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In spatio-temporal disease mapping models, identifiability constraints affect PQL and INLA results

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Abstract Disease mapping studies the distribution of relative risks or rates in space and time, and typically relies on generalized linear mixed models (GLMMs) including fixed effects and spatial, temporal, and spatio-temporal random effects. These GLMMs are typically not identifiable and constraints are required to achieve sensible results. However, automatic specification of constraints can sometimes lead to misleading results. In particular, the penalized quasi-likelihood (PQL) fitting technique automatically centers the random effects even when this is not necessary. In the Bayesian approach, the recently-introduced INLA (integrated nested Laplace approximations) computing technique can also produce wrong results if constraints are not carefully chosen. In this paper the spatial, temporal, and spatio-temporal interaction random effects are reparameterized using the spectral decompositions of their precision matrices to establish the appropriate identifiability constraints. Breast cancer mortality data from Spain is used to illustrate the ideas.

Keywords Breast cancer · INLA · Leroux CAR prior · PQL · Space-time interactions

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1 Introduction

Statistical techniques for disease mapping have developed tremendously in the last few years. The availability of information from modern registers with high quality data recorded for many years and regions has brought about new goals and challenges, which in turn have made possible the development of new and more flexible statistical models, faster and less computationally demanding fitting techniques, and new free software to implement these advances. These methodological developments are now ready for policy makers, epidemiologists, health researchers, and health professionals to use in a more or less automated form. However, this abundance of ready-to-use statistical resources can lead to errors and misleading results when analyzing mortality or incidence data in space and time due, among other causes, to incorrect specification of identifiability constraints, which standard software usually fixes at default values.

Research into spatial and spatio-temporal disease mapping has been carried out within a Bayesian framework, with generalized linear mixed models (GLMM) playing a major role. Two main approaches have been followed for model fitting and inference, the empirical Bayes (EB) and fully Bayes (FB) approaches. Model fitting and estimation in the EB approach commonly rely on penalized quasi-likelihood (PQL) (see Breslow and Clayton, 1993), while the FB approach usually uses Markov chain Monte Carlo (McMC) techniques (Gilks, 2005). In addition to McMC, a new strategy based on integrated nested Laplace approximations (INLA) has recently been derived for estimating posterior quantities of interest (Rue et al, 2009). This technique is becoming very popular in disease mapping because it allows fairly complex space-time models to be fit much more quickly than McMC.

The GLMMs traditionally used in disease mapping are not identifiable (Gelfand and Sahu, 1999) and although some identifiability problems have been dealt with, this matter deserves further attention and needs clarification for practitioners. For example, one of the first identifiability concerns arose with the work by Besag et al (1991). They proposed an areal model (the BYM model) for the log-relative risks of a disease considering two random area effects: one with an exchangeable distribution and one with an intrinsic conditional autoregressive (ICAR) distribution. The ICAR distribution is specified conditionally and the parameters are uniquely determined up to a constant, so the overall intercept is implicit in the ICAR specification. Hence, if the model includes an explicit intercept as well, the model is not identified. The solution is to omit the explicit intercept or to add sum-to-zero constraints for the random effects.

Counts in space and time demand more flexible models to unveil the underlying geographical patterns and their temporal evolution. However, as terms are added to the model, identifiability problems arise. The literature in spatio-temporal disease mapping is abundant, describing different models with parametric (see for example Bernardinelli et al, 1995; Ugarte et al, 2009a) as well as non parametric trends (Knorr-Held and Besag, 1998). A key research paper is Knorr-Held (2000), which specifies spatio-temporal models including four

different types of spatio-temporal interactions. In these models, identifiability problems arise because the overall level can be absorbed by the spatial and the time main effects, and the interaction terms are confounded with the main effects. A different type of spatio-temporal model in disease mapping combines CAR spatial random effects with temporal trends based on B-splines (see, e.g., MacNab and Gustafson, 2007; MacNab, 2007). In most of this research, sum-to-zero constraints are considered as guaranteeing model identifiability but no clear guidance is given about why these constraints have to be considered. The foregoing papers took a FB approach using McMC, while other papers took the EB approach, using PQL for model fitting. For example, Ugarte et al (2010) consider spatio-temporal CAR models and P-spline models from an EB perspective to study brain cancer mortality in Spain, and Etxeberria et al (2014) consider spatio-temporal CAR and P-spline models for smoothing and forecasting mortality risks. However, identifiability issues have not received much attention because the PQL method automatically centers the spatial, temporal, and spatio-temporal random effects, that is, automatically imposes sum-to-zero constraints.

This paper considers space-time disease mapping models including an overall risk level (intercept) and spatial, temporal, and spatio-temporal random effects. In particular, conditional autoregressive (CAR) spatial random effects, first- or second-order random walks for time, and the corresponding space-time interactions are considered. To deal with identifiability problems, models will be reparameterized using the spectral decomposition of the precision matrices to remove the combinations of the random effects that are in the span of the fixed effects (Reich et al, 2006; Hodges and Reich, 2010). These authors treat the problem as a collinearity issue and restrict the spatial random effects to the subspace orthogonal to the fixed effects. Using this reparameterization it is easy to see that deleting repeated columns in certain model matrices is equivalent to specific sum-to-zero constraints. This is important for practitioners as some statistical software requires the specification of such constraints. In particular, we will focus on specifying constraints in the R-INLA package for approximate Bayesian inference, which has become popular because it provides quick fits of complex models.

The rest of the paper is laid out as follows. Section 2 reviews a simple spatial model and a more general spatio-temporal model with identifiability problems. Section 3 considers a reparameterization to make the models identifiable. Section 4 provides insight into model estimation and the use of linear constraints with PQL. Section 5 illustrates the previous sections' results using a case study. The paper closes with a discussion.

2 Spatial and spatio-temporal models in disease mapping

This section briefly reviews spatial and spatio-temporal disease mapping models to highlight the identifiability problems arising in this field.

Consider a large domain (let us say a country) divided into small areas (for example provinces or counties) that will be labelled by $i = 1, \ldots, S$, and denote by Y_i the number of deaths (or incident cases) in the i^{th} small area. Then conditional on the relative risk r_i, Y_i is assumed to be Poisson distributed with mean $\mu_i = e_i r_i$, where e_i is the number of expected cases. That is

$$Y_i|r_i \sim Pois(\mu_i = e_i r_i),\ \log(\mu_i) = \log(e_i) + \log(r_i).$$

Here $\log(e_i)$ is an offset and $\log(r_i)$ is modeled as

$$\log(r_i) = \eta + \xi_i, \tag{1}$$

where η is an overall risk and ξ_i is the spatial random effect. An intrinsic conditional autoregressive (ICAR) prior is considered for the vector of spatial effects $\boldsymbol{\xi} = (\xi_1, \ldots, \xi_S)'$. Namely,

$$\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2 \mathbf{Q}_\xi^-),$$

where $^-$ indicates the Moore-Penrose inverse of a matrix, and $\mathbf{Q}_\xi$ is the spatial neighbourhood matrix with (i, j) element defined as $\mathbf{Q}_{\xi(ij)} = -1$ if areas i and j are neighbours and 0 otherwise. The i^{th} diagonal element equals the number of neighbours of the i^{th} region. Typically, two regions are neighbours if they share a common border. Clearly, $\sum_j \mathbf{Q}_{\xi(ij)} = 0$, $\forall i$, that is $\mathbf{Q}_\xi \mathbf{1}_S = 0$, where $\mathbf{1}_S$ is a vector of ones of length S, and the intercept is implicit in the ICAR specification as will be shown in Section 3.1. Hence, an identifiability problem with the intercept arises. The problem can be solved either by deleting the intercept or by imposing sum-to-zero constraints $\sum_i \xi_i = 0$ (see for example, Eberly et al, 2000).

Other priors for the spatial random effects have been proposed. Leroux et al (1999) considered the following specification (LCAR hereafter in the paper) taking account of spatially structured and unstructured variability

$$\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2 \mathbf{D}^{-1}),\ \mathbf{D} = (\lambda_\xi \mathbf{Q}_\xi + (1 - \lambda_\xi)\mathbf{I}_\xi), \tag{2}$$

where $\lambda_\xi \in [0, 1]$ is a spatial smoothing parameter and $\mathbf{I}_\xi$ is an $S \times S$ identity matrix. If $\lambda_\xi = 1$, Model (2) becomes the ICAR distribution. If $0 \leq \lambda_\xi < 1$, the matrix $\mathbf{D}$ is of full rank, but the identifiability issue still remains, as we will see in Section 3.

Suppose now that for each small area i, data are available for different time periods labelled by $t = 1, \ldots, T$. Then, conditional on the relative risk r_{it}, the count of events in region i at time t, Y_{it}, is assumed to follow a Poisson distribution with mean $\mu_{it} = e_{it} r_{it}$, where e_{it} is the number of expected events. That is

$$Y_{it}|r_{it} \sim Pois(\mu_{it} = e_{it} r_{it}),\ \log(\mu_{it}) = \log(e_{it}) + \log(r_{it}).$$

The term $\log(r_{it})$ can include spatial and temporal random effects additively, as well as space-time interactions. Let us focus first on the following spatio-

temporal additive model

$$\log(r_{it}) = \eta + \xi_i + \gamma_t, \tag{3}$$

where here the vector of temporal random effects $\boldsymbol{\gamma} = (\gamma_1, \ldots, \gamma_T)'$ is assumed to follow a random walk of first (RW1) or second (RW2) order, that is,

$$\boldsymbol{\gamma} \sim N(\mathbf{0}, \sigma_\gamma^2 \mathbf{Q}_\gamma^-),$$

where the matrix $\mathbf{Q}_\gamma$ has rank deficiency equal to 1 or 2 for a RW1 and a RW2 respectively (see Rue and Held, 2005, chap. 3). If the temporal random effect is assumed to follow a RW1 distribution, then $\mathbf{Q}_\gamma \mathbf{1}_T = 0$, where $\mathbf{1}_T$ is a vector of ones of length T, and the intercept is implicit in the RW1, leading to an identifiability problem. As in the spatial case, the problem can be solved either by deleting the intercept or by imposing the sum-to-zero constraint $\sum_t \gamma_t = 0$. If the spatial random effect follows an ICAR distribution, we can delete the intercept and impose sum-to-zero constraints on the spatial or the temporal random effects, or leave the intercept and impose sum-to-zero constraints on both the spatial and the temporal random effects. If the temporal random effect is distributed as RW2, then $\mathbf{Q}_\gamma \mathbf{1}_T = 0$, $\mathbf{Q}_\gamma \mathbf{t}^* = 0$, where $\mathbf{t}^* = (1, 2, \ldots, T)'$, and the slope in time is implicit in the RW2 specification. As the model does not include a linear trend, no extra constraints are needed.

Spatio-temporal models including area and time effects additively may be very restrictive in practice, so interaction terms are usually added to Model (3). Knorr-Held (2000) proposes four types of interactions, namely Type I (interaction random effects with any spatial or temporal structure), Type II (interaction random effects spatially unstructured but temporally correlated), Type III (interaction random effects spatially correlated but with no temporal structure), and finally Type IV (interaction random effects spatially and temporally correlated). Here we focus on Type IV interactions, the most complex type (constraints for Type I, Type II and Type III interactions can be found in Appendix B). Then Model (3) becomes

$$\log(r_{it}) = \eta + \xi_i + \gamma_t + \delta_{it}, \tag{4}$$

where the vector of spatio-temporal random effects $\boldsymbol{\delta} = (\delta_{11}, \ldots, \delta_{S1}, \ldots, \delta_{1T}, \ldots, \delta_{ST})'$ is assumed to follow the multivariate normal distribution

$$\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2 (\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)^-).$$

The rank of the matrix $\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi$ is $(T-1) \times (S-1)$ or $(T-2) \times (S-1)$ if $\boldsymbol{\gamma}$ follows a RW1 or a RW2 respectively. Consequently, the rank deficiency is $T+S-1$ (RW1) or $T+2S-2$ (RW2). Note that $(\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)\mathbf{1}_{TS} = 0$, where $\mathbf{1}_{TS}$ is a vector of ones of length TS, leading to an identifiability problem with the intercept. In addition, the interaction term is confounded with the main effects, creating further identifiability issues. In the next section, we reparameterize the models using the spectral decomposition of the precision matrices of the random effects to solve these identifiability problems.

3 Model reparameterization

In this section, the random effects are transformed using appropriate matrices to express them as independent Gaussian random effects. Deleting repeated columns in the design matrices circumvents the identifiability issues, which implies suitable constraints.

3.1 Spatial model

Consider again the spatial Model (1)

$$\log(r_i) = \eta + \xi_i,$$

or in matrix form

$$\log(\mathbf{r}) = (\mathbf{1}_S)\eta + \mathbf{I}_\xi \boldsymbol{\xi}, \quad \boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2 \mathbf{Q}_\xi^-), \tag{5}$$

where $\mathbf{r} = (r_1, \ldots, r_S)'$. The neighbourhood matrix $\mathbf{Q}_\xi$ has rank deficiency 1 assuming the spatial domain is connected. Consider the spectral decomposition of $\mathbf{Q}_\xi$,

$$\mathbf{Q}_\xi = \mathbf{U}_\xi \boldsymbol{\Sigma}_\xi \mathbf{U}_\xi^{'} = [\mathbf{U}_{\xi n} : \mathbf{U}_{\xi r}] \begin{pmatrix} 0 & \mathbf{0} \\ \mathbf{0} & \widetilde{\boldsymbol{\Sigma}}_\xi \end{pmatrix} \begin{bmatrix} \mathbf{U}_{\xi n}^{'} \\ \mathbf{U}_{\xi r}^{'} \end{bmatrix}, \tag{6}$$

where $\mathbf{U}_\xi = [\mathbf{U}_{\xi n} : \mathbf{U}_{\xi r}]$ is an orthogonal matrix with columns the eigenvectors of $\mathbf{Q}_\xi$, $\mathbf{U}_{\xi n} = \mathbf{1}_S$ (up to a normalizing constant) and $\mathbf{U}_{\xi r}$ are the matrices of eigenvectors having null and non-null eigenvalues respectively, and $\widetilde{\boldsymbol{\Sigma}}_\xi$ is a diagonal matrix with the non-null eigenvalues of $\mathbf{Q}_\xi$ in the main diagonal. Then, as $\mathbf{U}_\xi$ is orthogonal,

$$\boldsymbol{\xi} = \mathbf{U}_\xi \mathbf{U}_\xi^{'} \boldsymbol{\xi} = [\mathbf{U}_{\xi n} : \mathbf{U}_{\xi r}] \begin{bmatrix} \mathbf{U}_{\xi n}^{'} \\ \mathbf{U}_{\xi r}^{'} \end{bmatrix} \boldsymbol{\xi}.$$

If we define

$$\begin{aligned} \mathbf{X} = \mathbf{U}_{\xi n} = \mathbf{1}_S, \;\; \beta_\xi = \mathbf{U}_{\xi n}^{'} \boldsymbol{\xi} = \mathbf{1}_S^{'} \boldsymbol{\xi} \\ \mathbf{Z} = \mathbf{U}_{\xi r}, \qquad\quad \boldsymbol{\alpha}_\xi = \mathbf{U}_{\xi r}^{'} \boldsymbol{\xi}, \end{aligned}^{,}$$

then

$$\boldsymbol{\xi} = \mathbf{X}\beta_\xi + \mathbf{Z}\boldsymbol{\alpha}_\xi,$$

where β_ξ plays the role of a fixed effect and the spatial Model (5) can be reformulated as

$$\log(\mathbf{r}) = (\mathbf{1}_S)\eta + (\mathbf{1}_S)\beta_\xi + \mathbf{U}_{\xi r}\boldsymbol{\alpha}_\xi, \quad \boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \sigma_\xi^2 \widetilde{\boldsymbol{\Sigma}}_\xi^{-1}). \tag{7}$$

Note that the reparameterized Model (7) has two intercepts, revealing the identifiability problem. Consequently, removing or setting to zero the intercept β_ξ makes the model identifiable, and now the precision matrix of the

reparameterized random effect has full rank. Setting β_ξ to zero leads to the usual sum-to-zero constraint $\sum_{i=1}^{S} \xi_i = 0$, as $\beta_\xi = \mathbf{1}_S^{'}\boldsymbol{\xi} = \sum_{i=1}^{S} \xi_i$. The identifiable spatial model is then

$$\log(\mathbf{r}) = (\mathbf{1}_S)\eta + \mathbf{U}_{\xi r}\boldsymbol{\alpha}_\xi, \quad \boldsymbol{\alpha} \sim N(\mathbf{0}, \sigma_\xi^2 \widetilde{\boldsymbol{\Sigma}}_\xi^{-1}).$$

If the prior for the spatial random effect is the LCAR given in Equation (2), the covariance matrix is of full rank whenever $0 \leq \lambda_\xi < 1$, but identifiability problems still remain. In particular, the matrix $\mathbf{D}$ has spectral decomposition

$$\begin{aligned}\mathbf{D} &= (\lambda_\xi \mathbf{Q}_\xi + (1-\lambda_\xi)\mathbf{I}_\xi) = (\lambda_\xi \mathbf{U}_\xi \boldsymbol{\Sigma}_\xi \mathbf{U}_\xi^{'} + (1-\lambda_\xi)\mathbf{I}_\xi) \\ &= \mathbf{U}_\xi(\lambda_\xi \boldsymbol{\Sigma}_\xi + (1-\lambda_\xi)\mathbf{I}_\xi)\mathbf{U}_\xi^{'},\end{aligned}$$

because $\mathbf{U}_\xi$ is orthogonal, so that $\mathbf{D}$ has the same eigenvectors as $\mathbf{Q}_\xi$ but different eigenvalues. Defining $\mathbf{X} = \mathbf{U}_{\xi n} = \mathbf{1}_S$, $\beta_\xi = \mathbf{U}_{\xi n}^{'}\boldsymbol{\xi} = \mathbf{1}_S^{'}\boldsymbol{\xi}$, $\mathbf{Z} = \mathbf{U}_{\xi r}$, and $\boldsymbol{\alpha} = \mathbf{U}_{\xi r}^{'}\boldsymbol{\xi}$ as before, the spatial random effect can be expressed as $\boldsymbol{\xi} = \mathbf{X}\beta_\xi + \mathbf{Z}\boldsymbol{\alpha}$ and again we have a redundant intercept. Setting $\beta_\xi = 0$ leads to the usual sum-to-zero constraint $\sum_{i=1}^{S} \xi_i = 0$.

3.2 Spatio-temporal model

In the following we consider the spatio-temporal Model (4), with the LCAR prior (2) for the spatial random effect. We consider this prior as it takes account of both structured and unstructured variability. The matrix form of this model is

$$\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_T \otimes \mathbf{I}_\xi)\boldsymbol{\xi} + (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\boldsymbol{\gamma} + \mathbf{I}_\delta\boldsymbol{\delta}, \tag{8}$$

where $\mathbf{r} = (r_{11}, \ldots, r_{S1}, \ldots, r_{1T}, \ldots, r_{ST})'$, and $\mathbf{I}_\gamma$ and $\mathbf{I}_\delta$ are $T \times T$ and $TS \times TS$ identity matrices respectively. The temporal main effect $\boldsymbol{\gamma}$ is assumed to follow a RW1 or a RW2, and the interaction random effect is assumed to be completely structured in space and time, that is, $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2(\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)^-)$. Now consider the spectral decomposition of $\mathbf{Q}_\xi$ given by (6), and the spectral decomposition of $\mathbf{Q}_\gamma$

$$\mathbf{Q}_\gamma = \mathbf{U}_\gamma \boldsymbol{\Sigma}_\gamma \mathbf{U}_\gamma^{'} = [\mathbf{U}_{\gamma n} : \mathbf{U}_{\gamma r}] \begin{pmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \widetilde{\boldsymbol{\Sigma}}_\gamma \end{pmatrix} \begin{bmatrix} \mathbf{U}_{\gamma n}^{'} \\ \mathbf{U}_{\gamma r}^{'} \end{bmatrix},$$

where $\mathbf{U}_\gamma = [\mathbf{U}_{\gamma n} : \mathbf{U}_{\gamma r}]$ is the matrix of eigenvectors, $\mathbf{U}_{\gamma n}$ is the matrix of eigenvectors having null eigenvalue, $\mathbf{U}_{\gamma r}$ is the matrix of eigenvectors having non-null eigenvalues, and $\widetilde{\boldsymbol{\Sigma}}_\gamma$ is a diagonal matrix with the non-null eigenvalues in the main diagonal. If the distribution of the temporal random effect is a RW1, then the rank deficiency of $\mathbf{Q}_\gamma$ is 1, and $\mathbf{U}_{\gamma n} = \mathbf{1}_T$ (up to a normalizing constant). If the temporal random effect is distributed according to a RW2,

the rank deficiency of $\mathbf{Q}_\gamma$ is 2, and $\mathbf{U}_{\gamma n} = [\mathbf{1}_T : \mathbf{t}^*]$, where $\mathbf{t}^* = (1, 2, \ldots, T)'$ up to a normalizing constant. The spectral decomposition of $\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi$ can be expressed as

$$\mathbf{Q}_\delta = \mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi = \mathbf{U}_\delta \boldsymbol{\Sigma}_\delta \mathbf{U}_\delta^{'} = [\mathbf{U}_{\delta n} : \mathbf{U}_{\delta r}] \begin{pmatrix} \mathbf{0} & \mathbf{0} \\ \mathbf{0} & \widetilde{\boldsymbol{\Sigma}}_\delta \end{pmatrix} \begin{bmatrix} \mathbf{U}_{\delta n}^{'} \\ \mathbf{U}_{\delta r}^{'} \end{bmatrix},$$

where $\mathbf{U}_\delta = [\mathbf{U}_{\delta n} : \mathbf{U}_{\delta r}]$ is the matrix of eigenvectors, $\mathbf{U}_{\delta n}$ is the matrix of eigenvectors having null eigenvalue, $\mathbf{U}_{\delta r}$ is the matrix of eigenvectors having non-null eigenvalues, and $\widetilde{\boldsymbol{\Sigma}}_\delta = \widetilde{\boldsymbol{\Sigma}}_\gamma \otimes \widetilde{\boldsymbol{\Sigma}}_\xi$ is a diagonal matrix with the non-null eigenvalues in the main diagonal. The matrix with eigenvectors spanning the null space can be expressed in terms of the eigenvectors spanning the null space of $\mathbf{Q}_\gamma$ and $\mathbf{Q}_\xi$, that is

$$\mathbf{U}_{\delta n} = [\mathbf{U}_{\gamma n} \otimes \mathbf{U}_{\xi n} : \mathbf{U}_{\gamma n} \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi n}].$$

Similarly,

$$\mathbf{U}_{\delta r} = [\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r}].$$

The key now is to define transformations so that the spatio-temporal Model (8) is reformulated to achieve identifiability. Define the transformation matrices as $\mathbf{U}_\gamma$ and $\mathbf{U}_\delta$ such that

$$\begin{aligned}(\mathbf{I}_\gamma \otimes \mathbf{1}_S)\boldsymbol{\gamma} &= (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_\gamma \mathbf{U}_\gamma^{'}\boldsymbol{\gamma} = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\left[\mathbf{U}_{\gamma n} : \mathbf{U}_{\gamma r}\right] \begin{bmatrix} \mathbf{U}_{\gamma n}^{'} \\ \mathbf{U}_{\gamma r}^{'} \end{bmatrix} \boldsymbol{\gamma} \\ &= [\mathbf{X}_\gamma : \mathbf{Z}_\gamma] \begin{bmatrix} \beta_\gamma \\ \boldsymbol{\alpha}_\gamma \end{bmatrix} = \mathbf{X}_\gamma \beta_\gamma + \mathbf{Z}_\gamma \boldsymbol{\alpha}_\gamma\end{aligned}$$

and

$$\mathbf{I}_\delta \boldsymbol{\delta} = \mathbf{U}_\delta \mathbf{U}_\delta^{'} \boldsymbol{\delta} = [\mathbf{U}_{\delta n} : \mathbf{U}_{\delta r}] \begin{bmatrix} \mathbf{U}_{\delta n}^{'} \\ \mathbf{U}_{\delta r}^{'} \end{bmatrix} \boldsymbol{\delta} = [\mathbf{X}_\delta : \mathbf{Z}_\delta] \begin{bmatrix} \boldsymbol{\beta}_\delta \\ \boldsymbol{\alpha}_\delta \end{bmatrix} = \mathbf{X}_\delta \boldsymbol{\beta}_\delta + \mathbf{Z}_\delta \boldsymbol{\alpha}_\delta.$$

If the temporal random effect follows a RW1, then

$$\begin{aligned} \mathbf{X}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma n} = \mathbf{1}_{TS}, \;\; \beta_\gamma = \mathbf{U}_{\gamma n}^{'}\boldsymbol{\gamma} = \mathbf{1}_T^{'}\boldsymbol{\gamma}, \\ \mathbf{Z}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma r} = \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S, \qquad \boldsymbol{\alpha}_\gamma = \mathbf{U}_{\gamma r}^{'}\boldsymbol{\gamma}, \\ \mathbf{X}_\delta = \mathbf{U}_{\delta n} = [\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S], \qquad \boldsymbol{\beta}_\delta = \mathbf{U}_{\delta n}^{'}\boldsymbol{\delta}, \\ \mathbf{Z}_\delta = \mathbf{U}_{\delta r} = [\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r}], \qquad \boldsymbol{\alpha}_\delta = \mathbf{U}_{\delta r}^{'}\boldsymbol{\delta}. \end{aligned}$$

Consequently, Model (8) can be expressed as

$$\begin{aligned}\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_{TS})\beta_\xi + (\mathbf{1}_T \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\xi + (\mathbf{1}_{TS})\beta_\gamma + (\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)\boldsymbol{\alpha}_\gamma \\ + [\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S]\boldsymbol{\beta}_\delta + (\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\delta, \end{aligned} \tag{9}$$

where $\boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \sigma_\xi^2(\lambda_\xi \widetilde{\boldsymbol{\Sigma}}_\xi + (1-\lambda_\xi)\mathbf{I}_{\xi-1})^{-1})$, $\mathbf{I}_{\xi-1}$ is an identity matrix of dimension $(S-1)$, $\boldsymbol{\alpha}_\gamma \sim N(\mathbf{0}, \sigma_\gamma^2 \widetilde{\boldsymbol{\Sigma}}_\gamma^{-1})$, and $\boldsymbol{\alpha}_\delta \sim N(\mathbf{0}, \sigma_\delta^2 \widetilde{\boldsymbol{\Sigma}}_\delta^{-1})$. If we remove the repeated columns $\mathbf{1}_{TS}$ (corresponding to β_ξ, β_γ, and $\boldsymbol{\beta}_\delta$), $\mathbf{1}_T \otimes \mathbf{U}_{\xi r}$, and $\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S$ (corresponding to $\boldsymbol{\beta}_\delta$), this leaves the following model

$$\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_T \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\xi + (\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)\boldsymbol{\alpha}_\gamma + (\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\delta. \quad (10)$$

Removing the repeated columns leads to the linear constraints $\sum_{i=1}^{S} \xi_i = 0$, $\sum_{t=1}^{T} \gamma_t = 0$, $\sum_{i=1}^{S} \delta_{it} = 0$, $\forall t$ and $\sum_{t=1}^{T} \delta_{it} = 0$, $\forall i$. Note that if the ICAR prior is considered for the spatial random effect, then $(\mathbf{1}_T \otimes \mathbf{I}_\xi)\boldsymbol{\xi}$ is transformed into $\mathbf{1}_{TS}\boldsymbol{\beta}_\xi + (\mathbf{1}_T \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\xi$, and the identifiable model takes the same form as Model (10), where now $\boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \widetilde{\boldsymbol{\Sigma}}_\xi^{-1})$. For details about the derivation of these sum-to-zero constraints see Appendix A.

If the temporal random effect follows a RW2, then

$$\begin{aligned}
&\mathbf{X}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma n} = [\mathbf{1}_{TS} : \mathbf{t}^* \otimes \mathbf{1}_S], && \boldsymbol{\beta}_\gamma = \mathbf{U}_{\gamma n}^{'}\boldsymbol{\gamma} = [\mathbf{1}_T : \mathbf{t}^*]^{'}\boldsymbol{\gamma},\\
&\mathbf{Z}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma r} = \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S, && \boldsymbol{\alpha}_\gamma = \mathbf{U}_{\gamma r}^{'}\boldsymbol{\gamma},\\
&\mathbf{X}_\delta = \mathbf{U}_{\delta n} = [\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{U}_{\xi r}], && \boldsymbol{\beta}_\delta = \mathbf{U}_{\delta n}^{'}\boldsymbol{\delta},\\
&\mathbf{Z}_\delta = \mathbf{U}_{\delta r} = [\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r}], && \boldsymbol{\alpha}_\delta = \mathbf{U}_{\delta r}^{'}\boldsymbol{\delta}.
\end{aligned}$$

Consequently, Model (8) can be expressed as

$$\begin{aligned}
\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_{TS})\beta_\xi + (\mathbf{1}_T \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\xi + [\mathbf{1}_{TS} : \mathbf{t}^* \otimes \mathbf{1}_S]\boldsymbol{\beta}_\gamma + (\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)\boldsymbol{\alpha}_\gamma\\
+[\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{U}_{\xi r}]\boldsymbol{\beta}_\delta + (\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\delta.
\end{aligned} \quad (11)$$

where $\boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \sigma_\xi^2(\lambda_\xi \widetilde{\boldsymbol{\Sigma}}_\xi + (1-\lambda_\xi)\mathbf{I}_{\xi-1})^{-1})$, $\boldsymbol{\alpha}_\gamma \sim N(\mathbf{0}, \sigma_\gamma^2 \widetilde{\boldsymbol{\Sigma}}_\gamma^{-1})$, and $\boldsymbol{\alpha}_\delta \sim N(\mathbf{0}, \sigma_\delta^2 \widetilde{\boldsymbol{\Sigma}}_\delta^{-1})$. If we remove the repeated columns $\mathbf{1}_{TS}$ (corresponding to $\boldsymbol{\beta}_\xi$, $\boldsymbol{\beta}_\gamma$, and $\boldsymbol{\beta}_\delta$), $\mathbf{1}_T \otimes \mathbf{U}_{\xi r}$, $\mathbf{t}^* \otimes \mathbf{1}_S$ and $\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S$ (corresponding to $\boldsymbol{\beta}_\delta$), this leaves the following model

$$\begin{aligned}
\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_T \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\xi + (\mathbf{t}^* \otimes \mathbf{1}_S)\boldsymbol{\beta}_\gamma + (\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)\boldsymbol{\alpha}_\gamma\\
+[\mathbf{t}^* \otimes \mathbf{U}_{\xi r}]\boldsymbol{\beta}_\delta + (\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\delta.
\end{aligned} \quad (12)$$

If the ICAR prior were considered for the spatial random effect the identifiable model would be (12), but then $\boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \widetilde{\boldsymbol{\Sigma}}_\xi^{-1})$. The equivalent linear constraints are the same as in the RW1 case because the model does not include a linear trend and no additional identifiability issue arises. See Appendix A for more details about the derivation of these sum-to-zero constraints.

It is important to highlight that in Models (9) and (11) we have deleted the repeated terms $(\mathbf{1}_T \otimes \mathbf{U}_{\xi r})$ and $(\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)$ from the fixed effects arising from the reparameterization of the interaction random effect $\boldsymbol{\delta}$. We could have deleted the same terms in the reparameterization of the main spatial and

temporal random effect $\boldsymbol{\xi}$ and $\boldsymbol{\gamma}$ respectively, but if so this would imply that the spatial and temporal main effects were fixed instead of random, as $(\mathbf{1}_T \otimes \mathbf{U}_{\xi r})$ and $(\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)$ would only appear in the fixed part arising from the reparameterization of the interaction random effect $\boldsymbol{\delta}$. In particular, treating the spatial and temporal main effects as fixed effects would imply that they are not smoothed at all.

4 Model fitting

Model fitting and inference with spatial and spatio-temporal disease mapping models have usually been done using either an empirical Bayes (EB) or fully Bayes (FB) approach. In the EB approach, penalized quasi-likelihood (PQL) has been widely used (see for example MacNab and Dean, 2001; Dean et al, 2004; Ugarte et al, 2008, 2009b, 2010, 2012). From a FB perspective, Markov chain Monte Carlo (McMC) techniques have been used because the posterior distributions usually cannot be obtained in closed form (see, for example Bernardinelli et al, 1995; Knorr-Held and Besag, 1998; Knorr-Held, 2000; Best et al, 2005; Ainsworth and Dean, 2006; Martínez-Beneito et al, 2008; Ugarte et al, 2009a). Although these techniques have been widely used, the implementation may not be easy for practitioners as algorithms have to be carefully chosen (Knorr-Held and Rue, 2002; Schmid and Held, 2004), and difficulties such as long computing times and large Monte Carlo errors usually appear with complex models (Schrödle et al, 2011). An alternative to McMC for Bayesian inference based on integrated nested Laplace approximations and known as INLA has been recently proposed (Rue et al, 2009). This technique can be easily used in the free software `R` using the package `R-INLA`. In this section we show how the PQL technique naturally applies linear constraints and we provide guidelines to include constraints in INLA. Linear constraints when the temporal random effect follows RW1 are easy to deal with. However, if the distribution of the temporal random effect is RW2, constraints are a bit more difficult to specify and place.

Consider the spatio-temporal Model (8). PQL requires a working vector and the restricted maximum likelihood equations Harville (1977). The components of the working vector are

$$\mathbf{Y}^* = \mathbf{X}\eta + \mathbf{Z}_1\boldsymbol{\xi} + \mathbf{Z}_2\boldsymbol{\gamma} + \mathbf{Z}_3\boldsymbol{\delta} + (\mathbf{Y} - \boldsymbol{\mu})g'(\boldsymbol{\mu}),$$

where $\mathbf{X}$ is the fixed effects matrix (here a column of ones), $\mathbf{Z}_1 = \mathbf{1}_T \otimes \mathbf{I}_\xi$ is the design matrix of the main spatial random effect $\boldsymbol{\xi}$, $\mathbf{Z}_2 = \mathbf{I}_\gamma \otimes \mathbf{1}_S$ is the design matrix of the main temporal random effect $\boldsymbol{\gamma}$, $\mathbf{Z}_3 = \mathbf{I}_\delta$ is the design matrix of the interaction term $\boldsymbol{\delta}$, $\boldsymbol{\mu}$ is the vector of means of the Poisson distribution, g is the link function (here the logarithmic function), and $g'(\boldsymbol{\mu}) = 1/\boldsymbol{\mu}$. Then a correspondence with a normal mixed model is attained as

$$\mathbf{Y}^* = \mathbf{X}\eta + \mathbf{Z}_1\boldsymbol{\xi} + \mathbf{Z}_2\boldsymbol{\gamma} + \mathbf{Z}_3\boldsymbol{\delta} + \boldsymbol{\epsilon},$$

where $\boldsymbol{\epsilon} = (\mathbf{Y} - \boldsymbol{\mu})g'(\boldsymbol{\mu}) \sim N(\mathbf{0}, \mathbf{W}^{-1})$, and $\mathbf{W} = diag(\mu_{it})$. The fixed effect estimator is obtained as $\hat{\eta} = (\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{Y}^*$, where $\mathbf{V} = \mathbf{W}^{-1} + \mathbf{Z}_1\mathbf{G}_1\mathbf{Z}_1^{'} + \mathbf{Z}_2\mathbf{G}_2\mathbf{Z}_2^{'} + \mathbf{Z}_3\mathbf{G}_3\mathbf{Z}_3^{'}$, and $\mathbf{G}_1 = \sigma_\xi^2\mathbf{D}^{-1}$ or $\mathbf{G}_1 = \sigma_\xi^2\mathbf{Q}_\xi^-$ depending on whether the spatial effect follows the LCAR prior (2) or the ICAR prior respectively, $\mathbf{G}_2 = \sigma_\gamma^2\mathbf{Q}_\gamma^-$, and $\mathbf{G}_3 = \sigma_\delta^2\mathbf{Q}_\delta^-$ (see for example Ugarte et al, 2010 for details). The random effects are predicted as

$$\begin{aligned}\hat{\boldsymbol{\xi}} &= \hat{\mathbf{G}}_1\mathbf{Z}_1^{'}\hat{\mathbf{V}}^{-1}(\mathbf{Y}^* - \mathbf{X}\hat{\eta}),\\ \hat{\boldsymbol{\gamma}} &= \hat{\mathbf{G}}_2\mathbf{Z}_2^{'}\hat{\mathbf{V}}^{-1}(\mathbf{Y}^* - \mathbf{X}\hat{\eta}),\\ \hat{\boldsymbol{\delta}} &= \hat{\mathbf{G}}_3\mathbf{Z}_3^{'}\hat{\mathbf{V}}^{-1}(\mathbf{Y}^* - \mathbf{X}\hat{\eta}).\end{aligned}$$

If $\mathbf{G}_1 = \sigma_\xi^2\mathbf{Q}_\xi^-$, then, the PQL technique automatically imposes the usual sum-to-zero constraint $\sum_{i=1}^S \xi_i = 0$. This is clear as $\mathbf{Q}_\xi\mathbf{1}_S = \mathbf{0}$, and hence $\sum_{i=1}^S \hat{\xi}_i = \hat{\sigma}_\xi^2(\mathbf{Q}_\xi^-\mathbf{Z}_1^{'}\hat{\mathbf{V}}^{-1}(\mathbf{Y}^* - \mathbf{X}\hat{\eta}))^{'}\mathbf{1}_S = \hat{\sigma}_\xi^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})^{'}\hat{\mathbf{V}}^{-1}\mathbf{Z}_1\mathbf{Q}_\xi^-\mathbf{1}_S = 0$. Note that if $\mathbf{x}$ is an eigenvector of $\mathbf{Q}_\xi$ that has zero eigenvalue, then $\mathbf{x}$ is an eigenvector of $\mathbf{Q}_\xi^-$ that has zero eigenvalue (see for example Harville, 2008, chap. 21, p. 546). Consequently, $\mathbf{Q}_\xi^-\mathbf{1}_S = \mathbf{0}$. Similarly, the sum-to-zero constraint is automatically imposed for the temporal random effects. Furthermore, if the LCAR prior is used for the spatial effect, i.e., if $\mathbf{G}_1 = \sigma_\xi^2\mathbf{D}^{-1} = \sigma_\xi^2(\lambda_\xi\mathbf{Q}_\xi + (1-\lambda_\xi)\mathbf{I}_\xi)^{-1}$, then the PQL technique also automatically imposes the sum-to-zero constraint $\sum_{i=1}^S \xi_i = 0$ when the intercept is included in the model. Note that in general, if $\mathbf{x}$ is an eigenvector of $\mathbf{A}$ that has non-zero eigenvalue λ, then $\mathbf{x}$ is an eigenvector of $\mathbf{A}^{-1}$ that has non-zero eigenvalue $1/\lambda$ (see for example Harville, 2008 chap 21, p. 527). Consequently, as $\mathbf{Q}_\xi\mathbf{1}_S = \mathbf{0}$ and $\mathbf{I}_\xi\mathbf{1}_S = \mathbf{1}_S$, $\mathbf{D}\mathbf{1}_S = (\lambda_\xi\mathbf{Q}_\xi + (1-\lambda_\xi)\mathbf{I}_\xi)\mathbf{1}_S = (1-\lambda_\xi)\mathbf{1}_S$, and then $\mathbf{D}^{-1}\mathbf{1}_S = \frac{1}{(1-\lambda_\xi)}\mathbf{1}_S$. Hence, $\sum_{i=1}^S \hat{\xi}_i = \hat{\sigma}_\xi^2(\hat{\mathbf{D}}^{-1}\mathbf{Z}_1^{'}\hat{\mathbf{V}}^{-1}(\mathbf{Y}^* - \mathbf{X}\hat{\eta}))^{'}\mathbf{1}_S = \hat{\sigma}_\xi^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})^{'}\hat{\mathbf{V}}^{-1}\mathbf{Z}_1\hat{\mathbf{D}}^{-1}\mathbf{1}_S = \frac{\hat{\sigma}_\xi^2}{(1-\hat{\lambda}_\xi)}(\mathbf{Y}^* - \mathbf{X}\hat{\eta})^{'}\hat{\mathbf{V}}^{-1}\mathbf{1}_{TS} = 0$ taking into account that

$$\begin{aligned}(\mathbf{Y}^* - \mathbf{X}\hat{\eta})^{'}\hat{\mathbf{V}}^{-1}\mathbf{X} &= (\mathbf{Y}^* - \mathbf{X}(\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{Y}^*)^{'}\hat{\mathbf{V}}^{-1}\mathbf{X} =\\ &= \mathbf{Y}^{*'}(\mathbf{I} - \hat{\mathbf{V}}^{-1}\mathbf{X}(\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}\mathbf{X}^{'})\hat{\mathbf{V}}^{-1}\mathbf{X} =\\ &= \mathbf{Y}^{*'}(\hat{\mathbf{V}}^{-1}\mathbf{X} - \hat{\mathbf{V}}^{-1}\mathbf{X}(\mathbf{X}'\hat{\mathbf{V}}^{-1}\mathbf{X})^{-1}\mathbf{X}^{'}\hat{\mathbf{V}}^{-1}\mathbf{X}) = \mathbf{0}.\end{aligned}$$

Then if the intercept is included in the model, the vector $\mathbf{1}_{TS}$ is one of the columns of $\mathbf{X}$ and therefore $(\mathbf{Y}^* - \mathbf{X}\hat{\eta})^{'}\hat{\mathbf{V}}^{-1}\mathbf{1}_{TS} = 0$.

PQL also automatically imposes sum-to-zero constraints $\sum_{i=1}^S \delta_{it} = 0$, $\forall t$ and $\sum_{t=1}^T \delta_{it} = 0$, $\forall i$ if the temporal random effect follows a RW1. This is also easy to see. If we define $\mathbf{e}_i$, $i = 1\ldots, S$, to be a vector of length S with a one in the i-th position and zero elsewhere, and $\mathbf{u}_t$, $t = 1\ldots, T$, to be a vector of

length T with a one in the t-th position and zero elsewhere, then

$$\begin{aligned}\sum_{i=1}^{S}\hat{\delta}_{it} &= \hat{\sigma}_\delta^2(\mathbf{Q}_\delta^- \mathbf{Z}_3^{'}\hat{\mathbf{V}}^{-1}(\mathbf{Y}^* - \mathbf{X}\hat{\eta}))'(\mathbf{u}_t \otimes \mathbf{1}_S)\\ &= \hat{\sigma}_\delta^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})'\hat{\mathbf{V}}^{-1}\mathbf{Z}_3\mathbf{Q}_\delta^-(\mathbf{u}_t \otimes \mathbf{1}_S)\\ &= \hat{\sigma}_\delta^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})'\hat{\mathbf{V}}^{-1}\mathbf{Z}_3(\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)^-(\mathbf{u}_t \otimes \mathbf{1}_S)\\ &= \hat{\sigma}_\delta^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})'\hat{\mathbf{V}}^{-1}\mathbf{Z}_3((\mathbf{Q}_\gamma^-\mathbf{u}_t) \otimes (\mathbf{Q}_\xi^-\mathbf{1}_S)) = 0,\end{aligned}$$

and

$$\begin{aligned}\sum_{t=1}^{T}\hat{\delta}_{it} &= \hat{\sigma}_\delta^2(\mathbf{Q}_\delta^- \mathbf{Z}_3^{'}\hat{\mathbf{V}}^{-1}(\mathbf{Y}^* - \mathbf{X}\hat{\eta}))'(\mathbf{1}_T \otimes \mathbf{e}_i)\\ &= \hat{\sigma}_\delta^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})'\hat{\mathbf{V}}^{-1}\mathbf{Z}_3\mathbf{Q}_\delta^-(\mathbf{1}_T \otimes \mathbf{e}_i)\\ &= \hat{\sigma}_\delta^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})'\hat{\mathbf{V}}^{-1}\mathbf{Z}_3(\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)^-(\mathbf{1}_T \otimes \mathbf{e}_i)\\ &= \hat{\sigma}_\delta^2(\mathbf{Y}^* - \mathbf{X}\hat{\eta})'\hat{\mathbf{V}}^{-1}\mathbf{Z}_3((\mathbf{Q}_\gamma^-\mathbf{1}_T) \otimes (\mathbf{Q}_\xi^-\mathbf{e}_i)) = 0.\end{aligned}$$

Hence, if the distribution of the temporal random effect is RW1, PQL automatically places correct constraints. However, if the distribution of the temporal random effect is RW2, then PQL imposes more restrictions than needed unless extra terms — a common linear trend or linear trends for each area — are added to the model. A RW2 prior for the temporal random effect implies that PQL automatically imposes the constraint $\mathbf{Q}_\gamma\mathbf{t}^* = \mathbf{0}$, so that $\sum_{t=1}^{T} t\hat{\gamma}_t = 0$, but this constraint is not needed unless a linear trend is present in the model. Similarly $(\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)(\mathbf{t}^* \otimes \mathbf{e}_i) = \mathbf{0}$, so that PQL automatically imposes the constraint $\sum_{t=1}^{T} t\hat{\delta}_{it} = 0$, $\forall i$. Consequently, PQL places more constraints than are needed unless we explicitly consider the model reformulation given in Equation (12). Using the reformulated Model (10), we avoid an additional inconvenience because if the full Model (8) is fitted placing the appropriate sum-to-zero constraints, the variance of the intercept is larger than the one obtained by fitting the reformulated Model (10). The reason is that when we use the LCAR prior for the spatial effect, the eigenvalue corresponding to the eigenvector $\mathbf{1}_S$ is not null and hence it contributes to the variance of the intercept (see Appendix C). This does not happen if the ICAR prior is considered because the eigenvalue associated with the eigenvector $\mathbf{1}_S$ is equal to zero, so that it does not contribute to the variance of the intercept. When we consider the reformulated model, the redundant intercepts disappear from the model and the variance is not inflated.

Recently, a new approximate technique called INLA, based on integrated nested Laplace approximations, has been proposed for Bayesian inference in models using latent Gaussian Markov random fields (Rue et al, 2009), which includes the models described in this paper. An attractive feature of INLA is that it can easily be used in the free software `R` (R Core Team, 2016), with the package `R-INLA` (Martino and Rue, 2009). `R` code to fit some of these models

in INLA can be found in Ugarte et al (2014). Details about how to place constraints in disease mapping models using INLA can be found in Schrödle and Held (2011). We recommend a careful reading of this paper to avoid misunderstandings. According to the authors, "...the identifiability of $\boldsymbol{\delta}$ can be ensured by computing the null space of the respective structure matrix $\mathbf{R}$ and using the obtained eigenvectors as linear constraints for the estimation of $\boldsymbol{\delta}$. As a consequence, the number of linear constraints which are necessary is *always* equal to the rank deficiency of $\mathbf{R}$ [emphasis added]". This is true if the model includes an intercept and the temporal effect is modeled as a RW1. However, if a RW2 prior is used for the temporal random effect, constraints are not in fact needed for all the eigenvectors corresponding to the null eigenvalues of the precision matrix *unless* a common linear trend and area specific linear trends are included in the model, as shown in Section 3.2. Section 5 below shows the consequences of adding these needless constraints in a model with a RW2 prior for the temporal random effect. Appendices A and B show the appropriate constraints.

5 Illustration

This section uses female breast cancer mortality data (ICD-10 code 50) in Spanish provinces during the period 1990-2010 to illustrate how estimates can change if unnecessary linear constraints are unintentionally included in the model. The models are fitted in an EB approach using PQL and in a FB approach using INLA. In all of the models, a global intercept η has been included in estimating the log-risks, so we must center the spatial random effects by including the constraint $\sum_{i=1}^{S} \xi_i = 0$. Regarding estimation of the intercept using PQL, if a RW1 prior is used for time and the LCAR prior is used for the spatial random effect, the estimated standard error of the the intercept is inflated when we fit the complete Model (8) with appropriate sum-to-zero constraints. In this case, $\hat{\eta} = -0.034$ and $s.e.(\hat{\eta}) = 0.036$. However, if we fit the reparameterized Model (10), $\hat{\eta} = -0.034$ and $s.e.(\hat{\eta}) = 0.0039$. If an ICAR prior is used for the spatial random effect, the same estimates are obtained from the full Model (8) with appropriate sum-to-zero constraints and from the reparameterized Model (10), i.e., the estimate and the standard error for the intercept are $\hat{\eta} = -0.034$ and $s.e.(\hat{\eta}) = 0.0039$ respectively. Using INLA (placing uniform distributions on the standard deviations), the estimate of the intercept ($\hat{\eta} = -0.035$) and its standard error ($s.e.(\hat{\eta}) = 0.004$) are identical for the complete Model (8) and the the reduced Model (10) regardless of we use the ICAR or the LCAR prior for the spatial random effect.

We now focus on the estimated temporal pattern $\hat{\gamma}_t$ common to all small areas. As shown in Section 4, if a RW2 prior is used for the temporal random effect, PQL automatically sets the constraints $\sum_{t=1}^{T} \gamma_t = 0$ and $\sum_{t=1}^{T} t\gamma_t = 0$, the latter being unnecessary because no explicit linear trend is included in the model. Figure 1 on the upper-left shows the estimated temporal patterns obtained with a RW1 and a RW2 using PQL with Model (8). If we compare

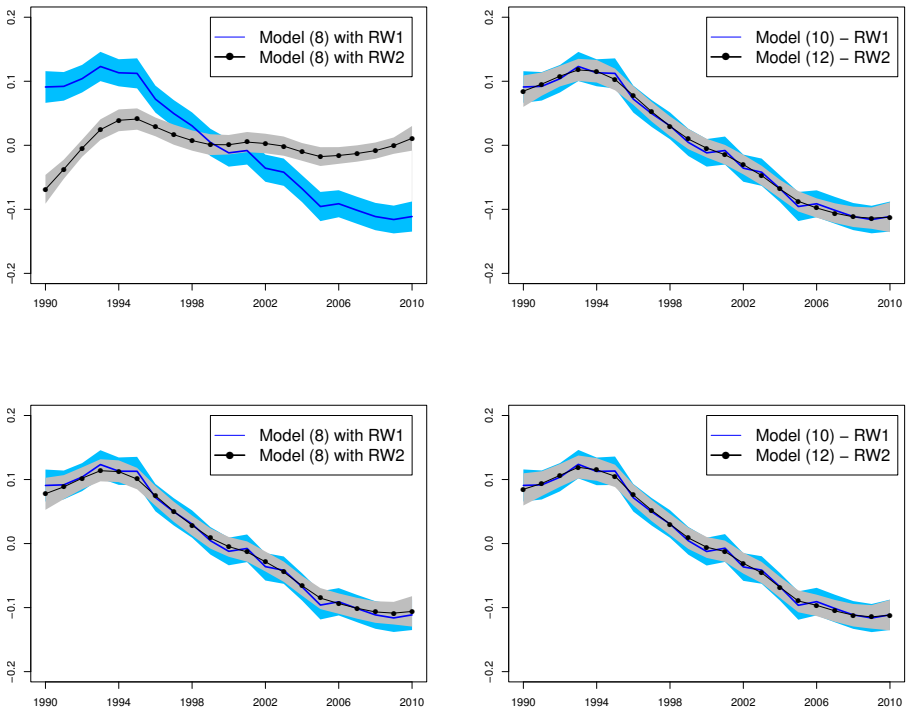

Fig. 1 Estimated temporal trend $\hat{\gamma}_t$ with PQL (top) and INLA (bottom)

the fits, we see a different trend for the RW2 due to the unnecessary constraint $\sum_{t=1}^{T} t\gamma_t = 0$, instead of the expected smoother version of the RW1 fit. However, if the reparameterized Models (10) and (12) are fitted (upper-right hand in Figure 1), where the repeated (or linearly dependent) columns of the fixed effect matrix are deleted, the results of the two fits are much more consistent. Because only the repeated columns are removed, the unnecessary constraint $\sum_{t=1}^{T} t\gamma_t = 0$ is not placed on the fit. If the models are fitted using INLA, once the appropriate constraints are specified for the temporal effect γ_t, the temporal pattern estimated for the original Model (8) (Figure 1 on the bottom-left) and the reparameterized Models (10) and (12) (Figure 1 on the bottom-right) are almost identical, indicating that INLA does not inherently place unnecessary constraints on the temporal effects.

Now consider the estimates of the spatio-temporal random effect $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2(\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)^-)$. If a RW2 prior is considered for the temporal random effect and the model is fitted using PQL, the following linear constraints are automatically imposed: $\sum_{i=1}^{S} \delta_{it} = 0$, $\forall t$, $\sum_{t=1}^{T} \delta_{it} = 0$, $\forall i$ and $\sum_{t=1}^{T} t\delta_{it} = 0$, $\forall i$. The latter constraints are unnecessary and force the area-specific risk evolution to have a very restricted shape. Figure 2 shows the estimated interaction effects for three selected provinces using PQL. The top row in Figure 2 shows the estimates when both RW1 and RW2 are considered in the original Model (8). Clearly the unnecessary constraints for a RW2 make the fit very different

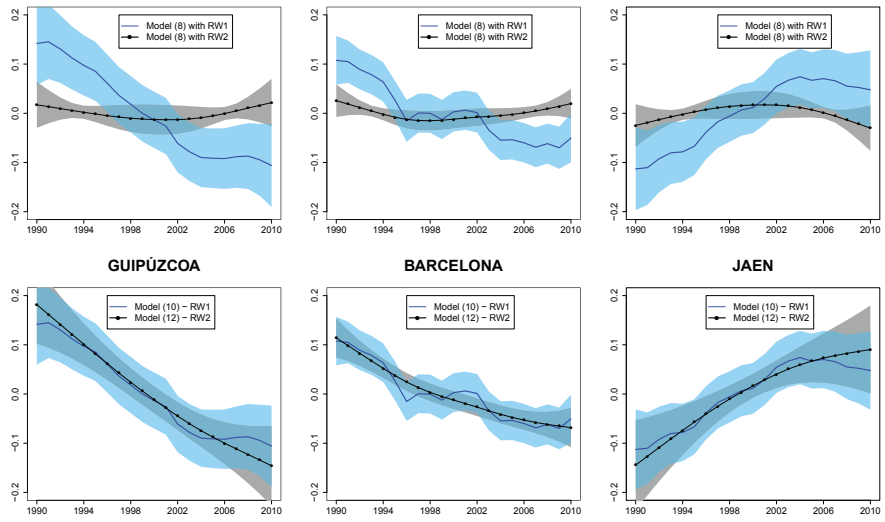

Fig. 2 Space-time interaction random effect $\hat{\delta}_{it}$ estimated with PQL

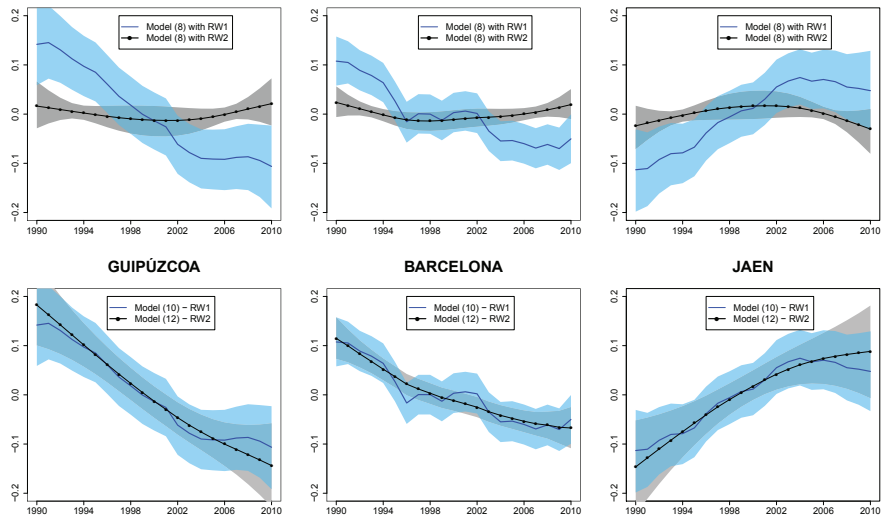

Fig. 3 Space-time interaction random effect $\hat{\delta}_{it}$ estimated with INLA

from that obtained with a RW1: the linear component of the RW1 fit is absent in the RW2 fit. The bottom row in Figure 2 shows the estimates using the reparameterized Models (10) and (12). The results seem to be more sensible as similar fits are obtained with RW1 and RW2, with the RW2 fits being smoother, as expected.

The results obtained with INLA are also interesting. Proceeding as suggested in Schrödle and Held (2011), with all eigenvectors in the null space of $\mathbf{Q}_\delta = \mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi$ used as constraints to identify $\boldsymbol{\delta}$, when the RW2 prior is used the interaction fit given by INLA is very similar to the restricted interaction fit using PQL (top row of Figure 3). This problem is solved if the reparameterized Models (10) and (12) are used instead (bottom row of Figure 3). If instead of reparameterizing the model, we fit the original model using INLA and apply only the appropriate sum-to-zero constraints to $\boldsymbol{\delta}$, the resulting fit is similar to those from the re-paramterized models with slight differences in some areas with low populations. Figure 4 shows the estimated interaction random effect in two low-population provinces when fitting Model (8) using INLA with a RW1 (solid line) and with a RW2 and appropriate sum-to-zero constraints (dashed line), and fitting the reparameterized Model (12) (dotted line). The estimates with the correct sum-to-zero constraints and with the reparameterized model differ, the latter being similar to estimates using PQL. However, these differences do not have a great impact on the final risk estimates.

Finally, to see the effects of unnecessary constraints on the final risk estimates, Figure 5 displays the estimated relative risks with PQL and INLA for two provinces, Guipuzcoa (left column) and Barcelona (right column). Top row corresponds to the PQL fit and bottom row displays the INLA fit. If model (8) is fitted using PQL, the estimated relative risk (black continuos line with grey confidence band) do not track the SMR's trend (red line). On the other hand, if the reparameterized model 12 is fitted, the estimated relative risks (blue line with blue confidence band) track the SMR's very well. The confidence band for the estimated relative risks has been constructed using the estimated mean squared error of the logrisk and the delta method (see Ugarte et al, 2008, 2010; Adin et al, 2016). The same effect is also observed in the INLA fit (bottom row). If model (8) is fitted using as many constraints in the interaction as eigenvectors expanding the null space of the interaction covariance matrix, the estimated relative risks (black continuos line with grey credibility band) are wrong. However, if model (8) with appropriate constraints or the reparameterized model (12) are fitted, the estimated relative risks (blue line with blue credibility band) are correct. It should be noticed that PQL is placing unnecessary constraints in the main temporal effect and in the interaction effect, whereas INLA only uses extra constraints in the interaction term. Consequently, the effect of the unnecessary constraints is stronger in the PQL fit. Nevertheless, the effect of unnecessary constraints in the final risk is serious enough to be taken into account.

To compare models with constraints versus reparameterized models, we computed AIC (PQL fitting) and DIC (INLA fitting). Table 1 shows AIC for models fit using PQL and DIC for models fit using INLA. Regarding PQL, the two models have similar AICs when the temporal distribution is a RW1, showing equivalent results using constraints in the original model or fitting the reparameterised model. However, when the temporal random effect is a RW2, the high AIC for the original model indicates that PQL imposes more constraints than needed. Results with INLA are similar to those from PQL.

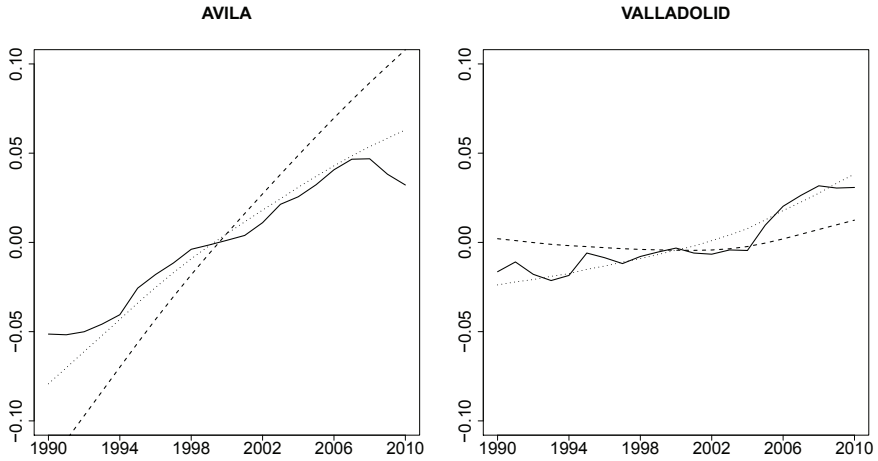

Fig. 4 Space-time interaction random effect $\hat{\delta}_{it}$ estimated with INLA for Model (8) with RW1 (solid line), Model (8) with RW2 and appropriate sum-to-zero constraints (dashed line) and the reparameterized Model (12) (dotted line)

Table 1 Model comparisons in the analysis of female breast cancer mortality data in Spain

		PQL							
		RW1				RW2			
		Deviance	Df	AIC	Time	Deviance	Df	AIC	Time
ICAR models	Model 8	7410.9	145.6	7702.1	75	8802.3	66.1	8934.6	100
	Model 10/12	7411.8	145.2	7702.1	240	7494.5	110.8	7716.1	400
LCAR models	Model 8	7409.9	146.0	7701.8	95	8801.3	66.5	8934.3	125
	Model 10/12	7411.1	145.4	7701.8	170	7493.7	111.1	7716.0	240
		INLA							
		$\bar{D}$	p.eff	DIC	Time	$\bar{D}$	p.eff	DIC	Time
ICAR models	Model 8	7555.0	149.7	7704.8	60	7798.1	71.5	7869.6	120
	Model 8*					7601.9	120.4	7722.4	55
	Model 10/12	7555.0	149.7	7704.8	1030	7601.7	117.2	7718.9	705
LCAR models	Model 8	7554.2	150.3	7704.5	100	7797.5	71.7	7869.2	235
	Model 8*					7601.2	120.9	7722.1	95
	Model 10/12	7554.2	150.3	7704.5	1640	7600.9	117.9	7718.8	1215

For RW1, the recommended constraints are appropriate, but for RW2 using more constraints than needed leads to poor fits. Table 1 uses "Model 8*" to denote Model (8) fitted in INLA with the appropriate sum-to-zero constraints. The DICs obtained with Model 8* are slightly higher than the analogous DICs from the reparameterized model. This may reflect the effect shown in Figure 4. Finally, Table 1 also displays computing time (in seconds) required to fit the models. The PQL fits were run in a personal computer LENOVO with 3.1 GHz Intel Core i5 processor and 6GB RAM using R (version 3.2.2). The INLA fits

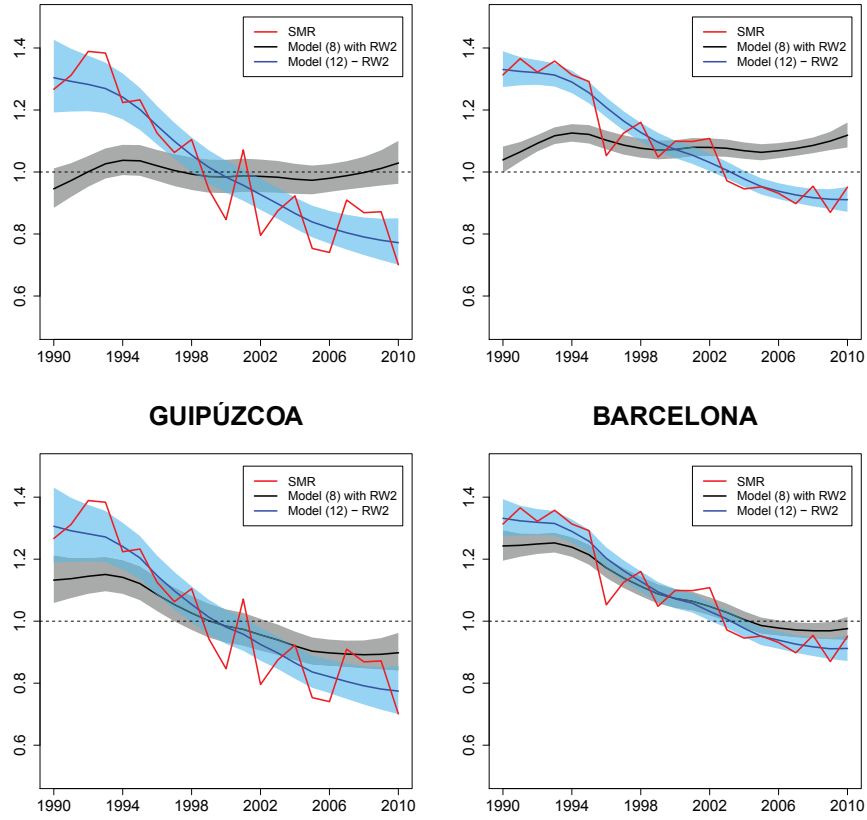

Fig. 5 Standardized mortality ratios (red lines), and estimated relative risks with PQL (top row) and INLA (bottom row) for the provinces of Guipuzcoa (left column) and Barcelona (right column). Black lines corresponds to model (8) with unnecessary constraints, and blue lines represents the estimates from the reparameterized model (12)

were run in a twin superserver with four processors Intel Xeon 6C and 96GB RAM using R (version 3.2.2) and the R package INLA (version 0.0-1455098891, dated 2016-02-10). Computing time is higher for the reparameterized models. Consequently, if INLA is used to fit the spatio-temporal model (8) with a RW2 prior for the temporal component, it is recommended to place appropriate constraints instead of reparameterizing the model.

6 Discussion

Statistical models used in spatial and spatio-temporal disease mapping have become more and more sophisticated to allow proper analyses of real data. This complexity has brought some challenges, model identifiability being one of the

most important. There are plenty of papers on spatial and spatio-temporal disease mapping; most consider sum-to-zero constraints to achieve identifiability but do not clearly establish why and how the constraints should be imposed.

The main objective of this paper was to clarify this issue, providing practical guidelines when spatio-temporal disease mapping models are fitted using PQL or INLA. In both approaches (empirical or fully Bayes), one of the more widely used priors for spatial random effects is the intrinsic CAR (ICAR). Recently, certain disadvantages of this prior have been reported, for example, it produces negative correlations among regions located far apart. These limitations have led some authors to use the Leroux prior (LCAR) as a possible alternative to the ICAR. The LCAR prior does not produce such negative correlations and it has the advantage of including a parameter that quantifies spatial dependence as well as unstructured heterogeneity. However, if the LCAR prior is used and Model (8) (a spatio-temporal model with a RW1 prior for the main temporal effect) is fitted using PQL, an undesired variance inflation of the intercept estimate occurs even if adequate restrictions on the spatial effects are used. In addition, if a RW2 prior is used for the temporal random effects, PQL automatically places unnecessary constraints on the estimates, which leads to an erroneous estimate of the temporal trend. Both problems can be fixed with a reparameterization of the model based on the spectral decomposition of the precision matrices of the spatial, temporal, and spatio-temporal random effects, as shown in this paper. If additional spatially varying fixed effects were included in the model, collinearity problems with the spatial main effect could appear (see Reich et al, 2006) affecting the standard error of the estimates. However, this is beyond the scope of this paper and deserves further research. Here, our focus is on putting adequate restrictions in disease mapping models commonly used for map production in vital agencies, public health institutions, and research centers.

For Bayesian inference, model fitting can be done using McMC or INLA; INLA is popular nowadays and we have focused on it. In this paper, we provided details on how to specify appropriate constraints in INLA when fitting the more common spatio-temporal models, including four types of spatio-temporal interactions (Knorr-Held, 2000; see Appendices A and B). Previous papers have not clarified this aspect of using INLA in enough detail and proper constraint specification is crucial for practitioners. In particular it is *not* the case that the number of linear constraints needed to identify the interaction effect is always equal to the rank deficiency of the precision matrix (Schrödle and Held, 2011). Placing more restrictions than needed again leads to erroneous estimates.

Summing up, when using PQL for fitting spatio-temporal disease mapping models, our recommendation is to reparameterize the model using the spectral decomposition of the precision matrices of the random effects before fitting. If model fitting is carried out using INLA, the appropriate constraints must be identified and used. Doing so gives correct results without incurring the extra computing time required to fit the reparameterized model in R-INLA.

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Appendix A

Appendix A shows how the usual sum-to-zero constraints are derived.

Appendix A.1

Given the spatio-temporal model of Equation (8)

$$\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_T \otimes \mathbf{I}_\xi)\boldsymbol{\xi} + (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\boldsymbol{\gamma} + \mathbf{I}_\delta\boldsymbol{\delta},$$

where η is the log of the global risk, the spatial random effect $\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2\mathbf{Q}_\xi^-)$ follows an ICAR distribution, the temporal random effect $\boldsymbol{\gamma} \sim N(\mathbf{0}, \sigma_\gamma^2\mathbf{Q}_\gamma^-)$ follows a RW1 distribution, and the interaction random effect $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2(\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)^-)$ is completely structured (Type IV interaction) in space and time, the linear constraints that make this model identifiable are

$$\sum_{i=1}^{S}\xi_i = 0, \quad \sum_{t=1}^{T}\gamma_t = 0 \qquad \text{and} \qquad \begin{array}{l} \sum_{t=1}^{T}\delta_{it} = 0, \quad \text{for} \quad i = 1,\ldots,S \\ \sum_{i=1}^{S}\delta_{it} = 0, \quad \text{for} \quad t = 1,\ldots,T \end{array}$$

As shown in Section 3.2, the random effects of Equation (8) can be reparameterized using the spectral decomposition of their covariance matrices, so this model becomes

$$\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + [\mathbf{X}_\xi : \mathbf{Z}_\xi]\begin{bmatrix}\beta_\xi \\ \boldsymbol{\alpha}_\xi\end{bmatrix} + [\mathbf{X}_\gamma : \mathbf{Z}_\gamma]\begin{bmatrix}\beta_\gamma \\ \boldsymbol{\alpha}_\gamma\end{bmatrix} + [\mathbf{X}_\delta : \mathbf{Z}_\delta]\begin{bmatrix}\boldsymbol{\beta}_\delta \\ \boldsymbol{\alpha}_\delta\end{bmatrix}$$

where

$$\begin{aligned}
\mathbf{X}_\xi = (\mathbf{1}_T \otimes \mathbf{I}_\xi)\mathbf{U}_{\xi n} = \mathbf{1}_{TS}, \quad & \beta_\xi = \mathbf{U}_{\xi n}^{'}\boldsymbol{\xi} = \mathbf{1}_S^{'}\boldsymbol{\xi} \\
\mathbf{Z}_\xi = (\mathbf{1}_T \otimes \mathbf{I}_\xi)\mathbf{U}_{\xi r} = \mathbf{1}_T \otimes \mathbf{U}_{\xi r}, \quad & \boldsymbol{\alpha}_\xi = \mathbf{U}_{\xi r}^{'}\boldsymbol{\xi}, \\
\mathbf{X}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma n} = \mathbf{1}_{TS}, \quad & \beta_\gamma = \mathbf{U}_{\gamma n}^{'}\boldsymbol{\gamma} = \mathbf{1}_T^{'}\boldsymbol{\gamma} \\
\mathbf{Z}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma r} = \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S, \quad & \boldsymbol{\alpha}_\gamma = \mathbf{U}_{\gamma r}^{'}\boldsymbol{\gamma}, \\
\mathbf{X}_\delta = \mathbf{U}_{\delta n} = [\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S], \quad & \boldsymbol{\beta}_\delta = \mathbf{U}_{\delta n}^{'}\boldsymbol{\delta} \\
\mathbf{Z}_\delta = \mathbf{U}_{\delta r} = [\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r}], \quad & \boldsymbol{\alpha}_\delta = \mathbf{U}_{\delta r}^{'}\boldsymbol{\delta}.
\end{aligned}$$

Consequently, the model can be re-expressed as

$$\begin{aligned}
\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_{TS})\beta_\xi + (\mathbf{1}_T \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\xi + (\mathbf{1}_{TS})\beta_\gamma + (\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)\boldsymbol{\alpha}_\gamma \\
+[\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S]\boldsymbol{\beta}_\delta + (\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\delta.
\end{aligned}$$

where $\boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \sigma_\xi^2 \widetilde{\boldsymbol{\Sigma}}_\xi^{-1})$, $\boldsymbol{\alpha}_\gamma \sim N(\mathbf{0}, \sigma_\gamma^2 \widetilde{\boldsymbol{\Sigma}}_\gamma^{-1})$ and $\boldsymbol{\alpha}_\delta \sim N(\mathbf{0}, \sigma_\delta^2 \widetilde{\boldsymbol{\Sigma}}_\delta^{-1})$.
To obtain the identifiable model of Equation (10), the repeated columns $\mathbf{1}_{TS}$, $\mathbf{1}_T \otimes \mathbf{U}_{\xi r}$ and $\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S$ must be removed, which is equivalent to set $\beta_\xi = 0$, $\beta_\gamma = 0$ and $\boldsymbol{\beta}_\delta = \mathbf{0}$. For the first two constraints, it is straightforward that

$$\beta_\xi = 0 \Longleftrightarrow \mathbf{1}_S^{'}\boldsymbol{\xi} = 0 \Longleftrightarrow \sum_{i=1}^{S} \xi_i = 0 \quad \text{and} \quad \beta_\gamma = 0 \Longleftrightarrow \mathbf{1}_T^{'}\boldsymbol{\gamma} = 0 \Longleftrightarrow \sum_{t=1}^{T} \gamma_t = 0.$$

Now decompose the constraint $\boldsymbol{\beta}_\delta = \mathbf{0}$ into its three terms:

- As in the previous case, $\mathbf{1}_{TS}^{'}\boldsymbol{\delta} = 0 \Longleftrightarrow \sum_{i=1}^{S}\sum_{t=1}^{T} \delta_{it} = 0$.
- Denoting $\boldsymbol{\delta} = (\delta_{11}, \ldots, \delta_{S1}, \ldots, \delta_{1T}, \ldots, \delta_{ST})^{'}$ it can be shown that

$$(\mathbf{1}_T \otimes \mathbf{U}_{\xi r})^{'}\boldsymbol{\delta} = [\mathbf{U}_{\xi r}^{'} : \cdots : \mathbf{U}_{\xi r}^{'}] \begin{pmatrix} \delta_{11} \\ \vdots \\ \delta_{ST} \end{pmatrix} = \mathbf{U}_{\xi r}^{'}[\mathbf{I}_\xi : \cdots : \mathbf{I}_\xi] \begin{pmatrix} \delta_{11} \\ \vdots \\ \delta_{ST} \end{pmatrix} = \mathbf{U}_{\xi r}^{'} \begin{pmatrix} \sum_{t=1}^{T} \delta_{1t} \\ \vdots \\ \sum_{t=1}^{T} \delta_{St} \end{pmatrix},$$

and

$$(\mathbf{1}_T \otimes \mathbf{U}_{\xi r})^{'}\boldsymbol{\delta} = \mathbf{0} \Longleftrightarrow \mathbf{U}_{\xi r}^{'} \begin{pmatrix} \sum_{t=1}^{T} \delta_{1t} \\ \vdots \\ \sum_{t=1}^{T} \delta_{St} \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix}.$$

$\mathbf{U}_{\xi r}^{'}$ is a $(S-1)\times S$ matrix with rank $S-1$ and the previous homogenous linear system has an infinite number of solutions. However, as the $\sum_{i=1}^{S}\sum_{t=1}^{T}\delta_{it}=0$ sum-to-zero constraint is satisfied, adding this constraint to the linear system:

$$\begin{bmatrix}\mathbf{U}_{\xi r}^{'}\\ \mathbf{1}_S^{'}\end{bmatrix}\begin{pmatrix}\sum_{t=1}^{T}\delta_{1t}\\ \vdots\\ \sum_{t=1}^{T}\delta_{St}\end{pmatrix}=\begin{pmatrix}0\\ \vdots\\ 0\end{pmatrix}\Longleftrightarrow\begin{pmatrix}\sum_{t=1}^{T}\delta_{1t}\\ \vdots\\ \sum_{t=1}^{T}\delta_{St}\end{pmatrix}=\begin{pmatrix}0\\ \vdots\\ 0\end{pmatrix}\Longleftrightarrow\sum_{t=1}^{T}\delta_{it}=0,\ \forall i.$$

– In a similar way, it can be shown that

$$(\mathbf{U}_{\gamma r}\otimes\mathbf{1}_S)^{'}\boldsymbol{\delta}=\mathbf{U}_{\gamma r}^{'}\begin{pmatrix}\mathbf{1}_S^{'}&\dots&0\\ 0&\ddots&0\\ 0&0&\mathbf{1}_S^{'}\end{pmatrix}\boldsymbol{\delta}=\mathbf{U}_{\gamma r}^{'}(\mathbf{I}_\gamma\otimes\mathbf{1}_S^{'})\boldsymbol{\delta}=\mathbf{U}_{\gamma r}^{'}\begin{pmatrix}\sum_{i=1}^{S}\delta_{i1}\\ \vdots\\ \sum_{i=1}^{S}\delta_{iT}\end{pmatrix}$$

and consequently,

$$(\mathbf{U}_{\gamma r}\otimes\mathbf{1}_S)^{'}\boldsymbol{\delta}=\mathbf{0}\Longleftrightarrow\mathbf{U}_{\gamma r}^{'}\begin{pmatrix}\sum_{i=1}^{S}\delta_{i1}\\ \vdots\\ \sum_{i=1}^{S}\delta_{iT}\end{pmatrix}=\begin{pmatrix}0\\ \vdots\\ 0\end{pmatrix}$$

$\mathbf{U}_{\gamma r}^{'}$ is a $(T-1)\times T$ matrix with rank $T-1$, and the previous homogenous linear system has an infinite number of solutions. However, as the $\sum_{i=1}^{S}\sum_{t=1}^{T}\delta_{it}=0$ sum-to-zero constraint is satisfied, adding this constraint to the linear system

$$\begin{bmatrix}\mathbf{U}_{\gamma r}^{'}\\ \mathbf{1}_T^{'}\end{bmatrix}\begin{pmatrix}\sum_{i=1}^{S}\delta_{i1}\\ \vdots\\ \sum_{i=1}^{S}\delta_{iT}\end{pmatrix}=\begin{pmatrix}0\\ \vdots\\ 0\end{pmatrix}\Longleftrightarrow\begin{pmatrix}\sum_{i=1}^{S}\delta_{i1}\\ \vdots\\ \sum_{i=1}^{S}\delta_{iT}\end{pmatrix}=\begin{pmatrix}0\\ \vdots\\ 0\end{pmatrix}\Longleftrightarrow\sum_{i=1}^{S}\delta_{it}=0,\ \forall t.$$

Appendix A.2

Given the spatio-temporal model of Equation (8)

$$\log(\mathbf{r})=(\mathbf{1}_{TS})\eta+(\mathbf{1}_T\otimes\mathbf{I}_\xi)\boldsymbol{\xi}+(\mathbf{I}_\gamma\otimes\mathbf{1}_S)\boldsymbol{\gamma}+\mathbf{I}_\delta\boldsymbol{\delta},$$

where η is the log of the global risk, the spatial random effect $\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2 \mathbf{Q}_\xi^-)$ follows an ICAR distribution, the temporal random effect $\boldsymbol{\gamma} \sim N(\mathbf{0}, \sigma_\gamma^2 \mathbf{Q}_\gamma^-)$ follows a RW2 distribution, and the interaction random effects $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2 (\mathbf{Q}_\gamma \otimes \mathbf{Q}_\xi)^-)$ are completely structured (Type IV interaction) in space and time, the linear constraints that make this model identifiable are

$$\sum_{i=1}^{S} \xi_i = 0, \quad \sum_{t=1}^{T} \gamma_t = 0 \qquad \text{and} \qquad \begin{array}{ll} \sum_{t=1}^{T} \delta_{it} = 0, & \text{for} \quad i = 1, \ldots, S \\ \sum_{i=1}^{S} \delta_{it} = 0, & \text{for} \quad t = 1, \ldots, T \end{array}$$

Additionally, the constraints $\sum_{t=1}^{T} \sum_{i=1}^{S} t\delta_{it} = 0$ have to be considered, but they are automatically placed with $\sum_{i=1}^{S} \delta_{it} = 0$, as $\sum_{t=1}^{T} \sum_{i=1}^{S} t\delta_{it} = \sum_{t=1}^{T} t \sum_{i=1}^{S} \delta_{it} = 0$.

If the temporal random effect $\boldsymbol{\gamma}$ follows a RW2 distribution, the random effects of Equation (8) can be reparameterized using the spectral decomposition of the covariance matrix, so this model becomes

$$\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + [\mathbf{X}_\xi : \mathbf{Z}_\xi] \begin{bmatrix} \beta_\xi \\ \boldsymbol{\alpha}_\xi \end{bmatrix} + [\mathbf{X}_\gamma : \mathbf{Z}_\gamma] \begin{bmatrix} \beta_\gamma \\ \boldsymbol{\alpha}_\gamma \end{bmatrix} + [\mathbf{X}_\delta : \mathbf{Z}_\delta] \begin{bmatrix} \boldsymbol{\beta}_\delta \\ \boldsymbol{\alpha}_\delta \end{bmatrix}$$

where

$$\begin{aligned}
&\mathbf{X}_\xi = (\mathbf{1}_T \otimes \mathbf{I}_\xi)\mathbf{U}_{\xi n} = \mathbf{1}_{TS}, && \beta_\xi = \mathbf{U}_{\xi n}^{'} \boldsymbol{\xi} = \mathbf{1}_S^{'} \boldsymbol{\xi} \\
&\mathbf{Z}_\xi = (\mathbf{1}_T \otimes \mathbf{I}_\xi)\mathbf{U}_{\xi r} = \mathbf{1}_T \otimes \mathbf{U}_{\xi r}, && \boldsymbol{\alpha}_\xi = \mathbf{U}_{\xi r}^{'} \boldsymbol{\xi}, \\
&\mathbf{X}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma n} = [\mathbf{1}_{TS} : \mathbf{t}^* \otimes \mathbf{1}_S], && \boldsymbol{\beta}_\gamma = \mathbf{U}_{\gamma n}^{'} \boldsymbol{\gamma} = [\mathbf{1}_T : \mathbf{t}^*]^{'} \boldsymbol{\gamma}, \\
&\mathbf{Z}_\gamma = (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\mathbf{U}_{\gamma r} = \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S, && \boldsymbol{\alpha}_\gamma = \mathbf{U}_{\gamma r}^{'} \boldsymbol{\gamma}, \\
&\mathbf{X}_\delta = \mathbf{U}_{\delta n} = [\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{U}_{\xi r}], && \boldsymbol{\beta}_\delta = \mathbf{U}_{\delta n}^{'} \boldsymbol{\delta}, \\
&\mathbf{Z}_\delta = \mathbf{U}_{\delta r} = [\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r}], && \boldsymbol{\alpha}_\delta = \mathbf{U}_{\delta r}^{'} \boldsymbol{\delta}.
\end{aligned}$$

Consequently, this model can be re-expressed as

$$\begin{aligned}
\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_{TS})\beta_\xi + (\mathbf{1}_T \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\xi + [\mathbf{1}_{TS} : \mathbf{t}^* \otimes \mathbf{1}_S]\boldsymbol{\beta}_\gamma + (\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)\boldsymbol{\alpha}_\gamma \\
+ [\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{U}_{\xi r}]\boldsymbol{\beta}_\delta + (\mathbf{U}_{\gamma r} \otimes \mathbf{U}_{\xi r})\boldsymbol{\alpha}_\delta.
\end{aligned}$$

where $\boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \sigma_\xi^2 \widetilde{\boldsymbol{\Sigma}}_\xi^{-1})$, $\boldsymbol{\alpha}_\gamma \sim N(\mathbf{0}, \sigma_\gamma^2 \widetilde{\boldsymbol{\Sigma}}_\gamma^{-1})$ and $\boldsymbol{\alpha}_\delta \sim N(\mathbf{0}, \sigma_\delta^2 \widetilde{\boldsymbol{\Sigma}}_\delta^{-1})$.

To obtain the identifiable model of Equation (12), the repeated columns $\mathbf{1}_{TS}$ (corresponding to $\boldsymbol{\beta}_\gamma$), $\mathbf{1}_T \otimes \mathbf{U}_{\xi r}$, $\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S$ and $\mathbf{t}^* \otimes \mathbf{1}_S$ (corresponding

to $\boldsymbol{\beta}_\delta$) must be removed, which is equivalent to set $\mathbf{1}_S^{'}\boldsymbol{\xi} = 0$, $\mathbf{1}_T^{'}\boldsymbol{\gamma} = 0$ and $[\mathbf{1}_{TS} : \mathbf{1}_T \otimes \mathbf{U}_{\xi r} : \mathbf{U}_{\gamma r} \otimes \mathbf{1}_S : \mathbf{t}^* \otimes \mathbf{1}_S]^{'}\boldsymbol{\delta} = \mathbf{0}$.

Similar to the RW1 case, it can be shown that:

- $\mathbf{1}_S^{'}\boldsymbol{\xi} = 0 \Longleftrightarrow \sum_{i=1}^{S} \xi_i = 0$, $\mathbf{1}_T^{'}\boldsymbol{\gamma} = 0 \Longleftrightarrow \sum_{t=1}^{T} \gamma_t = 0$ and $\mathbf{1}_{TS}^{'}\boldsymbol{\delta} = 0 \Longleftrightarrow \sum_{i=1}^{S}\sum_{t=1}^{T} \delta_{it} = 0$.
- $(\mathbf{t}^* \otimes \mathbf{1}_S)^{'}\boldsymbol{\delta} = 0 \Longleftrightarrow (\mathbf{1}_S^{'}, 2\mathbf{1}_S^{'}, \ldots, T\mathbf{1}_S^{'})\boldsymbol{\delta} = 0 \Longleftrightarrow \sum_{i=1}^{S}\sum_{t=1}^{T} t\delta_{it} = 0$.
- $(\mathbf{1}_T \otimes \mathbf{U}_{\xi r})^{'}\boldsymbol{\delta} = \mathbf{0} \Longleftrightarrow \mathbf{U}_{\xi r}^{'} \begin{pmatrix} \sum_{t=1}^{T} \delta_{1t} \\ \vdots \\ \sum_{t=1}^{T} \delta_{St} \end{pmatrix} = \mathbf{0} \Longleftrightarrow \sum_{t=1}^{T} \delta_{it} = 0, \forall i.$
- Finally,

$$(\mathbf{U}_{\gamma r} \otimes \mathbf{1}_S)^{'}\boldsymbol{\delta} = \mathbf{0} \Longleftrightarrow \mathbf{U}_{\gamma r}^{'} \begin{pmatrix} \sum_{i=1}^{S} \delta_{1i} \\ \vdots \\ \sum_{i=1}^{S} \delta_{Ti} \end{pmatrix} = \mathbf{0},$$

$\mathbf{U}_{\gamma r}^{'}$ is a $(T-2)\times T$ matrix with rank $T-2$, and the previous homogenous linear system has an infinite number of solutions. However, adding both $\sum_{i=1}^{S}\sum_{t=1}^{T} \delta_{it} = 0$ and $\sum_{i=1}^{S}\sum_{t=1}^{T} t\delta_{it} = 0$ sum-to-zero constraints to the linear system

$$\begin{bmatrix} \mathbf{U}_{\gamma r}^{'} \\ \mathbf{1}_T^{'} \\ \mathbf{t}^{*'} \end{bmatrix} \begin{pmatrix} \sum_{i=1}^{S} \delta_{i1} \\ \vdots \\ \sum_{i=1}^{S} \delta_{iT} \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix} \Longleftrightarrow \begin{pmatrix} \sum_{i=1}^{S} \delta_{i1} \\ \vdots \\ \sum_{i=1}^{S} \delta_{iT} \end{pmatrix} = \begin{pmatrix} 0 \\ \vdots \\ 0 \end{pmatrix} \Longleftrightarrow \sum_{i=1}^{S} \delta_{it} = 0, \forall t.$$

The reader should note that if the Leroux et al. (1999) reparameterization is used, the same sum-to-zero constraints have to be considered because the linear combination $\sum_{i=1}^{S} \xi_i$ is in the span of the intercept.

Appendix B

In this section we provide the constraints for interactions of Type I, II, and III.

Appendix B1: RW1

Given the spatio-temporal model of Equation (8)

$$\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_T \otimes \mathbf{I}_\xi)\boldsymbol{\xi} + (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\boldsymbol{\gamma} + \mathbf{I}_\delta\boldsymbol{\delta},$$

where η is the log of the global risk, the spatial random effect $\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2\mathbf{Q}_\xi^-)$ follows an ICAR distribution, the temporal random effect $\boldsymbol{\gamma} \sim N(\mathbf{0}, \sigma_\gamma^2\mathbf{Q}_\gamma^-)$ follows a RW1 distribution.

1. If the interaction effects are unstructured in space and time, that is, the interaction is of Type I with $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2\mathbf{I}_\delta)$, the linear constraints that make this model identifiable are

$$\boxed{\sum_{i=1}^{S}\xi_i = 0, \quad \sum_{t=1}^{T}\gamma_t = 0 \qquad \text{and} \qquad \sum_{t=1}^{T}\sum_{i=1}^{S}\delta_{it} = 0}$$

2. If the interaction effects are unstructured in space and structured in time, that is, the interaction is of Type II with $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2(\mathbf{Q}_\gamma \otimes \mathbf{I}_\xi)^-)$, the linear constraints that make this model identifiable are

$$\boxed{\sum_{i=1}^{S}\xi_i = 0, \quad \sum_{t=1}^{T}\gamma_t = 0 \qquad \text{and} \qquad \sum_{t=1}^{T}\delta_{it} = 0, \quad i = 1, \ldots, S.}$$

3. If the interaction effects are structured in space and unstructured in time, that is, the interaction is of Type III with $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2(\mathbf{I}_\gamma \otimes \mathbf{Q}_\xi)^-)$, the linear constraints that make this model identifiable are

$$\boxed{\sum_{i=1}^{S}\xi_i = 0, \quad \sum_{t=1}^{T}\gamma_t = 0 \qquad \text{and} \qquad \sum_{i=1}^{S}\delta_{it} = 0, \quad t = 1, \ldots, T.}$$

Appendix B2: RW2

Given the spatio-temporal model of Equation (8)

$$\log(\mathbf{r}) = (\mathbf{1}_{TS})\eta + (\mathbf{1}_T \otimes \mathbf{I}_\xi)\boldsymbol{\xi} + (\mathbf{I}_\gamma \otimes \mathbf{1}_S)\boldsymbol{\gamma} + \mathbf{I}_\delta\boldsymbol{\delta},$$

where η is the log of the global risk, the spatial random effect $\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2\mathbf{Q}_\xi^-)$ follows an ICAR distribution, the temporal random effect $\boldsymbol{\gamma} \sim N(\mathbf{0}, \sigma_\gamma^2\mathbf{Q}_\gamma^-)$ follows a RW2 distribution.

1. If the interaction effects are unstructured in space and time, that is, the interaction is of Type I with $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2\mathbf{I}_\delta)$, the linear constraints that

make this model identifiable are

$$\boxed{\sum_{i=1}^{S}\xi_i = 0, \quad \sum_{t=1}^{T}\gamma_t = 0, \qquad \text{and} \qquad \begin{array}{l}\sum_{t=1}^{T}\sum_{i=1}^{S}\delta_{it} = 0,\\ \sum_{t=1}^{T}\sum_{i=1}^{S} t\delta_{it} = 0.\end{array}}$$

2. If the interaction effects are unstructured in space and structured in time, that is, the interaction is of Type II with $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2(\mathbf{Q}_\gamma \otimes \mathbf{I}_\xi)^-)$, the linear constraints that make this model identifiable are

$$\boxed{\sum_{i=1}^{S}\xi_i = 0, \sum_{t=1}^{T}\gamma_t = 0, \sum_{t=1}^{T} t\gamma_t = 0 \text{ and } \sum_{t=1}^{T}\delta_{it} = 0, \quad \text{for} \quad i = 1, \ldots, S.}$$

3. If the interaction effects are structured in space and unstructured in time, that is, the interaction is of Type III with $\boldsymbol{\delta} \sim N(\mathbf{0}, \sigma_\delta^2(\mathbf{I}_\gamma \otimes \mathbf{Q}_\xi)^-)$, the linear constraints that make this model identifiable are

$$\boxed{\sum_{i=1}^{S}\xi_i = 0, \quad \sum_{t=1}^{T}\gamma_t = 0 \qquad \text{and} \qquad \sum_{i=1}^{S}\delta_{it} = 0, \quad \text{for} \quad t = 1, \ldots, T.}$$

Appendix C

This section shows that the variance of the intercept is inflated if the LCAR prior is used for the spatial random effect and the model is fitted using PQL with appropriate constraints. If the model is reparameterized, the variance is not inflated. It also shows that the ICAR prior does not present this problem. We consider this spatial linear mixed model:

$$\mathbf{Y} = (\mathbf{1}_S)\eta + \boldsymbol{\xi} + \boldsymbol{\epsilon}. \tag{13}$$

Appendix C: ICAR prior

Assume an ICAR prior for the spatial random effect $\boldsymbol{\xi}$, that is, $\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2\mathbf{Q}_\xi^-)$, and $\boldsymbol{\epsilon} \sim N(\mathbf{0}, \sigma_\epsilon^2\mathbf{I})$. Then

$$\text{var}(Y) = \mathbf{V} = \sigma_\epsilon^2\mathbf{I}_S + \sigma_\xi^2\mathbf{Q}_\xi^- = \sigma_\epsilon^2(\mathbf{I}_S + k\mathbf{U}_\xi\boldsymbol{\Sigma}_\xi^-\mathbf{U}_\xi')$$

where $\mathbf{I}_S$ is an $S \times S$ identity matrix, $\mathbf{U}_\xi = [\mathbf{U}_{\xi n} : \mathbf{U}_{\xi r}] = [\mathbf{1}_S/\sqrt{S} : \mathbf{U}_{\xi r}]$, and $k = \sigma_\xi^2/\sigma_\epsilon^2$. Clearly

$$\mathbf{V}^{-1} = \frac{1}{\sigma_\epsilon^2}(\mathbf{I}_S + k\mathbf{U}_\xi \boldsymbol{\Sigma}_\xi^- \mathbf{U}_\xi')^{-1} = \frac{1}{\sigma_\epsilon^2}\mathbf{U}_\xi(\mathbf{I}_S + k\boldsymbol{\Sigma}_\xi^-)^{-1}\mathbf{U}_\xi'.$$

Then

$$\begin{aligned}(\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}) &= \frac{1}{\sigma_\epsilon^2}\mathbf{1}_S'\mathbf{U}_\xi(\mathbf{I}_S + k\boldsymbol{\Sigma}_\xi^-)^{-1}\mathbf{U}_\xi'\mathbf{1}_S \\ &= \frac{1}{\sigma_\epsilon^2}\left[S/\sqrt{S}, 0, \ldots, 0\right] \operatorname{diag}(1, 1 + k/d_2, \ldots, 1 + k/d_S)^{-1} \left[S/\sqrt{S}, 0, \ldots, 0\right]' \\ &= \frac{S}{\sigma_\epsilon^2}\end{aligned}$$

where $\mathbf{X} = 1_S, d_2, \ldots, d_S$ are the non-null eigenvalues of $\mathbf{Q}_\xi$ (note that $d_1 = 0$), and finally

$$\operatorname{var}(\hat{\eta}) = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})^{-1} = \frac{\sigma_\epsilon^2}{S}.$$

Now reparameterize Model (13). Then

$$\mathbf{Y} = (\mathbf{1}_S)\eta + \mathbf{U}_{\xi r}\boldsymbol{\alpha}_\xi + \boldsymbol{\epsilon},$$

where $\boldsymbol{\alpha} \sim N(\mathbf{0}, \sigma_\xi^2 \widetilde{\boldsymbol{\Sigma}}_\xi^{-1})$. Then,

$$\operatorname{var}(Y) = \mathbf{V} = \sigma_\epsilon^2(\mathbf{I}_S + k\mathbf{U}_{\xi r}\widetilde{\boldsymbol{\Sigma}}_\xi^{-1}\mathbf{U}_{\xi r}').$$

Using matrix inversion formulas and noting that $\mathbf{U}_{\xi r}'\mathbf{U}_{\xi r} = \mathbf{I}_{S-1}$, it follows that

$$\begin{aligned}\mathbf{V}^{-1} &= \left[\sigma_\epsilon^2(\mathbf{I}_S + k\mathbf{U}_{\xi r}\widetilde{\boldsymbol{\Sigma}}_\xi^{-1}\mathbf{U}_{\xi r}')\right]^{-1} = \frac{1}{\sigma_\epsilon^2}\left[\mathbf{I}_S - \mathbf{I}_S\mathbf{U}_{\xi r}(\mathbf{U}_{\xi r}'\mathbf{I}_S\mathbf{U}_{\xi r} + k^{-1}\widetilde{\boldsymbol{\Sigma}}_\xi)^{-1}\mathbf{U}_{\xi r}'\mathbf{I}_S\right] \\ &= \frac{1}{\sigma_\epsilon^2}\left[\mathbf{I}_S - \mathbf{U}_{\xi r}(\mathbf{I}_{S-1} + k^{-1}\widetilde{\boldsymbol{\Sigma}}_\xi)^{-1}\mathbf{U}_{\xi r}'\right],\end{aligned}$$

and

$$\begin{aligned}(\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}) &= \frac{1}{\sigma_\epsilon^2}\mathbf{1}_S'\left[\mathbf{I}_S - \mathbf{U}_{\xi r}(\mathbf{I}_{S-1} + k^{-1}\widetilde{\boldsymbol{\Sigma}}_\xi)^{-1}\mathbf{U}_{\xi r}'\right]\mathbf{1}_S \\ &= \frac{1}{\sigma_\epsilon^2}\left[\mathbf{1}_S'\mathbf{1}_S - \mathbf{1}_S'\mathbf{U}_{\xi r}(\mathbf{I}_{S-1} + k^{-1}\widetilde{\boldsymbol{\Sigma}}_\xi)^{-1}\mathbf{U}_{\xi r}'\mathbf{1}_S\right]. \\ &= \frac{1}{\sigma_\epsilon^2}(S - 0) = \frac{S}{\sigma_\epsilon^2},\end{aligned}$$

because $\mathbf{1}_S$ and the columns of $\mathbf{U}_{\xi r}$ are orthogonal. Consequently,

$$\text{var}(\hat{\eta}) = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})^{-1} = \frac{\sigma_\epsilon^2}{S},$$

and the variance is the same if the model is fitted with appropriate sum-to-zero constraints or in the reparameterized version.

Appendix C: LCAR prior

Assume an LCAR prior for the spatial random effect $\boldsymbol{\xi}$, that is $\boldsymbol{\xi} \sim N(\mathbf{0}, \sigma_\xi^2 \mathbf{D}_\xi^{-1})$, $\mathbf{D} = \lambda_\xi \mathbf{Q}_\xi + (1-\lambda_\xi)\mathbf{I}_S$. Then

$$\begin{aligned}\text{var}(Y) = \mathbf{V} &= \sigma_\epsilon^2 \mathbf{I}_S + \sigma_\xi^2 \mathbf{D}_\xi^{-1} = \sigma_\epsilon^2 (\mathbf{I}_S + k\mathbf{D}^{-1}) \\ &= \sigma_\epsilon^2 \left[\mathbf{I}_S + k\mathbf{U}_\xi((1-\lambda_\xi)\mathbf{I}_S + \lambda_\xi \boldsymbol{\Sigma}_\xi)^{-1}\mathbf{U}_\xi'\right]\end{aligned}$$

where as before, $\mathbf{I}_S$ is an $S \times S$ identity matrix, $\mathbf{U}_\xi = [\mathbf{U}_{\xi n} : \mathbf{U}_{\xi r}] = [\mathbf{1}_S/\sqrt{S} : \mathbf{U}_{\xi r}]$, and $k = \sigma_\xi^2/\sigma_\epsilon^2$. Clearly

$$\begin{aligned}\mathbf{V}^{-1} &= \frac{1}{\sigma_\epsilon^2}\left[\mathbf{I}_S + k\mathbf{U}_\xi((1-\lambda_\xi)\mathbf{I}_S + \lambda_\xi \boldsymbol{\Sigma}_\xi)^{-1}\mathbf{U}_\xi'\right]^{-1} \\ &= \frac{1}{\sigma_\epsilon^2}\mathbf{U}_\xi\left[\mathbf{I}_S + k((1-\lambda_\xi)\mathbf{I}_S + \lambda_\xi \boldsymbol{\Sigma}_\xi)^{-1}\right]^{-1}\mathbf{U}_\xi' \\ &= \frac{1}{\sigma_\epsilon^2}\mathbf{U}_\xi \text{diag}\left(1 + \frac{k}{\lambda_\xi d_1 + (1-\lambda_\xi)}, \ldots, 1 + \frac{k}{\lambda_\xi d_S + (1-\lambda_\xi)}\right)^{-1}\mathbf{U}_\xi'\end{aligned}$$

Note that the eigenvalues of the precision matrix $\lambda_\xi \mathbf{Q}_\xi + (1 - \lambda_\xi \mathbf{I}_S)$ are all positive whenever $\lambda_\xi < 1$. They take the form $\lambda_\xi d_i + (1-\lambda_\xi)$, $i = 1, \ldots, S$, where $d_1 = 0$ and $d_i > 0$, $i = 2, \ldots, S$ are the eigenvalues of $\mathbf{Q}_\xi$. Then

$$\begin{aligned}(\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}) &= \frac{1}{\sigma_\epsilon^2}\mathbf{1}_S'\mathbf{U}_\xi \text{diag}\left(1 + \frac{k}{(1-\lambda_\xi)}, \ldots, 1 + \frac{k}{\lambda_\xi d_S + (1-\lambda_\xi)}\right)^{-1}\mathbf{1}_S \\ &= \frac{1}{\sigma_\epsilon^2}\left[S/\sqrt{S}, 0, \ldots, 0\right] \text{diag}\left(1 + \frac{k}{(1-\lambda_\xi)}, \ldots, 1 + \frac{k}{\lambda_\xi d_S + (1-\lambda_\xi)}\right)^{-1}\left[S/\sqrt{S}, 0, \ldots, 0\right]' \\ &= \frac{S}{\sigma_\epsilon^2}\left(1 + \frac{k}{(1-\lambda_\xi)}\right)^{-1}.\end{aligned}$$

Finally

$$\text{var}(\hat{\eta}) = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})^{-1} = \frac{\sigma_\epsilon^2}{S}\left(1 + \frac{k}{(1-\lambda_\xi)}\right).$$

Now reparameterize Model (13). Then

$$\mathbf{Y} = (\mathbf{1}_S)\eta + \mathbf{U}_{\xi r}\boldsymbol{\alpha}_\xi + \boldsymbol{\epsilon},$$

where $\boldsymbol{\alpha}_\xi \sim N(\mathbf{0}, \sigma_\xi^2(\lambda_\xi \widetilde{\boldsymbol{\Sigma}}_\xi + (1-\lambda_\xi)\mathbf{I}_{S-1})^{-1})$. Denoting by $\widetilde{\mathbf{D}} = \lambda_\xi \widetilde{\boldsymbol{\Sigma}}_\xi + (1-\lambda_\xi)\mathbf{I}_{S-1}$,

$$\text{var}(Y) = \mathbf{V} = \sigma_\epsilon^2(\mathbf{I}_S + k\mathbf{U}_{\xi r}\widetilde{\mathbf{D}}^{-1}\mathbf{U}'_{\xi r}).$$

Using matrix inversion formulas and taking into account that $\mathbf{U}'_{\xi r}\mathbf{U}_{\xi r} = \mathbf{I}_{S-1}$,

$$\begin{aligned}\mathbf{V}^{-1} &= \left[\sigma_\epsilon^2(\mathbf{I}_S + k\mathbf{U}_{\xi r}\widetilde{\mathbf{D}}^{-1}\mathbf{U}'_{\xi r})\right]^{-1} = \frac{1}{\sigma_\epsilon^2}\left[\mathbf{I}_S - \mathbf{I}_S\mathbf{U}_{\xi r}(\mathbf{U}'_{\xi r}\mathbf{I}_S\mathbf{U}_{\xi r} + k^{-1}\widetilde{\mathbf{D}})^{-1}\mathbf{U}'_{\xi r}\mathbf{I}_S\right] \\ &= \frac{1}{\sigma_\epsilon^2}\left[\mathbf{I}_S - \mathbf{U}_{\xi r}(\mathbf{I}_{S-1} + k^{-1}\widetilde{\mathbf{D}})^{-1}\mathbf{U}'_{\xi r}\right],\end{aligned}$$

and

$$\begin{aligned}(\mathbf{X}'\mathbf{V}^{-1}\mathbf{X}) &= \frac{1}{\sigma_\epsilon^2}\mathbf{1}'_S\left[\mathbf{I}_S - \mathbf{U}_{\xi r}(\mathbf{I}_{S-1} + k^{-1}\widetilde{\mathbf{D}})^{-1}\mathbf{U}'_{\xi r}\right]\mathbf{1}_S \\ &= \frac{1}{\sigma_\epsilon^2}\left[\mathbf{1}'_S\mathbf{1}_S - \mathbf{1}'_S\mathbf{U}_{\xi r}(\mathbf{I}_{S-1} + k^{-1}\widetilde{\mathbf{D}})^{-1}\mathbf{U}'_{\xi r}\mathbf{1}_S\right]. \\ &= \frac{1}{\sigma_\epsilon^2}(S-0) = \frac{S}{\sigma_\epsilon^2}\end{aligned}$$

Consequently,

$$\text{var}(\hat{\eta}) = (\mathbf{X}'\mathbf{V}^{-1}\mathbf{X})^{-1} = \frac{\sigma_\epsilon^2}{S}.$$

Thus it is clear that if the model is fitted with sum-to-zero constraints the variance of the intercept estimator is inflated. This is avoided by reparameterizing the model.

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