Web-based Supplementary Materials for:

A penalized framework for distributed lag non-linear models

Antonio Gasparrini, Fabian Scheipl, Ben Armstrong, Michael G. Kenward

Summary. This appendix contains additional details on the simulation study and additional results from the analyses of the illustrative examples. Updated information on the methodology and a version of the R code compatible with future versions of the package dlnm are available from the personal website of the first author (www.ag-myresearch.com) and in GitHub (github.com/gasparrini).

Web Appendix A

The three scenarios of the simulation studies are defined by different dose-lag-response surfaces. These are constructed by different marginal dose-response functions $f(x)$:

$$f_{\text{lin}}(x) = 0.1 \cdot (x - 2) \ ,$$
$$f_{\text{flex}}(x) = \sum_{p=0}^{4} \delta_p (x - 5)^p \ ,$$
$$f_{\text{dnorm1}}(x) = \big(\Phi_{1.5,2}(x) - \Phi_{1.5,2}(5)\big) + \big(\Phi_{7.5,1}(x) - \Phi_{7.5,1}(5)\big) \ ,$$

centered at different values, and lag-response functions $w(\ell)$:

$$w_{\text{const}}(\ell) = 0.20 \ ,$$
$$w_{\text{decay}}(\ell) = \exp(-\ell/2) \ ,$$
$$w_{\text{peak1}}(\ell) = 12 \cdot \Phi_{8,5}(\ell) \ ,$$
$$w_{\text{peak2}}(\ell) = 15 \cdot \Phi_{8,10}(\ell) \ ,$$
$$w_{\text{dnorm}}(\ell) = 5 \cdot \Phi_{4,6}(\ell) + 5 \cdot \Phi_{25,4}(\ell) \ ,$$

with $\boldsymbol{\delta} = [0.2118881, 0.1406585, -0.0982663, 0.0153671, -0.0006265]^{\mathsf{T}}$ and $\boldsymbol{\Phi}_{m,s}(z)$ as a normal density function of z with mean m and standard deviation s. The dose-response and lag-response curves are represented graphically in Figure 1. The bi-dimensional dose-lag-response functions $f_j \cdot w_j(x_{t-\ell}, \ell)$ for the three scenarios $j = 1, 2, 3$ representing a plane, a shape resembling previously estimated temperature-mortality associations, and a complex surface, respectively, are computed as:

$$f_1 \cdot w_1(x_{t-\ell}, \ell) = 0.1 \cdot f_{\text{lin}}(x_{t-\ell}) \cdot w_{\text{const}}(\ell) \ ,$$
$$f_2 \cdot w_2(x_{t-\ell}, \ell) = \begin{cases} f_{\text{flex}}(x_{t-\ell}) \cdot w_{\text{decay}}(\ell) & \text{if } x \geq 5 \\ f_{\text{flex}}(x_{t-\ell}) \cdot w_{\text{peak1}}(\ell) & \text{if } x < 5 \end{cases} \ ,$$
$$f_3 \cdot w_3(x_{t-\ell}, \ell) = \begin{cases} f_{\text{dnorm}}(x_{t-\ell}) \cdot w_{\text{dnorm}}(\ell) & \text{if } x \geq 5 \\ f_{\text{dnorm}}(x_{t-\ell}) \cdot w_{\text{peak2}}(\ell) & \text{if } x < 5 \end{cases} \ ,$$

and are represented in Figure 1 of the main text.

Web Appendix B

In each of the $i = 1, \ldots, 1000$ simulation replicates in each of the three scenarios, estimated effects $\hat{\beta}_{i,x_p,\ell_p}$ were computed on a grid of predictor values $x_p = 0, 0.25, \ldots, 9.75, 10$ and lag values $\ell_p = 0, \ldots, 40$, and compared with the true effects β_{i,x_p,ℓ_p}. The *across-the-surface* statistics (Marra and Wood, 2012) were computed as the average across the 40×41 values. Specifically, coverage and root mean square error (RMSE) were defined as:

$$\text{Coverage} = \sum_{x_p=0}^{10} \sum_{\ell_p=0}^{40} \left[\sum_{i=1}^{m} I\left(\left| \hat{\beta}_{i,x_p,\ell_p} - \beta_{x_p,\ell_p} \right| \leq \Phi^{-1}(1-\alpha/2) \cdot \sqrt{V\left(\hat{\beta}_{i,x_p,\ell_p}\right)} \right) /m \right] /(40 \times 41) \,,$$

$$\text{RMSE} = \sum_{x_p=0}^{10} \sum_{\ell_p=0}^{40} \left[\frac{\sqrt{\sum_{i=1}^{m} \left(\hat{\beta}_{i,x_p,\ell_p} - \beta_{x_p,\ell_p} \right)^2 /m}}{\sum_{i=1}^{m} \left(\beta_{x_p,\ell_p} \right) /m} \right] /(40 \times 41) \,.$$

These statistics, averaged across the whole surface, are used in Table 1 of the main text, while the actual coverage for specific values of doses and lags are graphically represented in Web Figures 4–5 below.

Web Appendix C

The extension described in this contribution is implemented in R (R Core Team, 2015, version 3.3.0) by embedding the packages dlnm (Gasparrini, 2011, version 2.3.0) and mgcv (Wood, 2006, version 1.8-12), both available in the Comprehensive R Archive Network (CRAN).

Specifically, at the time of writing two alternative methods were proposed. In the *internal* method, a new function `smooth.construct.cb.smooth.spec()` defines smoothers and penalties internally within the regression function `gam()` of mgcv. Other functions in the package dlnm are applied to produce predictions and plotting. Alternatively the *external* method, possibly less stable but slightly more flexible, uses the dlnm function `crossbasis()` to obtain the transformation in Eq.(1)–(3) through new functions `ps()` and `cr()` defining the PS and CR marginal smoothers, and a new function `cbPen()` generating the penalty matrices of the cross-basis in Eq.(4). These are used as penalized 'parametric' terms in the regression function `gam()`.

It should be noted that the current implementation of GAMs in mgcv does not include regression models such as the Cox proportional hazard or conditional logistic (see Section 5.2 in the manuscript). However, the form of penalized DLNMs described in this contribution can be easily applied in these settings as well.

Additional details are provided in the documentation of the R packages dlnm and mgcv. The code to reproduce the results of the simulation study and the two examples is included in the Web-based Supplementary Material, with an updated version available from GitHub (github.com/gasparrini) or from the personal website of the first author (www.ag-myresearch.com).

Web Figures

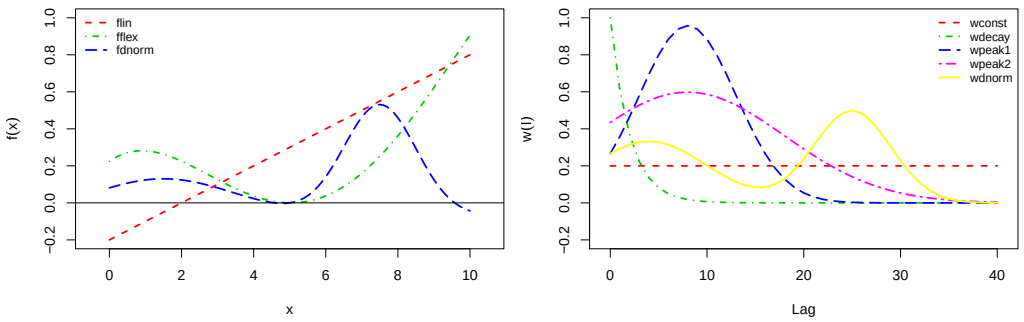

Fig. 1: Simulated shapes for the dose-response function $f(x)$ (left panel) and lag-response function $w(\ell)$ (right panel), used to produce the three scenarios of dose-lag-response surfaces illustrated in Figure 1 in the main text.

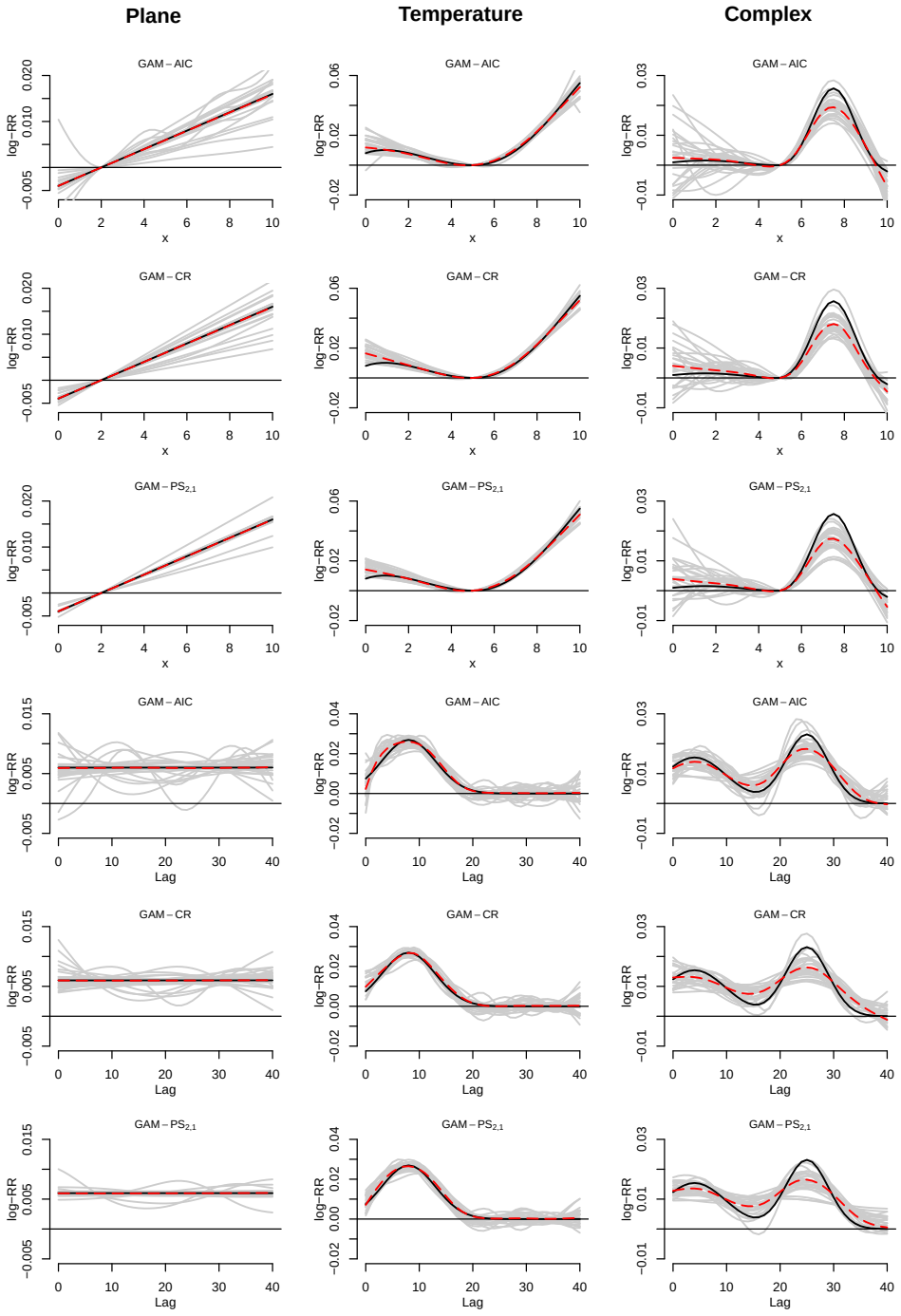

Fig. 2: Results of the simulation study, illustrating the performance of three different models (see Table 1 in the main text). The panels represent the dose-response (rows 1–3) and lag-response curves (rows 4–6) corresponding to the bold black lines in the three simulated surfaces (by column) in Figure 1 in the main text. Continuous grey, and dashed red and continuous black lines represent the fit from 25 random replicates, the average across all replicates, and the true simulated curves, respectively.

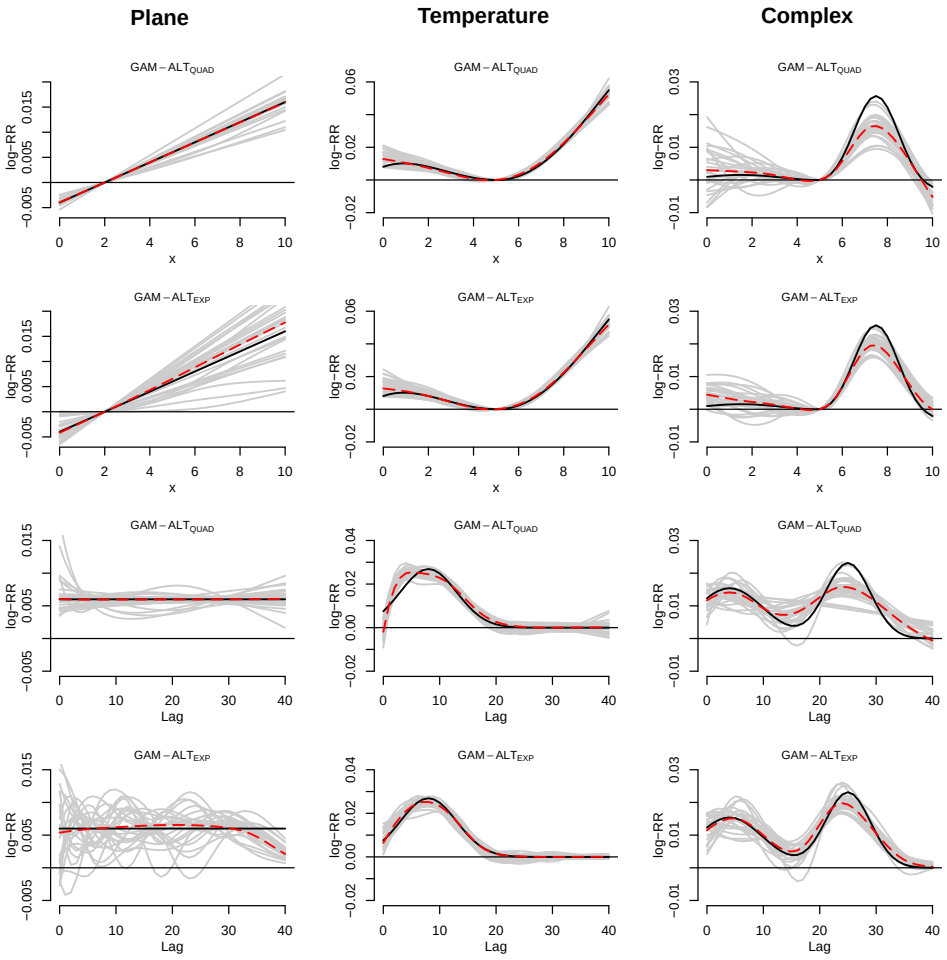

Fig. 3: Results of the simulation study, illustrating the performance of two different models (see Table 1 in the main text). The panels represent the dose-response (rows 1–2) and lag-response curves (rows 3–4) corresponding to the bold black lines in the three simulated surfaces (by column) in Figure 1 in the main text. Continuous grey, and dashed red and continuous black lines represent the fit from 25 random replicates, the average across replicates, and true simulated curves, respectively.

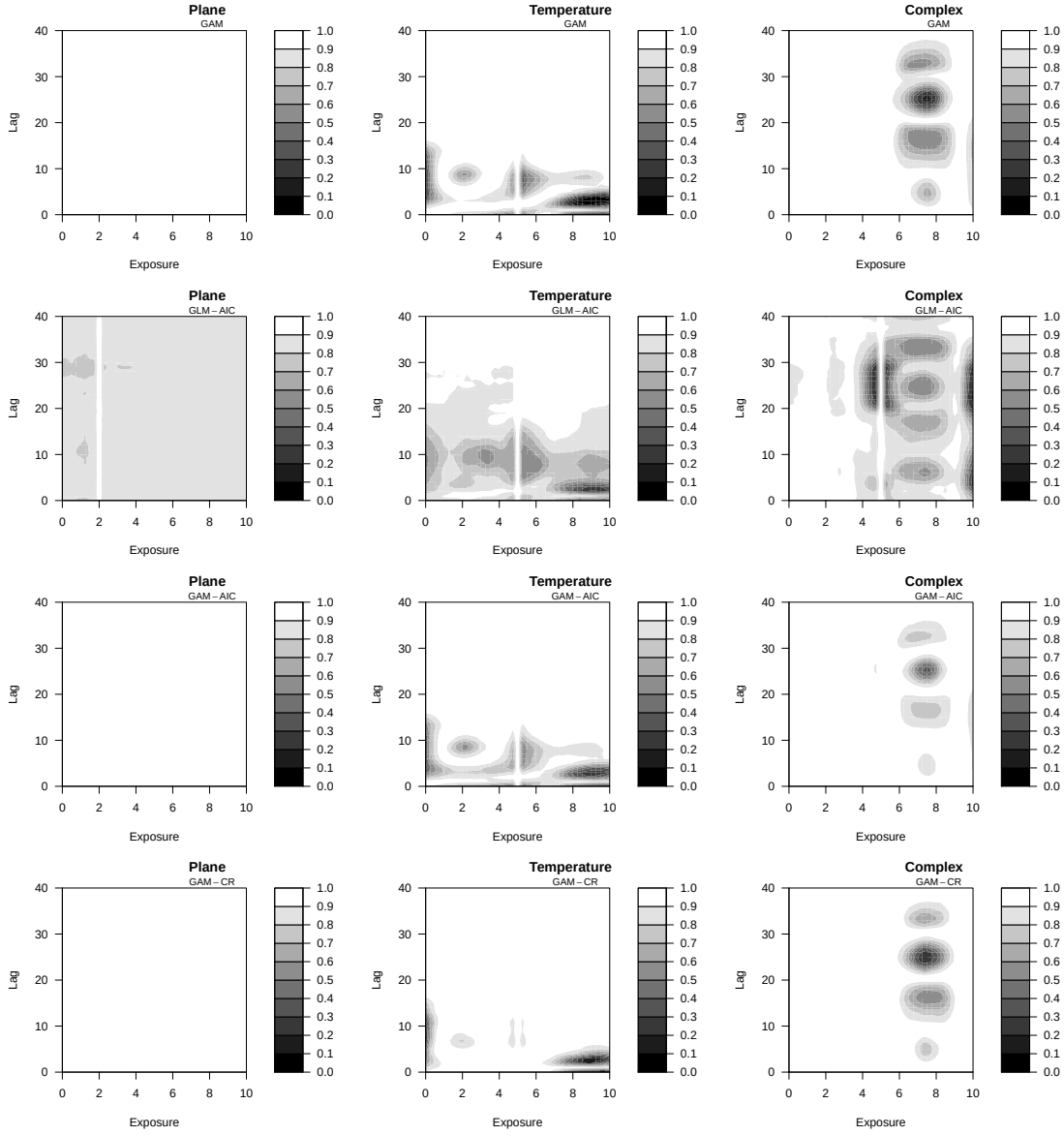

Fig. 4: Results of the simulation study, illustrating the empirical coverage across the risk surfaces of the first four models in Table 1 in the main text (by row), for the three simulated surfaces (by column) in Figure 1 in the main text.

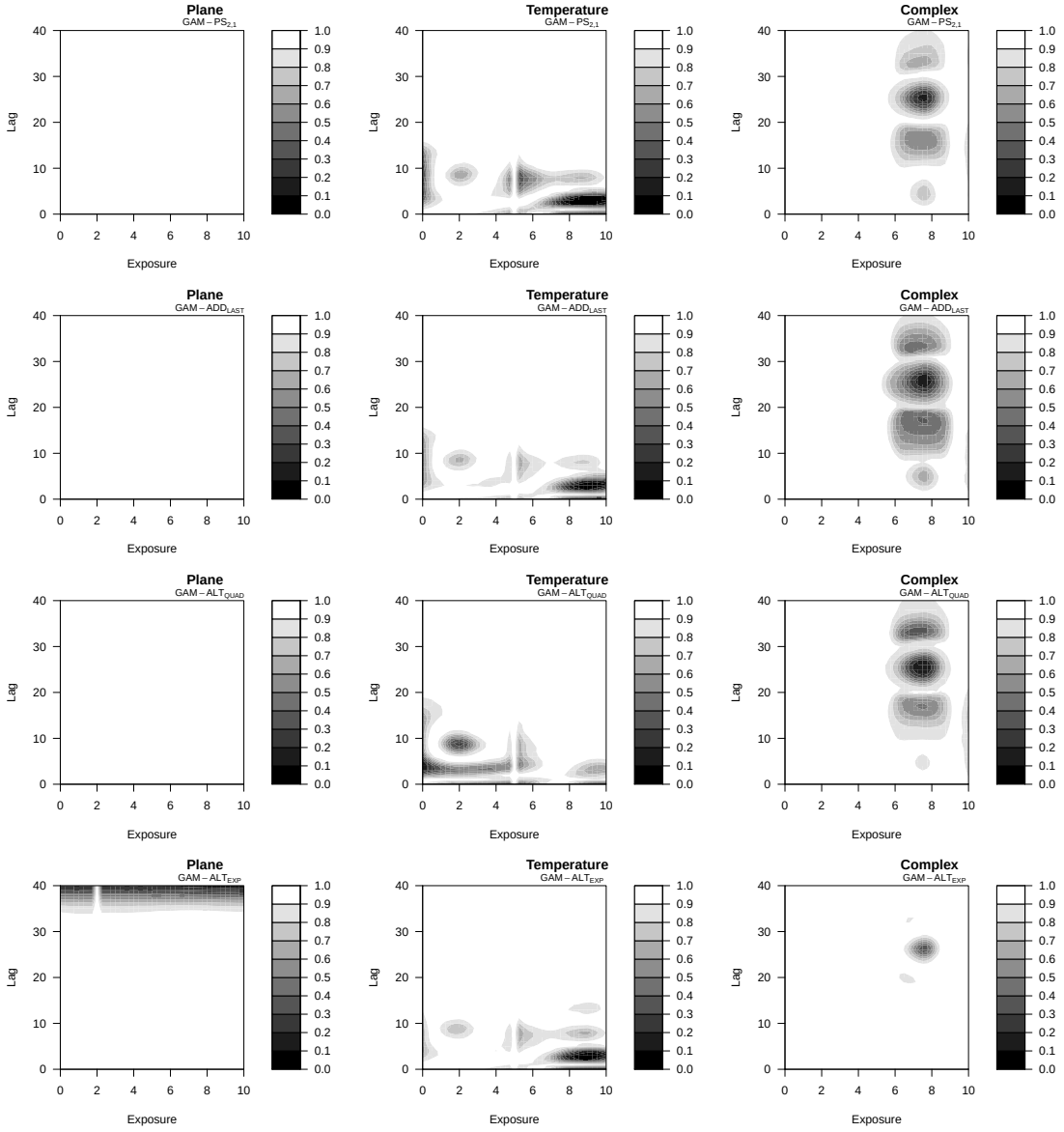

Fig. 5: Results of the simulation study, illustrating the empirical coverage across the risk surfaces of the last four models in Table 1 in the main text (by row), for the three simulated surfaces (by column) in Figure 1 in the main text.

References

Gasparrini, A. (2011) Distributed lag linear and non-linear models in R: the package dlnm. *Journal of Statistical Software*, **43**, 1–20.

R Core Team (2015) *R: A Language and Environment for Statistical Computing*. R Foundation for Statistical Computing, Vienna, Austria. URL`http://www.R-project.org/`.

Wood, S. N. (2006) *Generalized Additive Models: an Introduction with R*. Chapman & Hall/CRC.