Constant optimization of oral drug absorption kinetics in the compartment absorption and transit models using particle swarm optimization algorithm

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Abstract. Simulation of predictive modeling oral drug namely Compartment Absorption and Transit (CAT) using Particle Swarm Optimization (PSO) algorithm has been performed. This research will be carried out optimization of kinetic constant value oral drug use PSO algorithm to obtain the best global transport constant values for CAT equation that can predict drug concentration in plasma. The value of drug absorption rate constant for drug atenolol 25 mg is k10, k12, k21, k13 and k31 with each value is 0.8562, 0.3736, 0.2191, 0.4334 and 1.000 have been obtained thus raising the value of the coefficient of determination of a model CAT. From the experimental data plasma drug concentrations used are Atenolol, the coefficient of determination (R²) obtained from simulations atenolol 25 mg (PSO) was 81.72% and 99.46%. Better correlation between the dependent variable as the drug concentration and explanatory variables such as mass medication, plasma volume, and rate of absorption of the drug has increased in CAT models using PSO algorithm. Based on the results of CAT models fit charts can predict drug concentration in plasma.

1. Introduction

Modern drug design is not only focused on the pharmacological activity but also reach the area where the drug is working and the ability of the drug to be absorbed by the body. A few of mathematical models that can predict the oral bioavailability of a drug, where bioavailability is the extent to which the drug is absorbed in the body. Predictive modeling oral drug that made Yu et al
namely Compartment Absorption and Transit (CAT) has provided an understanding of oral drug absorption since the 1995's until the present[1-2]. The mathematical model is an interesting tool that provides an understanding of oral drug absorption since the 1650s until now.

Particle Swarm Optimization (PSO) is a method of optimization solutions that is adapted from the behavior of animals such as birds flock movements are then each object animals consider to be a particle. A particle in D-dimensional space has a position that is encoded as a vector coordinates. This position vector is considered as a condition of the particle in the search space. Each position in the search space is an alternative solution that can be evaluated using the objective function. Each particle moves with a certain speed. Particle Swarm Optimization (PSO) to apply the nature of each individual in a large group. Then combine these properties to solve problems. Particle Swarm Optimization was introduced in 1995, since then that the researchers who developed the method of PSO. The unique thing of the PSO algorithm is heuristic particle speed settings and probabilistic. If a particle has a constant speed so if the position of a particle visualized trail will form a straight line. With the external factors that alter the line will then move the particle in the search space it is expected that the particles can lead, approached, and ultimately achieve an optimal point. External factors in question include the best position ever skipped a particle and the best position of the entire particles (each particle is assumed to know the best position of any other particles).

In this simulation, to optimize the absorption of orally administered drugs in the small intestine are used PSO algorithm. Given the effectiveness of the concept and simple, PSO optimizer has become popular and has been widely applied in practical problem solving. Thus, the theoretical study and improvement of the performance of the algorithm has become an important and attractive[3-18]. This research will be carried out optimization of kinetic constant value oral drug use PSO algorithm to obtain the best global transport constant values for CAT equation that can predict drug concentration in plasma.

2. Theory

2.1. Particle Swarm Optimization

There are n particles in a space dimension D, the position of the i-th particle in a room is \( r_i = (r_{i1}, r_{i2}, ..., r_{id}) \), \( i = 1, 2, 3, ..., n \), the particle velocity is \( \dot{r}_i = (\dot{r}_{i1}, \dot{r}_{i2}, ..., \dot{r}_{id}) \), \( i = 1, 2, 3, ..., n \) and the best position of a particle is \( P_i = (P_{i1}, P_{i2}, ..., P_{id}) \), \( i = 1, 2, 3, ..., n \). The position of the particle swarms is \( P_g = (P_{g1}, P_{g2}, ..., P_{gd}) \), \( i = 1, 2, 3, ..., n \), where the PSO algorithm is as follows:

\[
\begin{align*}
    r_{id} &= r_{id} + \dot{r}_{id} \\
    \dot{r}_{id} &= \dot{r}_{id} + c_1 \beta_1 (r_{id} - r_{id}) + c_2 \beta_2 (p_{gd} - r_{id})
\end{align*}
\]

Where, \( i = 1, 2, ..., n \), \( d = 1, 2, ..., D \), \( c_1 \) and \( c_2 \) is the coefficient identifier on each swarm and are positive. The relative coefficient value expressing the degree of the relative importance of Pi and Pg with developments. \( \beta_1 \) and \( \beta_2 \) is a random value between 0-1, is determined by the user, equation (1) and (2) can be modified into

\[
\begin{align*}
    r_{id} &= \gamma r_{id} + \dot{r}_{id} \\
    \dot{r}_{id} &= \omega \dot{r}_{id} + c_1 \beta_1 (r_{id} - r_{id}) + c_2 \beta_2 (p_{gd} - r_{id})
\end{align*}
\]

Where \( \gamma \) and \( \omega \) each is a constant factor and the factor of inertia. This model will be simulated in space with specific dimensions with a number of iterations so that in each iteration, the particle's
position will increasingly lead to the intended target (minimizing or maximizing functions). This is done until the maximum iteration can also be used to achieve or other termination criteria.

2.2. Compartment Absorption and Transit (CAT) models

The distribution of the different compartments have been used to simulate and explain the oral drug absorption. Therefore it is necessary defining the number of compartments closest to the small intestine absorption characteristics in humans. CAT models created to describe the transit flow of drugs in the human intestine. This model can explain the problem and estimate the plasma concentrations of oral absorption of oral medications. This model defines that the drug crosses the small intestine passes through a series of compartments. Each compartment has a linear transfer kinetics. Each compartment is smoothly flow rate and volume are different but have Kt (constant transit) are the same. In this model the digestive system is divided into three segments, namely the stomach, small intestine, and large intestine. Human small intestine is divided into seven compartments with drug transfer from one compartment to the other compartment occurs in the first order.

![Figure 1 CAT diagram with linear transit and absorption kinetics][1]

Figure 1 illustrates the CAT models to calculate the flow of transit in the stomach, duodenum, jejunum, ileum and colon. Drugs should not be described soon after entry into the human body where $M_s$, $M_c$ and $M_a$ are the mass of the drug in the stomach, small intestine and colon, $K_s$, $K_a$ and $K_i$ are rate constant of gastric emptying, intrinsic absorption and small intestine transit. So that modeling transit and gastrointestinal absorption can be formulated as follows.

Stomach:

$$\frac{dM_s}{dt} = -K_s M_s, \quad \text{where, } K_s = \frac{1}{T_{ge}}$$

Small Intestine:

$$\frac{dM_1}{dt} = K_s M_s - K_1 M_1 - K_0 M_1,$$
$$\frac{dM_2}{dt} = K_0 M_1 - K_1 M_2 - K_0 M_2,$$
$$\frac{dM_3}{dt} = K_1 M_2 - K_2 M_3 - K_0 M_3,$$
$$\frac{dM_4}{dt} = K_2 M_3 - K_3 M_4 - K_0 M_4,$$
$$\frac{dM_5}{dt} = K_3 M_4 - K_4 M_5 - K_0 M_5,$$  

(6)
\[ \frac{dM_6}{dt} = K_5 M_5 - K_6 M_6 - K_7 M_6, \]
\[ \frac{dM_7}{dt} = K_6 M_6 - K_7 M_7 - K_8 M_7, \]

Where, \( K_a = 2(P_{off}^{*}R) \), \( K_i = 7/T_{ai} = 7/3.32 \) jam and \( K_0 = K_1 \).

Colon:
\[ \frac{dM_a}{dt} = -K_a M_a, \quad (7) \]

The amount of drug absorbed by the small intestine:
\[ \frac{dM_n}{dt} = K_n \sum_{a=n}^{2} M_n, \quad n = 1, \ldots, 7 \quad (8) \]

Yu et al provide modeling compartment as follows[1]:
\[ \frac{dC_1}{dt} = \frac{1}{V_1} \frac{dM_n}{dt} - (k_{12} + k_{13} + k_{10})C_1 + k_{21}C_2 + k_{31}C_3 \quad (9) \]
\[ \frac{dC_2}{dt} = k_{12}C_1 + k_{21}C_2 \quad (10) \]
\[ \frac{dC_3}{dt} = k_{13}C_1 + k_{31}C_3 \quad (11) \]

where \( V_1 \) is the volume of the central compartment, \( k_{10}, k_{12}, k_{21}, k_{13} \) and \( k_{31} \) are the value of drug absorption rate constant.

### 3. Result and Discussion

Parameter values such as \( k_{10}, k_{12}, k_{31}, k_{13} \) and \( k_{31} \) is used as a constant transport of (Compartment Absorption and Transit) CAT models can be optimized using (Particle Swarm Optimization) PSO algorithm. The value of drug absorption rate constant for drug atenolol 25 mg is \( k_{10}, k_{12}, k_{21}, k_{13} \) and \( k_{31} \) with each value is 0.8562 , 0.3736 , 0.2191 , 0.4334 and 1.000 have been obtained thus raising the value of the coefficient of determination of a model CAT. From the experimental data plasma drug concentrations used are Atenolol, the coefficient of determination \( R^2 \) obtained from simulations atenolol 25 mg and 25 mg (PSO) was 81.72\% and 99.46\%. Based on the picture, the drug experienced three phase process in which plasma absorption, post absorption phase and elimination phase. Undergo drug absorption phase indicated by the increase in concentrations of the drug, and the drug experienced post absorption phase is indicated by a decrease in drug concentration. The last stage is the elimination phase which is characterized by a decrease in medication to near zero. Based on the results of CAT models fit charts can predict drug concentration in plasma.
Figure 2. CAT models without PSO (Atenolol 25mg). $R^2=81.72\%$

Figure 3. CAT models with PSO (Atenolol 25mg). $R^2=99.46\%$

Table 1. CAT model parameters for drug atenolol 25 mg and 25 mg (PSO)

| Parameters | 25 (PSO) | 25 |
|------------|----------|----|
| $F$        | 0.56 $^a$ | 0.56 $^a$ |
| $P_{eg}$ (cm/hr) | 0.19 $^a$ | 0.19 $^a$ |
| $T_{ge}$ (hr) | 2 $^a$ | 2 $^a$ |
| $K_S$ (hr$^{-1}$) | 0.2171 $^a$ | 0.2171 $^a$ |
| $K_a$ (hr$^{-1}$) | 0.5 $^a$ | 0.5 $^a$ |
| $K_{12}$ (hr$^{-1}$) | 0.3736 $^c$ | 0.05 $^b$ |
| $K_{13}$ (hr$^{-1}$) | 0.4334 $^c$ | 0.9 $^b$ |
| $K_{21}$ (hr$^{-1}$) | 0.2191 $^c$ | 11.32 $^b$ |
| $K_{31}$ (hr$^{-1}$) | 1.0 $^c$ | 0.39 $^b$ |
| $K_{10}$ (hr$^{-1}$) | 0.8562 $^c$ | 0.9 $^b$ |

$^a$ Yu et al (1999).
$^b$ estimates.
$^c$ Using PSO with upper and lower bound that has been determined from 0 to 1.

4. Conclusion

This study reported that the PSO algorithm can determine the rate constant of drug absorption and also increases the coefficient of determination of CAT models in order to estimate the oral drug absorption in plasma.

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