Common Intervention Analysis in Multivariate Nonstationary Time Series

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EXTENDED ABSTRACT

The cynomolgus monkey, one of a number of primate species phylogenetically close to humans, is commonly used in cardiovascular research. Assessment of cardiac safety of drug candidates is important in drug development. The objectives of this study were to present a set of time series analysis technique that enables us to detect 'significant' change in heart rate, respiration rate, diastolic blood pressure and systolic blood pressure coming from drug administration. However, it is not easy to detect or extract the effects of dosing from observed heart rate, blood pressures and so on. It is just because the monkey is alive and heart rate and blood pressures are continuously fluctuating according to his activities. Hence some suitable time series modeling of a monkey's 'usual' activity is required, and side effects of drug administration should be estimated as an 'add-on' over the regular time series variations. In this paper we propose a method based on a structural time series model which has an intervention term in the observational equation.

In this study, data are taken from observing seventy-five male cynomolgus monkeys (aged 4–6 years, weighting 3–6 kg) that were housed in a controlled environment. In the animal room, a light/dark cycle of 12h (lights on at 08:00) was set.A telemetry transmitter was implanted intraperitonearlly, and fixed inside the abdominal wall under ketamine hydrochloride anesthesia. An antibiotic was administrated intramuscularly at 0.05 mL/kg to the animals once daily for three days including the day of plantation. Under these experiment settings, we especially focus on heart rate, respiration rate, systolic blood pressure and diastolic blood pressure.

Plot of the data suggests the nonstationarity, so we employ structural type unobserved component models. We assume second order random walk for trend component, and include stationary autoregressive component if necessary. To express the effect of dosing, we put additional regressor which is basically generated from an exponential function with two unknown parameters. Once a state space representation of the model is obtained, the model can be estimated by the method of maximum likelihood, and model comparison will be done by AIC.

The results shows trend plus AR with an intervention is supported in most of the cases. Except respiration rate data, this model was almost always selected. It turns out that a stationary AR component is indispensable to express the variation incurred by regular activities of a monkey. When a simple trend model (with or without an intervention term) is assumed, the cases where the estimated intervention terms are significant are just 9 to 15 cases out of 75 cases. This just comes from the poor fit of the data, and the intervention terms are generally buries in the noise.

The time series analysis done in this paper can be a basis of the estimation of dose response curve. Even if an intervention term is found to be significant, it does not always mean an acute toxicity. For example, we might set some threshold for the height of the function. Suppose we set 20 rise or more in systolic blood pressure should be regarded as the evidence of acute toxicity. Then the case is classified as a toxic case. Changing dose levels and repeating experiments, finally we obtain a set of dose level times response data. Then the usual dose response analysis can be applicable.

1 INTRODUCTION

The cynomolgus monkey, one of a number of primate species phylogenetically close to humans, is commonly used in cardiovascular research. Assessment of cardiac safety of drug candidates is important in drug development.

The objectives of this study were to present a set of time series analysis technique that enables us to detect 'significant' change in heart rate, respiration rate, diastolic blood pressure and systolic blood pressure coming from drug administration.

However, it is not easy to detect or extract the effects of dosing from observed heart rate, blood pressures and so on. It is just because the monkey is alive and heart rate and blood pressures are continuously fluctuating according to his activities.

Hence some suitable time series modeling of a monkey's 'usual' activity is required, and side effects of drug administration should be estimated as an 'add-on' over the regular time series variations. In this paper we propose a method based on a structural time series model which has an intervention term in the observational equation.

The rest of the paper is organized as follows. In section 2, we explain how the data are acquired, and also details of experimental settings. In section 3, we explain our statistical model to be used here. It is so-called a structural time series model, which inevitably exploits state space form and related algorithm. In section 4, we present the results of our analysis on 75 male cynomolgus monkey data. In section 5, we discuss some issues related to the results, and issues that has something to do our future work. Section 6 concludes.

2 DATA

2.1 Animals

All procedures involving animals were approved by the Animal Care and Use Committee of Shin Nippon Biomedical Laboratories, Ltd. (Kagoshima Japan), and were performed in accordance with the standards published by the National Research Council (Guide for the Care and Use of Laboratory Animals, NIH OACU) and the National Institute of Health Policy on Human Care and Use of Laboratory Animals. All data retrieving work was performed at Shin Nippon Biomedical Laboratories, Ltd. (Kagoshima, Japan).

Seventy-five male cynomolgus monkeys (aged 4–6 years, weighting 3–6 kg) were housed in a controlled environment maintained at a temperature of between 23° C and 29° C and relative humidity of between 35% and 75% . The animal room was ventilated with a minimum of 15 air changes/h, and a light/dark cycle of 12h (lights on at 08:00) was set.

2.2 Surgical implantation

A Data Sciences International (DSI) telemetry transmitter (TL11M2-D70-PCT, Data Sciences International Inc.) was implanted intraperitonearlly, and fixed inside the abdominal wall under ketamine hydrochloride (10 mg/kg, intramuscular, Fuji Chemical Industry Co., Ltd.) anesthesia. Two unipolar lead electrodes for the electrocardiogram (ECG) were inplanted subcutaneously at predetermined locations on the right manubrial border of the sternum and left anterior auxiliary line sixth rib. An antibiotic [aqueous suspended injection of dihydrostreptomycin sulfate (250 mg potency/mL), benzyl penicillin procane (200,000 units/mL)] was administrated intramuscularly at 0.05 mL/kg to the animals once daily for three days including the day of plantation (Horii et al., 2002). All animals were allowed approximately two or three weeks to recover from surgery and were used in the present study after the ECG parameters stabilized.

2.3 Sample Data and Problem

In Figure 1, data for a cynomolgus monkey are plotted. From above, heart rate, respiration rate, diastolic blood pressure, and systolic blood pressure. All the data are sampled with equally interval of 5 minutes, so the length of a time series is 288. Each data starts from 08:00, and the final interval is 07:55. An antibiotic was administered at 11:00, so the 37th observation is expected to reflect the effects of dosing.

Looking at these sample plots, we find a seemingly stationary fluctuation around a slowly changing diurnal pattern. Even if we discard all the dark time data, still some kind of trend might exist. This leads to the idea of employing structural time series models.

Based on our experiments, we expect a kind of jump and decay after $t = 37$. Looking at these graphs, it seems subtle whether or not we could detect such an acute toxicity. The aim of our analysis is to device a statistical tool that enables us to find 'significant' exogenous effect from data. Whether or not an extracted effect should be regarded as an acute toxicity needs some external knowledge on toxicity.

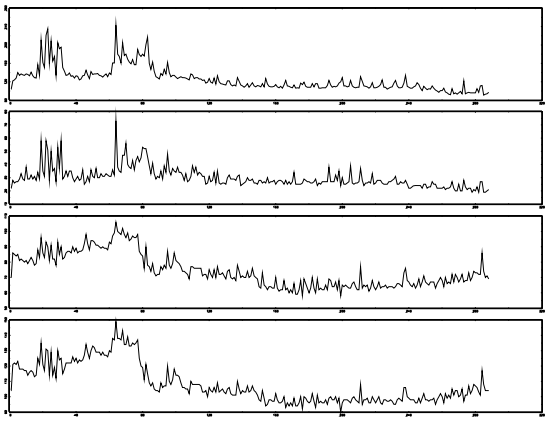

Figure 1. Plot of data obtained for a certain cynomolgus monkey. From above, heart rate, respiration rate, diastolic blood pressure, and systolic blood pressure.

3 TIME SERIES MODELS

3.1 Structural Time Series Model

As a basis of the discussion of this article, this section explains a popular model called basic structural model. Modeling trend-seasonality with state-space form have been explored since the end of 1970's. Trend and seasonal are regarded as unobservable components, and for each unobservable component a stochastic model is assumed. One of the most popular specification is a set of the equations described as follows.

$$
\begin{aligned}
y_t &= \mu_t + \psi_t + d_t + \epsilon_t && (1)\\
\mu_t &= \mu_{t-1} + \beta_{t-1} + \eta_t && (2)\\
\beta_t &= \beta_{t-1} + \zeta_t && (3)\\
\psi_t &= \sum_{j=1}^{m} a_j \psi_{t-j} + \omega_t && (4)
\end{aligned}
$$

In above equations, we assume that each of ϵ_t, η_t, ζ_t, ω_t follows zero mean normal distributions but with different variance; σ_ϵ^2, σ_η^2, σ_ζ^2 and σ_ω^2 respectively. This set of equations together with seasonal component is often referred to as Harvey's basic structural model (BSM hereafter), see Harvey (1989, p.47). In our data, although there might be some diurnal pattern, we have data just for one day, so we expect trend part will represent the intraday seasonal pattern. Equation (1) is called observational (or measurement) equation. This reflects our observation that the salient features of economic time series are trend μ_t and stationary AR part γ_t, and the rest is regarded as irregular component ϵ_t. The term d_t expresses some deterministic effects, and actually works as an intervention term or as a pulse in our model. Specification of d_t will be stated in subsection 3.3.

Trend component consists of two latent variables μ_t and β_t, which is respectively referred to 'stochastic level' and 'stochastic slope'. The equation (2) plus (3) is called the local linear trend model. The name comes from the fact that the drift term β_t plays a role of a linear trend rather than a constant in (2). In practice, it is often observed that either $\hat{\sigma}_\eta^2$ or $\hat{\sigma}_\zeta^2$ is almost equal to zero. Because of this redundancy, some researchers assume that $\sigma_\zeta^2 = 0$ a priori. On the other hand, it is also possible to consider the following trend model in stead of (2) plus (3);

$$\mu_t = 2\mu_{t-1} - \mu_{t-2} + \eta_t. \qquad (5)$$

If we rewrite (5) as $\mu_t = \mu_{t-1} + (\mu_{t-1} - \mu_{t-2}) + \eta_t$, it is easily understood that (5) is a special case of the local linear trend model in the sense that the stochastic slope β_t is also driven by the same process η_t rather than by a different process ζ_t. From now on, trend model is fixed to (5) in this article.

3.2 State Space Form

So far I have just introduced a couple of models for components, none of which does not correspond to the pulse effect due to antibiotic administration. That will be expressed as an exogenous term in measurement equation, so in this subsection we put everything in a state space form, and the model estimation via a state space form.

Due to the assumption of no correlation among innovation and noise process, the state space representation can be built up as a composition of small state space models for the individual components. For the simplicity of presentation, we put $m = 2$ throughout this paper. From equation (5) and (4), it turns out that the essential quantity that determines the present distribution of μ_t and ψ_t will be given by a vector

$$\alpha_{t-1} = (\mu_{t-1}, \mu_{t-2}, \psi_{t-1}, \psi_{t-2})' \qquad (6)$$

where the prime ($'$) denotes the transpose of a vector or a matrix. By setting submatrices as follows,

$$T_1 = \begin{bmatrix} 2 & -1 \\ 1 & 0 \end{bmatrix}, \; T_2 = \begin{bmatrix} a_1 & a_1 \\ 1 & 0 \end{bmatrix},$$

$$R_1 = R_2 = \begin{bmatrix} 1 & 0 \\ 0 & 0 \end{bmatrix},$$

new matrices T and R are defined as

$$T = \begin{bmatrix} T_1 & O \\ O & T_2 \end{bmatrix}, \quad R = \begin{bmatrix} R_1 \\ R_2 \end{bmatrix}, \quad \eta_t = \begin{bmatrix} \eta_t \\ \omega_t \end{bmatrix}. \qquad (7)$$

Then the transition of the state vector can be written in a matrix notation as

$$\alpha_t = T\alpha_{t-1} + R\eta_t. \qquad (8)$$

As we observe that the measurement equation (1) just extracts and adds the components μ_t and γ_t, defining $z' = (1, 0, 1, 0)$ yields the relation between the observation and the state as

$$y_t = z'\alpha_t + d_t + \epsilon_t. \tag{9}$$

Now the structural model is put in a state space form by (8) and (9). Note that the specification of α_t, T, R and z' described above is not a unique one because the transformations of these vectors and matrices by a regular square matrix still give rise to the same state space model.

3.3 Intervention Term

We introduce an intervention term d_t so that it should express rapid increase in heart rate, blood pressure and so on provided the administration quantity is big enough to incur such an increase. A simple but mostly acceptable modeling is to assume exponential function. That is,

$$d_t = \begin{cases} 0 & , t = 1, \ldots, 36 \\ \rho \exp(-\lambda(t-36)) & t = 37, \ldots, 288. \end{cases}$$

We expect both ρ and λ are nonnegative. A big ρ value suggests acutely toxic effects, while a big λ value implies quick decay of such an effect. Adding this term needs two extra parameters.

3.4 Model and State Estimation

Let a_{t-1} denote the minimum mean squared error (MMSE) estimator of α_{t-1} based on the observations up to time $t-1$. Let P_{t-1} denote the 4×4 (in our situation) covariance matrix of the estimation error, i.e.

$$P_{t-1} = \mathrm{E}[(\alpha_{t-1} - a_{t-1})(\alpha_{t-1} - a_{t-1})'].$$

Given a_{t-1} and P_{t-1}, the MMSE estimator of α_t and the covariance matrix of the estimation error is given by

$$\begin{aligned} a_{t|t-1} &= T a_{t-1} \\ P_{t|t-1} &= T P_{t-1} T' + RQR' \end{aligned}$$

where $Q = \mathrm{diag}(\sigma_\eta^2, \sigma_\omega^2)$. These two equations are known as the *prediction equations*.

Once the new observation, y_t, becomes available, the estimator of α_t, $a_{t|t-1}$, can be updated. The *updating equations* are given by the following two equations,

$$\begin{aligned} a_t &= a V_{t|t-1} + P_{t|t-1} z' f_t^{-1} (y_t - z' a_{t|t-1} - d_t) \\ P_t &= P_{t|t-1} - P_{t|t-1} z' f_t^{-1} z P_{t|t-1} \end{aligned}$$

where $f_t = z' P_{t|t-1} z + \sigma_\epsilon^2$. Repetition of prediction and updating constitutes so-called the Kalman filter.

Unless $\sigma_\epsilon^2 = 0$, the estimation problem of a state space model is double-folded. Given the unknown hyperparameters $\theta = (a_1, a_2, \sigma_\epsilon^2, \sigma_\eta^2, \sigma_\omega^2)'$, running Kalman filter and fixed interval smoother yields the estimates of unobservable components $\{\hat{\mu}_t\}_{t=1}^T$, $\{\hat{\psi}_t\}_{t=1}^T$ and hence $\{\hat{\epsilon}_t\}_{t=1}^T$. The vector of unknown parameters, θ, can be estimated by the maximum likelihood method. The likelihood function for a time series can be decomposed into the product of the density functions of one step ahead prediction error $v_t = y_t - z' a_{t|t-1}$. The variance of observation noise σ_ϵ^2 usually can be concentrated out of the likelihood function. Let $\theta^* = (a_1, a_2, \sigma_\eta^2, \sigma_\omega^2)'$, then

$$\log L_c(\theta^*) = -\frac{1}{2} \left\{ T \log 2\pi \tilde{\sigma}^2(\theta^*) + \sum_{t=1}^T \log f_t + T \right\}$$

must be maximized with respect to the unknown parameters θ^*, while $\tilde{\sigma}^2(\theta^*)$ is given by

$$\tilde{\sigma}^2(\theta^*) = \frac{1}{T} \sum_{t=1}^T \frac{v_t^2}{f_t}.$$

Model comparison will be done based on AIC (Akaike, 1973). We will compare a simple trend model, trend model with an intervention term, trend plus AR model, and finally trend plus AR with an intervention term. As regards the initial state settings, we employ the 'large κ approximation' (Harvey, 1989, p.121). As for stationary AR part, we could express unconditional distribution of an AR process via its parameters so that they should give proper initial distributions. Once the unknown hyperparameters are estimated, then the unobserved components are estimated by the fixed interval smoother. For the algorithm of the fixed interval smoother, see Anderson and Moore (1979, p.187–190), Harvey (1989, p.154) or Kitagawa and Gersch (1996, p.58).

As for the coefficients of AR component model, we restrict partial autocorrelations take their values between -1 and 1 so that $\{\psi_t\}$ should be a stationary autoregressive process. Hence the partial autocorrelations are transformed to have infinite support, by logit transformation for example, then their inverse transformations will be performed inside the filtering subroutine.

4 RESULTS

In this section, we first present the results concerning simple trend model and its extension. A simple illustration reveals a problem of this approach, and it will be shown that including stationary AR component leads to much better modeling, and makes it possible to detect intervention effects more often.

4.1 Trend Model

Here the trend model is fixed to the second order random walk model, namely to (5), while we have two choices for the observation equation. One has d_t term,

$$y_t = \mu_t + d_t + \epsilon_t,$$

while the other is without d_t,

$$y_t = \mu_t + \epsilon_t.$$

The results are summarized in Table 1. Out of 75 samples (72 for diastolic blood pressure only), how often the model with or without intervention is preferred is reported.

Data	without d_t	with d_t
Heart Rate	66	9
Resp. Rate	66	9
Diastolic BP	57	15
Systolic BP	61	14

Table 1. Results of model selection. Comparison based on simple trend model.

Figure 2 shows one of the cases in heart rate where the intervention is found to be significant. Height of exponential function is about 53, and decay rate parameter is estimated to be 0.45, which suggests persistent effect in this case.

Looking at the upper panel of Figure 2, one might think the goodness of fit of the simple trend model (with an intervention term at most) would not be sufficient to explain the total variability of the given data. In the next subsection, we report the results after including stationary AR component.

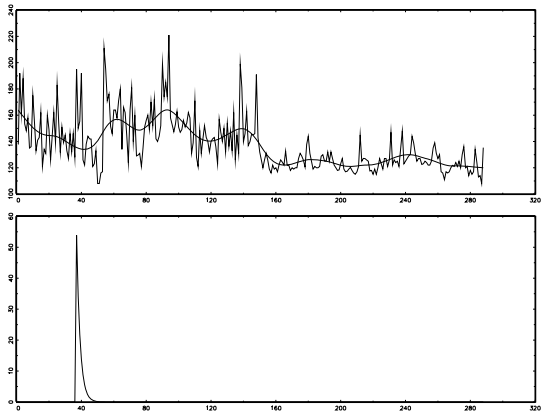

Figure 2. An intervention effect on a heart rate series. Original and trend (upper), estimated intervention (lower).

4.2 Trend plus AR Model

Now we incorporate a second order AR component,

$$\psi_t = a_1\psi_{t-1} + a_2\psi_{t-2} + \omega_t.$$

It is possible to increase the order of AR, to 4 or 6 say, but we do not perform further specification searches. This can be justified in terms of detecting the reaction to dosing. Trend order is fixed to 2 as with the previous section. Models in comparison are different only by the term d_t. Namely, we compare (1) and

$$y_t = \mu_t + \psi_t + \epsilon_t.$$

The results are summarized in Table 2. In sum, trend plus AR type decomposition accompanied with an intervention term is very frequently selected by minimum AIC procedure.

	Trend only		Trend+AR	
Data	/wo d_t	/w d_t	/wo d_t	/w d_t
Heart Rate	2	0	0	72
Resp. Rate	17	0	0	58
Diastolic BP	1	0	0	71
Systolic BP	1	0	0	74

Table 2. Results of model selection. Comparison based on simple trend model.

Figure 3 is based on the results of working on the same data as in Figure 2. Much of the fluctuations are absorbed into AR component, which might lead to better fit or lower AIC value. Height of exponential function is about 50 which is alike in the simple trend model with an intervention case, while the decay rate parameter is estimated to be almost 10, so the effect is immediate.

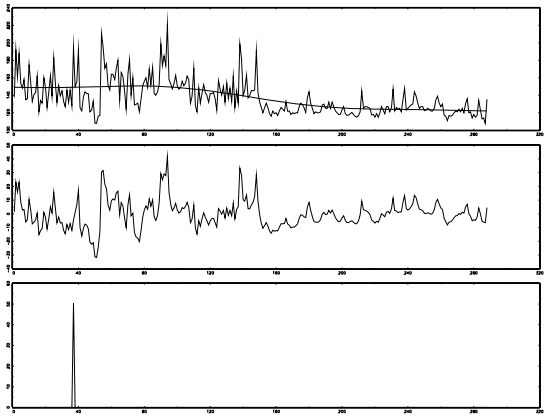

Figure 3. An intervention effect on a heart rate series. Trend+AR+Intervention effect. Original and trend (upper), AR component (middle), and estimated intervention effect (bottom).

5 DISCUSSION

5.1 Role of AR Component

How should I understand the difference between Table 1 and 2? The plausible answer seems to come after comparing Figure 2 with Figure 3. Without an intervention term, the model has poor explanatory power, and much of the fluctuation around the trend has to be put to residuals. Then, the height of the exponential function at its origin sometimes buries in the noise level. If so, it is parsimonious to regard the intervention effect just a part of irregular component.

Whatever the data, heart rate or blood pressures, they vary according to a cynomolgus monkey's activity, so their fluctuations are inevitable. Our aim is to estimate the effect of antibiotic administration, so the inclusion of AR term gives us good description of various measurements assuming monkey's activities.

5.2 Toward Dose Response Analysis

The methodology presented in this paper is a basis of future dose response analysis. Even if an intervention term is found to be significant (in minimum AIC sense), it does not always mean an acute toxicity; it depends on the estimated height of exponential function or also on the decay rate.

To understand this, it helps to look at actual form of estimated functions (or dummies). Figure 4 and 5 show overlayed exponential functions of systolic blood pressure and respiration rate respectively. For example, we might set some threshold for the height of the function. For example, we might set 20 rise or more in systolic blood pressure should be regarded as the evidence of acute toxicity. Then the case is classified as a toxic case.

So far, we only have data set under the single dose level. After increasing quantity of administration, we run the time series analysis proposed in this paper, and finally we obtain a set of dose level times response data. Then the usual dose response analysis can be applicable.

5.3 Box-Tiao Parameterization

In this paper we simply placed the exponential function with two parameters. In the context of intervention analysis, Box and Tiao (1975) is the most well-known paper. It would be possible to adapt their parameterization. Let $P_t^{(T)}$ be a pulse indicator where

$$P_t^{(T)} = \begin{cases} 0, & t \neq T \\ 1, & t = T. \end{cases}$$

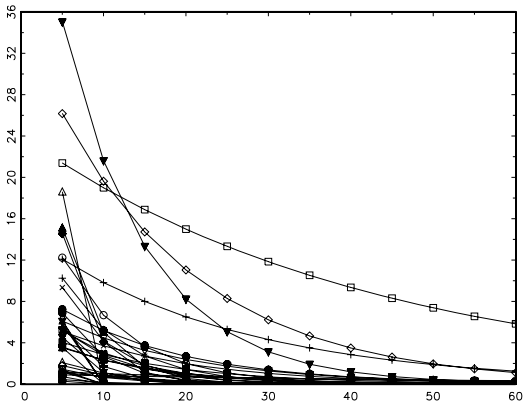

Figure 4. Intervention effects on systolic blood pressure.

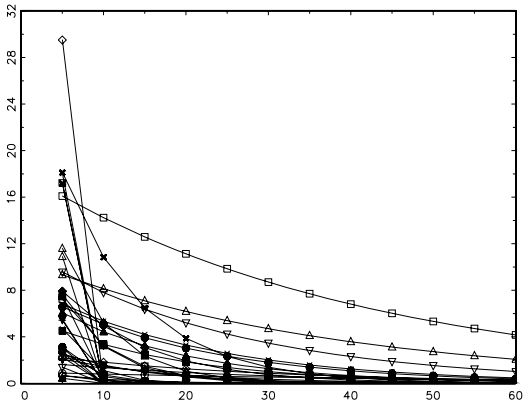

Figure 5. Intervention effects on respiration rate.

Then the model suitable to our problem is

$$d_t = \omega_1 B/(1-\delta B)P_t^{(T)}.$$

Obviously, the parameter ω_1 corresponds to ρ in our model, while δ determines the decay of the pulse effects, therefore plays the same role of λ in our model.

6 CONCLUSION

A structural time series model with an intervention has been proposed to model the data from embedded telemetry in a cynomolgus monkey. Not only the trend term but stationary AR term plays an important role to extract dose effects accurately. Estimated effects can form a basis of the judgement of acute toxicity, then the time series analysis done here enables usual dose response analysis.

7 ACKNOWLEDGEMENT

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Ltd., Kagoshima, Japan.

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