Study of Parameters Estimation of The Three-Compartment Pharmacokinetic Model using Particle Swarm Optimization Algorithm

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Abstract. The accuracy of the numerical solution of the three-compartment pharmacokinetic model is generally related to the rate parameter. Therefore, in this research, the numerical solution will be applied to the pharmacokinetic model which is shaped by the nonlinear coupled ordinary differential equations. Then the particle swarm optimization (PSO) algorithm which used random numbers is used to estimate the parameters of the pharmacokinetic model. The accuracy of the estimation parameters can be predicted using the experimental data of the drug absorption concentration by using the shape suitability of the curve. Based on these study results, the PSO algorithm is very simple but provides accurate parameter estimates for predicting drug concentrations in the central compartment over the entire time span after oral drug administration. This numerical method has been tried in experimental literature data for the drug atenolol. The prediction accuracy of the drug absorption indicates that the $R^2$ value of all numerical results has reached above 90%.

1. Introduction

The pharmacokinetic models have been used to describe the distribution and concentration of oral drugs in the human body. This model is commonly used in many clinical applications and drug designs. Pharmacokinetic models can be applied to estimate optimal drug scheduling and appropriate drug dosages. In the pharmaceutical industry, pharmacokinetic models will be applied to help design drug systems. Pharmacokinetic models are very helpful in clinical applications, and for obtaining the basic concepts of drug transport and metabolism in vivo [1].

The pharmacokinetic models can describe the process of absorption, distribution, and elimination of drugs in the human body. In this model, human body tissue is usually described by one or more compartments to represent the mechanism of the drug being absorbed, transferred, and removed according to the function of the kinetic parameters in the compartment. These kinetic parameters are time-dependent but can be categorized as the independent variable [2]. The numerical solution of the pharmacokinetic equations will give the absorbed drug concentration in each compartment as a function of time. The parameters of the pharmacokinetic models will be estimated with experimental data for the plasma drug atenolol concentration based on the literature [3]. This study will estimate the parameters of the pharmacokinetic models which are shaped by the coupled ordinary differential equation by using the PSO algorithm. This algorithm uses random numbers to estimate the parameters of the pharmacokinetic models.
In general, the human body can be described in the pharmacokinetic models as the many compartments including a central compartment. The process of absorption and elimination usually takes place only in the central compartment. However, the drug distribution process can occur in all compartments. Nonetheless, the pharmacokinetic models for most drugs can be described by single or two-compartment models. The pharmacokinetic equation for the two-compartment model with the oral drug dose is formed by the central compartment and the compartment combination between the shallow and deep compartments. The central compartment is assumed to be the first-order absorption compartment with the absorption rate parameter \( k_a \). The development of pharmacokinetic models based on accurate methods and sensitive analytical techniques has shown that some oral drugs follow the pattern of a three-compartment pharmacokinetic model. After oral drug administration into the central compartment, the drug is then slowly distributed to other tissues. However, the distribution of drugs to some networks is much slower than the distribution to the central network. The three-compartment pharmacokinetic model consists of two peripheral compartments connected to a central compartment. The central compartment itself is a site for drug absorption and elimination.

The PSO algorithm is inspired by the behaviour of animal populations. James Kennedy and Russell C. Eberhart introduced simulation of the behaviour of flocking birds that are looking for food as a simulation used to find solutions to optimization problems. In a conference in 1995, they have been published their ideas for the optimization of sustainable nonlinear functions \([4, 5]\). The PSO algorithm has two main concepts, that is velocity and coordinates for each particle. Each particle has an initial coordinate and an initial velocity in the solution space. As the algorithm develops, all the particles will converge to the coordinates of the best solution. The PSO algorithm is quite simple to implement as it requires less memory. Therefore, the simplicity of this PSO makes this algorithm have a high speed compared to other algorithms \([6]\).

In the basic formula of the PSO algorithm, the velocity of each particle is calculated using the current velocity, best personal, and best local values then multiplied by the stochastic variable. The current particles will update at previous rates, not only the best before but also the best in the global. Stochastic variables are used as the total probability to find and distribute the best local and global best \([6]\).

The dynamic systems models have an important role in applied science. In many fields of science and engineering, dynamic systems can be analyzed using compartment models. The compartment models are usually used in the pharmacokinetic models. In the pharmacokinetic models, the compartment model can describe how much time-dependent drug concentration is in the blood plasma. In other words, compartments can describe the body tissues pharmacokinetic. Parameters, such as volume and rate constant, for connecting the two compartments are assumed to be constant. They will be estimated to find the best solution. The estimation of pharmacokinetic parameters has been studied in the literature \([7]\).

This study is aimed to estimate the parameters of the three-compartment of the pharmacokinetic models using a population-based artificial intelligence algorithm, which is the PSO algorithm. This paper proposes a PSO algorithm for obtaining the estimation of compartment model parameters since this simple algorithm has a better consistent convergence to the best fitness value than the others.

## 2. Methods

### 2.1. Three-Compartmental Pharmacokinetic Model

For reducing complexity in drug metabolism problems, the pharmacokinetic models commonly use the compartment models. A single well-mixed compartment is the simplest pharmacokinetic model which usually for describing the administration of drug fluids that are transferred intravenously to enter the entire blood system in the human body. This model cannot describe the drug absorption process because it is without oral drug administration procedures. Therefore, this model does not require the calculation of the oral drug absorbed through the Gastro-Intestinal (GI) tract membrane \([8]\).

In the two-compartment pharmacokinetic model, this model is supplemented by extravascular administration (first compartment) for modeling the drug dosage administered orally and the oral drug
pass through to the bloodstream (second compartment). The second compartment should be able to describe the phase of absorption into the bloodstream and also be able to describe the phase of elimination or excretion. All processes must comply with the conservation law of mass [8].

The three-compartment pharmacokinetic model still assumes the first and second compartments have the same role as the two-compartment pharmacokinetic model, namely as blood flow and oral administration sites. In this model, blood flow should always be considered positive according to physiological realities. The main compartment can distribute drugs in two ways, which can be inserted into the third compartment or removed from the system as a whole. The coupled ordinary differential equation for the three-compartment pharmacokinetic model can be written as follows:

\[
\frac{dC_1}{dt} = \frac{dM_a}{dt} - (k_{12} + k_{13} + k_{10})C_1 + k_{21}C_2 + k_{13}C_3
\]  

(1)

\[
\frac{dc_2}{dt} = k_{12}C_1 - k_{21}C_2
\]  

(2)

\[
\frac{dc_3}{dt} = k_{13}C_1 - k_{31}C_3
\]  

(3)

The definitions of the pharmacokinetic parameters used in the equations of the three-compartment pharmacokinetic model are presented in Table 1.

**Figure 1.** Schematic Diagram of The Three-Compartment Pharmacokinetic Model and Compartmental Absorption and Transit Model
Table 1. The Compartment Symbol and Parameters of The Three-Compartment Pharmacokinetic Model

| Symbol | Definition |
|--------|------------|
| $C_1$  | the mass of oral drug in the central compartment and has units of mg/ml |
| $C_2$  | the mass of oral drug in the shallow compartment and has units of mg/ml |
| $C_3$  | the mass of oral drug in the deep compartment and has units of mg/ml |
| $k_{12}$ | the first-order transfer rate parameter from the central compartment to the shallow compartment and has units of min$^{-1}$ |
| $k_{21}$ | the first-order transfer rate parameter from the shallow compartment to the central compartment and has units of min$^{-1}$ |
| $k_{10}$ | the first-order elimination rate parameter from the central compartment and has units of min$^{-1}$ |
| $k_{13}$ | the first-order transfer rate parameter from the central compartment to the deep compartment and has units of min$^{-1}$ |
| $k_{31}$ | the first-order transfer rate constant from the deep compartment to the central compartment and has units of min$^{-1}$ |
| $V_1$  | the volume of the central compartment and has units of ml. This term relates the administered dose to the initial plasma drug concentration (central compartment concentration) after administration of an oral drug dosage |
| $M_a$  | the amount of drug absorbed in the small intestine |

2.2. Modified Compartmental Absorption and Transit Model

Yu and Amidon have introduced a compartmental absorption and transit (CAT) model to describe the drug transit flow rate and the drug absorption rate in the small intestine. The CAT model can also calculate the dose fraction of the drug that has been absorbed. This model proposes a small intestine consisting of seven compartments because it is the best compartment model [9, 10]. The seven-compartment model consists of the first compartment representing the duodenum, the second and third compartments representing the jejunum, and the other compartments representing the ileum. As long as the drug passes through the duodenum, jejunum, and ileum compartments, they take transit times of about 14, 71, and 114 minutes, respectively. Meanwhile, the GI tract in the CAT model consists of three compartments, namely the stomach, small intestine, and large intestine (colon).

After oral drug administration, the bioavailability of the drug sometimes depends nonlinearly on its concentration. The nonlinear phenomenon of drug absorption in the small intestine can be caused by several factors, one of which is a complex nonlinear bioavailability pattern. This nonlinear behaviour is due to the interaction between the small intestinal absorption and the secretory transport system when the concentration of the oral drug in the small bowel fluid falls outside the range of the linearly operating system. The nonlinear mechanism and kinetic properties of absorption in the small intestine are of great importance for the development of orally active drugs, especially in clinical applications. [11].

In this study, the original CAT model will be modified by assuming that nonlinear phenomena in the small intestinal absorption need to be considered in the previously CAT model [9, 10]. The modification of the original CAT model proposed in this study is written in the equations [12, 13]:

a. The equation in the stomach:
\[
\frac{dM_t}{dt} = -k_sM_s \quad \text{where} \quad k_s = \frac{1}{T_{ge}} \quad (4)
\]

b. The equation in the small intestine:
\[
\frac{dM_1}{dt} = \left( k_sM_s^2 - k_tM_1^2 \right) / M_0 - k_aM_1, \quad (5)
\]
\[
\frac{dM_2}{dt} = k_tM_1 - k_tM_2 - 2k_aM_2, \quad (6)
\]
\[
\frac{dM_3}{dt} = k_tM_2 - k_tM_3 - 2k_aM_3, \quad (7)
\]
\[
\frac{dM_4}{dt} = \left( k_tM_3^2 - k_tM_4^2 \right)a \times F / M_0 - k_aM_4, \quad (8)
\]
\[
\frac{dM_5}{dt} = \left( k_tM_4^2 - k_tM_5^2 \right)a \times F / M_0 - k_aM_5, \quad (9)
\]
\[
\frac{dM_6}{dt} = \left( k_tM_5^2 - k_tM_6^2 \right)a \times F / M_0 - k_aM_6, \quad (10)
\]
\[
\frac{dM_7}{dt} = \left( k_tM_6^2 - k_tM_7^2 \right)a \times F / M_0 - k_aM_7, \quad (11)
\]
c. The equation in the colon:
\[
\frac{dM_c}{dt} = k_tM_n, \quad (12)
\]

where \( k_a = \frac{2}{P_{eff} \times R} \) and \( k_t = \frac{7}{T_{se}} \). The definitions of the variables and parameters of the modified CAT model used in the equations above are presented in Table 2. The intestine permeability \( (P_{eff}) \) is one of the main biopharmaceutical parameters that determine the rate and extent of intestine drug absorption. Constant \( a = P_{eff} \times \frac{T_{ileum}}{T_{ileum}} = 0.0475P_{eff} \) for \( T_{ileum} = 1.9 \) hours and \( l_{ileum} = 400 \) cm. Notation \( F \) is a unitless ratio, \( 0 < F \leq 1 \), which is a ratio between the availability of the drug given via the non-oral route and the availability of the drug obtained when the drug is given via the oral route. The \( F \) value is also known as the dose fraction that reaches the small intestine transit process. This pharmacokinetic ratio parameter, \( F \), can also be used to represent absolute bioavailability in the steady-state and serves for the chronic treatment of a patient. While the rate of absorption of oral drugs from the small intestine into the plasma can be calculated by the equation:
\[
\frac{dM_a}{dt} = k_a \sum_{n=1}^{7} M_n, \quad n = 1, ..., 7. \quad (13)
\]
Table 2. Variables and Parameter of Modified Compartmental Absorption and Transit Model

| Symbol | Definition |
|--------|------------|
| $M_s$  | the mass of oral drug in the stomach |
| $M_n$  | the mass of oral drug in the $n$th compartment |
| $M_c$  | the mass of oral drug in the colon |
| $k_s$  | the rate constants of gastric emptying |
| $k_t$  | the rate constants of small intestine transit |
| $k_a$  | the rate constants of intrinsic absorption |
| $T_{ge}$ | the time constant for gastric emptying, |
| $T_{se}$ | the time constant for stomach emptying, |
| $P_{eff}$ | the effective intestine permeability coefficient through a cylindrical intestine segment of radius $R$. |
| $t$    | the time |

2.3. Particle Swarm Optimization

The main attractive nature of the PSO algorithm is its simplicity, due to it involves only two model equations. In this algorithm, the coordinates of each particle represent a possible solution which relates to two vectors, that is the position ($x_i$) and velocity ($v_i$) vectors. A swarm consists of a number of particles (or possible solutions) in N-dimensional search space. Position vectors, $X_i = [x_{i1}, x_{i2}, ..., x_{iN}]$, and velocity vectors, $V_i = [v_{i1}, v_{i2}, ..., v_{iN}]$, are the two vectors associated with each particle. These two vectors will continue (fly) through the feasible solution space to derive optimal solutions [14]. Each particle position will be updated based on its own exploration to achieve the best position and also based on the best swarm overall experience. Its previous velocity vector according to the following equation:

$$V_j(i) = V_j(i-1) + c_1 r_3 |P_{best,j} - X_j(i-1)| + c_2 r_2 |G_{best,j} - X_j(i-1)|,$$

(14)

$$X_j(i) = X_j(i-1) + V_j(i)$$

(15)

The definitions of the variables and parameters of PSO used in the equations above are presented in Table 3. The outline of a PSO algorithm in this case is as follows:

```
% PSO algorithm
global k10 k12 k13 k31
atenolol_data = load('atenolol_data.txt');
s = atenolol_data (:,1)
C25_50_100 = atenolol_data (:,2)
upbnd= [k10 k12 k13 k31];
lwbnd= [k10 k12 k13 k31];
N = maximum of particles;
M = maximum of iterations;
X = zeros(N,5);
V = zeros(N,5);
% Initializing positions and velocities
for i = 1: N
    for j = 1:5
        X(i,j) = (upbnd(j)-lwbnd(j)).*rand + lwbnd(j);
        V(i,j) = 4*rand;
    end
end
```
```matlab
[line, colom] = size(X);
for i = 1 : N
    k_{10} = X(i,1);
    k_{12} = X(i,2);
    k_{21} = X(i,3);
    k_{13} = X(i,4);
    k_{31} = X(i,5);
    Xhimel = X; Vhimel = V;
    Xhimel = Xhimel + Vhimel;
    for i = 1: N
        for j = 1:5
            if lbwbd(j) <= Xhimel(i,j) && Xhimel(i,j) <= upbnd(j)
                X(i,j) = Xhimel(i,j);
            else
                X(i,j) = X(i,j);
            end
        end
    end
    rhomax = 0.9; rhomin = 0.4;
    for it = 1: M
        rho(it) = rhomax - ((rhomax-rhomin)/M)*it;
    end
    it = 1;
    Pbest = X;
    [minf, idk] = min(errorC_kuadrat);
    CATbest = X(idk,:);
    while it < M
        it;
        r_1 = rand; r_2 = rand;
        for i = 1: line
            Vhimel(i,:) = rho(it).*Vhimel(i,:) + r_1.*(Pbest(i,:)-...Xhimel(i,:)) + r_2.*(CATbest-Xhimel(i,:));
            Xhimel(i,:) = Xhimel(i,:) + Vhimel(i,:);
        end
    end
end
```

```matlab
[70x777]Seminar Nasional Fisika (SNF) Unesa 2020
[70x763]Journal of Physics: Conference Series
[274x763]1805 (2021) 012032
[368x763]IOP Publishing
doi:10.1088/1742-6596/1805/1/012032
```
### Table 3. Variables and Parameter of Modified Compartmental Absorption and Transit Model

| Symbol | Definition |
|--------|------------|
| $c_1$ and $c_2$ | two “trust” positive constants |
| $r_1$ and $r_2$ | two randomly generated numbers with a range of [0,1] |
| $\text{best}_j$ | the best position particle achieved based on its own experience |
| $G_{\text{best},j}$ | the best particle position based on overall swarm’s experience |
| $j$ | the iteration index |
| $i$ | the particle index |

For evaluating the best numerical solution. The coefficient of determination, $R^2$, is calculated to show the graphic method between the numerical solution results and experimental data is the best solution. In general, the value of $R^2$ is above 0.9 indicates the best solution. The $R^2$ value of the best graphic method between the numerical solution results and the experimental data is calculated by the following equation:

$$ R^2 = \left(1 - \frac{X^2}{\text{sst}}\right) \times 100 \%, $$

where $X^2$ and SST are:

$$ X^2 = \sum_{i=1}^{N} (y_{\text{exp}i} - y_{\text{sim}i})^2, $$

$$ \bar{y} = \sum_{i=1}^{N} \frac{(y_{\text{sim}i} + y_{\text{exp}i})}{2N}, $$

$$ \text{sst} = \sum_{i=1}^{N} (y_i - \bar{y})^2, $$

where $y_{\text{exp}}$ is experimental data, $y_{\text{sim}}$ is the numerical solution results of the pharmacokinetic equations and $\bar{y}$ is the averaged data.

### 3. Results and Discussion

The In this study, a pharmacokinetic model behavior in form of a three-compartment model have been done. The PSO algorithm was applied for analysis of clinical data from a previous literature for atenolol. The initialization of pharmacokinetic parameters which will be estimated from both the graphical method and the PSO algorithm represented in this study are represented in Table 4. The available clinical data and numerical solution results are shown in Figure 2, 3, and 4 for atenolol, respectively, represent oral drug doses for 25, 50, and 100 mg [15].

The coefficient of determination $R^2$ obtained from all drug doses was more than 90 %, so this parameters estimation was said to be feasible to use. From Figure 2, 3, and 4 indicate that the parameters estimation procedure calculated in this study have comparable accuracy in predicting the drug concentration in the central compartment. Nevertheless, the most graphics only show good accuracy in predicting the drug concentration in the early stages after an oral drug administration.
Figure 2. Atenolol Concentration in The Central Compartment After 25 mg Bolus Dose for A Subject. A Solid Line Represents A Numerical Solution and A Red Circle Represents an Experimental Data.

Figure 3. Atenolol Concentration in The Central Compartment After 50 mg Bolus Dose for A Subject. A Solid Line Represents A Numerical Solution and A Red Circle Represents an Experimental Data.
Figure 4. Atenolol Concentration in The Central Compartment After 100 mg Bolus Dose for A Subject. A Solid Line Represents A Numerical Solution and A Red Circle Represents an Experimental Data

Table 4. The Pharmacokinetic Parameters Estimated from Experimental Data

| Parameters | Lower bound | Upper bound |
|------------|-------------|-------------|
| $k_{12}$   | 0.50        | 1.00        |
| $k_{21}$   | 0.20        | 0.60        |
| $k_{10}$   | 0.10        | 2.40        |
| $k_{13}$   | 0.50        | 2.00        |
| $k_{31}$   | 0.50        | 0.70        |

Estimation of the parameters of the modified model using PSO shows good and efficient results in predicting the absorption rate of oral drugs in the human small intestine. The PSO method has a better ability in estimating, because the position and velocity of the particles can affect changes with each iteration, and only requires less memory than other optimization methods.

At the oral drug dose of 25 mg, the value of $R^2 = 94\%$ was obtained with the respective rate parameters $k_{10} = 0.1259$, $k_{12} = 0.3370$, $k_{13} = 0.6243$, $k_{21} = 0.37364$, and $k_{31} = 0.35735$. Meanwhile, for the oral drug dose of 50 mg, it was obtained that the value of $R^2 = 95\%$ with rate parameters were $k_{10} = 0.1620$, $k_{12} = 0.3043$, $k_{13} = 0.5764$, $k_{21} = 0.3677$, and $k_{31} = 0.3827$, respectively. Then for the oral drug dose of 100 mg, the value of $R^2 = 96.5\%$ was obtained with the respective rate parameters $k_{10} = 0.1257$, $k_{12} = 0.5126$, $k_{13} = 0.6622$, $k_{21} = 0.29587$, and $k_{31} = 0.6379$.

4. Conclusions
In this study, the parameters estimation process has been applied to estimate the parameters of the pharmacokinetic equations for the three-compartment model. A fairly simple PSO algorithm that provides accurate parameter estimates for predicting drug concentrations in the central compartment was used in this study. Based on the curve it appears that the accuracy has not yet reached the entire
time span after oral drug administration, however, the estimation of these parameters is consistent with a random search within a predetermined parameter range.

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