

Spatial Bayesian distributed lag non-linear models (SB-DLNM) with R-INLA

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In a recent paper published in this journal,¹ we introduced spatial Bayesian distributed lag non-linear models (SB-DLNMs) as a novel framework for estimating the short-term lagged health effects of environmental exposures in small areas. We extended the state-of-the-art approach for exposure-lag-response epidemiological modelling, distributed lag non-linear models (DLNMs),² by incorporating spatial models within a single-stage Bayesian framework to account for spatial dependence in risks. To evidence the practicality of SB-DLNMs, we conducted a case study estimating temperature-lag-mortality relationships in the 73 neighbourhoods of Barcelona. SB-DLNMs can be implemented using various Bayesian statistical software tools. We used WinBUGS for its flexibility in specifying complex hierarchical Bayesian models.³ However, besides the need of conducting simulation studies that validates the robustness of the models, we acknowledged in the original paper that the biggest limitation of SB-DLNMs is their long execution times and high computational demands. As an alternative, R-INLA, based on integrated nested Laplace approximations,⁴ offers faster computation compared to software alternatives using Markov chain Monte Carlo (MCMC),⁵ such as WinBUGS. In this letter, we present the implementation of SB-DLNMs with R-INLA providing the illustrative code to reproduce the results of the same case study of small-area temperature-mortality associations in the Supplementary Text S1 and in a GitHub repository (https://github.com/marcosqz/sbdlm_rinla_implementation).

The complete formulation of SB-DLNMs is detailed in the original SB-DLNM paper.¹ The approach involves considering the spatial arrangement of the data by assuming spatial distribution for the coefficients that define the exposure-lag-response association. This concept is feasible in R-INLA by using pre-implemented spatial models within the package.⁶ Moreover, the flexibility inherent in Bayesian models is maintained in R-INLA by sampling from the joint posterior distribution using the function `"inla.posterior.sample"` in R.⁶

We executed both implementations of SB-DLNMs for the case study. In the new R-INLA implementation, each cross-basis coefficient has independent BYM2 spatial models,⁷ whereas in the WinBUGS implementation, all Leroux spatial models share a common parameter. These changes are motivated by R-INLA's own limitations and in order to set, in our opinion, a good practical guidance for potential R-INLA users of this methodology. Nevertheless, the results obtained with the new R-INLA implementation are comparable to those presented in the original case study using the WinBUGS implementation (Figure 1 and Supplementary Figure S1). Both approaches give similar regional cumulative temperature-mortality associations and a consistent spatial distribution of heat-related mortality risks. The most notable finding however consists in the reduction in execution time for SB-DLNMs, from approximately two weeks in the original WinBUGS implementation to just 25 minutes with R-INLA in the case-crossover design (Figure 1).

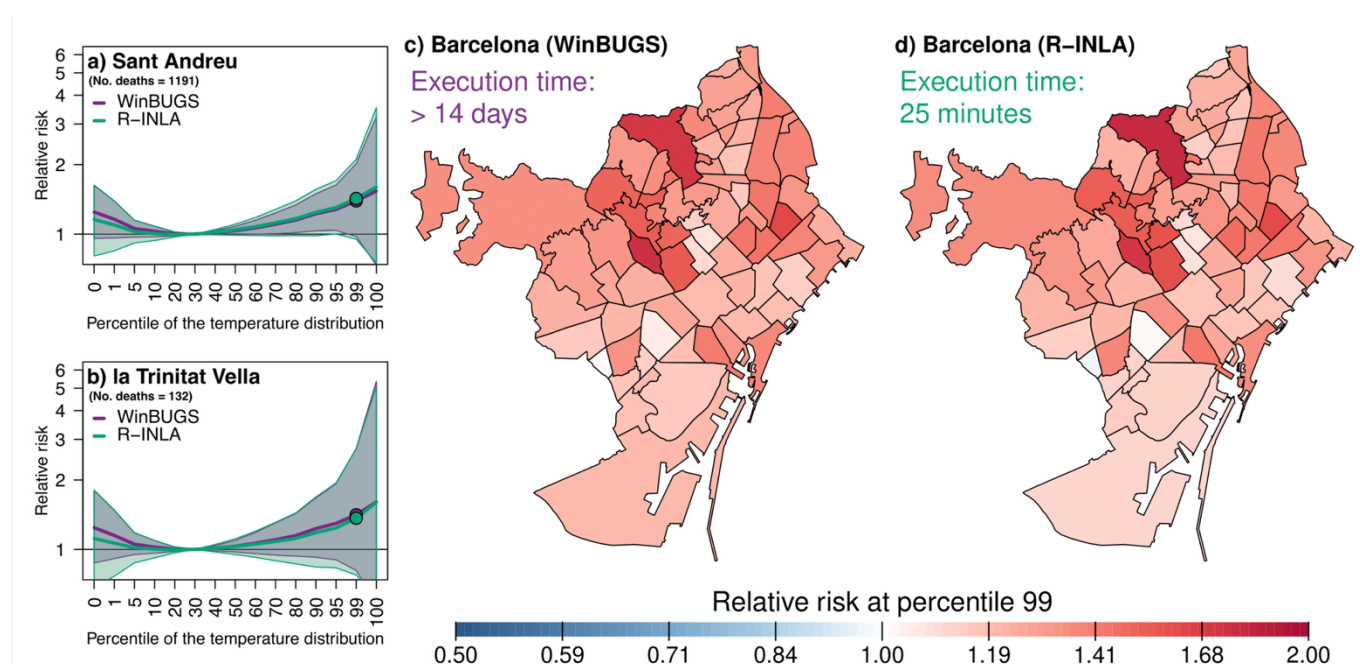


Figure 1: Overall cumulative temperature-mortality association in two adjacent neighbourhoods and spatial distribution of heat-related mortality risks in Barcelona (2007-2016) for WinBUGS and R-INLA implementations of spatial Bayesian distributed lag non-linear models (SB-DLNMs) with the case-crossover design. Panels (a) and (b) show the association between the percentile of the neighbourhood

temperature distribution and the relative risk of mortality. Curves are centred at the 30th percentile of the neighbourhood temperature distribution in both neighbourhoods. The thick curves represent the points estimates (ie median values) and the coloured areas represent the 95% credible interval of the estimates. Panels (c) and (d) show the point estimates of the relative risk of death at the 99th percentile of the neighbourhood temperature distribution, compared with the risk at the centring temperature in the 30th percentile, for the WinBUGS and R-INLA implementations respectively. **Alt text: Graphs show small differences in the estimation of temperature-mortality associations between spatial Bayesian distributed lag non-linear models run in WinBUGS and R-INLA, but large differences in execution time.**

In general, Table 1 shows the significantly faster execution times achieved with R-INLA compared to WinBUGS. The shift from several days to only a few seconds or minutes in the independent Bayesian DLNMs (B-DLNMs) shows the potential for implementing these models in single-location analyses. We note that the relative improvement in the execution times are higher in the case-crossover design than in the time-series design, though refining the R-INLA implementation or relaxing assumptions in the seasonality splines could narrow this gap.

MODEL	DESIGN	EXECUTION TIME WinBUGS	EXECUTION TIME R-INLA	RATIO EXECUTION TIME WinBUGS / R-INLA
Independent B-DLNM	Case-crossover	>2 days	59 seconds	~ 3.000
Independent B-DLNM	Time-series	>3 days	43 minutes	~ 100
SB-DLNM	Case-crossover	>14 days	25 minutes	~ 800
SB-DLNM	Time-series	>14 days	2.4 days	~ 6

Table 1: Execution times of the case-study of small-area temperature-associations for the WinBUGS and R-INLA implementations of independent Bayesian distributed lag non-linear models (B-DLNMs) and spatial Bayesian distributed lag non-linear models (SB-DLNMs). The models were run on a desktop computer with an Intel(R) Xeon(R) Gold 6230 CPU 2.10GHz processor (12 threads used in WinBUGS, 10 threads for R-INLA), and 64GB of RAM. The case-study models the short-term associations between temperature and mortality during the summer months (June-September) in 73 small-areas of Barcelona (2007-2016). The dataset included 39,569 deaths, with 19 (1,454) deaths in the neighbourhood with the lowest (highest) number of deaths. Distributed lag non-linear models modelling choices were based on previous studies, and specified in the original SB-DLNM paper.¹ Execution times could vary depending on many factors such as the specification of the models, the convergence criteria and the number of iterations in WinBUGS, the integration method and the approximation method for the posterior marginals in R-INLA. However, the importance of these results lies in the large differences in the magnitudes of the execution times.

To extend the applicability range of SB-DLNM to larger range of case studies, it was necessary to improve the implementation from the original SB-DLNM paper.¹ We achieved this by rewriting SB-DLNMs in R-INLA, which significantly reduced execution times compared with the WinBUGS implementation. Despite some differences in model implementations, the results for this case study are almost identical. However, it is important to acknowledge that model specification in R-INLA can be less flexible. For example, specifying common parameters across all spatial models, which is straightforward in WinBUGS, become more complex in R-INLA. Additionally, R-INLA, as an inference tool, has its own limitations, such as being an approximation method to the posterior distribution (similar to MCMC). However, its increased speed compared to many MCMC algorithms strengthens its practicality and usability.

The new R-INLA implementation offers several advantages. In contrast to WinBUGS, R-INLA allows for easy implementation on Linux clusters, which facilitates the parallelisation of the model in high-performance computing systems. This R-INLA implementation could allow future studies to use SB-DLNMs in cases involving large-scale datasets,⁵ facilitating more direct comparisons with other small-area approaches using more spatial units,⁸ or continent-wide datasets representing the intersection of small groups of age, sex, cause of disease and/or comorbidities, as it is currently being developed within the framework of the EARLY-ADAPT project.⁹ By providing the R-INLA reproducible code for the case study (Supplementary Text S1 and in https://github.com/marcosqz/sbdlm_rinla_implementation), we aim to encourage other researchers to use SB-DLNMs for both small-area and large-scale environmental epidemiology.

Ethics approval

This study is based on a secondary analysis of administrative data, and does not contain any studies with human participants performed by any of the authors. Informed consent of individuals, or approval by a medical ethics board, was not required under national regulations.

Data availability

The mortality data underlying this article were gathered from the mortality registry of Barcelona, which draws on both the mortality registry of the Department of Health of Catalonia and the municipal population registry. Data will be shared upon request to the corresponding author with permission from both the Department of Health of Catalonia and the municipal population registry. The temperature data underlying this article were provided by VITO [<https://vito.be/en>] by permission. Temperature data will be shared on request to the corresponding author with permission of VITO.

Author contributions

M.Q-Z. and M.M-D. conceptualized the study. M.Q-Z. and M.M-D. performed the statistical analysis. M.Q-Z. wrote the original draft. All authors contributed to the study design, the interpretation of the results and the drafting of the manuscript.

Use of Artificial intelligence (AI) tools

AI was used to improve readability and English grammar.

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Conflict of interest

None declared.

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Text S1: R-INLA code for Bayesian and spatial Bayesian distributed lag non-linear models (B-DLNM and SB-DLNM) in the case study of small-area short-term associations between temperature and mortality in Barcelona.

In the original SB-DLNM paper (<https://doi.org/10.1093/ije/dyae061>) we provided the WinBUGS implementation of SB-DLNMs. While WinBUGS provides flexibility in specifying complex hierarchical Bayesian models, R-INLA is a faster and computationally efficient method.

We provide in a GitHub repository (https://github.com/marcosqz/sbdlnm_rinla_implementation) the R-INLA implementation of SB-DLNMs with all the necessary files to reproduce the analysis of the temperature-mortality association in small areas presented in the original SB-DLNM paper: the shapefile of the city of Barcelona, the exposure temperature data at the regional level, and daily mortality data re-simulated from the fitted model (not the original due to confidentiality restrictions). With this reproducible code is possible to replicate the entire process of SB-DLNMs in R-INLA.

Here, in the supplementary data, we show the three scripts in which the code is divided:

1. *01_data_preparation.R*. The first code is for data preparation, transforming the usual time-series datasets of temperature and mortality into data ready to use for SB-DLNMs.
2. *02_run_sbdlm.R*. The second code presents the model specification and execution of independent B-DLNMs and SB-DLNMs in R-INLA.
3. *03_plot_sbdlm.R*. The last code shows how to handle the output from the models in this Bayesian context: build and plot the three-dimensional exposure-lag-response surfaces, the overall associations, and map the risks showing the spatial patterns.

```

1 #####
2 # IMPORTANT: THE MORTALITY DATA provided are simulated FROM MODEL 4 (SB-DLNM
3 # WITH TIME-SERIES DESIGN) IN THE ORIGINAL SB-DLNM PAPER
4 # (https://doi.org/10.1093/ije/dyae061)
5 # due to confidentiality restrictions of the original dataset. Original data
6 # may be requested to the data owner (The Barcelona Public Health Agency) who
7 # should share them in similar terms than those applying to this study. The
8 # supplied mortality, with exactly the same structure than the original dataset,
9 # allows reproducing the code provided so that interested readers may run it as
10 # an example of use. However, the results from the original data are
11 # additionally supplied (input/result_inla folder). We provide here the
12 # implementation of B-DLNMs and SB-DLNMS in R-INLA, a significantly faster and
13 # user-friendly software compared to WinBUGS.
14 # We used R version 4.4.2 and INLA version 24.12.11
15 #####
16 #####
17 # In this R project we implement Bayesian and spatial Bayesian distributed
18 # lag non-Linear models (B-DLNM and SB-DLNM) for the case study of short-term
19 # associations between temperature and mortality in the city of Barcelona.
20 #####
21 #####
22 #####
23 # CODE 1: DATA PREPARATION
24 # Data preparation: Transforming time-series temperature and mortality datasets
25 # for B-DLNMs and SB-DLNMs.
26 #####
27
28 # Load libraries
29
30 library(sf)
31 library(spdep)
32 library(lubridate)
33 library(dlnm)
34
35 # Load data
36
37 load("input/daily_data.RData")
38 shapefile_bcn <- read_sf("input/shapefile_bcn.shp")
39
40 # Subset data to only summer months of 2007 to 2016
41
42 data <- subset(data, month(date) %in% 6:9)
43 data <- subset(data, year(date) %in% 2007:2016)
44
45 # Generate a list of spatial structure from the shapefile for use in INLA.
46 list_neig <- nb2mat(poly2nb(shapefile_bcn), style = "B")
47 save(list_neig, file = "output/list_neighbours.RData")
48
49 # Set variables defining the dlnm model
50
51 dlnm_var <- list(
52   var_prc = c(0.50, 0.90),
53   var_fun = "ns",
54   max_lag = 8,
55   lagnk = 2,
56   n_reg = 73,
57   n_coef = 12)
58
59 # Set variables for trend and seasonality
60
61 df_seas <- 4
62 df_trend_10years <- 1 # 1 df every 10 years to control for long-term trends
63 df_trend <- round(
64   length(min(year(data$date)):max(year(data$date))) / df_trend_10years / 10) # Here
65   we assume the time period for all regions is the same
66 rm(df_trend_10years)
67
68 dlnm_var$df_seas <- df_seas
69 dlnm_var$df_trend <- df_trend
70
71 rm(df_seas, df_trend)

```

```

72 save(dlnm_var, file = "output/dlnm_configuration.RData")
73
74 # Create crossbasis for each region
75
76 # Ensure that the data is ordered by region to maintain alignment between
77 # crossbasis and regions
78 if(is.unsorted(data$region)) {
79   stop("data needs to be ordered by region for the next loop")}
80
81 list_cb <- lapply(formatC(1:dlnm_var$n_reg, width = 2, flag = "0"),
82   function(i_reg) {
83
84     temp <- subset(data, region == i_reg,
85       select = c("temp", paste0("lag", 1:dlnm_var$max_lag)))
86
87     temp_knots <- quantile(temp$temp, dlnm_var$var_prc, na.rm = TRUE)
88     temp_boundary <- range(temp, na.rm = TRUE)
89
90     cb <- crossbasis(temp,
91       argvar = list(fun = dlnm_var$var_fun,
92         knots = temp_knots,
93         Boundary.knots = temp_boundary),
94       arglag = list(fun = "ns",
95         knots = logknots(dlnm_var$max_lag,
96           dlnm_var$lagnk),
97         intercept = TRUE))
98
99     cb
100
101   })
102 cb <- do.call(rbind, list_cb)
103 rm(list_cb)
104
105 # Create different objects for the case-crossover and time-series designs
106
107 data_cco <- data; cb_cco <- cb
108 data_ts <- data; cb_ts <- cb
109
110 rm(data, cb)
111
112 # PREPARE DATA FOR THE CASE-CROSSOVER DESIGN
113
114 # Create strata for the case-crossover
115 # (neighborhood - year - month - day of week)
116 data_cco$strata <- paste(data_cco$region,
117   year(data_cco$date),
118   formatC(month(data_cco$date), width = 2, flag = "0"),
119   wday(data_cco$date, week_start = 1),
120   sep = ":")
121
122 # We exclude stratum without cases as they do not contribute to the
123 # likelihood in the case-crossover design
124 keep <- sapply(split(data_cco$mort, data_cco$strata), sum)
125 keep <- data_cco$strata %in% names(keep[keep != 0])
126 data_cco <- data_cco[keep,]
127 cb_cco <- cb_cco[keep,]
128 rm(keep)
129
130 save(data_cco, file = "output/data_casecrossover.RData")
131 save(cb_cco, file = "output/crossbasis_casecrossover.RData")
132
133 # PREPARE DATA FOR THE TIME-SERIES DESIGN
134
135 # Define day of week and year
136 data_ts$day_of_week <- wday(data_ts$date, week_start = 1)
137 data_ts$year <- year(data_ts$date)
138
139 # Create the trend matrix
140
141 trend <- onebasis(data_ts$date, fun = "ns", df = dlnm_var$df_trend)
142
143 # Create the seasonality matrix
144

```

```

145 # Ensure that the data is ordered by region and year to maintain alignment
146 # between seasonality and data
147 if(is.unsorted(order(data_ts$region, data_ts$year))) {
148   stop("data needs to be ordered by region and year for the next loop")}
149
150 seas <- lapply(formatC(1:dlm_var$n_reg, width = 2, flag = "0"),
151   function(i_reg) {
152     lapply(unique(year(data_ts$date)), function(i_year) {
153       date <- subset(data_ts, region == i_reg & year(date) == i_year)$date
154       seas <- onebasis(yday(date), fun = "ns", df = dlm_var$df_seas)
155       return(seas)
156     })
157   })
158 seas <- do.call(rbind, do.call(rbind, seas))
159
160 save(data_ts, file = "output/data_timeseries.RData")
161 save(cb_ts, file = "output/crossbasis_timeseries.RData")
162 save(trend, file = "output/trend_timeseries.RData")
163 save(seas, file = "output/seasonality_timeseries.RData")

```

```

1 #####
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8 # supplied mortality, with exactly the same structure than the original dataset,
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10 # an example of use. However, the results from the original data are
11 # additionally supplied (input/result_inla folder). We provide here the
12 # implementation of B-DLNMs and SB-DLNMs in R-INLA, a significantly faster and
13 # user-friendly software compared to WinBUGS.
14 # We used R version 4.4.2 and INLA version 24.12.11
15 #####
16 #####
17 # In this R project we implement Bayesian and spatial Bayesian distributed
18 # lag non-Linear models (B-DLNM and SB-DLNM) for the case study of short-term
19 # associations between temperature and mortality in the city of Barcelona.
20 #####
21 #####
22 # CODE 2: RUN B-DLNMs AND SB-DLNMs
23 # Model specification and execution: independent B-DLNMs and SB-DLNMs in R and
24 # R-INLA with simulated mortality data.
25 #####
26 #####
27
28 # Load libraries
29 library(INLA)
30
31 # 10 threads were used to generate the results
32 # Use "inla.setOption("num.threads", 10)" only if your computer has at least
33 # 10 threads
34
35 # inla.setOption("num.threads", 10)
36
37 # Load data for case-crossover design
38 load("output/data_casecrossover.RData")
39 load("output/crossbasis_casecrossover.RData")
40
41 # Load data for time-series design
42 load("output/data_timeseries.RData")
43 load("output/crossbasis_timeseries.RData")
44 load("output/trend_timeseries.RData")
45 load("output/seasonality_timeseries.RData")
46
47 # Load spatial data structure and DLNM configuration
48 load("output/list_neighbours.RData")
49 load("output/dlnm_configuration.RData")
50
51 # For INLA implementation, add variables identifying different categories
52
53 # (1) Case-crossover
54 colnames(cb_cco) <- paste0("cb", 1:ncol(cb_cco))
55 data_cco <- cbind(data_cco, cb_cco) # Add cross-basis to the dataset
56 for (i in 1:dlnm_var$n_coef) {
57   col_name <- paste0("id_cb", i)
58   data_cco[[col_name]] <- as.numeric(data_cco$region) # One estimate per region for
59   cb coefficients
60 } rm(i, col_name)
61
62 # (2) Time-series
63 colnames(cb_ts) <- paste0("cb", 1:ncol(cb_ts)) # Add cross-basis to the dataset
64 data_ts <- cbind(data_ts, cb_ts)
65 for (i in 1:dlnm_var$n_coef) {
66   col_name <- paste0("id_cb", i)
67   data_ts[[col_name]] <- as.numeric(data_ts$region) # One estimate per region for cb
68   coefficients
69 } rm(i, col_name)
70
71 data_ts$trend <- trend[,1] # Add trend to the dataset
72 data_ts$id_trend <- as.numeric(data_ts$region) # One estimate per region for trend

```

```

coefficients
71
72 colnames(seas) <- paste0("seas", 1:dlnm_var$df_seas)
73 data_ts <- cbind(data_ts, seas) # Add seasonality to the dataset
74 for (i in 1:dlnm_var$df_seas) {
75   data_ts[[paste0("id_year", i)]] <- lubridate::year(data_ts$date) # One estimate per
   year and region for seasonality coefficients
76   data_ts[[paste0("id_region", i)]] <- as.numeric(data_ts$region)
77 }; rm(i)
78
79 data_ts$intercept_dow <- paste0("dow_", data_ts$day_of_week, "_", data_ts$region) #
Add day of week to the dataset
80
81 #.....
82 ### MODEL 1 (Independent B-DLNM - case-crossover design) ###
83 #.....
84
85 ### INLA - MODEL 1 Independent B-DLNM - case-crossover design
86
87 inla_formula <- mort ~ -1 +
88   f(strata, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed = TRUE
   ))) +
89   f(id_cb1, cb1, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
90   f(id_cb2, cb2, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
91   f(id_cb3, cb3, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
92   f(id_cb4, cb4, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
93   f(id_cb5, cb5, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
94   f(id_cb6, cb6, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
95   f(id_cb7, cb7, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
96   f(id_cb8, cb8, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
97   f(id_cb9, cb9, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
   TRUE))) +
98   f(id_cb10, cb10, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
   = TRUE))) +
99   f(id_cb11, cb11, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
   = TRUE))) +
100  f(id_cb12, cb12, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
   = TRUE)))
101
102 # In order to sample from the posterior distribution model need to be fitted
103 # with config = TRUE
104 inla_model <- inla(inla_formula,
105                   data = data_cco, family = "poisson",
106                   control.compute = list(config = TRUE),
107                   control.inla = list(strategy = "laplace",
108                                       int.strategy = "grid"))
109
110 # Extract the ensemble of sample coefficients of the crossbasis
111 inla_res <- inla.posterior.sample(1000, inla_model,
112                                  selection = list("id_cb1" = 1:dlnm_var$n_reg,
113                                                  "id_cb2" = 1:dlnm_var$n_reg,
114                                                  "id_cb3" = 1:dlnm_var$n_reg,
115                                                  "id_cb4" = 1:dlnm_var$n_reg,
116                                                  "id_cb5" = 1:dlnm_var$n_reg,
117                                                  "id_cb6" = 1:dlnm_var$n_reg,
118                                                  "id_cb7" = 1:dlnm_var$n_reg,
119                                                  "id_cb8" = 1:dlnm_var$n_reg,
120                                                  "id_cb9" = 1:dlnm_var$n_reg,
121                                                  "id_cb10" = 1:dlnm_var$n_reg,
122                                                  "id_cb11" = 1:dlnm_var$n_reg,
123                                                  "id_cb12" = 1:dlnm_var$n_reg))
124
125 cb_res <- lapply(1:dlnm_var$n_reg, function(i_reg) {
126   beta_reg <- sapply(inla_res, function(x) {
127     sapply(1:dlnm_var$n_coef, function(i) {

```

```

128     x$latent[paste0("id_cb", i, ":", i_reg),]
129   })
130 })
131 t(beta_reg)
132 })
133
134 # save(cb_res, file = "output/predicted_inla_model1_independent_casecrossover.RData")
135
136 rm(inla_formula, inla_model, inla_res, cb_res)
137
138 #.....
139 ### MODEL 2 (Independent B-DLNM - time-series design) ###
140 #.....
141
142 ### INLA - MODEL 2 Independent B-DLNM - time-series design
143
144 inla_formula <- mort ~ -1 +
145   f(intercept_dow, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
146     = TRUE))) +
147   f(id_cb1, cb1, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
148     TRUE))) +
149   f(id_cb2, cb2, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
150     TRUE))) +
151   f(id_cb3, cb3, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
152     TRUE))) +
153   f(id_cb4, cb4, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
154     TRUE))) +
155   f(id_cb5, cb5, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
156     TRUE))) +
157   f(id_cb6, cb6, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
158     TRUE))) +
159   f(id_cb7, cb7, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
160     TRUE))) +
161   f(id_cb8, cb8, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
162     TRUE))) +
163   f(id_cb9, cb9, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed =
164     TRUE))) +
165   f(id_cb10, cb10, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
166     = TRUE))) +
167   f(id_cb11, cb11, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
168     = TRUE))) +
169   f(id_cb12, cb12, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
170     = TRUE))) +
171   f(id_trend, trend, model = "iid", hyper = list(prec = list(initial = log(1e-04),
172     fixed = TRUE))) +
173   seas1:factor(id_year1):factor(id_region1) +
174   seas2:factor(id_year2):factor(id_region2) +
175   seas3:factor(id_year3):factor(id_region3) +
176   seas4:factor(id_year4):factor(id_region4)
177
178 # In order to sample from the posterior distribution model need to be fitted
179 # with config = TRUE
180 inla_model <- inla(inla_formula,
181   data = data_ts, family = "poisson",
182   control.compute = list(config = TRUE),
183   control.inla = list(strategy = "laplace",
184     int.strategy = "grid"))
185
186 # Extract the ensemble of sample coefficients of the crossbasis
187 inla_res <- inla.posterior.sample(1000, inla_model,
188   selection = list("id_cb1" = 1:dlnm_var$n_reg,
189     "id_cb2" = 1:dlnm_var$n_reg,
190     "id_cb3" = 1:dlnm_var$n_reg,
191     "id_cb4" = 1:dlnm_var$n_reg,
192     "id_cb5" = 1:dlnm_var$n_reg,
193     "id_cb6" = 1:dlnm_var$n_reg,
194     "id_cb7" = 1:dlnm_var$n_reg,
195     "id_cb8" = 1:dlnm_var$n_reg,
196     "id_cb9" = 1:dlnm_var$n_reg,
197     "id_cb10" = 1:dlnm_var$n_reg,
198     "id_cb11" = 1:dlnm_var$n_reg,
199     "id_cb12" = 1:dlnm_var$n_reg))

```

```

187 cb_res <- lapply(1:dlnm_var$n_reg, function(i_reg) {
188   beta_reg <- sapply(inla_res, function(x) {
189     sapply(1:dlnm_var$n_coef, function(i) {
190       x$latent[paste0("id_cb", i, ":", i_reg),]
191     })
192   })
193   t(beta_reg)
194 })
195
196 # save(cb_res, file = "output/predicted_inla_model2_independent_timeseries.RData")
197
198 rm(inla_formula, inla_model, inla_res, cb_res)
199
200 #.....
201 ### MODEL 3 (SB-DLNM - case-crossover design) ###
202 #.....
203
204 ### INLA - MODEL 3 SB-DLNM - case-crossover design
205
206 inla_formula <- mort ~ -1 +
207   cb1 + cb2 + cb3 + cb4 + cb5 + cb6 +
208   cb7 + cb8 + cb9 + cb10 + cb11 + cb12 +
209   f(strata, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed = TRUE
210   ))) +
211   f(id_cb1, cb1, model = "bym2", graph = list_neig) +
212   f(id_cb2, cb2, model = "bym2", graph = list_neig) +
213   f(id_cb3, cb3, model = "bym2", graph = list_neig) +
214   f(id_cb4, cb4, model = "bym2", graph = list_neig) +
215   f(id_cb5, cb5, model = "bym2", graph = list_neig) +
216   f(id_cb6, cb6, model = "bym2", graph = list_neig) +
217   f(id_cb7, cb7, model = "bym2", graph = list_neig) +
218   f(id_cb8, cb8, model = "bym2", graph = list_neig) +
219   f(id_cb9, cb9, model = "bym2", graph = list_neig) +
220   f(id_cb10, cb10, model = "bym2", graph = list_neig) +
221   f(id_cb11, cb11, model = "bym2", graph = list_neig) +
222   f(id_cb12, cb12, model = "bym2", graph = list_neig)
223
224 # In order to sample from the posterior distribution model need to be fitted
225 # with config = TRUE
226 inla_model <- inla(inla_formula,
227   data = data_cco, family = "poisson",
228   control.compute = list(config = TRUE),
229   control.inla = list(strategy = "laplace",
230     int.strategy = "grid"))
231
232 # Extract the ensemble of sample coefficients of the crossbasis
233 inla_res <- inla.posterior.sample(1000, inla_model,
234   selection = list(cb1 = 1,
235     cb2 = 1,
236     cb3 = 1,
237     cb4 = 1,
238     cb5 = 1,
239     cb6 = 1,
240     cb7 = 1,
241     cb8 = 1,
242     cb9 = 1,
243     cb10 = 1,
244     cb11 = 1,
245     cb12 = 1,
246     "id_cb1" = 1:dlnm_var$n_reg,
247     "id_cb2" = 1:dlnm_var$n_reg,
248     "id_cb3" = 1:dlnm_var$n_reg,
249     "id_cb4" = 1:dlnm_var$n_reg,
250     "id_cb5" = 1:dlnm_var$n_reg,
251     "id_cb6" = 1:dlnm_var$n_reg,
252     "id_cb7" = 1:dlnm_var$n_reg,
253     "id_cb8" = 1:dlnm_var$n_reg,
254     "id_cb9" = 1:dlnm_var$n_reg,
255     "id_cb10" = 1:dlnm_var$n_reg,
256     "id_cb11" = 1:dlnm_var$n_reg,
257     "id_cb12" = 1:dlnm_var$n_reg))
258
259 cb_res <- lapply(1:dlnm_var$n_reg, function(i_reg) {

```

```

259   beta_reg <- sapply(inla_res, function(x) {
260     sapply(1:dlnm_var$n_coef, function(i) {
261       x$latent[paste0("cb", i, ":1"),] +
262       x$latent[paste0("id_cb", i, ":", i_reg),]
263     })
264   })
265   t(beta_reg)
266 })
267
268 # save(cb_res, file = "output/predicted_inla_model3_spatial_casecrossover.RData")
269
270 rm(sdunif, inla_formula, inla_model, inla_res, cb_res)
271
272 #.....
273 ### MODEL 4 (SB-DLNM - time-series design) ###
274 #.....
275
276 ### INLA - MODEL 4 SB-DLNM - time-series design
277
278 inla_formula <- mort ~ -1 +
279   cb1 + cb2 + cb3 + cb4 + cb5 + cb6 +
280   cb7 + cb8 + cb9 + cb10 + cb11 + cb12 +
281   f(intercept_dow, model = "iid", hyper = list(prec = list(initial = log(1e-04), fixed
282     = TRUE))) +
283   f(id_cb1, cb1, model = "bym2", graph = list_neig) +
284   f(id_cb2, cb2, model = "bym2", graph = list_neig) +
285   f(id_cb3, cb3, model = "bym2", graph = list_neig) +
286   f(id_cb4, cb4, model = "bym2", graph = list_neig) +
287   f(id_cb5, cb5, model = "bym2", graph = list_neig) +
288   f(id_cb6, cb6, model = "bym2", graph = list_neig) +
289   f(id_cb7, cb7, model = "bym2", graph = list_neig) +
290   f(id_cb8, cb8, model = "bym2", graph = list_neig) +
291   f(id_cb9, cb9, model = "bym2", graph = list_neig) +
292   f(id_cb10, cb10, model = "bym2", graph = list_neig) +
293   f(id_cb11, cb11, model = "bym2", graph = list_neig) +
294   f(id_cb12, cb12, model = "bym2", graph = list_neig) +
295   f(id_trend, trend, model = "iid", hyper = list(prec = list(initial = log(1e-04),
296     fixed = TRUE))) +
297   seas1:factor(id_year1):factor(id_region1) +
298   seas2:factor(id_year2):factor(id_region2) +
299   seas3:factor(id_year3):factor(id_region3) +
300   seas4:factor(id_year4):factor(id_region4)
301
302 # In order to sample from the posterior distribution model need to be fitted
303 # with config = TRUE
304 inla_model <- inla(inla_formula,
305   data = data_ts, family = "poisson",
306   control.compute = list(config = TRUE),
307   control.inla = list(strategy = "laplace",
308     int.strategy = "grid"))
309
310 # Extract the ensemble of sample coefficients of the crossbasis
311 inla_res <- inla.posterior.sample(1000, inla_model,
312   selection = list(cb1 = 1,
313     cb2 = 1,
314     cb3 = 1,
315     cb4 = 1,
316     cb5 = 1,
317     cb6 = 1,
318     cb7 = 1,
319     cb8 = 1,
320     cb9 = 1,
321     cb10 = 1,
322     cb11 = 1,
323     cb12 = 1,
324     "id_cb1" = 1:dlnm_var$n_reg,
325     "id_cb2" = 1:dlnm_var$n_reg,
326     "id_cb3" = 1:dlnm_var$n_reg,
327     "id_cb4" = 1:dlnm_var$n_reg,
328     "id_cb5" = 1:dlnm_var$n_reg,
329     "id_cb6" = 1:dlnm_var$n_reg,
330     "id_cb7" = 1:dlnm_var$n_reg,
331     "id_cb8" = 1:dlnm_var$n_reg,

```

```

330                                     "id_cb9" = 1:dlnm_var$n_reg,
331                                     "id_cb10" = 1:dlnm_var$n_reg,
332                                     "id_cb11" = 1:dlnm_var$n_reg,
333                                     "id_cb12" = 1:dlnm_var$n_reg))
334
335 cb_res <- lapply(1:dlnm_var$n_reg, function(i_reg) {
336   beta_reg <- sapply(inla_res, function(x) {
337     sapply(1:dlnm_var$n_coef, function(i) {
338       x$latent[paste0("cb", i, ":1"),] +
339       x$latent[paste0("id_cb", i, ":", i_reg),]
340     })
341   })
342   t(beta_reg)
343 })
344
345 # save(cb_res, file = "output/predicted_inla_model4_spatial_timeseries.RData")
346
347 rm(sdunif, inla_formula, inla_model, inla_res, cb_res)

```

```

1 #####
2 # IMPORTANT: THE MORTALITY DATA provided are simulated FROM MODEL 4 (SB-DLNM
3 # WITH TIME-SERIES DESIGN) IN THE ORIGINAL SB-DLNM PAPER
4 # (https://doi.org/10.1093/ije/dyae061)
5 # due to confidentiality restrictions of the original dataset. Original data
6 # may be requested to the data owner (The Barcelona Public Health Agency) who
7 # should share them in similar terms than those applying to this study. The
8 # supplied mortality, with exactly the same structure than the original dataset,
9 # allows reproducing the code provided so that interested readers may run it as
10 # an example of use. However, the results from the original data are
11 # additionally supplied (input/result_inla folder). We provide here the
12 # implementation of B-DLNMs and SB-DLNMS in R-INLA, a significantly faster and
13 # user-friendly software compared to WinBUGS.
14 # We used R version 4.4.2 and INLA version 24.12.11
15 #####
16 #####
17 # In this R project we implement Bayesian and spatial Bayesian distributed
18 # lag non-Linear models (B-DLNM and SB-DLNM) for the case study of short-term
19 # associations between temperature and mortality in the city of Barcelona.
20 #####
21 #####
22 #####
23 # CODE 3: PLOT SB-DLNMS
24 # Handling with output from SB-DLNMs: Construct and plot 3D surface associations,
25 # overall cumulative associations, and mapping spatial patterns in R.
26 #####
27
28 # Load libraries
29
30 library(dlnm)
31 library(leaflet)
32 library(sf)
33 library(lubridate)
34
35 # Load necessary files
36
37 load("input/daily_data.RData")
38 shapefile_bcn <- read_sf("input/shapefile_bcn.shp")
39 # WARNING: WE LOAD THE OUTPUT FROM MODEL 3 EXECUTED WITH R-INLA AND THE
40 # REAL MORTALITY DATA. IT CAN BE REPLACED FOR ANY OF THE OTHER OUTPUTS OBTAINED
41 # WITH REAL DATA OR OBTAINED WITH THE PREDICTED DATA FROM CODE 02_run_sbdlm.R
42 load("input/result_inla/final_inla_model3_spatial_casecrossover.RData")
43 load("output/dlnm_configuration.RData")
44
45 # DATA PREPARATION
46
47 # Subset data to only summer months of 2007 to 2016
48
49 data <- subset(data, month(date) %in% 6:9)
50 data <- subset(data, year(date) %in% 2007:2016)
51
52 # Define the percentiles of temperature to be calculated
53 percentiles <- c(seq(0, 1, by = 0.1),
54                  seq(2, 98, by = 1),
55                  seq(99, 100, by = 0.1)) /100
56
57 # Create the temperature values used in the DLNM models
58 list_temp <- lapply(1:dlnm_var$n_reg, function(i_reg) {
59
60   label_reg <- formatC(i_reg, width = 2, flag = "0")
61   temp <- subset(data, region == label_reg,
62                  select = c("temp", paste0("lag", 1:dlnm_var$max_lag)))
63   temp_knots <- quantile(temp[["temp"]], dlnm_var$var_prc, na.rm = TRUE)
64   temp_boundary <- range(temp, na.rm = TRUE)
65   x_temp <- quantile(temp[["temp"]], percentiles, na.rm = TRUE)
66
67   return(list(temp_knots = temp_knots, # knots of the exposure-response function
68              temp_boundary = temp_boundary, # range of temperatures
69              x_temp = x_temp)) # temperatures in which risk are calculated
70
71 })
72

```

```

73 temp_knots <- sapply(list_temp, function(x) x[["temp_knots"]])
74 temp_boundary <- sapply(list_temp, function(x) x[["temp_boundary"]])
75 x_temp <- sapply(list_temp, function(x) x[["x_temp"]])
76 rm(list_temp)
77
78 # Create a list with the basis for exposure and the basis for lags
79 # in each neighbourhood
80
81 basis_all <- lapply(1:dlnm_var$n_reg, function(i_reg) {
82
83   f.temp_knots <- temp_knots[,i_reg]
84   f.temp_boundary <- temp_boundary[,i_reg]
85   f.x_temp <- x_temp[,i_reg]
86
87   # basis temperatures
88   Q <- onebasis(f.x_temp, fun = dlnm_var$var_fun, knots = f.temp_knots,
89                 Boundary.knots = f.temp_boundary)
90
91   # basis lags
92   C <- onebasis(0:dlnm_var$max_lag, fun = "ns",
93                 knots = logknots(dlnm_var$max_lag, dlnm_var$lagnk),
94                 intercept = TRUE)
95
96   return(list(basis_exp = Q, basis_lag = C))
97
98 })
99
100 # Create a list with the cross-basis in each neighbourhood
101
102 cb <- lapply(1:dlnm_var$n_reg, function(i_reg) {
103
104   cb <- crossbasis(matrix(rep(x_temp[,i_reg], dlnm_var$max_lag + 1),
105                             ncol = dlnm_var$max_lag + 1),
106                     argvar = list(fun = dlnm_var$var_fun,
107                                   knots = temp_knots[,i_reg],
108                                   Boundary.knots = temp_boundary[,i_reg]),
109                     arglag = list(fun = "ns",
110                                   knots = logknots(dlnm_var$max_lag, dlnm_var$lagnk),
111                                   intercept = TRUE))
112
113   return(cb)
114
115 })
116
117 #-----
118 # A) PANEL 3-DIMENSIONAL TEMPERATURE-LAG-RISK ASSOCIATION
119 # FOR REGION 1 / ITERATION 1 (EQUIVALENT TO PANEL FIGURE 1 IN THE ORIGINAL SB-DLNM
120 # PAPER)
121 #-----
122
123 # Specify the neighborhood of Barcelona (any integer from 1 to 73)
124 i_reg <- 1
125
126 basis_exp <- basis_all[[i_reg]]$basis_exp
127 basis_lag <- basis_all[[i_reg]]$basis_lag
128 f.x_temp <- x_temp[,i_reg]
129
130 # Extract the ensemble of sample coefficients of the crossbasis
131 beta_reg <- cb_res[[i_reg]]
132
133 # Initialize the array to store the RR for each temperature and lag combination
134 cp <- array(NA, dim = c(nrow(beta_reg), length(f.x_temp), dlnm_var$max_lag + 1))
135
136 for(i_iter in 1:nrow(beta_reg)) {
137   for(i_temp in 1:length(f.x_temp)) {
138     for(i_lag in 1:(dlnm_var$max_lag + 1)) {
139       cp[i_iter, i_temp, i_lag] <- sum(
140         (t(basis_exp[i_temp,,drop = FALSE]) %*% basis_lag[i_lag,,drop = FALSE]) *
141         matrix(beta_reg[i_iter,], ncol = ncol(basis_lag), byrow = TRUE))
142     }
143   }
144   rm(i_iter, i_temp, i_lag)

```

```

145
146 # Position of the temperature percentile where we center the associations
147 i_cen <- percentiles == 0.3
148
149 # New array to store the centered association
150 cp_cen <- array(NA, dim = c(nrow(beta_reg), length(f.x_temp), dlnm_var$max_lag + 1))
151
152 for(i in 1:length(f.x_temp)){
153   cp_cen[,i,] <- cp[,i,]-cp[,i_cen,]
154 }; rm(i, cp)
155
156 # Choose an iteration for plotting (e.g., the first iteration)
157 cp_plot <- exp(cp_cen[1,,])
158
159 # Plot three-dimensional associations
160 pdf("plot/figureA_exposure_lag_response_surface.pdf",
161     width = 5, height = 5)
162 par(mex = 0.3)
163 association <-
164   persp(x = f.x_temp, y = 0:dlnm_var$max_lag, z = cp_plot, border = NA,
165         ticktype = "detailed", theta = 240, phi = 50,
166         xlab = "\nTemperature (°C)", ylab = "\nLag (days)", zlab = "\nRelative risk",
167         col = "lightskyblue", zlim = c(min(cp_plot), max(cp_plot)),
168         ltheta = 170, shade = 0.75, r = sqrt(3), d = 5,
169         cex.lab = 0.8, cex.axis = 0.8, main = "A) Exposure-lag-response surface")
170
171 # Add lines for risk at lag 1, risk at percentile 99, and centring temperature
172 lines(trans3d(x = f.x_temp, y = 1,
173             z = cp_plot[,2],
174             pmat = association), lwd = 2, col = "red")
175 lines(trans3d(x = f.x_temp[percentiles == 0.99], y = 0:dlnm_var$max_lag,
176             z = cp_plot[percentiles == 0.99,],
177             pmat = association), lwd = 2, col = "orange")
178 lines(trans3d(x = f.x_temp[i_cen], y = 0:dlnm_var$max_lag,
179             z = cp_plot[i_cen,],
180             pmat = association), lwd = 2, col = "black")
181
182 dev.off()
183
184 # Clean up variables
185 rm(i_reg, basis_exp, basis_lag, f.x_temp, beta_reg, cp_cen, i_cen, association,
186     cp_plot)
187
188 #-----
189 ### B) OVERALL CUMULATIVE TEMPERATURE-MORTALITY ASSOCIATION FOR REGION 1
190 ### (EQUIVALENT TO FIGURE 2 IN THE ORIGINAL SB-DLNM PAPER)
191 #-----
192
193 # Specify the neighborhood of Barcelona (any integer from 1 to 73)
194 i_reg <- 1
195
196 # Extract the ensemble of sample coefficients of the crossbasis
197 beta_reg <- cb_res[[i_reg]]
198
199 # Calculate directly the RR of the overall cumulative temperature-mortality
200 # associations for region i_reg
201 rr <- apply(beta_reg, 1, function(x) {
202   sapply(1:length(x_temp[i_reg]), function(i) cb[[i_reg]][i,] %*% x)
203 })
204
205 # Keep the exposure variable for the region
206 x_plot <- x_temp[, 1]
207
208 # Center the curve
209 i_cen <- percentiles == 0.3
210 rr_plot <- t(apply(rr, 1, function(x) x - rr[i_cen,]))
211
212 # Plot the overall cumulative temperature-mortality association
213 pdf("plot/figureB_overall_cumulative-temperature_mortality_association.pdf",
214     width = 6, height = 5)
215 plot(x_plot, rep(1, length(x_plot)), type = "n", log = "y",
216     xlim = range(x_plot), ylim = c(0.5, 5),
217     xlab = "Temperature (°C)", ylab = "Relative risk",

```

```

218     main = "B) Overall cumulative temperature-mortality association",
219     axes = FALSE)
220 axis(1, at = seq(15, 40, by = 5))
221 axis(2, at = c(0.5, seq(1, 5, by = 1)), labels = c(0.5, seq(1, 5, by = 1)))
222
223 # Draw the ensemble of overall accumulated associations
224 for(i in 1:ncol(rr_plot)){
225     lines(x_plot, exp(rr_plot[,i]), lwd = 0.2, col = "lightgrey")
226 }; rm(i)
227 abline(h = 1)
228
229 # Calculate and draw the summary associations
230 rr_plot_summary <- apply(rr_plot, 1, quantile, c(0.025, 0.5, 0.975))
231 lines(x_plot, exp(rr_plot_summary[2,]), lwd = 3)
232 lines(x_plot, exp(rr_plot_summary[1,]), lwd = 2, lty = 2)
233 lines(x_plot, exp(rr_plot_summary[3,]), lwd = 2, lty = 2)
234
235 dev.off()
236
237 # Clean up variables
238 rm(i_reg, beta_reg, rr, x_plot, i_cen, rr_plot, rr_plot_summary)
239
240 #-----
241 ### C) MAP OF THE RISKS AT PERCENTILE 99
242 ### (SAME AS FIGURE 4C IN THE ORIGINAL SB-DLNM PAPER)
243 #-----
244
245 # Calculate directly the RR of the overall cumulative temperature-mortality
246 # associations for all regions
247 rr <- lapply(1:dlm_var$n_reg, function(i_reg) {
248
249     # Extract all the samples of the coefficients of the crossbasis
250     beta_reg <- cb_res[[i_reg]]
251
252     # The RR in each temperature x is the sum of the product of x transformed
253     # through the crossbasis function and the coefficients of the crossbasis
254     rr <- apply(beta_reg, 1, function(x) {
255         sapply(1:length(x_temp[,i_reg]), function(i) cb[[i_reg]][i,] %*% x)
256     })
257
258     rr
259
260 })
261
262 # Create a function for centring the risk in each region
263 Center_RR <- function(f.rr, f.cen, f.temp){
264
265     cen <- f.temp[which.min(abs(f.temp - f.cen))]
266     rr <- apply(f.rr, 2, function(x) x - x[f.temp == cen])
267     rr
268
269 }
270
271 # Center the relative risk in each region and extract the point estimate at
272 # percentile 99
273 rr_plot <- sapply(1:dlm_var$n_reg, function(i_reg) {
274     x_plot <- x_temp[, i_reg]
275     cen_plot <- x_plot[percentiles == 0.3]
276     rr_plot <- Center_RR(f.rr = rr[[i_reg]],
277                         f.cen = cen_plot,
278                         f.temp = x_plot)
279
280     # Point estimate as the median of the values at percentile 99
281     median(exp(rr_plot[percentiles == 0.99,]))
282
283 })
284
285 # Set the minimum and maximum RR in the plots
286 rr_max <- 2
287 rr_min <- exp(-log(rr_max))
288
289 # Force RR are between the maximum and minimum values to avoid NAs
290 rr_plot[rr_plot < rr_min] <- rr_min

```

```

291 rr_plot[rr_plot > rr_max] <- rr_max
292
293 # Palette of colours for the maps
294 pal <- colorNumeric(palette = rev(
295   c("#A90C38", "#C52A40", "#E24848", "#F16B61", "#F89183", "#FEB6A8", "#FEDAD3",
296     "#FFFFFF", "#D3E5F2", "#A8CCE5", "#88B4D5", "#6D9CC3", "#5585B1", "#416F9C",
297     "#2E5A87")), domain = c(log(rr_min), log(rr_max)), reverse = FALSE)
298
299 # Plot the map with the risks
300 pdf("plot/figureC_map_relative_risks.pdf",
301     width = 3, height = 5)
302
303 par(mar = c(1, 1, 1, 1), omi = c(0, 0, 0.4, 0))
304 plot(shapefile_bcn$geometry, col = pal(log(rr_plot)),
305     main = "C) Map relative risks")
306
307 dev.off()
308
309 # Clean up variables
310 rm(rr, Center_RR, rr_plot, rr_max, rr_min, pal)

```

Figure S1: Overall cumulative temperature-mortality associations for SB-DLNMs using the WinBUGS and R-INLA implementations in the 73 neighbourhoods of Barcelona (2007-2016).

Neighbourhoods are identified with their identification number in the plot titles. Panels labelled with a) (first and third column) show results from the case-crossover design, while panels labelled with b) (second and fourth column) show results from the time-series design. The list of adjacent regions, and the number of deaths in the study period are listed in top of the plots. In each neighbourhood the results for the WinBUGS (purple) and R-INLA implementations (green) are represented. The thick curves represent the points estimates (i.e., median values) of the association between the percentile of the neighbourhood temperature distribution and the relative risk of mortality. To facilitate the comparison, the baseline risk is centred at the 30th percentile of the neighbourhood temperature distribution. The coloured areas represent the 95% credible interval of the estimates. The relative risks (RRs) at the 99th percentile (P99) are provided at the top of the figures, including the point estimates (also marked with dots in the curves) and their corresponding 95% credible intervals.

