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人體藥物動力學模式考慮動態模式的參數估計

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中文摘要

人體藥物動力學模式（physiologically-based pharmaco-kinetic model, or PBPK model）為用以描述環境暴露於有害化學物質情況下，體內相對隨時間變化的濃度的動態關係最直接的証據與有力的工具。但是由於 PBPK 模式包含了約二十個因人而異的參數，而參與實驗的人數與重複測量的次數通常極為有限，因此建立體內濃度與外在暴露濃度的動態關係所需的統計分析也存在許多的不確定性。 Bois 等人利用貝氏統計的架構以馬可夫鍊蒙地卡羅(MCMC)方法算出 PBPK 模式的眾多參數分布，再得到體內濃度與環境暴露隨時間變化的動態關係（Bois, Jackson, Pekari, & Smith, 1996;Gelman, Bois, & Jiang, 1996）。雖然上述做法成功的引進 MCMC 方法克服了 PBPK 模式太多未知參數的問題，但是在考慮模式預測值與實際量取值的差異時，Bois 等人將此歸諸於來自測量誤差(measurement error)，然而由於體內濃度隨環境暴露變化的動態濃度實際上為一隨機過程，而人體代謝機制也極為複雜，因此必須將過程誤差(process error)一併考慮。此外，由於實驗室儀器的進步，測量誤差的影響可能遠不及於過程誤差。本計畫成果基於 Bois 等人的方法架構，同時考慮過程誤差與測量誤差。首先將 PBPK model 簡化成線性隨機微分方程式，積分後同時考慮測量誤差，很自然的轉換成時間數列的 state-space model。利用 Kalman filter 的方法，可以產生各空腔隨時間變化的濃度以及各參數的事後分布，再利用 MCMC 的方法，即可得到眾多參數理論上收斂時的穩定分布。

關鍵詞：馬可夫鍊蒙地卡羅、過程誤差、測量誤差、環境暴露濃度、隨機微分方程式

英文摘要

Physiologically-based pharmacokinetic models (PBPK models) have been playing an important role in assessing the dynamic relationship between internal dose and environmental exposure to hazardous chemicals. However, numerous model parameters with often very limited study subjects make statistical analysis difficult to justify. Bois et al (1996) and Gelman, Bois, and Jiang (1996) successfully applied the MCMC simulation technique in PBPK model parameter estimation problem. However, their approach attributed the random variations in internal concentrations to measurement error only, which may not be the case in real life. Due to the complexity of body metabolic mechanism, stochastic variations (process error) other than the deterministic model should be taken into account. In addition, this source of variation may surpass measurement error owing to advances in laboratory techniques nowadays. This report considers both process error and measurement error simultaneously. First, by adding random variations to the deterministic model and simplified to linear case, we obtain system of stochastic differential equations. Integrating through Ito integral, the resultant equations of internal concentrations become familiar state-space model with measurement error. The Kalman filter technique is then employed to obtain the posterior distributions of concentrations and parameters given concentrations. The MCMC technique is finally applied to generate the required samples after convergence.

Key words: Markov Chain Monte Carlo, process error, measurement error, environmental exposure concentration, stochastic differential equation

報告內容

1. 前言

The assessment of biological concentrations of a person exposed to hazardous chemicals helps industrial hygienists in determining how much risk one may develop certain diseases more precisely than environmental exposure monitoring. To find the relationship between environmental exposure and the corresponding internal concentrations, physiologically based pharmacokinetic (PBPK) models that describe the dynamic internal concentrations within body tissues have become popular in recent years (Leung, 1992; Thomas, et al, 1996; Reitz, et al, 1996). Specifically, PBPK models not only helps industrial hygienists to propose biological exposure indexes (BEIs) in more biological media and at different sampling times, it can also be used to simulate a wide variety of exposure conditions (Leung, 1992).

By dividing the whole body of a person into 4 (or 5) different groups of tissues: fat, muscle (slowly perfused), richly perfused, liver, and assuming that all metabolism takes place in the liver, dynamic concentrations within each compartment at time *t* can be determined by solving the mass-balance equations for each of the compartments. Specifically, let the fat, muscle, richly perfused, and liver compartments be denoted by $k = 1,2,3,4$, respectively. The concentrations for the non-liver compartments satisfy the equation

$$V_k \frac{d}{dt} C_k(t) = Q_k \left[C_{art}(t) - C_k(t)/\lambda_k \right], k = 1,2,3, \qquad (1)$$

and the concentration for the liver compartment satisfies the equation

$$V_4 \frac{d}{dt} C_4(t) = Q_4 \left[C_{art}(t) - C_4(t)/\lambda_4 \right] - \frac{V_{\max} C_4(t)}{K_m + C_4(t)} - K_f C_4(t) V_4/\lambda_4, \qquad (2)$$

where

$$C_{art}(t) = \left(Q_c C_{ven}(t) + Q_{alv} C_{inh}(t) \right) / \left(Q_c + Q_{alv}/\lambda_b \right), \qquad (3)$$

and

$$C_{ven}(t) = \sum_{k=1}^{4} \left(Q_k C_k(t)/\lambda_k \right) / Q_c \qquad (4)$$

are the concentrations in the arterial blood and venous blood at time *t*, respectively, $C_{inh}(t)$ is the chemical concentration in inhaled air, $C_k(t)$ is the chemical concentration in the *k-th* compartment at time *t*, Q_{alv} is the alveolar ventilation, Q_k, V_k, and λ_k are the blood flow rate, volume, and tissue-blood partition coefficient of the *k-th* compartment, respectively. Also, λ_b is blood-air partition coefficient, Q_c is the cardiac output, $V_{\max}$ is the maximum rate of metabolism, K_m is the Michaelis-Menten kinetic constant, and K_f is the first order metabolic constant.

To fit in the unknown parameters of the PBPK model for internal concentrations in practice, researchers of the field often obtain the partition coefficients λ_k and λ_b from literature, V_k and Q_{alv} are proportional to individual body weight, and Q_k are proportional to Q_{alv}. And the metabolic constants $V_{\max}$, K_m, and K_f are obtained by scaling allometrically the in vivo value

determined in laboratory animals with gas uptake techniques (see, e.g., Leung, 1992). Variations of the internal concentrations are then obtained by assigning statistical distributions to the parameters (Thomas, et al, 1996; Wu, et al, 2002). However, since these unknown model parameters are different for each individual, and the best fitting values are only empirical based on often very limited measurements, the results may not be legitimate for statistical inferences.

2. 研究目的

In this report, to estimate the PBPK model parameters more adequately, we consider the stochastic variations of internal concentrations together with measurement error. The most important direct impact would be statistical inferences based on the estimated model parameters, especially body burden calculated from accumulated predicted compartment (such as liver or fatty tissue) concentrations. Another important application is retrospectively from sample internal concentrations to assess environmental exposure concentration, which is difficult to assess in most cases. However, the latter case is of direct concern to public population. The latter serves as two major goals in our follow-up projects.

3. 文獻探討

To estimate the PBPK model parameters with formal statistical approach, Bois et al (1996) and Gelman, Bois, and Jiang (1996) employed the Markov Chain Monte Carlo (MCMC) simulation technique for population modeling with informative prior distributions for the parameters. Given the observations and the prior information, random samples of the parameters are generated from their posterior distributions. These values are then fitted into the PBPK model to obtain the internal concentrations at time t using the Runge-Kutta numerical integration method. Differences of the expectations and the observations are attributed to measurement error. Updated observations can be obtained from the posterior distribution of the measurement error, from which new set of parameters are again generated. The procedure is repeated until large enough samples are generated from their stationary distributions after convergence.

Though the approach using MCMC simulations successfully reflects population parameters distributions upon convergence. Due to complexity of human body metabolic mechanism, the deterministic models represented by the mass-balance equations (1) and (2) are subject to stochastic variations, which should also be taken into account. That is, successive observations in time may depart from the trajectory predicted by the deterministic model. And special attention should be dealt with this source of error other than measurement error as well.

4. 研究方法

In this report, we approximate equation (2) into a linear form, and rewrite equations (1) and (2) as stochastic differential equations by adding stochastic variations. The solutions together with equations (3) and (4) are then transformed into a dynamic linear state-space model, the established Bayesian methodology using the Kalman filter is then employed for the unobserved compartment concentrations. Together with the MCMC simulations, samples of the unknown population parameters are then generated for statistical inferences.

5. 結果與討論

The methodology of the proposed approach has already been completed. Numerical results such as real example analysis and simulations are working in progress. It is expected that the complete manuscript for submission for publication is no later than the end of February, 2005. The results are expected to be the mainstream in PBPK model statistical research. Not only the results correct Bois et al's main framework, which is oversimplified. But it also successfully brings in state-space model structure naturally together with MCMC simulation technique. The developed methodology is further applied to backward estimation of (unknown) individual environmental exposure based on blood sampling measurements.

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