

A multivariate statistical approach to predict COVID-19 count data with epidemiological interpretation and uncertainty quantification

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Outline

- We propose *statistical autoregressive models to analyze* the observed time series of count data referred to different categories
- We apply the approach to *Italian COVID-19 data* (at national level and for Lombardy) considering different categories of patients further to susceptible individuals and deceased
- For the *COVID-19*, $K = 6$ categories are considered:
 1. *susceptible* not previously ill (**S**)
 2. *recovered* (**R**)
 3. positive cases in *quarantine* (**Q**)
 4. *hospitalized* in regular wards (**H**)
 5. patients in *intensive care units* (**ICU**)
 6. *deceased* (**D**)
- The main assumption is that observed frequencies correspond to margins of a sequence of *unobserved contingency tables*

Model assumptions

- We observe *counts* for K categories over T time occasions, which are denoted by

$$y_{tk}, \quad t \in \mathcal{T} = \{1, \dots, T\}, \quad k \in \mathcal{K} = \{1, \dots, K\},$$

and are realizations of the random variables Y_{tk} collected in the vectors $\mathbf{Y}_t = (Y_{t1}, \dots, Y_{tK})'$

- The proposed approach is based on *three main assumptions*
- The *1st assumption* is that for $t \in \mathcal{T}' = \{2, \dots, T\}$,

$$Y_{tk} = \sum_{j \in \mathcal{K}} X_{tjk}, \quad k \in \mathcal{K},$$

under the constraint

$$\sum_{k \in \mathcal{K}} X_{tjk} = Y_{t-1,j}, \quad j \in \mathcal{K}$$



- The X_{tjk} are frequencies of a “*transition table*” with row totals equal to $Y_{t-1,k}$ and column totals Y_{tk} , which are collected in the vectors $\mathbf{X}_{tj} = (X_{tj1}, \dots, X_{tjK})'$
- The transition tables have *structural zeros* from any category different from S to S and from D to any category different from D

| | S | R | Q | H | ICU | D | Total |
|-------|-----------|-----------|-----------|-----------|-----------|-----------|-------------|
| S | X_{t11} | X_{t12} | X_{t13} | X_{t14} | X_{t15} | X_{t16} | $Y_{t-1,1}$ |
| R | 0 | X_{t22} | X_{t23} | X_{t24} | X_{t25} | X_{t26} | $Y_{t-1,2}$ |
| Q | 0 | X_{t32} | X_{t33} | X_{t34} | X_{t35} | X_{t36} | $Y_{t-1,3}$ |
| H | 0 | X_{t42} | X_{t43} | X_{t44} | X_{t45} | X_{t46} | $Y_{t-1,4}$ |
| ICU | 0 | X_{t52} | X_{t53} | X_{t54} | X_{t55} | X_{t56} | $Y_{t-1,5}$ |
| D | 0 | 0 | 0 | 0 | 0 | X_{t66} | $Y_{t-1,6}$ |
| Total | Y_{t1} | Y_{t2} | Y_{t3} | Y_{t4} | Y_{t5} | Y_{t6} | N |

- X_{t35} corresponds to the number of individuals who moved from category Q at time $t - 1$ into category ICU at occasion t
- The *overall frequency* N is kept fixed across time



- The *2nd assumption* concerns the distribution of every random vector \mathbf{X}_{tj} ; there are two options:
 - Multinomial distribution
 - Dirichlet-Multinomial distribution
- Multinomial formulation*:

$$\mathbf{X}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1} \sim \text{Mult}(y_{t-1,j}; \mathbf{p}_{tj}),$$

where $\mathbf{p}_{tj} = (p_{tj1}, \dots, p_{tjK})'$ is a vector of “transition probabilities” from category j to the other categories

- The first two *moments* are:

$$\mathbb{E}(\mathbf{X}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}) = y_{t-1,j} \mathbf{p}_{tj},$$

$$\text{Var}(\mathbf{X}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}) = y_{t-1,j} [\text{diag}(\mathbf{p}_{tj}) - \mathbf{p}_{tj} \mathbf{p}_{tj}']$$



- To account for **overdispersion**, we can alternatively assume a Dirichlet-Multinomial distribution:

$$\mathbf{X}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1} \sim \text{Dir} - \text{Mult}(y_{t-1,j}; \boldsymbol{\alpha}_{tj}),$$

where $\boldsymbol{\alpha}_{tj}$ is a vector of K positive parameters α_{tjk}

- The first two **moments** are:

$$\mathbb{E}(\mathbf{X}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}) = y_{t-1,j} \frac{\boldsymbol{\alpha}_{tj}}{\alpha_{tj+}},$$

$$\text{Var}(\mathbf{X}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}) = y_{t-1,j} \left[\text{diag} \left(\frac{\boldsymbol{\alpha}_{tj}}{\alpha_{tj+}} \right) - \frac{\boldsymbol{\alpha}_{tj}}{\alpha_{tj+}} \frac{\boldsymbol{\alpha}'_{tj}}{\alpha_{tj+}} \right] \frac{y_{t-1,j} + \alpha_{tj+}}{1 + \alpha_{tj+}},$$

$$\text{with } \alpha_{tj+} = \sum_{k \in \mathcal{K}} \alpha_{tjk}$$

- Letting $p_{tjk} = \alpha_{tjk} / \alpha_{tj+}$, the expected value is the same as the Multinomial one; the variance terms **tend to the Multinomial ones** as $\alpha_{tj+} \rightarrow \infty$

- The *3rd assumption* concerns the parametrization of the assumed distribution
- Under the *Multinomial model*, we assume that

$$p_{tjk} = \frac{\exp(\mathbf{f}'_{tjk}\boldsymbol{\beta}_{jk})}{\sum_{l \in \mathcal{D}_j} \exp(\mathbf{f}'_{tjl}\boldsymbol{\beta}_{jl})}, \quad t \in \mathcal{T}', j \in \mathcal{K}, k \in \mathcal{D}_j,$$

where \mathcal{D}_j is the *set of non-zero cells* in the j -th row of each “transition table”

- For *model identifiability* we constrain $\boldsymbol{\beta}_{jj} \equiv 0$ for each j
- The *design column vectors* \mathbf{f}_{tjk} contain the terms of a polynomial (or spline) of time t of a suitable order and may include indicator variables for interventions (e.g., $\mathbf{f}_{tjk} = (1, t, t^2, t^3)'$ when 3rd order polynomials are adopted)

- Under the *Dirichlet-Multinomial parametrization*, we directly assume

$$\alpha_{tjk} = \exp(\mathbf{f}'_{tjk}\boldsymbol{\beta}_{jk}), \quad t \in \mathcal{T}', j \in \mathcal{K}, k \in \mathcal{D}_j,$$

without constraining any regression vector $\boldsymbol{\beta}_{jk}$ to 0

- The resulting model has a straightforward interpretation, but the *distribution of the frequencies* Y_{tk} is difficult to deal with as it derives from the convolution of

$$\prod_{j \in \mathcal{K}} p(\mathbf{X}_{tj} = \mathbf{x}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1})$$

- The proposed approach may be seen as an *extension* of that for 2×2 contingency tables proposed in Eleftheraki et al. (2009); a related model is also described in Zhang et al. (2020) and Whiteley & Rimella (2021)

Bayesian inference

- The β_{jk} *parameters* are assumed to be *a priori* independent with distribution

$$\beta_{jk} \sim N(0, \sigma^2 \mathbf{I}), \quad j \in \mathcal{K}, k \in \mathcal{D}_j,$$

where σ^2 is a large value (*diffuse prior distributions*)

- To incorporate specific *a priori* hypotheses and for stability reasons, *we also assume constrains* of type

$$a_{jk} \leq o_{tjk} \leq b_{jk}, \quad j, k \in \mathcal{K}, t \in \mathcal{T}^* = \{2, \dots, T^*\}, a_{jk}, b_{jk} \in \mathbb{R}^+,$$

where $o_{tjk} = p_{tjk}/p_{tjj}$ is the odds referred to category k with respect to category j at time occasion t

- Informative priors* may alternatively be considered by suitably choosing the hyperparameters of the prior distributions



- The model is estimated through a *data augmentation* (Tanner and Wong, 1987) MCMC algorithm based on a Metropolis sampler repeating two steps:
 1. for all $t > 1$ *update every contingency table* with elements x_{tjk} given the observe margins y_{tk} and the current parameter vectors β_{jk}
 2. *draw the model parameters* β_{jk} given the current values of the count variables X_{tjk}
- The *algebraic algorithm* of Diaconis (1998) is employed to sample tables with fixed margins, whereas the model parameters are drawn by a series of Metropolis-Hastings moves



- Updating “transition tables”:

- randomly select (several times) two rows and two columns of the current table so that a 2×2 subtable is identified
- propose a switch by adding (or subtracting) to the two cells in the main diagonal of the subtable a random integer number, which is subtracted (or added) to the off-diagonal cells

$$\begin{pmatrix} + & - \\ - & + \end{pmatrix} \quad \text{or} \quad \begin{pmatrix} - & + \\ + & - \end{pmatrix} \quad \text{with probability } 1/2$$

- accept the new table with probability

$$\min \left(1, \prod_{j \in \mathcal{K}} \frac{\rho(\mathbf{X}_{tj} = \mathbf{x}_{tj}^* | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}, \beta_j)}{\rho(\mathbf{X}_{tj} = \mathbf{x}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}, \beta_j)} \right),$$

where \mathbf{x}_{tj} is the vector of the frequencies in the j -th row of the current table, \mathbf{x}_{tj}^* is that of the proposed table, and β_j is the matrix containing all current regression vectors β_{jk} , $k \in \mathcal{D}_j$

- *Drawing new parameter vectors:*

1. for all j and $k \in \mathcal{D}_j$ a new value of β_{jk} , denote by β_{jk}^* , is drawn from the **proposal distribution** $N(\beta_{jk}, \tau^2 I)$
2. the proposed vector is **accepted** with probability

$$\min \left(1, \frac{\prod_{t \in \mathcal{T}'} p(\mathbf{X}_{tj} = \mathbf{x}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}, \beta_{jk}^\dagger) \pi(\beta_{jk}^*)}{\prod_{t \in \mathcal{T}'} p(\mathbf{X}_{tj} = \mathbf{x}_{tj} | \mathbf{Y}_{t-1} = \mathbf{y}_{t-1}, \beta_j) \pi(\beta_{jk})} \right),$$

where β_{jk}^\dagger is the same matrix as β_j with β_{jk} substituted with β_{jk}^* , and $\pi(\beta_{jk})$ is the prior density of the regression parameters

- The simulated posterior distribution of the parameters and tables is **summarized** in the usual way also providing variability measures in order to quantify the uncertainty

- At each step, the algorithm also performs *in-sample and out-sample predictions*
- For $t \in \mathcal{T}$, *(in-sample) predictions* of the frequencies y_{tk} at step s of the algorithm are computed as

$$\hat{y}_{tk}^{(s)} = \sum_{j \in \mathcal{K}} y_{t-1,j} p_{tjk}^{(s)}$$

- For $t > T$, *(out-sample) predictions* are based on the recursive rule

$$\hat{y}_{tk}^{(s)} = \sum_{j \in \mathcal{K}} \hat{y}_{t-1,j}^{(s)} p_{tjk}^{(s)},$$

initialized with $\hat{y}_{Tj}^{(s)} = y_{Tj}$



- For the COVID-19 application, at each step of the MCMC algorithm, the *net reproduction number* R_t is predicted as

$$\widehat{R}_t^{(s)} = \frac{\widehat{\Delta I}_t^{(s)}}{\sum_{r=1}^{t-1} \omega_{s,t-1} \widehat{\Delta I}_{t-r}^{(s)}}$$

- $\omega_{r,t-1}$ is a *weight* obtained by normalizing the density of the *Gamma* distribution with parameters 1.87 and 0.28
- $\widehat{\Delta I}_t^{(s)}$ is the number of *new positive* individuals predicted by the model for day t
- This method *directly derives* from Riccardo et al. (2020) for the Italian context

Model checking

- The *goodness-of-fit* of the model is assessed by a discrepancy measure between observed counts and in-sample predictions

$$\widehat{\text{Dist}}^{(s)} = \sum_{t \in \mathcal{T}'} \sum_{k \in \mathcal{K}} \frac{(y_{tk} - \hat{y}_{tk}^{(s)})^2}{\hat{y}_{tk}^{(s)}}$$

- When data are available, the quality of (*out-sample*) predictions is assessed by

$$\widehat{\text{Dist}}_t^{(s)} = \sum_{k \in \mathcal{K}} \frac{(y_{tk} - \hat{y}_{tk}^{(s)})^2}{\hat{y}_{tk}^{(s)}}, \quad t > T$$

- A similar discrepancy measure is used to check the *prediction power* for each specific category and denoted by $\widehat{\text{Dist}}_k^{*(s)}$

- The discrepancy measures computed across iterations are *summarized* by simple means obtaining $\widehat{\text{Dist}}$, $\widehat{\text{Dist}}_t$, and $\widehat{\text{Dist}}_k^*$
- For $\widehat{\text{Dist}}$, a *posterior predictive (PP) p-value* is also obtained; it is computed as the proportion of iterations for which $\widetilde{\text{Dist}}^{(s)}$ is greater than $\widehat{\text{Dist}}^{(s)}$, where $\widetilde{\text{Dist}}^{(s)}$ is obtained by substituting each observed frequency y_{tk} with a simulated frequency
- Particular care is necessary to *assess the PP p-values*; for in-sample predictions we expect a value close to 0.5 when the model has an adequate fit (Gelman, 2013)

Application: Italian COVID-19 data at the beginning of the pandemic

- We examined the *daily Italian data collected from February 24 until April 24, 2020* (61 days)
- We considered *different models* based on:
 - Multinomial or Dirichlet-Multinomial distribution
 - polynomials of 2nd or 3rd order of the time and intervention dummies
 - with or without constraints on the odds:

| | S | R | Q | H | ICU | D |
|-----|---|-----------|-----------|-----------|-----------|-----------|
| S | - | 10^{-7} | 0.001 | 10^{-4} | 10^{-6} | 10^{-7} |
| R | - | - | 0.001 | 10^{-4} | 10^{-6} | 10^{-7} |
| Q | - | 0.1 | - | 0.1 | 10^{-5} | 10^{-6} |
| H | - | 0.1 | 0.1 | - | 0.1 | 0.01 |
| ICU | - | 10^{-7} | 10^{-7} | 0.25 | - | 0.25 |
| D | - | - | - | - | - | - |

- All the models also included two dummy variables to account for *the effect of for public health non-pharmaceutical interventions* enforced on February 24th and on March 8th 2020 in Italy
- Goodness-of-fit* of the estimated models:

| Multinomial | $\widehat{\text{Dist}}$ | $\widetilde{\text{Dist}}$ | p -value |
|--|-------------------------|---------------------------|--------------|
| Model 1 (2nd order, without constraints) | 1,658.011 | 124.670 | 0.000 |
| Model 2 (2nd order, with constraints) | 2,347.274 | 68.474 | 0.000 |
| Model 3 (3rd order, without constraints) | 1,565.587 | 122.793 | 0.000 |
| Model 4 (3rd order, with constraints) | 2,203.832 | 70.512 | 0.000 |
| Dirichlet-Multinomial | $\widehat{\text{Dist}}$ | $\widetilde{\text{Dist}}$ | p -value |
| Model 5 (2nd order, without constraints) | 2,608.502 | 3,060.236 | 0.679 |
| Model 6 (2nd order, with constraints) | 2,992.213 | 3,629.419 | 0.750 |
| Model 7 (3rd order, without constraints) | 2,414.970 | 2,811.524 | 0.536 |
| Model 8 (3rd order, with constraints) | 2,915.772 | 3,344.208 | 0.661 |

- We considered in particular *Models 7 and 8*

- Discrepancy measures for the *forecasted cases* (Model 8, 3rd order with constraints) according to the posterior predictive distribution:

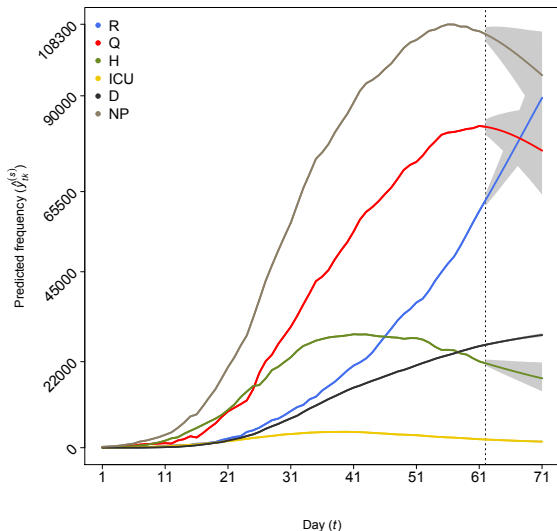
| Day | $\widehat{\text{Dist}}_t$ | $\widetilde{\text{Dist}}_t$ | p -value |
|------------|---------------------------|-----------------------------|------------|
| 25th April | 3,231.755 | 24.523 | 0.769 |
| 26th April | 3,347.780 | 36.457 | 0.403 |
| 27th April | 2,976.716 | 19.313 | 0.198 |
| 28th April | 3,105.249 | 26.695 | 0.161 |
| 29th April | 3,216.649 | 31.738 | 0.137 |
| 30th April | 3,095.463 | 31.599 | 0.164 |
| 1st May | 2,979.734 | 37.135 | 0.118 |
| 2nd May | 3,169.230 | 47.058 | 0.103 |
| 3rd May | 3,223.772 | 58.826 | 0.095 |
| 4th May | 3,112.596 | 44.670 | 0.069 |

- The *best predicted counts* are for categories ICU and D:

| | S | R | Q | H | ICU | D | Total |
|-----------------------------|-------|-------|-------|-----|-----|----|-------|
| $\widehat{\text{Dist}}_k^*$ | 0.000 | 1,409 | 1,397 | 372 | 31 | 12 | 3,220 |



- Daily *observed and predicted counts* for each category with a time horizon of 10 days and estimated 95% prediction intervals (in grey):



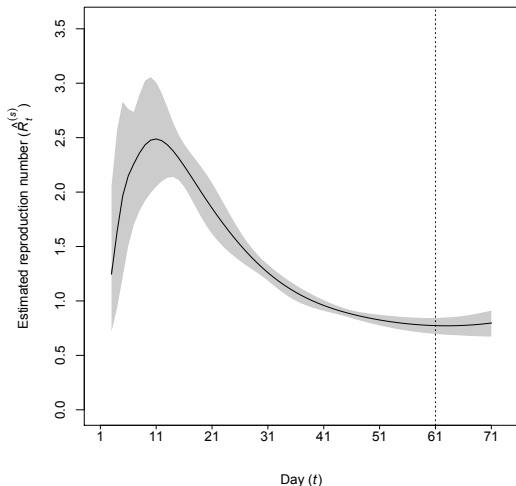
- Estimated posterior means of the *predicted transitions* between categories from 25th to 26th of April, 2020 (from the 61st to the 62nd day) and 95% prediction upper and lower bounds:

| | S | R | Q | H | ICU | D |
|-----|------------|--------|--------|--------|-------|--------|
| S | 60,121,632 | 0 | 2,219 | 154 | 1 | 0 |
| R | 0 | 60,489 | 9 | 0 | 0 | 0 |
| Q | 0 | 2,665 | 79,105 | 516 | 0 | 0 |
| H | 0 | 116 | 757 | 20,925 | 73 | 197 |
| ICU | 0 | 0 | 0 | 0 | 2,023 | 149 |
| D | 0 | 0 | 0 | 0 | 0 | 25,969 |

| | S | R | Q | H | ICU | D |
|-----|---|------------------|------------------|------------------|----------------|------------|
| S | - | (0, 0) | (1,217, 3,188) | (0, 718) | (0, 2) | (0, 0) |
| R | - | (60,471, 60,498) | (0, 26) | (0, 0) | (0, 0) | (0, 0) |
| Q | - | (1,269, 4,357) | (77,182, 80,672) | (32, 1,479) | (0, 0) | (0, 0) |
| H | - | (0, 506) | (463, 1,129) | (20,438, 21,321) | (25, 137) | (123, 282) |
| ICU | - | (0, 0) | (0, 0) | (0, 40) | (1,963, 2,075) | (98, 210) |
| D | - | - | - | - | - | - |



- Estimated and predicted (from the vertical line) *reproduction number* R_t (61 observed days, prediction from 25th of April to 4th of May). Estimated 95% credibility and prediction intervals (in grey):



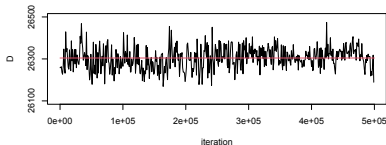
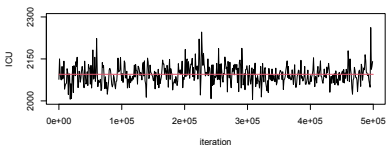
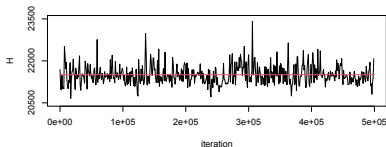
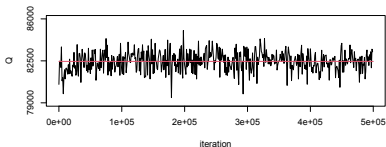
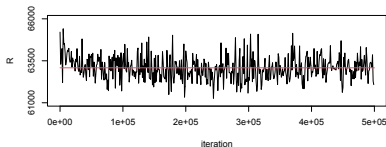
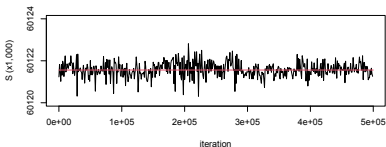


- We repeated the same analysis with Model 7 on Italian data and with Models 7 and 8 on data referred to the *Lombardy region*, obtaining similar results from several points of view
- The MCMC algorithms were run for *500,000 iterations* after a burnin of 100,000 iterations and a thinning of 10 iterations
- Diagnostics of the MCMC output reveals that the *effective sample size (ESS)* for the forecasted frequencies is satisfactory:

| | Model 8 | | | Model 7 | | |
|-----|---------|-------|-------|---------|-------|-------|
| | Day 1 | Day 2 | Day 3 | Day 1 | Day 2 | Day 3 |
| S | 12,893 | 5,641 | 3,677 | 6,911 | 2,049 | 897 |
| R | 11,605 | 4,611 | 2,865 | 4,768 | 2,129 | 1,603 |
| Q | 12,257 | 4,288 | 3,672 | 4,660 | 2,731 | 1,046 |
| H | 20,548 | 3,968 | 2,892 | 3,928 | 2,459 | 1,546 |
| ICU | 16,892 | 4,067 | 2,914 | 14,014 | 3,280 | 1,767 |
| D | 16,512 | 6,712 | 3,447 | 3,757 | 2,463 | 1,538 |

- The *ESS computed for the parameters* in β_{jk} are much lower and overall not completely satisfactory

- *Trace plots* for 1-day ahead forecasts (one iteration every 1,000):

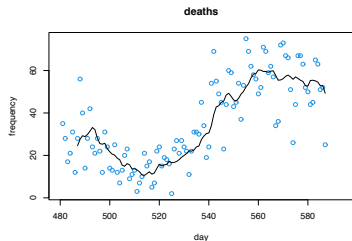
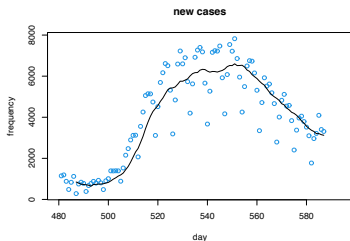


Weekly Italian data

- We use the proposed approach to perform *weekly forecasts* of the number of new cases and deaths for *Italy*, trying different model specifications
- These forecasts are published in the “*European Covid-19 Forecast Hub*” (<https://covid19forecasthub.eu/index.html>)
- We use the models based on the Dirichlet-Multinomial with a 3rd or 2nd order polynomial. We publish predictions of one of them or their averages
- The approach seems to perform *better for the weekly number of deaths* than for the number of new cases, even if the evaluated bias is particularly low with respect to that of the other research groups



- On the basis of the *observed data (from June 21 to October 3, 2021)* and with the mix of polynomial of 2nd and 3rd order, we predict 18227 (95% CI: 14212-22492) new cases and 299 (95% CI: 178-424) deaths for the week from October 04 to October 9



Main conclusions

- The approach allows us to *predict “transition tables”* on the basis of observed counts that may be useful in epidemiological contexts
- Being based on a *Bayesian approach*, it is possible to easily incorporate prior hypotheses on the basis of previous observations
- Despite the complexity of the distribution of the observed counts, *estimation is not particularly complex* by the MCMC algorithm that also allows us to easily perform predictions and quantify uncertainty
- We make our *implementation of the approach* available in R (<https://github.com/francescobartolucci/ARMultinomial>)
- This approach can also be used in several *other contexts*, whenever observed frequencies may be conceived as sums of “transition frequencies” (e.g., electoral flows)



Limits and possible developments

- The model is essentially *overparametrized* and the MCMC algorithm has a reduced ESS for the parameters → the parametrization of the transition probabilities p_{tjk} (or α_{tijk}) can be improved
- At the moment we do not use *covariates* apart from the temporal ones → we can easily include covariates (e.g., number of vaccinations)
- Under the Dirichlet-Multinomial formulation *prediction intervals* seem rather wide → explore restrictions on the parameters α_{tjk}
- In epidemiological contexts, the proposed model is closely related to models of type *Susceptible-Infected-Recovered* (SIR; e.g., Phenyó, 2006) → an accurate comparative analysis could be performed
- There are common points with *hidden Markov (HM) models* → try to cast the proposed model in the HM literature (Bartolucci et al., 2013; Zucchini, et al. 2017)



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