

Bayesian Change-point Mixed Models Applied to Data on Outpatient Antibiotic Use in Europe

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1 Introduction

Resistance to antibiotics is a major public-health problem and antibiotic use is being increasingly recognized as the main selective pressure driving this resistance. Quarterly data on outpatient antibiotic use are available from 25 European countries for the period 1997-2008 through the European project ESAC (www.esac.ua.ac.be). Antibiotic use was measured as defined daily doses per 1000 inhabitants per day (DID) for different Anatomical Therapeutic Chemical (ATC) levels, according to the WHO ATC classification. In this abstract we focus on the use of Tetracyclines. The main objective is to develop an appropriate statistical model to assess the significance of country-specific trends in Europe and to identify change-points, while accounting for country-specific global use as well as seasonal effects. The application of the model yields new important insights in the evolution of outpatient antibiotic use in Europe.

2 Methods

Change-point models have previously been used in several applications to model longitudinal data (see e.g. Ghosh et al., 2007; Dominicus et al., 2008). In this paper, an adaptive Bayesian linear spline model is proposed, where the number of knots (change-points) and their location are data-driven and determined by the deviance information criterion (DIC).

A linear model with country-specific mean can be written as

$$\begin{aligned} Y_{ij} &= \mu_i(t_{ij}) + \varepsilon_{ij} \\ &= \mu_i^T(t_{ij}) + \mu_i^S(t_{ij}) + \varepsilon_{ij}, \quad i = 1, 2, \dots, N; j = 1, 2, \dots, n_i \end{aligned} \quad (1)$$

where, Y_{ij} is the antibiotic use in DID for country i at time points t_{ij} , $\mu_i^T(t_{ij})$ is the trend component, $\mu_i^S(t_{ij})$ is the seasonal component and ε_{ij} is the measurement error which is assumed to be normally distributed with mean zero and constant variance σ_ε^2 . The country-specific mean components $\mu_i^T(t_{ij})$ and $\mu_i^S(t_{ij})$ are modelled as,

$$\begin{aligned} \mu_i^T(t_{ij}) &= (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \mu^{CP}(t_{ij}) \\ \mu_i^S(t_{ij}) &= (\beta_0^S + b_{0i}^S + \beta_1^S t_{ij}) \text{Sin}(\omega t_{ij} + \delta), \end{aligned} \quad (2)$$

where $\mu^{CP}(t_{ij})$ is a change-point component. If $\mu^{CP}(t_{ij})=0$ then there is no change point, β_0 is the intercept, β_1 is the regression coefficient describing the marginal linear time trend (t), β_0^S is the fixed amplitude, β_1^S is the amplitude varying over time, ω (in radians) is the frequency, δ (in radians) is the phase shift or phase angle, $\mathbf{b}_i = (b_{0i}, b_{1i}, b_{0i}^S)$ is the country-specific vector of random effects, ε_i is an n_i -dimensional vector of residuals, and we assume $b_i \sim N(0, D)$ and $\varepsilon_i \sim N(0, \Sigma_i)$. The matrix D is a covariance matrix with elements $d_{ij} = d_{ji}$ and Σ_i is an $n_i \times n_i$ covariance matrix. Often, Σ_i is assumed to be equal to $\sigma_\varepsilon^2 \mathbf{I}_{n_i}$, where \mathbf{I}_{n_i} is the n_i -dimensional identity matrix.

$$\mu^{CP}(t_{ij}) = \sum_{k=1}^K (\beta_{(k+1)} + b_{(k+1)i})(t_{ij} - K_{ki})_+, \quad (3)$$

where $x_+ = \max(x, 0)$, K ($k = 1, 2, 3, \dots, K$) is the number of unknown change-points, $K_{ki} = C_k$ or $K_{ki} = C_k + c_{ki}$ where C_k is the global change-point and c_{ki} is the country-specific change-point.

Substituting equations (2) and (3) in equation (1), yields to the final model

$$\begin{aligned} Y_{ij} &= (\beta_0 + b_{0i}) + (\beta_1 + b_{1i})t_{ij} + \sum_{k=1}^K (\beta_{(k+1)} + b_{(k+1)i})(t_{ij} - K_{ki})_+ \\ &\quad + (\beta_0^S + b_{0i}^S + \beta_1^S t_{ij}) \text{Sin}(\omega t_{ij} + \delta) + \varepsilon_{ij}. \end{aligned} \quad (4)$$

Random effects for the global level of use, the trend effects, the amplitude of the seasonal effect, and the location of the change-point are used to account for heterogeneity across countries. The number of change-points K and the location of the change-point(s) are data driven.

3 Results

Applying the proposed adaptive model indicates that the data support a model with two unknown fixed change-points. The first change-point in the trend of antibiotic use in DID is located at $t=17$ (first quarter of 2001) and the second change-point is located at $t=30$ (second quarter of 2004). The credible intervals for the change-points are given by (11.97, 21.86) and (27.01, 33.68), respectively. For the final model, fixed effect parameters (standard errors) were estimated to be 2.7436(0.3222), -0.0262(0.0079), 0.0207(0.0097) and 0.0038(0.0117), respectively for the intercept, the linear time effect, the change in the linear time effect before and after the first change-point, and the change in the linear time effect before and after the second change-point.

There is an overall decrease in the trend of outpatient antibiotic use in DID before the first change-point (slope=-0.0262), and a slight decrease in the trend after the first change-point (slope=-0.0055). There is no significant difference between the trend of DID before the second change-point and the trend after the second change-point. The location of the change-points may be related to points in time where public-health strategies were initiated, aiming to increase the awareness of the public to a more rational use of antibiotics or aiming to reduce overconsumption of antibiotics.

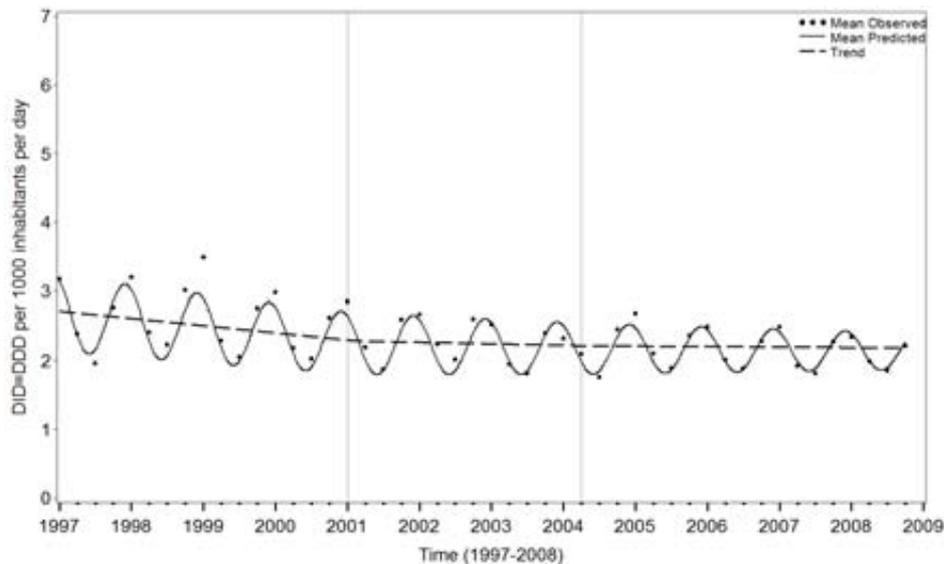


Figure 1: *The predicted mean profile (solid line), predicted trend (dashed line) and population averaged DID (dots).*

The predicted mean profile and the overall mean are shown in Figure 1. Figure 1 indicates that the model describes the data very well. The predicted mean is based on the predicted outcomes from the posterior distribution of the country-specific random effects. In Figure 1, the vertical lines indicate the estimated change-points.

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