Bayesian analysis of diffusion-driven multi-type epidemic models with application to COVID-19

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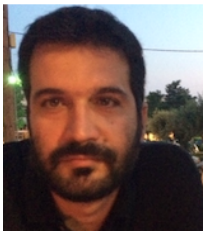
The BERNADETTE MSCA project



- **B**ayesian inf**ER**e**N**ce **A**nd mo**D**el s**E**lec**T**ion for s**T**ochastic **E**pidemics
- Collaborators: Demiris, Ntzoufras (AUEB), Kalogeropoulos (LSE)
- Webpage & R library
  - *https://bernadette-eu.github.io/*
  - *https://github.com/bernadette-eu/Bernadette*
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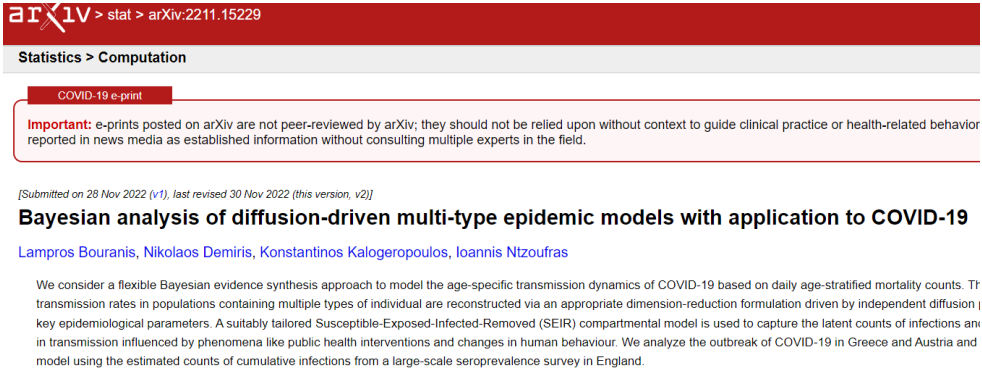


Motivation

- Large-scale seroprevalence studies to estimate actual number of infections
  - Severe under-ascertainment (Ward et al., 2021), varying in time and across countries.
  - Level of under-ascertainment depends on national testing and tracing policies, testing capacities and impact of false positives under different regimes.
  - Only a proportion of infections detected and reported at the early stages of the pandemic (Li et al., 2020).
- Methods that rely on reported counts of infections expected to yield biases in the inferred rates of transmission.

Motivation

- Challenges of under-ascertainment of COVID-19 infections and presence of heterogeneity in type, relevance, and granularity of the data
  - Seminal paper by Flaxman et al. (2020) and its extension to multiple age groups by Monod et al. (2021).
- A Bayesian evidence synthesis approach for the analysis of COVID-19 data
  - Infer the true number of infections using age-stratified daily COVID-19 attributable mortality counts.
  - Learn the age-specific transmission rates.
  - Reconstruct the epidemic drivers from publicly available data sources.

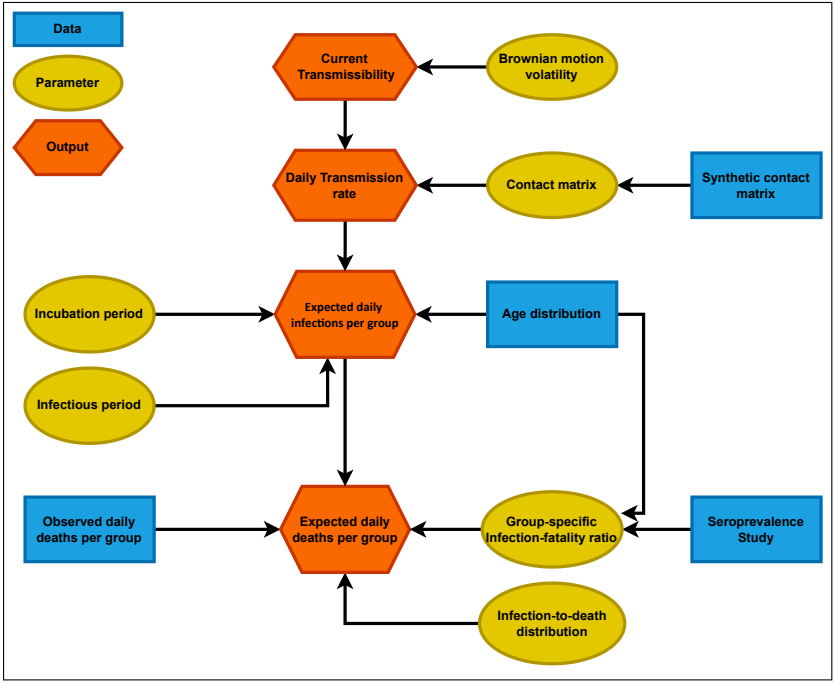
Introduction

- Allow for indirectly observed infections (Chatzilena et al., 2022).
- Age-stratified transmission model accounting for presence of social structures.
- Target the transmission rate matrix process:
  - Dimension increases quadratically with # of age groups.
  - Offer a dimension-reduction formulation projecting to latent diffusion processes.
- Desirable characteristics
  - Natural decomposition into underlying biological and social components.
  - Further evidence synthesis utilising information from contact surveys.
  - Driven by diffusion processes – capture temporal evolution of transmission rates & extrinsic environmental factors (NPIs and climatic changes).
  - Facilitates model determination at a latent level, performed here by appropriate model expansion.

Introduction

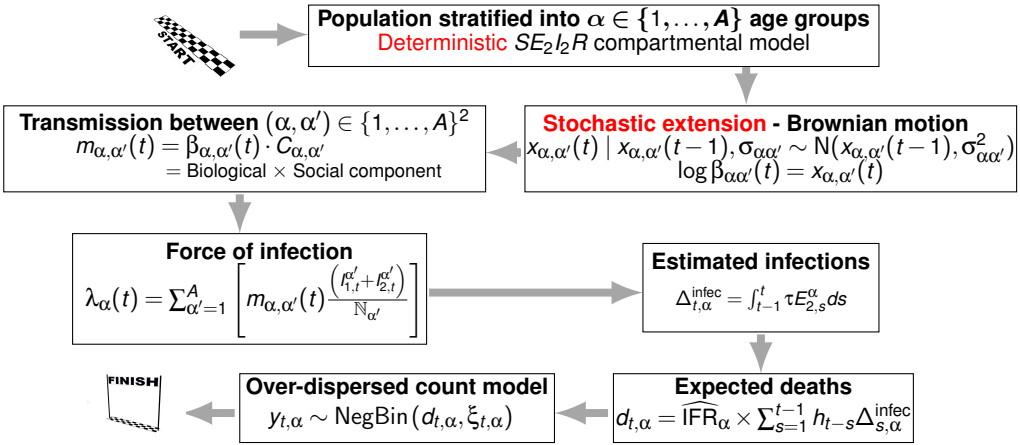
- Integration of multiple data sources, publicly available across countries:
  - Age-stratified daily COVID-19 attributable mortality counts and laboratory-confirmed COVID-19 infection counts.
  - Contact surveys.
  - Age distribution of the population.
- Contact survey data used to delineate potential identifiability issues (Britton, 1998) at the unobserved infection rate level when those rates are decomposed in their social and biological component.
- Uncertainty in contact structure is expressed via suitable prior distributions.

Model overview



Diffusion-driven multi-type transmission model

- Let $y_{t,\alpha}$ be the number of observed deaths on day $t = 1, \ldots, T$ in age group $\alpha \in \{1, \ldots, A\}$. A given infection may lead to observation events (i.e deaths) in the future.



Transmission rate matrix process

- Transmission between different age groups $(\alpha, \alpha') \in \{1, \ldots, A\}^2$:

$$\begin{aligned} m_{\alpha,\alpha'}(t) &= \beta_t^{\alpha\alpha'} \cdot C_{\alpha,\alpha'} \\ &= \text{Biological} \times \text{Social} \end{aligned}$$

- Diffusion process for modeling $\beta_t^{\alpha\alpha'}$ – Key advantages:
  - A data-driven approach; no need to specify the shape of change.
  - Tackles non-stationarity in the data.
  - Capture features like behavior changes, preventive measures, seasonal effects, holidays, etc.
  - Assess & interpret the evolution of transmission wrt mitigation strategies.

Transmission rate matrix process

- What we propose:
  - Independent diffusions to $\log(\beta_t^{11}), \log(\beta_t^{22}), \ldots, \log(\beta_t^{AA})$ with volatility parameters $\sigma_{x,\alpha}, \alpha \in \{1, \ldots, A\}$ [parsimony and interpretability]:

$$m_{\alpha,\alpha'}^{\text{MBM}}(t) = \beta_t^{\alpha\alpha'} \cdot C_{\alpha,\alpha'} \equiv \beta_t^{\alpha\alpha} \cdot C_{\alpha,\alpha'}.$$

  - Viewed as factor analysis, offering dimension reduction from elements of transmission rate matrix process to the Brownian motions $\beta_t^{\alpha\alpha}$ for $\alpha \in \{1, \ldots, A\}$.
  - Appealing feature – helps separate the contact matrix.
- Further reduction of the dimension of $m_{\alpha,\alpha'}^{\text{MBM}}(t)$:

$$m_{\alpha,\alpha'}^{\text{SBM}}(t) = \beta_t^{\alpha\alpha'} \cdot C_{\alpha,\alpha'} \equiv \beta_t \cdot C_{\alpha,\alpha'}.$$

- SBM is a nested model to MBM.

Observation process

- Denote the new COVID-19 attributable deaths occurring in day $t = 1, \ldots, T$ and age group $\alpha = 1, \ldots, A$ by $y_{t,\alpha}$.
- A given infection may lead to observation events (i.e deaths) in the future. Establish a link between $y_{t,\alpha}$ and the expected number of new infections via the function (Flaxman et al., 2020; Monod et al., 2021):

$$d_{t,\alpha} = \widehat{\text{IFR}}_{\alpha} \times \sum_{s=1}^{t-1} h_{t-s} \Delta_{s,\alpha}^{\text{infec}}.$$

- We link $d_{t,\alpha}$ under the proposed model to $y_{t,\alpha}$ through an over-dispersed count model (Birrell et al., 2021). The log-likelihood of the observed deaths is given by

$$\ell^{Deaths}(y \mid \phi) = \sum_{t=1}^{T} \sum_{\alpha=1}^{A} \text{logNegBin}\left(y_{t,\alpha} \mid d_{t,\alpha}, \xi_{t,\alpha}\right),$$

where $\xi_{t,\alpha} = \frac{d_{t,\alpha}}{\phi}$, such that $\mathbb{E}[y_{t,\alpha}] = d_{t,\alpha}$ and $\mathbb{V}[y_{t,\alpha}] = d_{t,\alpha}(1+\phi)$.

Observation process

- Infection-to-death distribution
  - Assumed to be Gamma distributed with mean 24.2 days and coefficient of variation 0.39 (Flaxman et al., 2020; Monod et al., 2021) and is given by

$$h \sim \text{Gamma}(6.29, 0.26).$$

- Infection fatality rate = deaths among all infected individuals
  - REal-time Assessment of Community Transmission-2 (REACT-2) national study of over 100,000 people in England (Ward et al., 2021): estimated total number of SARS-CoV-2 infections since start of the epidemic until mid-July 2020.

Age group	**15-44**	**45-64**	**65-74**	**75+**
IFR (%)	0.03	0.52	3.13	11.64

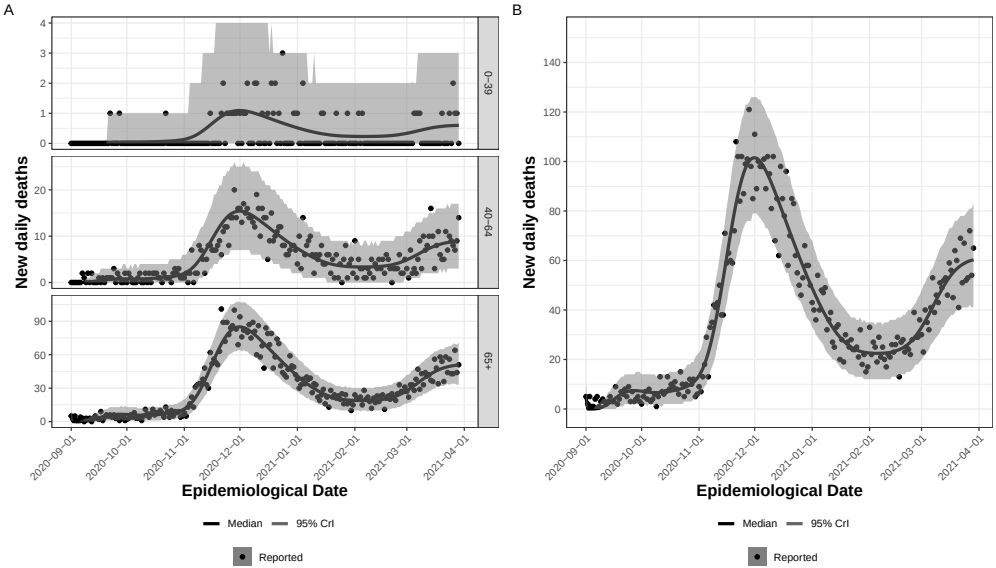
Parameter estimation - challenges

- Non-linear ODE system + SDE = hypo-elliptic diffusion $\rightarrow$ Intractable!
- Data augmentation framework of Dureau et al. (2013):
  - Latent sample path x of the diffusion is infinite-dimensional.
  - Indirectly observed through the time evolution of the disease states.
- Decrease dimensionality stochastic process:
  - Split study period $t = 1, \ldots, T$ into $k = 1, \ldots, K$ batches and model x_{k_t}.
  - Time-discretization via Euler-Maruyama approximation of x_{k_t}.

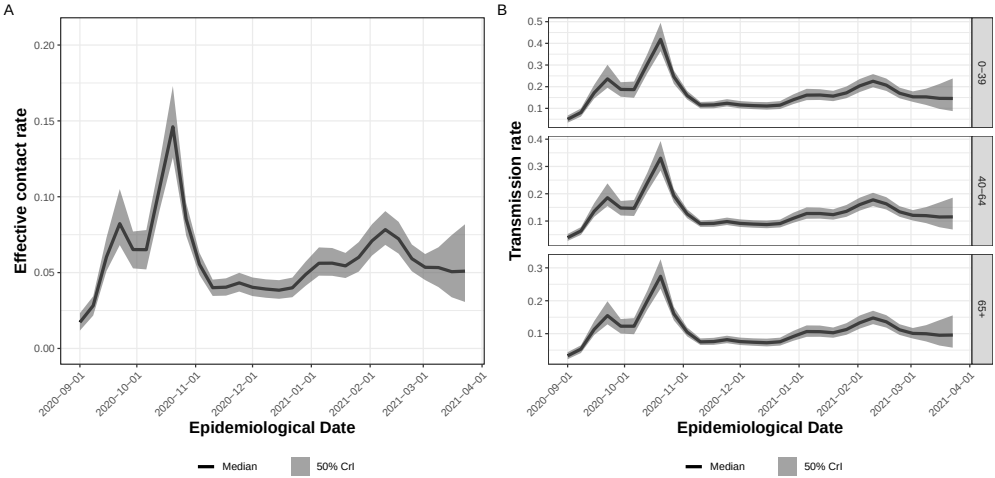
Parameter estimation - challenges

- Estimation of the volatilities $\sigma_{x,\alpha}, \alpha \in \{1, \ldots, A\}$.
- Longer time horizon $\rightarrow$ burden of ODE solver increases:
  - Numerical approximation via the Trapezoidal rule.
- Posterior sampling
  - Dynamic Hamiltonian Monte Carlo algorithm (Betancourt, 2018).
  - Can handle high-dim Θ and posteriors with weird shapes.
  - Volumes of data $\uparrow \Longrightarrow$ cost of solving ODEs $\uparrow$ (Birrell et al., 2021; Gosh et al., 2022): need for further developments.

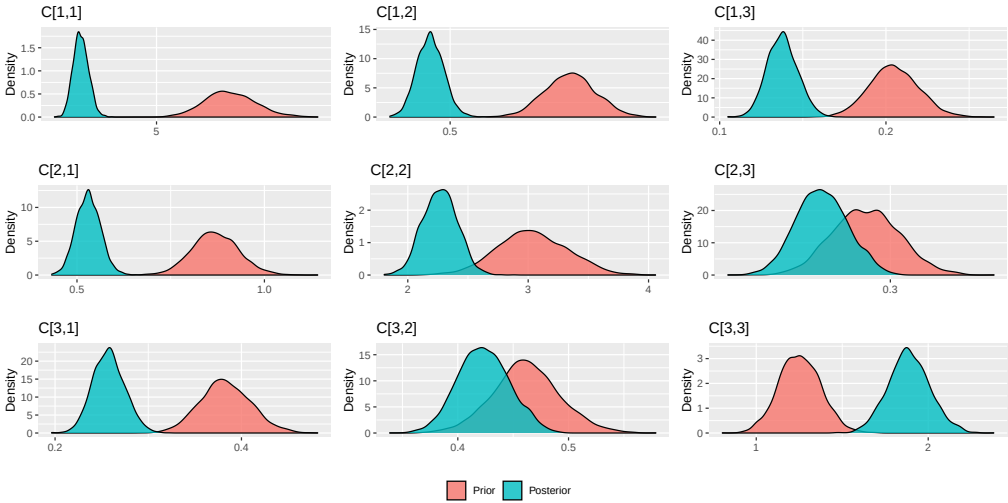
Greece – SBM model



Greece – SBM model



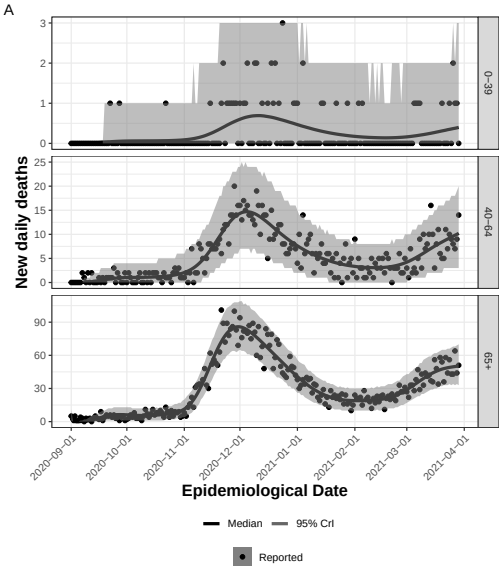
Greece – SBM model

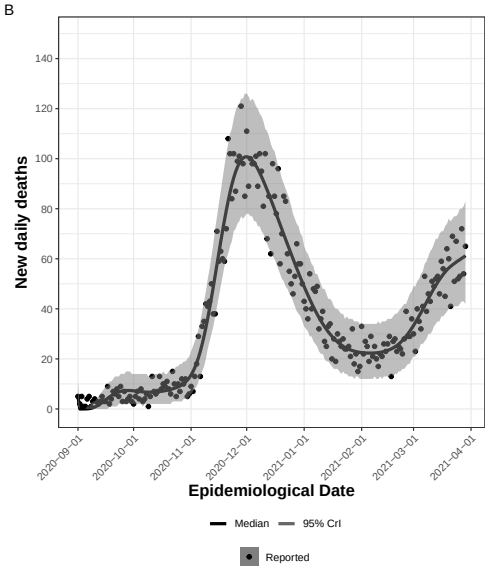


Greece – Model expansion

- The SBM model is not flexible enough to accommodate for age-specific trends in SARS-CoV-2 transmission.
- Assessment of the fidelity of the SBM model to the data at a latent level: prior-data conflict at a latent level.
- Expand the SBM model to the MBM model in the spirit of Gustafson (2005) and inspect the effect on the contact survey data.

Greece – Model expansion





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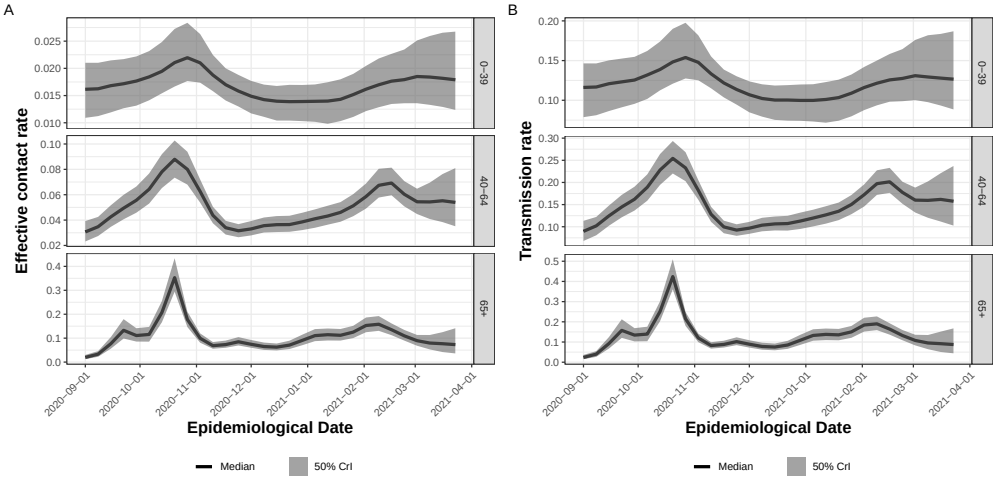

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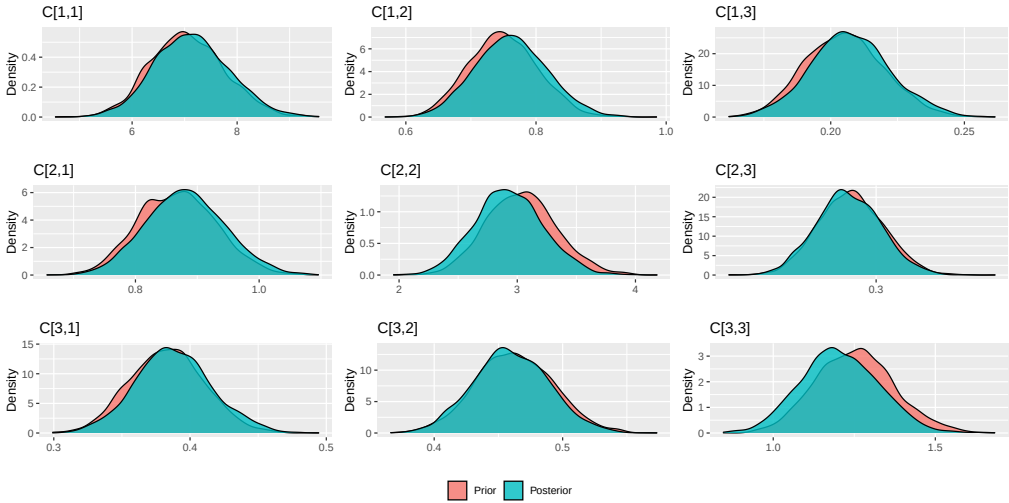
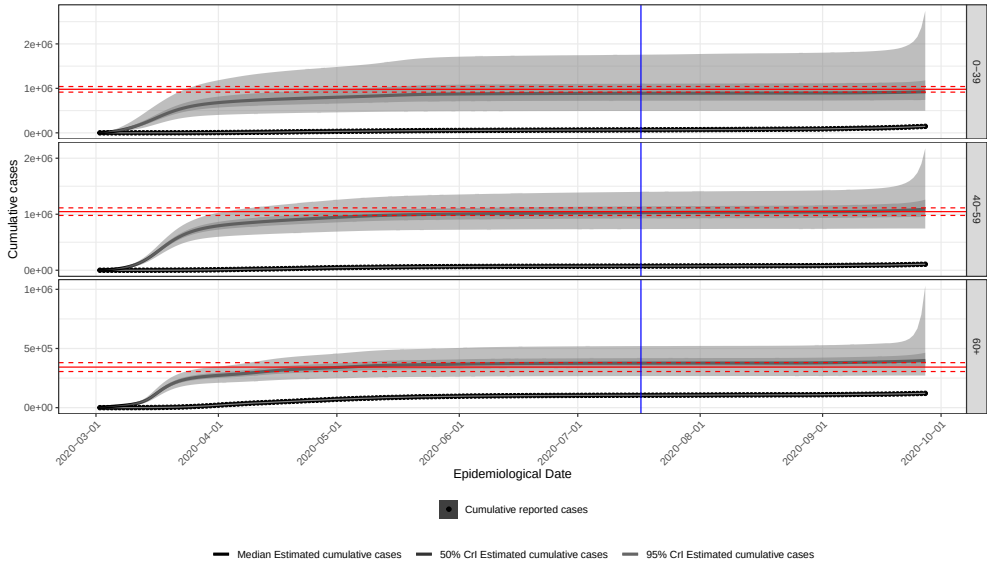


Greece – Model expansion

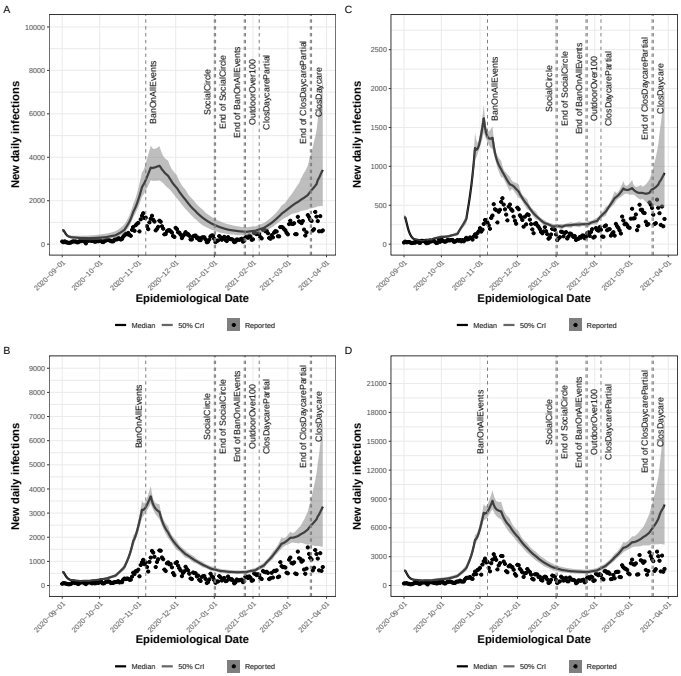
Table 1: Model determination. DIC: Deviance information criterion (Spiegelhalter et al., 2002); $\hat{p}_{DIC}$: estimated effective number of parameters using the DIC; LOOCV: Pareto smoothed importance sampling leave-one-out cross-validation information criterion and accompanying standard error (Vehtari et al., 2017) ; $\hat{p}_{loo}$: estimated effective number of parameters using LOOCV and accompanying standard error.

Model	DIC	$\hat{p}_{DIC}$	LOOCV (se)	$\hat{p}_{loo}$ (se)
SBM	2506.8	16.3	2507.4 (56.0)	15.9 (1.2)
MBM	2506.6	26.4	2506.2 (57.3)	24.6 (1.6)

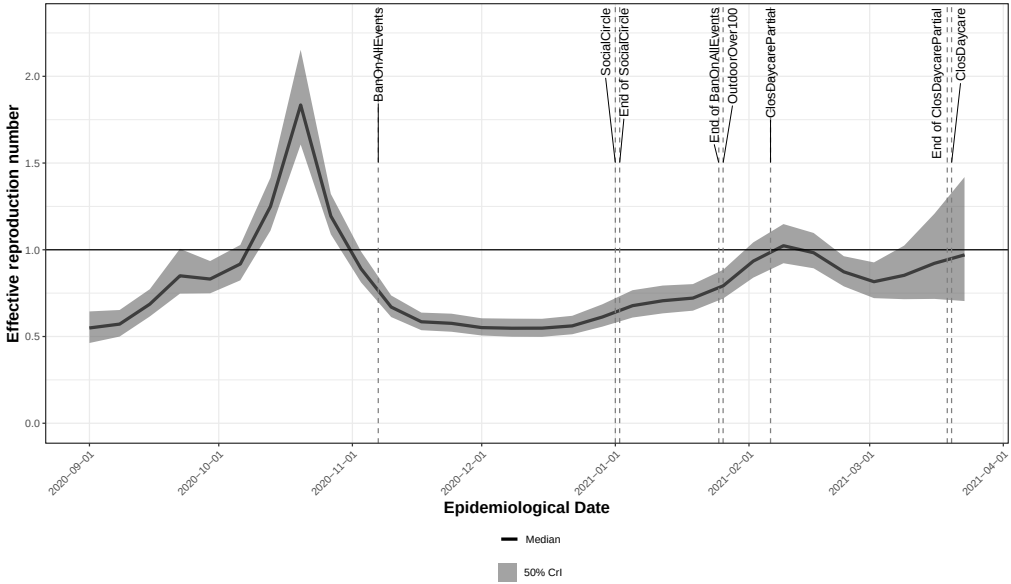
MBM External validation (England)



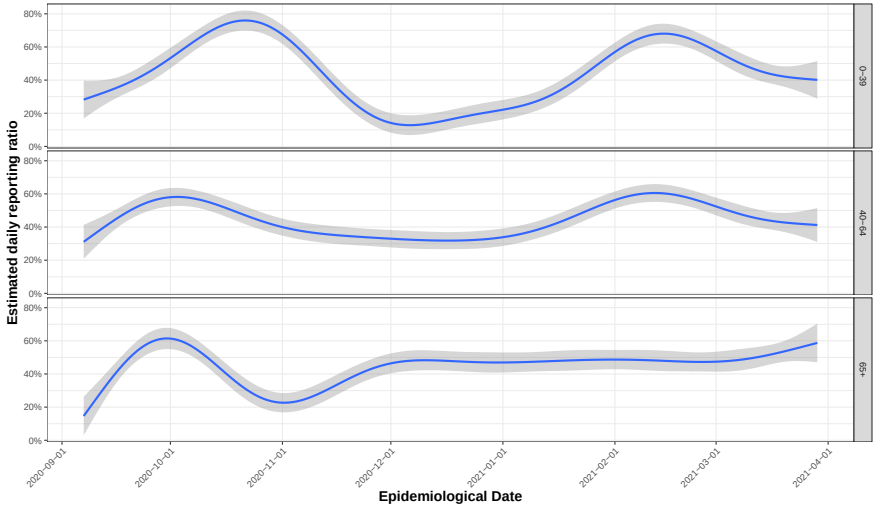
Greece – Age-specific infections (MBM)



Greece – Effective reproduction number (MBM)



Greece – Age-specific reporting ratio (MBM)



Exchangeable SDEs

- A Bayesian multi-task learning framework.
- Exchangeable GBMs - fall within the broad family of multi-output Gaussian Processes (GP).
- Multi-output GPs implemented for a simpler class of Bayesian infectious disease models (Seymour et al., 2022).
- Each Brownian motion path is drawn from an underlying population.
- Can be extended to include alternative Gaussian Processes to the GBM.

Exchangeable SDEs

- *A-priori* belief - shared structure across tasks.
- A Bayesian hierarchical model for:
  - Capturing cross-dependencies between tasks.
  - Introducing a natural interpretation based on the underlying mean stochastic process.
- Exchangeable GBMs improve predictive ability of the model compared to independent GBMs.

Concluding remarks

- Epidemic model driven by the distinct features of COVID-19 data:
  - A data-driven approach to inferring the mechanism governing COVID-19 transmission.
  - Diffusion processes that are a-priori independent.
  - Assess fidelity to the data at a latent level and resolve corresponding prior-data conflict via model expansion.
- Advantages:
  - Synthesis of multiple data sources, publicly available across countries.
  - Remove need for additional information on timing of interventions and hypotheses about their impact on transmission.
  - Model allows policymakers to assess effect of NPIs on each age group.

Concluding remarks

- Limitations:
  - Proposed hierarchical model better suited to the pre-vaccine era.
  - Variations in reporting procedure of deaths and mortality definitions across time and countries.
  - Parametric assumptions for infection-to-death distribution.
  - Account for hospital-acquired infections.
  - Time-invariant age-stratified IFRs.
- Moving forward:
  - Age-stratified IFRs & integration of further healthcare surveillance data.
  - Exchangeable diffusion processes: shared structure between dynamic transmission rates for individuals of different age groups.

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Data sources and definitions

Table 2: Data sources and definitions.

Data type	Description	Source	Reference
Mortality	Daily number of new deaths by age group according to the date of death, tested positive for COVID-19. For England, hospital-only.	NHS, England; Hellenic National Public Health Organization	National Health Service England (2022); Hellenic National Public Health Organization (2022)
Infections	Daily number of new cases by age group and specimen date	NHS, England; Hellenic National Public Health Organization	UK Health Security Agency (2022); Hellenic National Public Health Organization (2022)
Age distribution	Age distribution for a given year, broken down by 5-year age bands and gender	United Nations; Office for National Statistics, UK	United Nations: Department of Economic and Social Affairs: Population Division (2020); Office for National Statistics (2022)
Contact matrix	Rate of contacts between age groups		Prem et al. (2021)

Diffusion-driven multi-type transmission model (1)

- Age-stratified deterministic Susceptible-Exposed-Infected-Recovered ($\mathbb{N}_\alpha = S_t^\alpha + E_{1,t}^\alpha + E_{2,t}^\alpha + I_{1,t}^\alpha + I_{2,t}^\alpha + R_t^\alpha$) compartmental model
  - Force of infection:

$$\lambda_\alpha(t) = \beta_t^{\alpha\alpha'} \sum_{\alpha'=1}^{A} \left[C_{\alpha\alpha'} \frac{\left(I_{1,t}^{\alpha'} + I_{2,t}^{\alpha'} \right)}{\mathbb{N}_{\alpha'}} \right], \quad \alpha = 1, \ldots, A.$$

  - Non-linear system of ODEs:

$$\begin{cases} \frac{dS_t^\alpha}{dt} & = -\lambda_\alpha(t) S_t^\alpha, \\ \frac{dE_{1,t}^\alpha}{dt} & = \lambda_\alpha(t) S_t^\alpha - \tau E_{1,t}^\alpha, \quad \frac{dE_{2,t}^\alpha}{dt} = \tau \left(E_{1,t}^\alpha - E_{2,t}^\alpha \right) \\ \frac{dI_{1,t}^\alpha}{dt} & = \tau E_{2,t}^\alpha - \gamma I_{1,t}^\alpha, \quad \frac{dI_{2,t}^\alpha}{dt} = \gamma \left(I_{1,t}^\alpha - I_{2,t}^\alpha \right) \\ \frac{dR_t^\alpha}{dt} & = \gamma I_{2,t}^\alpha \\ \Delta_{t,\alpha}^{\text{infec}} & = \int_{t-1}^{t} \tau E_{2,s}^\alpha ds \end{cases} \tag{1}$$

- Mean Incubation period [$d_E = 2/\tau$]; Mean Infection period [$d_I = 2/\gamma$].

Prior distributions

- Initial conditions: t_0 = simulation start; most individuals assumed to be susceptible and are distributed across A according to $\mathbb{N}_\alpha$. The number of people in the exposed compartments at t_0 is controlled by a parameter π, and also distributed according to $\mathbb{N}_\alpha$. Other compartments are set to 0.

Table 3: Model parameters with assumed prior distributions or fixed values.

Symbol	Description	Prior source
Transmission model		
π	Initial proportion of exposed (at t_0)	Beta with $\mathbb{E}[\pi] = 0.1$, $\mathbb{V}[\pi] = 0.05 \cdot \mathbb{E}[\pi]$. Based on Hauser et al. (2020).
$F_{i,j}$	Entries of the contact matrix F	Half-Normal with $\mathbb{E}[F_{i,j}] = \mathcal{F}_{i,j}$, $\mathbb{V}[\pi] = (0.05 \cdot \mathcal{F}_{i,j})^2$ $i,j = 1,\ldots,A$.
x_0	Brownian motion at t_0	$\text{Normal}(0, 5^2)$
x_1	Brownian motion at t_1	$\text{Normal}(0, 4^2)$
x_t	Brownian motion	$x_t \mid x_{t-1}, \sigma_x^2 \sim \text{Normal}(x_{t-1}, \sigma_x^2)$, $t = 2,\ldots,T$.
σ_x	Volatility of the Brownian motion	$\text{Half-Normal}(0, 4)$.
Observational model		
ϕ	Negative Binomial over-dispersion	Exp(0.2). Based on Birrell et al. (2021).
Parameters assumed known		
$\widehat{\text{IFR}}_\alpha$	Infection-fatality rate	Based on Ward et al. (2021).
d_E	Mean Incubation period	3 days. Based on Liu et al. (2020).
d_I	Mean Infection period	4 days. Based on Liu et al. (2020).

Effective Reproduction number

- $R_t^{eff} =$ avg # of secondary infections a case infected at time t would generate, accounting for the finite population size and potential immunity in the population (Davies et al., 2020; Knock et al., 2021).
- The next-generation matrix was calculated as

$$\text{NGM}_{\alpha,\alpha'}(t) = m_{\alpha,\alpha'}(t) d_I \frac{S_\alpha(t)}{\mathbb{N}_{\alpha'}}.$$

- $R_t^{eff} =$ absolute value of the dominant eigenvalue of NGM(t).

Age-specific reporting ratio

- Combine daily laboratory-confirmed COVID-19 infections with estimated daily number of infections in the population.
- Age-specific posterior median of the number of infected individuals in the population at time $t - L$.
- Allows for a reporting delay of L days between infection and report.
- Laboratory-confirmed infections which are reported at time t denoted by $\Delta_{t,\alpha}^{\text{infec,rep}}$.
- Estimated age-specific daily reporting ratio for $\alpha \in \{1, \ldots, A\}$ expressed by

$$\hat{r}_{t,\alpha} = \frac{\Delta_{t,\alpha}^{\text{infec,rep}}}{\hat{\Delta}_{t-L,\alpha}^{\text{infec,pop}}}.$$

We considered a time delay between infection and report (L) equal to 6 days; a time-varying spline-based smoother was applied to $\hat{r}_{t,\alpha}$ via generalized additive model smoothing (Wood et al., 2016).