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STOCHASTIC PROCESSES FOR FINDING HPA AXIS FUNCTIONING ASSOCIATED WITH TRANSITION TO PSYCHOSIS COMBINED: DEX/CRH TEST USING BOX – COX TRANSFORMATION

Dr. N. Umamaheswari [*1], M. Monisha [2]

[*1]Assistant Professor, Department of Mathematics, Shrimati Indira Gandhi College, Affiliated to Bharathidasan University, Trichy, Tamil Nadu, India

[*2] M.Sc., Mathematics, Shrimati Indira Gandhi College, Affiliated to Bharathidasan University, Trichy, Tamil Nadu, India

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***Corresponding Author: Dr. N. Umamaheswari**
Assistant Professor, Department of Mathematics, Shrimati Indira Gandhi College, Affiliated to Bharathidasan University, Trichy, Tamil Nadu, India.
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ABSTRACT:

This Study exposes the functioning of the hypothalamic–pituitary–adrenal (HPA) axis in 12 young people at ultra high risk for developing psychosis, using the combined dexamethasone corticotrophin releasing hormone (DEX/CRH) test. Over a two year period, three of the 12 participants developed an acute psychosis. Descriptive analysis of the data indicated that contrary to expectations, participants who did not make the transition to psychosis had on average higher cortisol levels at the latter stages of the test, as well as a greater severity of depression and anxiety symptoms, than participants who subsequently developed psychosis by usingthe class of transformations that is considered is the Box-Cox power transformation, which applies to series measured on a ratio scale. We propose a nonparametric approach for estimating the optimal transformation parameter based on the frequency domain estimation of the prediction error variance, and also conduct an extensive recursive forecast experiment on a large set of seasonal monthly macroeconomic time series related to industrial production and retail turnover.

KEYWORDS: HPA, DEX, CRH , Psychosis, Dysregulation, Prediction, Prediction error variance , Specification.

INTRODUCTION

The diathesis-stress model of schizophrenia contends that a combination of factors, including genetic liability, abnormal maturation, early exposures, and stress combine to affect the abnormal substrate thought to underlie schizophrenia [10]. Indeed some research has suggested that stress and the associated rise in cortisol may be associated with increased psychopathology via a dynamic process involving increased dopamine activity and atrophy of cells in the hippocampus. In order to further elucidate the relationship between stress response and the pathophysiology of psychosis, it may be of special value to test HPA-axis reactivity during the sub-threshold stage of illness, prior to the onset of the first episode of psychosis. We applied the DEX/ CRH test in a small, specialized sample of individuals at ultra high risk of developing psychosis in order to assess whether HPA dysregulation is evident during the prodromal period.

Transformations aim at improving the statistical analysis of time series, by finding a suitable scale for which a model belonging to a simple and well known class, e.g. the normal regression model, has the best performance. An important class of transformations suitable for time series measured on a ratio scale with strictly positive support is the power transformation; originally proposed by [8], as a device for achieving a model with simple structure, normal errors and constant error variance, it was subsequently modified by Box and Cox . The objective of this paper is assessing whether transforming a variable leads to an improvement in forecasting accuracy. The issue has already been debated in the time series literature.

The use of the Box-Cox transformation as a preliminary specification step to fitting an ARIMA model was recommended in the book by [1]. In his discussion of the paper by [3], [9]advocated its use and showed that for the particular case study considered in the paper, the monthly sales of an engineering company, maximum likelihood estimation of the power transformation parameter could lead to superior forecasts. This point was elaborated further by [1].

Forecasting Box-Cox transformed series

Box and Cox proposed a transformation of a time series variable y_t,

t = 1, . . . ,n that depends on the power parameter λ in the following way:

$y_t(\lambda) = \frac{y_t^{\lambda} - 1}{\lambda}, \quad \lambda \neq 0$

$\ln y_t, \quad \lambda = 0$ (1)

where in denotes the natural logarithm. When λ is equal to 1, the series is analysed in its originalscale, whereas the case λ = 0 corresponds to the logarithmic transformation. Other importantspecial cases arise for fractional values of λ, e.g. the square root transform (λ = 1/2). Obviously,for the transformation to be applicable, the series has to be strictly positive.

Suppose the optimal forecast of the Box-Cox transformed series is denoted by $y_{t+h\backslash t}(\lambda)$, h =1, 2, . . ., where h is the forecast lead. Here optimality is intended in the mean square error sense,so that $y_{t+h\backslash t}(\lambda) = E[y_{t+h}(\lambda)|F_t]$ is the conditional mean of $y_{t+h}(\lambda)$, given the information set attime t, here denoted as F_t. The conditional mean is typically available in closed form. Finally, let$\sigma^2 h(\lambda) = E\{[y_{t+h}(\lambda) - y_{t+h\backslash t}(\lambda)]^2|F_t\}$ denote the h-step-ahead prediction error variance, which forsimplicity we assume time-invariant.

We now consider the prediction of$y_t$on its original scale of measurement. The naive forecast isobtained as the inverse Box-Cox transformation,

$$y_{t+h\backslash t} = \left(1 + \lambda y_{t+h\backslash t}(\lambda)\right)^{1\backslash\lambda}, \quad \lambda \neq 0$$

$$\mathrm{Exp}(y_{t+h\backslash t}(\lambda)), \lambda = 0 \quad (2)$$

This quantity corresponds to the median of the predictive distribution and, hence, it provides theminimum absolute error predictor.

The optimal predictor of y_{t+h}(i.e. its conditional expectation given the past), denoted by $y_{t+h\backslash t}$, is if the transformed series is normally distributed. In general a closed form expression for this integral is not available. However, if 1/λ is a positive integer, [7]provide a closed form expression. Table 1 presents the expressions of the optimal predictors as functions of the naive predictor $y_{t+h\backslash t}$for selected values of λ.

Deciding on the Box-Cox transformation for prediction

The Box-Cox transformation parameter is usually estimated by maximum likelihood, assuming a parametric model for $y_t(\lambda)$; the parameter λ can be concentrated out of the likelihood, which is corrected by the Jacobian so as to take into account the change of scale of the observations. This approach is plausible if the Box-Cox transformation converts the distribution to a normal. Unfortunately, the results by Nelson and Granger indicate that the normality assumptionfor the transformed series may be problematic. Moreover, even though the forecasts are typically based on a parametric model, there is usually uncertainty regarding the right model. Therefore, we propose a nonparametric approach, according to which the transformation parameter is estimatedas the value for which the prediction error variance (p.e.v.) of the series (after a normalization bythe Jacobian of the transformation), is a minimum.

Our procedure is based on the normalized Box-Cox (NBC) transformation which is obtained bydividing $y_t(\lambda)$ by$\sqrt[n]{j}$,where J $=\Pi_t \frac{\sigma_{yt}(\lambda)}{\sigma_{yt}}$is the Jacobian of the transformation, which is equaltog$_y{}^{\lambda-1}$with $g_y = [\Pi_t y_t]^{1\backslash n}$being the geometric average of the original observations. This yields

$z_t(\lambda) = g_y{}^{1-\lambda} y_t(\lambda)$ (3)

This normalization is relevant if the aim is minimizing the one-step-ahead across the different values of λ. Notice that whenλ = 1, the normalizing factor is unity, and the normalized transform sets the scale equal to that of the original observations.

We assume that $z_t = z_t(1)$ can be made stationary by differencing, that is, there exists a stationary representation$u_t = \Delta(L) z_t$, t = 1, . . . , n, where Δ(L) is a polynomial in the lag operator,L, e.g. $\Delta(L) = (1 - L)^d$or $\Delta(L) = (1 - L)(1 - L^s)$, for seasonal time series with seasonal periods. Obviously, if $z_t$is stationary, Δ(L)=1. Notice also that n has been reset so as to denote thenumber of observations available foru_t.

We estimate the transformation parameter by minimizing the prediction error variance. Notice that the one-stepahead prediction error variance (p.e.v.) for $z_t$is the same as that ofu_t, since $u_t - E(u_t|F_{t-1}) = z_t - E(z_t|F_{t-1})$.

If we let f(ω) denote the spectral density of u_t, and assume$\int_{-\pi}^{\pi} \ln 2\pi f(\omega)\, d\omega > -\infty$, the one-stepahead prediction error variance is defined, according to the usual Szego-Kolmogorov formula, as the geometric averageof the spectral density:

$\sigma^2 = \exp[\frac{1}{2\pi}\int_{-\pi}^{\pi} \ln 2\pi f(\omega)\, d\omega]$.

The prediction error variance can be estimated nonparametrically by a bias-corrected geometric average of theperiodogram. Letting $\omega_j = \frac{2\pi j}{n}$, j = 1, . . . , [n/2], denote the Fourier frequencies, where [·] is theinteger part of the argument, the sample spectrum is defined as

$I(\omega_j) = \frac{1}{2\pi n} [\sum_{t=1}^{n}(u_t - u)\, e^{-\omega_j t}]$

$u = \frac{1}{n}\Sigma_t u_t$ and ı is the imaginary unit. Letting n^* denote n/2 − 1, if n is even, and

(n − 1)/2, ifn is odd, proposed the following estimator:

$$\sigma 2 = \exp\, [\tfrac{1}{n^*} \sum_{j=1}^{n^*} \ln 2\pi I(\omega_j) + \gamma], \qquad (4)$$

where γ = 0.57722 is Euler’s constant.

[4] proposed replacing the raw periodogram ordinatesby their non-overlapping averages of m consecutive ordinates,

$$\sigma^2(m) = m\exp\, [\tfrac{1}{M} \sum_{j=0}^{M-1} \ln(\sum_{k=1}^{m} 2\pi I(\omega_{jm+k})) - \varphi(m)] \qquad (5)$$

where M = [(n − 1)/(2m)] and ψ(m) is the digamma function. The estimator (4) is obtained in the case m = 1. The large sample distributions of (5) and ln σ^2(m) are, respectively,

$$\sigma^2(m) \sim N(\sigma^2, \frac{2\sigma^4 m\psi'(m)}{n}), \quad \ln\sigma^2(m) \sim N(\sigma^2, \frac{2m\psi'(m)}{n})$$

The estimation of the optimal transformation parameter is carried out by a grid search overthe λ values in the range (a, b), where typically, b = −a = 2. For each value of λ in the selectedrange the NBC transformation of the series, $z_t(\lambda)$, is computed according to (3), the stationarity transformation is obtained as $u_t(\lambda) = \Delta(L) z_t(\lambda)$ and the HN estimator (5) is computed. The valueof λ that yields the minimum prediction error variance is the required estimate. Notice that a crucial assumption isthat the stationarity inducing transformation, Δ(L), does not vary with λ, which is appropriatefor the NBC.

When explanatory variables are present, such as trading days and Easter regressors for modeling calendar effects, interventions and seasonal dummy variables, the prediction error variance can be estimated from the frequency domain regression residual periodogram, as in Cameron. Alternatively, we could use a weighted estimate of the prediction error variance based on a similar idea toband spectral regression, that puts a zero weight to the sample spectrum ordinates around the trading days and seasonal frequencies.

The latter may also be advocated as a more general strategy aiming at robustifying the nonparametric estimator of the prediction error variance, by excluding some periodogram ordinates that could be affected by the stationarity inducing transformation. For instance, if $\Delta z_t = z_t - z_t - 1$ is analyzed, leavingout the seasonal frequency may be thought of as a way of eliminating a deterministic seasonal component from the series. If we focus on $\Delta s z_t = z_t -$ zt−s, instead, then the periodogram at the seasonal frequencies may get close to zero, so that the seasonal frequencies will contribute strongly and negatively to the prediction error variance estimate.

The priors

For the joint priors of the parameters $\alpha, \sigma^2, \psi, \lambda$ two categories of priors will be considered in this paper. In practice, we might use a uniform prior distribution if we reallyhave no prior knowledge about the parameters. Following the consideration of Box and Cox, the joint prior distribution is specified by

$\pi(\beta, \log\sigma, \psi, \lambda) = \pi(\beta, \log\sigma \backslash \lambda)\pi(\psi)\pi(\lambda)$(6)

where $m_1$is the dimension of β,$l_\lambda$denotes the geometric mean of the Jacobian

$l_\lambda = l_\lambda^{1\backslash n}$

and n =$\sum_{i=1}^{n} t_i$denotes the size of observations.

Forψ, we apply the Durbin–Levinson recursionto reparameterize

$\psi = (\emptyset, \theta)$in terms of $\boldsymbol{\gamma}_\psi = (\boldsymbol{\gamma}_\emptyset, \boldsymbol{\gamma}_\theta)$, which is confined within $\mathbb{R}_1^{p+q}$,

$\mathbb{R}_1 = (-1, 1)$, as discussed. Thus, we allow for a uniform prior on$\boldsymbol{\gamma}_\psi$. Forσ^2, we choose σ^{-2}as its prior. As for two possibilities are considered.We mayutilize the “principle of stable estimation” suggested, a uniformprior is appropriate.

Empirical determination of the functional form

It has been acknowledged in econometric studies that the determination of thefunctional relationship that may exist between some variables of interest need not be based on a priori economic rationale**.** The simplest procedure that hasbeen accepted and successfully applied is the Box-Cox transformation technique.In much of the research that has been undertaken, the following functional form has been accepted as standard:

$y_i^{\lambda} = \beta_0 + \sum_{j=1}^{q} \beta_j x_{ji} + \varepsilon_i$ (7)

Where x_{ji} are the transformed regressand and regressants, respectively, and $\varepsilon_i$represents the random errors. The presence of a model constant is a prerequisite to preserving the scale invariance as indicated by the functional form in the demand for money as related to both real income and interest rate with a common A while White estimated the liquidity trap with the same restrictions on A. [5]studied the relationship between earning, schooling and experience with a generalized A where asconsidered the functional form between population density and the distance from the central business district with λ_1 = 1. Khan & Ross determined the aggregate form of the import demand equation with a common A and Mills considered the functional form for the UK for money. Chang estimated the functional relationship for demand of meat in the USA with λ_0=λ_1, which has also been discussed by the relationship between the demand for money and the liquidity trap with a generalized Box- Cox parameter. An examination of the aggregate import demand equation by [2]was constrained to a common A and a further examination by constrained λ_1=λ_3,$\lambda_1 \neq \lambda_2$. This was further generalized by Boylan. Lin & Huang estimated the generalized functional form for the yield trend of wheat, corn and soybean. Newman estimated the relationship between the incidence of malaria and the mortality rate and concluded that the functional specification obtained by using the Box-Cox procedure was superior to earlier specifications. Some different procedures for estimating the transformation parameter in normal error models have been examined by Spitzer which, although leading to essentially the same estimates, differ in terms of computational time. Poirier studied some estimation methodology when the error terms are truncated normal. The generalized Box-Cox transformation has also been applied to model price changes and demand and supply elasticities. Soybean yield functions have been examined by Miner and Davison have modelled US soybean export. They concluded that the transformation provides approximately normally distributed error terms, a condition which is important for hypothesis testing and the construction of confidence intervals. It is important however, to point out that when certain a priori restrictions are placed on the transformation parameter, some behavioral properties are also unnecessarily forced upon the function. Since the Box- Cox transformation procedure calls for the resulting functional form to be entirely an outcome of the estimation process, any form of restrictions to be imposed on an a priori basis should be avoided as much as possible.

Example

For the DEX/CRH test, mean cortisol levels wereequivalent between the groups at baseline and duringthe early stages of the test, although higher mean cortisollevels were apparent among participants that did notsubsequently make the transition to psychosis, peakingat 60 min (see Fig. 1). the time of testing: sertraline 100 mg/d (one transition,one non-transition) and citalopram 30 mg/d (one transition,one non-transition).

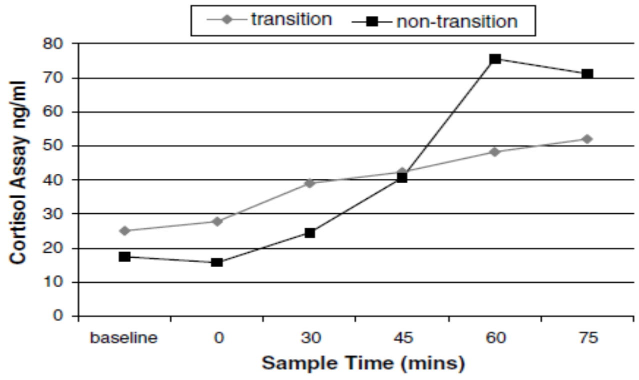

Fig. 1.

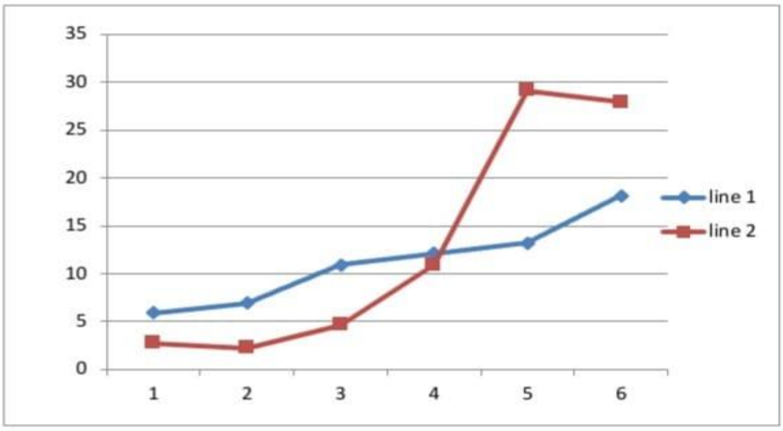

Fig. 2.

CONCLUSION

The Present study investigated the HPA axis functioning associated with transition to psychosis combined: DEX/CRH test from fig (1). We analyzed using Box – Cox Transformation.Finally from fig (2), we conclude that the results synchronize with Mathematical and Medicalreport.

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