 1)$.

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

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

$$\mathbb{P}\left(\forall (i, j, k) \in \mathcal{M}_0 : |\hat{\psi}_{ijk, T}| \leq c_{T, \text{Gauss}}(\alpha, h_k)\right) \geq 1 - \alpha + o(1)$$

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

$$\exists \mathcal{I}_k : \lambda_{i, T}(w) - \lambda_{j, T}(w) \geq c_T \sqrt{\log T / (Th_k)} \quad \forall w \in \mathcal{I}_k, \quad (1)$$

and $c_T \rightarrow \infty$ faster than $\frac{\sqrt{\log T} \sqrt{\log \log T}}{\log \log \log T}$.

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and $c_T \rightarrow \infty$ 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

$$\mathbb{P}\left(\forall (i, j, k) \in \mathcal{M}_1 : |\hat{\psi}_{ijk, T}| > c_{T, \text{Gauss}}(\alpha, h_k)\right) = 1 - o(1)$$

Application

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Minimal intervals

An interval $\mathcal{I}_k \in \mathcal{F}_{\text{reject}}(i, j)$ is called **minimal** if there is no other interval $\mathcal{I}_{k'} \in \mathcal{F}_{\text{reject}}(i, j)$ 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 very similar confidence statement about the set of minimal intervals as well:

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

Application setting

- Five countries: Germany, Italy, Spain, France and UK; $T = 120$.

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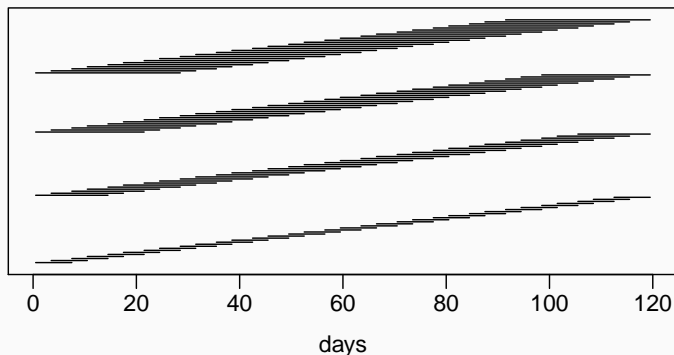
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- Five countries: Germany, Italy, Spain, France and UK; $T = 120$.
- $\alpha = 0.05$.
- Lengths of the time intervals 7, 14, 21, 28 days. The intervals start at days 1, 8, 15, ... and 4, 11, 19, ...

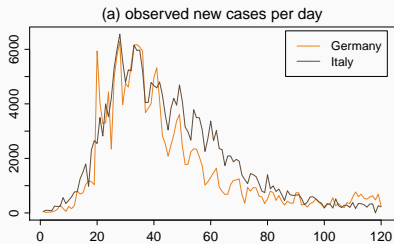
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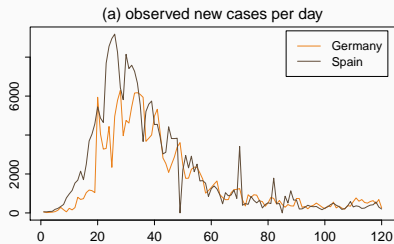
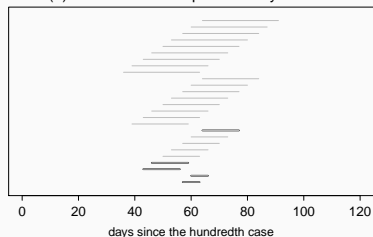
The family of intervals F



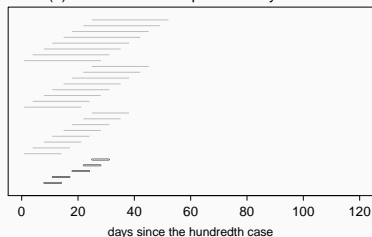
Application results



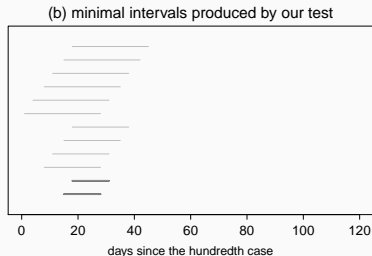
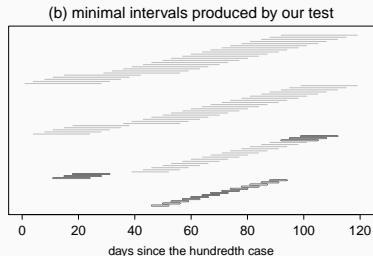
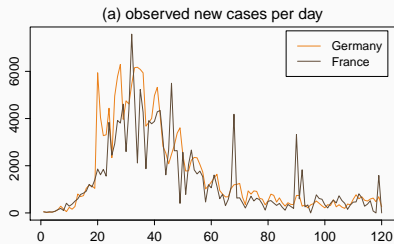
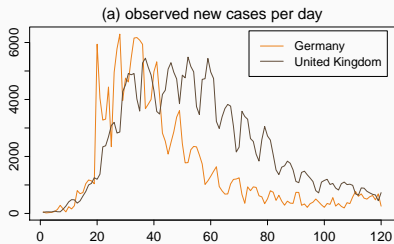
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Application results, part 2



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Further possible extensions:

- introduce scaling factor in the trend function, that allow for adjusting for the size of the country (population, density, testing regimes, etc.);

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- introduce scaling factor in the trend function, that allow for adjusting for the size of the country (population, density, testing regimes, etc.);
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- introduce scaling factor in the trend function, that allow for adjusting for the size of the country (population, density, testing regimes, etc.);
- connect with data-driven techniques such as machine learning;
- cluster the countries based on the trends they exhibit.

Thank you!

Simulation results for the size of the test

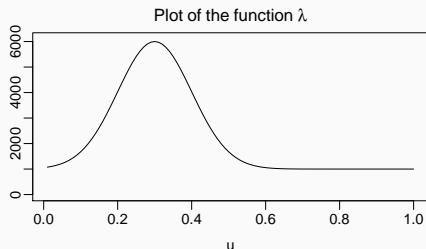


Table 1: Size of the multiscale test

	$n = 5$			$n = 10$			$n = 50$		
	significance level α			significance level α			significance level α		
	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

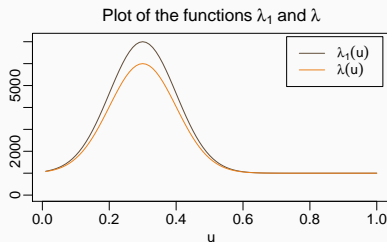


Table 2: Power of the multiscale test for scenario A

	$n = 5$			$n = 10$			$n = 50$		
	significance level α			significance level α			significance level α		
	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

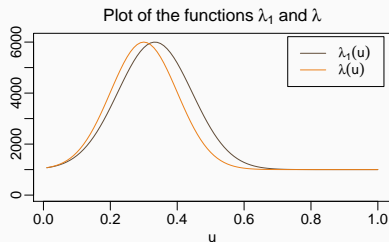
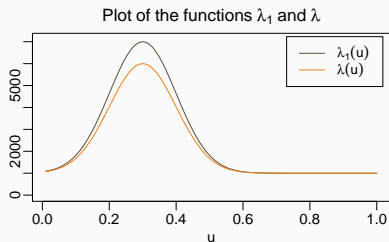


Table 3: Power of the multiscale test for scenario B

	$n = 5$			$n = 10$			$n = 50$		
	significance level α			significance level α			significance level α		
	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

Estimator of σ^2

We estimate the overdispersion parameter σ^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 λ_i is Lipschitz continuous. Then

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

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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 $\hat{\sigma}^2 = \sigma^2 + o_p(1)$.

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Notation

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

$$\begin{aligned}\hat{\psi}_{ijk,T} &= \frac{\sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right)(X_{it} - X_{jt})}{\hat{\sigma}\left\{\sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right)(X_{it} + X_{jt})\right\}^{1/2}} \\ \hat{\psi}_{ijk,T}^0 &= \frac{\sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right) \sigma \bar{\lambda}_{ij}^{1/2}\left(\frac{t}{T}\right)(\eta_{it} - \eta_{jt})}{\hat{\sigma}\left\{\sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right)(X_{it} + X_{jt})\right\}^{1/2}} & \hat{\Psi}_T &= \max_{(i,j,k)} a_k(|\hat{\psi}_{ijk,T}^0| - b_k) \\ \psi_{ijk,T}^0 &= \frac{1}{\sqrt{2Th_k}} \sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right)(\eta_{it} - \eta_{jt}) & \Psi_T &= \max_{(i,j,k)} a_k(|\psi_{ijk,T}^0| - b_k) \\ \phi_{ijk,T} &= \frac{1}{\sqrt{2Th_k}} \sum_{t=1}^T 1\left(\frac{t}{T} \in \mathcal{I}_k\right)(Z_{it} - Z_{jt}) & \Phi_T &= \max_{(i,j,k)} a_k(|\phi_{ijk,T}| - b_k)\end{aligned}$$

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

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

which in turn implies the desired statement.

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

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$\Rightarrow \max_m \dots = \sqrt{2 \log(1/h_l)} + o_P(1) \rightarrow \infty$ as $h \rightarrow 0$ and the stochastic behavior of Φ_T^{uncor} is dominated by the elements with small bandwidths h_l . [Go back](#)