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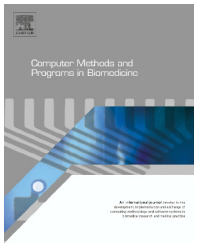

Statistical identifiability and convergence evaluation for nonlinear pharmacokinetic models with particle swarm optimization

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ABSTRACT

The statistical identifiability of nonlinear pharmacokinetic (PK) models with the Michaelis–Menten (MM) kinetic equation is considered using a global optimization approach, which is particle swarm optimization (PSO). If a model is statistically non-identifiable, the conventional derivative-based estimation approach is often terminated earlier without converging, due to the singularity. To circumvent this difficulty, we develop a derivative-free global optimization algorithm by combining PSO with a derivative-free local optimization algorithm to improve the rate of convergence of PSO. We further propose an efficient approach to not only checking the convergence of estimation but also detecting the identifiability of nonlinear PK models. PK simulation studies demonstrate that the convergence and identifiability of the PK model can be detected efficiently through the proposed approach. The proposed approach is then applied to clinical PK data along with a two-compartmental model.

1. Introduction

The nonlinear modeling is a routine but absolutely necessary statistical method in analyzing drug concentration data measured over time in pharmacokinetics (PK). In PK studies, Michaelis–Menten (MM) equation is often employed to describe the intrinsic clearance

$$CL_{\text{int}} = \frac{V_{\max}}{K_m + C(t)},$$

where $V_{\max}$ is the maximum enzyme activity; K_m is an inverse function of the affinity between drug and enzyme; $C(t)$ is an unbound drug concentration. K_m is also called the MM constant having the units of $C(t)$. The deterministic and statistical identifiabilities of parameters in the MM equation have been examined [1–3]. The deterministic identifiability is concerned with whether the model parameters can be identified with noise-free data, while the statistical identifiability is the possibility of identifying the model parameters with noise data.

Although numerous methods have been presented to detect the non-identifiable parameters deterministically, such as the Laplace transform [4], the similarity transformation approach [5], the Voterra and generating power series approaches [6], the differential algebra approach [7], and the alternating conditional expectation algorithm [8], there has been much less development in statistical identifiability analysis of PK models. One of the empirical approaches to assessing the statistical identifiability is the local sensitivity analysis. The local sensitivity analysis in the statistical identification uses the first partial derivatives of the differential

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equations with respect to the parameters, and depends on the non-singularity of the Fisher information matrix, which is equivalent to the Taylor series method and differential algebra method [9,10].

However, the local sensitivity analysis is likely to make a wrong decision if the estimate is far from the true value or the model has very complicated dynamics. Yue et al. [11] thus proposed the global sensitivity analysis for robust experimental design based on the modified Morris method [12], but it still requires an initial guess or prior knowledge concerning the underlying relation of the parameters. Therefore, we propose an approach not only to accessing the identifiability globally but also to requiring no preprocessing to obtain an initial guess or prior knowledge.

A number of estimation approaches were developed for population PK analysis [13–17]. Most approaches are a derivative-based local optimization method, however. A well-known challenge of the local optimization, such as the Newton and alike methods, is stuck at the saddle points or a local optimum so that the initial values are required to lie within a relatively small neighborhood of the true optimum to find a global optimum, and the derivative-based method is often terminated earlier due to the singularity. The singularity problem can become more prominent when the model is statistically non-identifiable. These issues urge us to use a derivative-free global optimization algorithm since it can avoid the singularity problem as well as seek the best parameter estimates of nonlinear models regardless of the presence of multiple local optima.

One interesting evolution based global optimization approach, particle swam optimization (PSO), was developed by Kennedy and Eberhart [18,19]. PSO algorithm is a derivative-free approach and becoming very popular due to its simplicity of implementation and robust convergence capability. Using PSO algorithm, Kim and Li [17] developed a global search algorithm, P-NONMEM, for nonlinear mixed-effects models to meet the challenges of the local optimization in NONMEM, which is one of the most popular approaches in PK studies. However, NONMEM uses a Broyden-Fletcher-Goldfarb-Shanno (BFGS) quasi-Newton algorithm, which is a derivative-based approach, so that it is not free from the singularity problem. For this reason, we develop a modified version of PSO algorithm, which is the PSO coupled with a derivative-free local optimization algorithm (LPSO), in order to estimate the parameters regardless of the identifiability.

One challenge of PSO algorithm is the lack of convergence criteria. The number of function evaluations is often used as a stopping criterion along with incorporating the choice of a problem-dependent parameter, which relies on the gradient or difference between the previous and the current estimates. However, this approach doesn't take the random or stochastic behavior of PSO into account so that it will make the estimation stopped before reaching a global optimum. It also focuses only on the identifiable situations. Therefore, it is desirable to have a reliable convergence criterion for detecting when the optimization process has found the global optimum even for non-identifiable conditions. We thus propose several approaches to not only diagnosing the convergence of PSO but also detecting the statistical identifiability.

In Section 2, a brief description of a two-compartment model with Michaelis–Menten kinetic equation is given. The nonlinear PK models with PSO are introduced in Section 3. In Section 4, the proposed PSO algorithm and its convergence criteria are described in details. Simulation studies are performed to evaluate the proposed approaches and real clinical PK data then are applied in Section 5. In Section 6, conclusions are reached.

2. Michaelis–Menten kinetic equation and two compartmental pharmacokinetics model

2.1. Statistical identifiability with the Michaelis–Menten kinetic equation

It is well known that the drug metabolism rate follows the Michaelis–Menten (MM) kinetics equation:

$$V(t) = \frac{dC(t)}{dt} = \frac{V_{max} \cdot C(t)}{K_m + C(t)},$$

where $V(t)$ is the velocity of the reaction, V_{max} is the maximum velocity, K_m is the MM constant, and $C(t)$ is the drug concentration. Monod [20] first applied the MM equation to microbiology for the growth rate of microorganisms.

The MM equation generally describes the relationship between the rates of substrate conversion by an enzyme to the concentration of the substrate. In this relationship, $V(t)$ is the rate of conversion, V_{max} is the maximum rate of conversion, and $C(t)$ is the substrate concentration. The MM constant K_m is equivalent to the substrate concentration at which the rate of conversion is half of V_{max}. K_m approximates the affinity of enzyme for the substrate. A small K_m indicates high affinity, and a substrate with a smaller K_m will approach V_{max} more quickly. Very high $C(t)$ values are required to approach V_{max}, which is reached only when $C(t)$ is high enough to saturate the enzyme [21].

In pharmacology research, the statistical identifiability often occurs with the MM equation. Suppose the observed data $y(t)$ follows a normal distribution with the MM equation at a time point t given the parameter $\theta = (V_{max}, K_m)$:

$$y(t) \sim ND\{\log \quad f(\theta, t), \sigma^2\},$$

where $f(\theta, t) = V(t)$ and ND stands for a normal distribution. However, when K_m is much higher than the concentration $C(t)$ (i.e., $K_m \gg C(t)$), the function $f(\theta, t)$ is close to $(V_{max}/K_m) \cdot C(t)$ in the equation below:

$$f(\theta, t) = \frac{V_{max} \cdot C(t)}{K_m + C(t)} \approx \frac{V_{max}}{Km} \cdot C(t) \quad \text{if} \quad C(t) \ll K_m.$$

In addition, when K_m is much smaller than the concentration $C(t)$ (i.e., $K_m \ll C(t)$), $f(\theta, t)$ is close to V_{max} in the equation below:

$$f(\theta, t) = \frac{V_{max} \cdot C(t)}{K_m + C(t)} \approx V_{max} \quad \text{if} \quad C(t) \gg K_m.$$

In other words, if the concentration $C(t)$ is much either less or greater than K_m, one will not be able to estimate both K_m and V_{max} separately due to identifiability.