Spatial association of bovine TB in wildlife badgers (Meles meles) and cattle.

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As humans have moved cattle around the world, bovine tuberculosis has also spread. It now has a global distribution and is especially problematic in Africa, where it was introduced by European livestock in the 1800s. The disease infects vital wildlife populations, such as buffalo and lions in Kruger National Park in South Africa, where tourism is an integral part of local economies.

In Ireland and the UK it infects cattle and the wildlife badgers (Meles meles) and the latter have been implicated in the spread of the disease in cattle. To understand how the disease spreads and to inform control policy, we determine here the joint spatial pattern in cattle and badgers. Previous work (Kelly, McGrath and More 2010; Kelly and More 2011) has established that TB spatially clusters in badgers and separately in cattle and the practical spatial ranges at which this occurs. Here we look at the spatial clustering pattern across the species. The analysis involves fitting linear geostatistical models (LGM's) with exponential covariance structure, adjusting where necessary for anisotropy.

Introduction

Bovine tuberculosis (bTB) is a disease that affects both cattle and badgers (see Figure below of these animals) and the latter are implicated in spreading the disease in cattle. Other countries have experienced problems with wildlife acting as a reservoir of *M. bovis* infection for domestic stock, including white-tailed deer in North America and possums in New Zealand. In developing countries, such as those in Africa, *M. bovis* affects both farmed and wild animals, with accompanying economic, environmental and social consequences. Infection of wildlife contributes to failure of TB eradication programmes. In Africa, consumption of raw milk and raw meat, and bushmeat consumption as a cheap source of proteins, represents one of the principal routes for human infection with bTB which is widespread (Etter *et al.* 2006). In this session we discuss modeling the effect of different interventions on badger-cattle transmission dynamics as well as spatial distribution of the disease - thus informing the design of control strategies (Griffin *et al.* 2005; Donnelly *et al.* 2006, 2007; Bourne *et al.* 2007; Jenkins, Woodroffe and Donnelly 2008, 2010). Without good estimates of epidemiological parameters and knowledge of the associated uncertainty in them, control programmes and preventive measures cannot be designed optimally nor evaluated appropriately. Spatial statistical methods applied to this problem are described (Kelly, McGrath and More 2010; Kelly and More 2010: Kelly 2011) and are applied in response to the complexities of the disease system - but always driven by the need to answer practical questions. Using h-likelihood methods (Lee, Nelder and Pawitan 2006), TB in cattle was shown to lower milk production in dairy herds (Boland, Kelly, Good and More 2010). However it was not related to udder health (Boland, Kelly, Good and More 2011) Will culling badgers always reduce the incidence of bovine TB in cattle? How can balance be maintained between the protection of farmer's livelihoods and the protection of wildlife and biodiversity? (Macdonald, Riordan and Mathews 2006; Paulsen *et al.* (eds), 2011). These are universal questions and in this session results from Ireland and the UK may be informative for other countries and for other disease control challenges. This paper presents spatial analyses that may also be of interest to researchers in environmental models where the methods are also applicable

The data

The data for this study are drawn from the Four Area Project (FAP), a formal badger removal project undertaken in Ireland from September 1997 to August 2002, to assess the effect of badger culling on the incidence of bovine tuberculosis (TB). The study design and its results are published in detail elsewhere in Griffin *et al.* (2005). Briefly, the FAP was conducted in matched removal and reference areas (average area of 245 km^2) in four counties in Ireland: Cork, Donegal, Kilkenny and Monaghan and badger culling was carried out proactively in the removal areas with minimal culling in the reference areas. These can be seen in the Figure below.

Here we consider herds in County Cork only, during the study period, as in Kelly (2011). A herd was regarded as positive for TB in any year if any animal in the herd tested positive for TB in that year by the Single Intradermal Comparative Tuberculin Test (SICTT) (Clegg *et al.* 2011). In addition we considered the covariates herd size and previous history of infection in a herd. As a herd may be located on multiple parcels of land, GIS co-ordinates of the herd are for the most part taken as the centroid of the main parcel of land of the herd.

Badger data is also taken from the FAP as in Kelly, McGrath and More (2010). Only data from County Cork is considered and we consider all badgers culled in the first year of the study for which the infection status, sex and age were known. The badger sett is the unit of analysis and number of badgers captured per sett is available as well as the GIS co-ordinates of the sett at capture. A sett was regarded as TB positive if any badger captured in the sett was TB positive.

Methods

Firstly, a logistic glm is fitted to the sett data using sett size (other covariates were not considered based on the results of Kelly, McGrath and More 2010) and Pearson residuals obtained. Secondly a logistic glm is fitted to the cattle data again using the covariates already established to be significant in Kelly and More (2010) or Kelly (2011). These were log of herd size (log(hs)) and previous history of infection (ph). The Pearson residuals from the model were obtained. Thirdly, the Pearson residuals for infected animals only are considered for further analyses.

Linear spatial geostatistical models (LGM's) with exponential covariance structure are fitted to the two sets of Pearson residuals separately (similar to Kelly, McGrath and More 2010; Kelly and More 2010; Kelly 2011). The residuals are assumed to be normally distributed but different models have different spatial covariance structure. Practical spatial ranges are estimated together with a measure of goodness-of-fit of the model -2 residual log(likelihood) AIC, or AICC (Schabenberger and Gotway 2005 Chapter 6).

Model (i): An LGM is fitted to the two sets of residuals combined. A fixed effect of animal is included in the model since the two sets of residuals may be of different order of magnitude and the practical spatial range is estimated together with measures of goodness-of-fit of the model as above. In this model the same spatial covariance exponential structure is fitted to all the animals of both species combined.

Model (ii): This model uses the same data as model (i). A fixed effect of animal is included but animal is assumed independent i.e. there is no covariance between badgers and cattle. One exponential covariance spatial structure is fitted to badgers and cattle combined.

Model (iii): This model uses the same data as model (i). A fixed effect of animal is included but animal is assumed independent i.e. no covariance between badgers and cattle. A different exponential covariance spatial structure is fitted to badgers and cattle.

The LGM model is given by: Let $r(s_i)$ be the residual for the infected animal at the ith location

s_i. Let $u(s_i)$ be a spatial random effect at location s_i. We assume the $u(s_i)$ follow an exponential isotropic covariance model F with (i,j)th element given by

$$Cov[u(s_i), u(s_j)] = \sigma^2[exp(-d_{ij}/\rho)]$$

where d_{ij} is the distance between the locations s_i and s_j. We thus have a Gaussian linear model with a constant term and a random effect $u(s_i)$ with spatial exponential covariance structure. The variance-covariance matrix of the data is modeled as

$$Var[r(s)] = F$$

The parameters σ^2 and ρ refer to the geostatistical parameters sill and "range", respectively. Covariance in this model reaches zero only asymptotically, thus the practical range is defined as the distance at which covariances are reduced to 5% of the sill i.e. 3ρ. Since we have repeated measures on cattle (data over 5 years), models including bovines have a nugget term. Thus, for the model with both species combined a nugget term is included by using

$$Var[r(s)] = \sigma_1^2 + F$$

Since the three models have the same mean structure but nested covariance structures, we can compare the three models by taking difference of -2 residual log(likelihood) and referring it to a χ^2 distribution with degrees of freedom the difference in number of covariance parameters in the models i.e. a likelihood ration type test. Since we are testing whether certain variance components are zero, the parameters lie on the boundary of the parameter space and thus we divide the p-value obtained from χ^2 by 2 (Self and Liang 1987; Littell, Milliken, Stroup and Wolfinger 2006).
All models are then re-fitted including possible terms for anisotropy i.e.

$$Cov[u(s_i), u(s_j)] = \sigma^2[-\theta_1|x_i - x_j|^{P_1} - \theta_2|y_i - y_j|^{p_2}]$$

where x and y denote eastings and northings of GIS co-ordinates respectively (Littell, Milliken, Stroup and Wolfinger 2006, Chapter 11). The models are again compared using the above methods.

The Gaussian and spherical covariance structures (Schabenberger and Gotway, 2005, Chapter 4; Littell *et al.* (2006) Chapter 11) are also fitted in all models to see if fit is improved. This is done by comparing AIC and AICC values of corresponding models.

Finally, the initial logistic glm's above are re-fitted to include the spatial co-ordinates x, y as fixed effects both for badger setts and cattle herds data.

The scale in all models is in km.

Effects with p-values < 0.05 are regarded as statistically significant.

Models are estimated and fitted using Proc Glimmix and Proc Mixed of SAS 9.2 version 9, SAS Institute Inc., Cary, NC, USA.

Results

Cattle : Over the 5 year period there were 1870 observations corresponding to 422 distinct herds. In the logistic non-spatial model, ph and log(hs) are statistically significant and observations on herd from year to year are correlated regardless of ph. (This is also true with year in model, although the models cannot be readily compared due to different fixed effects).
The data for models (i)-(iii) consisted of 83 cases i.e. 83 TB reports involving 68 distinct herds (i.e. 15 herds had more than 1 outbreak in the period 1).

Badgers: 207 setts were culled in the first year of badger culling in County Cork in period 1. The variable number of badgers culled in the sett constituted a significant fixed effect (p=.0037) in

the logistic model. The data for models (i)-(iii) consisted of 81 setts (81 had a badger with TB i.e. 39.1% of setts).

Model (i): The isotropic model gave partial sill 0.9301, $\rho = 0.0$ and nugget=0.2617. -2 res log likelihood model =478.5. A value $\rho = 0.0$ seems to imply observations separated by more than 0 km are not spatially correlated. However, the spatial parameter ρ was significantly different from zero by a likelihhod ratio type test. This was done by comparing -2 res log likelihood from the model fitting ρ, σ^2 and σ_1^2 to a model just fitting σ^2 and σ_1^2. The apparent contradiction may be due to just general spatial heterogeneity and a model with $\rho = 0$ and $\rho = \infty$ fit equally well. It may also be due to anisotropy.

When an exponential model with an anisotropy term was fitted, the model converged but the final Hessian was not positive definite. This covariance model was developed for a particular application by Littell, Milliken, Stroup and Wolfinger (2006, Chapter 11). At the last iteration -2 res log likelihood was 475.3 (3 additional parameters to the isotropic model), partial sill = 0.9511 and nugget = 0.2629 (similar to the isotropic model above). Comparing the models (i) with anisotropy terms included to not included via AIC or AICC they are somewhat similar. However the estimates of θ_1 and θ_2 were quite different - different in the two directions - again evidence of anisotropy. $\theta_1 = \infty$ in the x (easting) direction and $\theta_2 = 4.7514$ in the y (northing) direction, $p_1 = 4.1647$ and $p_2 = 0.1166$.

Model (ii): The isotropic or anisotropic model did not converge. We note however at the last iteration of the anisotropic model that $\theta_1 = 44.22$ in the x (easting) direction and $\theta_2 = 0.2227$ in the y (northing) direction, $p_1 = 2.3913$ and $p_2 = 0.01943$, $\sigma_1^2 = 0.3901$. So there is evidence of anisotropy. There is spatial correlation in both the x direction and to a lesser extent the y direction.

Model (iii): In the isotropic model convergence criteria are met but the final hessian is not positive definite. Model (iii) with anisotropy did not converge. However we note that at the last iteration for badgers $\theta_1 = 0.0$, $\theta_2 = 0.0$, $p_1 = 0.0$ and $p_2 = 0.0$ while for cattle $\theta_1 = 102.4$, $\theta_2 = 0.4744$, $p_1 = 2.8417$ and $p_2 = 0.01455$ and $\sigma_1^2 = 0.1173$.

In the initial logistic fixed effects model fitted to the badger data, with covariates spatial co-ordinates included, the number in the sett was a significant predictor of badger infection but x,y co-ordinates were not significant when this is accounted for.

In the initial logistic fixed effects model fitted to the cattle data, with covariates spatial co-ordinates included, log (hs) and ph have p-values < 0.05, the x coordinate was borderline significant and the y coordinate was not significant.

Discussion

Only data for the first year of the FAP for badgers is considered since the numbers of badgers captured in subsequent project years were too small to permit substantive analysis. Moreover, years were not amalgamated, to avoid possible distorting effects of recent badger culling on the distribution of infection (Tuyttens *et al.* 2000, Woodroffe *et al.* 2006) and to permit comparison with UK studies.

Since covariates such as herd size are important predictors of TB in cattle herds while this is not a relevant covariate for badger setts, and similarly number in sett is a significant predictor of sett infection and this is not relevant for cattle herds the effects of such explanatory variables are first removed from the response variable.

Secondly the residuals from the logistic models, separately for badgers and cattle were of a different scale. Thus all models included a categorical variable 'species' (i.e observation is either cattle herd or badger sett). Model (i) cannot be compared to a model fitted separately to cattle and to badgers as the mean structure is different (Schabenberger and Gotway 2005, Chapter 11). The results from these latter models are not presented here and conclusions from them are in agreement with Kelly, McGrath and More (2010) and Kelly and More (2010).

Convergence issues and Hessian issues in models (i)-(iii) :

Model (i): In the isotropic model some variance components are zero but is not directly possible to drop these terms from the model. In the anisotropic model an examination of why the convergence criteria are met but the final Hessian is not positive definite seems to be due to some final estimates of parameters are equal to the boundary constraints. Some variance components are zero but it is not directly possible to drop these terms from the model. It also indicates that parameter estimates for badgers and cattle are on a different scale.

Model (ii): Model did not converge - isotropic or anisotropic. An investigation of this problem revealed it may be due to covariance parameters for badgers and cattle are on a different scale. Re-scaling the effects in the model so that the covariance parameters are on the same scale was not directly possible.

Model (iii): The reason for a non-positive definite Hessian in the isotropic model may be due to final estimates of parameters equal to the boundary constraints. Some variance components are zero but is not directly possible to drop these terms from the model. Non-convergence in the anisotropic model is as described for model (ii)

Model (i) will give some kind of average of the spatial ranges for infected badger-infected badger, infected badger-infected cattle and infected cattle-infected cattle. This model gave $\rho = 0.0$ or equivalently $\rho = \infty$. When anisotropy is accounted for there is spatial correlation in the x-direction and some in the y-direction.

In model (iii) the indications are that when sett size is accounted for, there is little spatial correlation between badger setts. The values of -2 res log likelihood indicates this model may be a good fit in comparison to model (i) even when number of parameters is adjusted for.

In the logistic fixed effects model fitted to the badger data, with covariates spatial co-ordinates included, sett size was significant predictor while x, y coordinates are not. Kelly, McGrath and more (2010)) did not account for sett size and thus the results here are not a contradiction. They showed showed when only strain data is considered there is anisotropy in badgers and then this effect was small in County Cork. Moreover not all badgers were strain typed. For cattle, herd size and previous history of infection are important predictors, with borderline significance of the x coordinate but not the y. Comparing fixed effects models to spatial models, Cressie [1991, Chapter 4, 6], noted that anisotropy in one models error process cannot be distinguished from non-stationarity in another models mean process and there is non-identifiability of the deterministic and stochastic components of the models described in the Methods. Thus different models may fit equally well but practical conclusions from the models may be similar (Kelly(2011)).

Many other models were fitted separately to badgers and cattle and to the combined data. We follow the recommendations of Schabenberger and Gotway (2005, Chapter 11) in choosing the 'best' model: 'When fitting several competing models, for example, models that differ in their covariance structure ....One should not necessarily adopt the model with the smallest information criterion, but a model in the group that is parsimonious and interpretable'. However the overall results indicate that anisotropy terms are required in the model for cattle (as in Kelly (2011)). In cattle there is evidence of anisotropy, in badgers there is no anisotropy or remaining spatial correlation when sett size has been accounted for.

To investigate anisotropy further, all analyses should be carried out for the direction of spatial correlation for cattle in County Cork found in Kelly (2010) and Kelly (2011). However this will dilute the data and analysis will be reduced to perhaps 20 setts and 20 herds. This will be a subject of future work.

The models presented here are attempts to modeling infection between species and represent difficult computational and interpretability problems. Further work is needed in developing models

that will address this issue. A modeling approach enhances more descriptive data summaries such as K-functions or intensity functions as the effect of covariates can be taken into account more readily.

The TB status of cattle herds here is based on herd restriction due to TB. We note there may be a time lag in reporting of TB in cattle and there may be an incubation period. In addition badger data represent culled setts. These issues are discussed in Griffin *et al.* (2005) and Kelly *et al.* (2008)

It has already been established Griffin *et al.* (2005) and Bourne *et al.* (2007) that proactive culling of badgers decreases TB incidence in cattle herds.

The question of reactive badger culling remains unresolved in relation to scale and direction and whether it increases TB levels in badgers. These issues are outside the scope of this paper and there is an extensive literature (Kelly *et al.* 2008; Donnelly et al. 2006, Donnelly et al. 2007, Jenkins, Woodroffe and Donnelly 2010). Kelly *et al.* 2008 present a long-term observational study (over 16 years) from East Offaly, an area in the midlands of Ireland. The study indicates little perturbation effect when reactive policy is considered on a case-by-case and is localized. Jenkins, Woodroffe and Donnelly (2010) found that the reductions in cattle TB incidence achieved by repeated badger culling were not sustained in the long term after culling ended. For the East Offaly study and the FAP, they observed that badger culling was ongoing throughout (and in the case of East Offaly some periods having more intensive culling than others). However TB levels in East Offaly were consistently low in latter years of the study (between 5%-6% in all control type areas). Moreover reactive culling was minimal in the FAP in removal areas and perhaps levels could correspond to unofficial culling in the RBCT (Bourne *et al.* 2007). In Ireland land occupier compliance in the FAP was higher. This issue has been dealt with already extensively in the literature and many apparent difference are perhaps explainable by different policies in the UK and Ireland.

Farming plays an important part in Irish economy. In addition, good farming practice and biodiversity all contribute to the control of TB (OCorry-Crowe, Eves and Hayden 1993; Smal 1995; Griffin *et al.* 2005; Bourne *et al.* 2007; Woodroffe *et al.* 2006; MacDonald, Riordan and Mathews 2006).

Climatic factors may also affect TB incidence (Pfeiffer *et al.* 2008).

In conclusion, the anisotropy results here indicate the direction of culling is important and that a single scale may not be suitable for cattle, badgers separately or combined. This was already established in Kelly, McGrath and More (2010), Kelly and More (2010), Kelly (2010) and Kelly (2011).

There are numerous biological issues associated with the interpretation of these data. Many are discussed already in Griffin *et al.* (2005) and Kelly, McGrath and More (2010) and Kelly and More (2010). To address these is outside the scope of this paper. For example, due to both the nature of the infection and current diagnostic capacity, false negative cattle (SICTT negative but TB infected) are much more likely than false positive cattle (SICTT positive but not TB infected) with the most recent Irish data suggesting a sensitivity and specificity of 52.960.8% and 99.299.8%, respectively (Clegg *et al.* 2011). There are similar issues in relation to testing of badgers (Kelly, McGrath and More (2010) and Kelly and More (2010).

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