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An Application of Nelder-Mead Heuristic-based Hybrid Algorithms: Estimation of Compartment Model Parameters

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ABSTRACT

Compartment models are commonly used tools for nonlinear modeling in pharmacokinetic studies. Parameter estimation of compartment models play a crucial role in drug development. In order to estimate the model parameters, a derivative-based method, called stripping, has been commonly used in drug studies until now. In this study, a derivative free simple local search algorithm, Nelder-Mead Simplex (NMS), is hybridized with two artificial intelligence optimization algorithms, Genetic Algorithm (GA) and Particle Swarm Optimization (PSO). The hybridized algorithms are called GANMS and PSONMS which are used for parameter estimation. These hybrid algorithms are all population based and do not need any assumptions which make the calculations become easier. Two data sets with two compartment models are preferred as application from the literature. It is seen from the results that the suggested PSONMS is more preferable among the GA, PSO and GANMS with consistence parameter estimates and small error function values.

Keywords: Compartment models, parameter estimation, Genetic Algorithm (GA), Hybrid of GA with NMS (GANMS), Particle Swarm Optimization (PSO), Hybrid of PSO with NMS (PSONMS)

Mathematics Subject Classification: 97R40, 90C56, 65K10, 90-08

Computing Classification System: I.2, G.1

1. INTRODUCTION

Modeling of dynamical systems plays a crucial role in applied science. In order to analyse the dynamical systems in many field of science and engineering, compartment models are preferred as common modeling tools. One of the well-known field, in which the compartment models are widely used, is pharmacokinetic. A pharmacokinetic model explains how the concentration of a drug in blood plasma declines over time. In other words, what the body does to the drug is called pharmacokinetic. Since the development of drugs is time consuming and costly (Koch, 2012), mathematical modeling of pharmacokinetic is thought to be an important field in drug development.

Most pharmacokinetic models are deterministic in nature. Deviations and fluctuations attributed to experimental error. Parameters, such as volumes and rate constants, are assumed to be constant and wanted to be estimated. There are some studies about the estimation of pharmacokinetic parameters in the literature, e.g. Frome and Yakatan (1980); Booth (1991); Ozbek and Efe (2004). Besides, a derivative-based operation, called “back projection” or “stripping” method, is used to obtain the estimates of parameters in the literature (Wagner, 1975; Ağabeyoğlu, 2009). However, it has some drawbacks during the calculations. The major problem with performing the method is that each person who applies the method to the same set of data will usually obtain a different answer than the next person because of the preference knowledge during the linearization (Wagner, 1975). The stripping method, a kind of gradient based method, may cause loss of information. In order to make the calculations easier without any assumptions on the objective function, derivative-free optimization algorithms can be preferred. Rios and Sahinidis (2013) explained derivative-free optimization algorithms in detail and gave the comparison about them.

In this study, it is aimed to estimate the compartment model parameters by minimizing the error function, assumed as objective function, through derivative-free based hybridized algorithms. The hybrid algorithms are composed with a derivative-free simple local search algorithm (Nelder-Mead Simplex - NMS) and population based artificial intelligence algorithms (Genetic Algorithm – GA and Particle Swarm Optimization - PSO).

The GA is a population based heuristic algorithm, firstly introduced by John Holland (1975). It represents an intelligent global random search used to solve optimization problems. The GA is used for pharmacokinetic parameter estimation in compartment models in some previous studies, e.g. Murase et al. (1999), Zandkarimi et al. (2014), Holmes et al. (2000). The other population based heuristic algorithm, used in this study, is PSO. The PSO is firstly described by Eberhart and Kennedy (1995). In pharmacokinetic studies, Luo et al. (2013) used glow worm swarm optimization algorithm for solving parameters of pharmacokinetics. Both GA and PSO perform exploratory searches over their search spaces. However, it is important to balance this exploration with better exploitation by taking the solution towards the closest maximum fitness. This can be achieved by hybridizing a local search method. In this study, NMS, introduced by Nelder-Mead (1965), is preferred to improve the search process through hybridization. In pharmacokinetic studies, the PSO hybridization with NMS is done in the studies of Ouyang et al. (2011) and the hybrid algorithm is called AHPSO (adaptive hybrid particle swarm optimization). The other hybrid study is presented in the studies of Türkşen and Tez (2015). The GA is hybridized with NMS and called GAHNMS. The obtained estimates of compartment model parameters are compared with GA and PSO. It is seen that the GAHNMS has better performance.

The main idea behind the hybrid algorithms are obtaining an effective search mecanism by combining the advantages of each algorithm. It should be noted that various heuristic approaches e.g. Simulated Annealing (Kirkpatrick et al., 1983), Ant Colony Search Algorithm (Dorigo et al., 1996), Gravitational Search Algorithm (Rashedi et al., 2009) and also different hybridized combinations (Valdez et al.,

2011; David et al., 2013; Zavoianu et al., 2013; Khmelev and Kochetov, 2015) can be used for parameter estimation process.

This paper proposes a new hybrid algorithm by using PSO and NMS, called PSONMS, for obtaining the estimates of compartment model parameters. And also, it suggests that the proposed hybrid algorithm has the better consistent convergence to the best fitness value than the GA, PSO and GANMS. The rest of the paper is organized as follows. The detailed information about compartment models is given in Section 2. In Section 3, intelligence optimization algorithms and hybrid algorithms are presented. Two data sets from the literature are used for application purposes in Section 4. In Section 5, conclusion and future work are given.

2. COMPARTMENT MODELS

The compartment approach is the standard method in pharmacokinetic modeling because it allows the idendification of parts of the body with compartments in the model. A one-compartment model is shown in Figure 1 in which the body is depicted as a kinetically homogenous unit. In Figure 1, absorption and elimination rate constants, in h^{-1} unit, are represented as k_a and k, respectively.

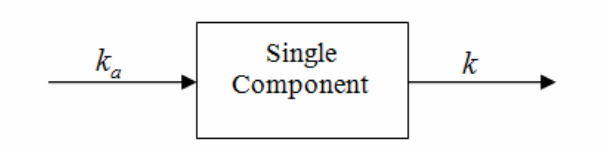

Figure 1. One-compartment model

In two-compartment model, the compartments are connected among each other in both directions and therefore, a distribution between the central and the peripheral compartment takes place (Koch, 2012). A schematic overview of the two-compartment model is presented in Figure 2.

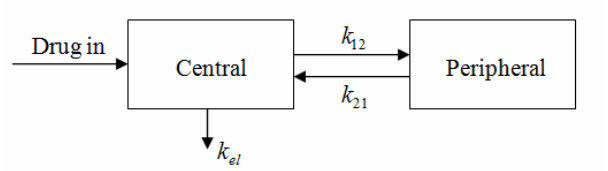

Figure 2. Two-compartment model

Here, the rate constants, which are rate of transfer from central to peripheral compartment, rate of transfer from peripheral to central compartment, and rate of elimination from central compartment are denoted as k_{12}, k_{21} and k_{el}, respectively.

It should be noted that the two-compartment model is called multi-compartment model in which the drug distributes into more than one-compartment. The compartment model is actually equation, or sets of equations, which describe the proposed system. One can easily define the changes in the concentration in the plasma by creating differential equations. The basic differential equation of a typical compartmental model with k components are

$$\frac{dx_i}{dt} = c_{i0} + \sum_{i=1,\, j\neq i}^{k} \left(c_{ij} x_j - c_{ji} x_i \right) - c_{0i} x_i \,, \quad 0 \le t < \infty \tag{2.1}$$

where c_{ij} are nonnegative constants and $x_i = x_i(t)$ is the amount of material in compartment i at time t (Lai, 1985). Under certain assumptions, integration of differential equation turns out to be polyexponential in form as

$$x_i(t) = \beta_i + \sum_{j=1}^{k} \alpha_{ij} e^{-\lambda_j t_i} \,,\ i = 1, 2, ..., n \tag{2.2}$$

where $\lambda_1, \lambda_2, ..., \lambda_k$ are positive constants depending only on the c_{ij}. Here, the β_i and α_{ij} are constants. The above equation expresses the observed response as a polyexponential function of time t. Therefore, the problem can be considered as parameter estimation for polyexponential regression model given as

$$Y_i = \beta + \sum_{j=1}^{k} \alpha_j e^{-\lambda_j t_i} + \varepsilon_i, \ i = 1, 2, ..., n \tag{2.3}$$

where ε_i, $i = 1, 2, ..., n$ represent random errors. The errors are usually assumed to be independent random variables with zero means. The set of parameters can be denoted as $\boldsymbol{\theta} = \left[\lambda_1 \ \lambda_2 ... \lambda_k ; \alpha_1 \ \alpha_2 ... \alpha_k ; \ \beta \right]$. In this study, β is chosen equal to zero ($\beta = 0$). In order to obtain the estimates of pharmacokinetic parameters root mean-squared error (*RMSE*) criteria is used as below:

$$RMSE = \phi(\boldsymbol{\theta}) = \sqrt{\frac{1}{n} \sum_{i=1}^{n} \left(Y_i - \hat{Y}_i \right)^2} \tag{2.4}$$

where $\hat{Y}_i$, $i = 1, 2, ..., n$ are the predicted response values. Error function, given in Equation (2.4), is considered as objective function, which is wanted to be minimized during the calculations. It is clear that the objective function is nonlinear in parameters. Because of this reason, gradient based methods may fail to obtain estimates of parameters. In this case, derivative-free methods are preferred to obtain the estimates of pharmacokinetic parameters.

3. DERIVATIVE-FREE OPTIMIZATION ALGORITHMS

It is well-known that the algorithms are called derivative-free optimization algorithms which use objective function values instead of derivative information during calculations. The development of these algorithms has long been studied (Rios and Sahinidis, 2013). The algorithms can be clasified as local or global with the latter having the ability to refine the search domain arbitrarily. And also clasified stochastic or deterministic, depending upon whether they require random search steps or not. In this study, local and global stochastic derivative-free algorithms and hybridized algorithms of them are used to estimate the pharmacokinetic parameters.

3.1. Local Search Algorithm: Nelder-Mead Simplex (NMS)

Nelder-Mead Simplex (NMS) algorithm, introduced by Nelder and Mead (1965), is one of the local search method. It is based upon the work of Spendley et al. (1962). It has been applied in physics, crystallography, biology, chemistry, and health care with various modifications (Rahami et al., 2011). In order to minimize the objective function, given in Equation (2.4), the NMS uses a simplex of $(n+1)$ points for n - dimensional $\boldsymbol{\theta}$, $\boldsymbol{\theta}=\left[\theta_1=\lambda_1,\theta_2=\lambda_2,...,\theta_k=\lambda_k,\theta_{k+1}=\alpha_1,\theta_{k+2}=\alpha_2,\theta_n=\alpha_n\right]$. It is well-known that a simplex in n - dimensional space is characterized by $(n+1)$ distinct vectors that are its vertices. e.g. in two space, a simplex is a triangle; in three space, it is a pyramid (Lagarias, 1998). And also, it is needed to calculate the associated function values of vertices $\phi(\theta_i),\ i=1,2,...,2k+1$.

At each step of the search, simplex move from vertex to vertex and can expand or contract. A new point in or near the current simplex is generated through a sequence of geometric operations: reflection, expansion, contraction and shrinkage. These operators are denoted with the parameters as ρ, γ, λ and η, respectively. The reflection operator is basic operator. By using this operator, it is wanted to find better solution. If reflection is resulted in best function value, then expansion is tried. If reflection resulted in worst, then contraction is tried. If all points are failed then the simplex shrinked around the best. The function value at the new point is compared with the function values at the vertices of the simplex and, usually, one of the vertices is replaced by the new point, giving a new simplex. The algorithm stops when the condition given as

$$\frac{1}{n}\sum_{i=1}^{n}\left\|\theta_i^{k+1}-\theta_i^{k}\right\|^2<\varepsilon \tag{3.1}$$

is satisfied. Here, k indicates the iteration number ($k=1,2,...,s$) and ε is a small real positive number which is used as stopping criteria. The algorithmic steps of the NMS is given below:

Step 2.1. Start with an initial solution vector of $\boldsymbol{\theta}$ in n-dimensions, $\boldsymbol{\theta}=\left[\theta_1\ \theta_2\ ...\theta_n\right]$.

Step 2.2. Let θ_i, $i=1,2,...,n+1$ denote the vertices in the current simplex and calculate the associated function values $\phi(\theta_i)$.

Step 2.3. Order the vertices in the simplex from lowest function value $\phi(\theta_1)$ to highest $\phi(\theta_{n+1})$.

Step 2.4. Calculate average of all the vertices except the worst, $\bar{\theta}=\sum_{i=1}^{n}\theta_i \Big/ n$.

Step 2.5. (Reflection)

- Compute the reflected point

$$\theta_r=\bar{\theta}+\rho\left(\bar{\theta}+\theta_{n+1}\right) \tag{3.2}$$

and evaluate the function value, $\phi(\theta_r)$.

- If $\phi_1 \le \phi_r \le \phi_n$, accept ϕ_r and terminate this iteration.

Step 2.6. (Expansion)

- If $\phi_r \le \phi_1$ then calculate the expansion point

$$\theta_e = \bar{\theta} + \gamma(\theta_r - \bar{\theta}) \tag{3.3}$$

and evaluate the function value, $\phi(\theta_e)$.

- If $\phi_e \le \phi_r$, accept θ_e and terminate iteration.
- Otherwise, accept θ_r and terminate iteration.

Step 2.7. (Shrink)

Calculate n points

$$\xi_i = \theta_i + \eta(\theta_i - \theta_1),\ i = 1, 2, ..., n+1 \tag{3.4}$$

and evaluate the $\phi(\xi_i)$. The vertices of the simplex at the next iteration are $\theta_1, \xi_2, \xi_3, ..., \xi_{n+1}$.

Step 2.8. Check the stopping condition, $\frac{1}{n}\sum_{i=1}^{n}\left\|\theta_i^{k+1} - \theta_i^k\right\|^2 < \varepsilon$. If it satisfies, set the final solution as an optimal solution. Otherwise, go to Step 2.2.

3.2. Global Search Algorithms

3.2.1. Genetic Algorithm

Genetic Algorithm (GA), introduced by Holland (1975), is one of the stochastic global search method. It has been successfully applied to a wide range of real-world problems of significant complexity (McCall, 2005). It starts with an initial population of artificial chromosomes (n_{pop}), which represent solutions to a problem, and let them evolve toward optimal solution according to basic principle of the survival of the fittest approach. In each generation, the fitness of every individual in the population is evaluated then stochastically selected from the current population and modified by using genetic operators, e.g. crossover, mutation, with simple GA parameters like crossover probability (Pr_{cr}), mutation probability (Pr_{mut}), number of population to form a new population. Then, the new population is considered as the current population in the next iteration of the algorithm (Rahami et al., 2011). The algorithm continues until the stopping condition is satisfied. The stopping conditions can be considered as a maximum number of generations ($maxgen$).

3.2.2. Particle Swarm Optimization

Particle Swarm Optimization (PSO), described by Eberhart and Kennedy (1995), Kennedy and Eberhart (1995), is a global optimization algorithm. The PSO belongs to the field of Swarm Intelligence and Collective Intelligence. And also, it is a subfield of Computational Intelligence. Its basic idea was originally inspired by simulation of the social behaviour of animals such as bird flocking, fish schooling and so on (Talukder, 2011). Similarly to GA, it is a population based method and it represents the state of the algorithm by a population. In the PSO system, each individual (agent) makes his decision according to his own experiences and other agent's experiences. The system initially has a population of random solutions. Each potential solution, called a particle (agent), is given a random velocity and is flown through the problem space. The agents have memory and each agent keeps track of its previous best position (called the P_{best}) and its corresponding fitness. There exists a number of P_{best} for the respective agents in the swarm and the agent with greatest fitness is called the global best (G_{best}) of the swarm. Each particle is treated as a point in n-dimensional space (Abd-El-Wahed, 2011). The ith particle is represented as $\boldsymbol{\theta}_i = \left[\theta_{i1}\ \theta_{i2} \ldots \theta_{in}\right]$, $i = 1, 2, \ldots, N$ where N denotes the number of particles (size of population). The best previous position of the ith particle (P_{besti}) that gives the best fitness value is represented as $\mathbf{P}_i = \left[P_{i1}\ P_{i2} \ldots P_{in}\right]$. The best particle among all the particles in the population is represented by $\mathbf{P}_g = \left[P_{g1}\ P_{g2} \ldots P_{gn}\right]$. The velocity, e.g., the rate of the position change for particle i is represented as $\mathbf{V}_i = \left[v_{i1}\ v_{i2} \ldots v_{in}\right]$. The particles are manipulated according to the following equations (the superscripts denote the iteration):

$$v_i^{k+1} = w \times v_i^k + c_1 \times r_1 \times \left(P_i - \theta_i^k\right) + c_2 \times r_2 \times \left(P_g - \theta_i^k\right) \tag{3.5}$$

$$\theta_i^{k+1} = \theta_i^k + v_i^{k+1} \tag{3.6}$$

where $i = 1, 2, \ldots, N$; w is the inertia weight which controls the momentum of the particle by changing in each iteration with $w = 0.5 + \frac{rand}{2}$; c_1 and c_2 are two positive constants, called the cognitive and social parameters respectively; r_1 and r_2 are random numbers uniformly distributed with in the range [0, 1]. Equation (3.5) is used to determine the ith particle's new velocity v_i^{k+1}, at each iteration, while Equation (3.6) provides the new position of the ith particle θ_i^{k+1}, adding its new velocity v_i^{k+1}, to its current position θ_i^k.

The algorithm is terminated after a given number of iterations ($maxiter$) or once the fitness value of the particles (or the particles themselves) are close enough in some sense.

3.3. Hybrid Algorithm of Local and Global Searches

Hybridizing is a combination of two algorithms. The main idea of composing the hybrid algorithm is to combine the advantages of each algorithm in a way to avoid their disadvantages. In this study, the proposed hybrid algorithm is based on exploration power of global search methods (GA and PSO) and exploitation feature of the local search method (NMS). The GA and PSO explore a promising area likely to contain global minima, and the NMS algorithm exploits the area to find the desired point would be promising if properly performed. The hybrid algorithms are called GANMS and PSONMS. In both the hybrid algorithms, firstly the global search method is runned and parameter values are obtained. Then the obtained parameter estimates are considered as the initial parameter values of local search method. Therefore, it would be promising to find global minima without trapping any local minima (Türkşen, 2014). The proposed algorithmic steps of the GANMS and PSONMS are given in below.

3.3.1. The Algorithmic Steps of the GANMS

Step 0: Initialize the tunable parameters.

Population size of artificial chromosomes, (n_{pop}); crossover probability, (Pr_{cr}); mutation probability, (Pr_{mut}); maximum number of generation, ($maxgen$); selection operator; crossover operator; mutation operator; reflection operator, (ρ); expansion operator, (γ); contraction operator, (λ); shrinkage operator, (η); stopping criteria, (ε); GA iteration counter, (s).

Step 1: *Exploration for an initial guess by using GA.*

Step 1.1. Determine the fitness value of each individual chromosome, $\boldsymbol{\theta}_i = \left[\theta_{i1}\ \theta_{i2} \ldots \theta_{in}\right]$, $i = 1, 2, \ldots, n_{pop}$ and compose current population. Set, $s = 1$.

Step 1.2. Select next generation by using selection operator from current population.

Step 1.3. Perform reproduction by using crossover operator and Pr_{cr}.

Step 1.4. Perform mutation by using mutation operator and Pr_{mut}.

Step 1.5. Replace the current population with the new population.

Step 1.6. Set $s = s + 1$. If $s < maxgen$ then go to Step 1.1. Otherwise, go to Step 2.

Step 2: *Exploitation for optimal solution by using NMS.*

Use the solution vector of GA, denoted with $\boldsymbol{\theta}$ in n-dimensions, as an initial guess for NMS. Make the evaluations from Step 2.2 to Step 2.8 given in Section 3.1.

3.3.2. The Algorithmic Steps of the PSONMS

Step 0: Initialize the tunable parameters.

Number of particles, (N); cognitive parameter, (c_1); social parameter, (c_2); maximum velocity of particles, ($v_{\max}$); inertia weight, (w); maximum number of iteration, ($maxiter$); reflection operator, (ρ); expansion operator, (γ); contraction operator, (λ); shrinkage operator, (η); stopping criteria, (ε); PSO iteration counter, (s).

Step 1: *Exploration for an initial guess by using PSO.*

Step 1.1. Determine the fitness value of each individual particle, $\boldsymbol{\theta}_i = \left[\theta_{i1}\ \theta_{i2} \ldots \theta_{in}\right],\ i = 1, 2, \ldots, N$ and compose current swarm. Set, $s = 1$.

Step 1.2. Select the P_{best} and G_{best}.

Step 1.3. Calculate the particle velocity according to Equation (3.2).

Step 1.4. Update particle position according to Equation (3.3).

Step 1.5. Evaluate the objective function value ϕ.

Step 1.6. Set $s = s + 1$. If $s < maxiter$ then go to Step 1.1. Otherwise, go to Step 2.

Step 2: *Exploitation for optimal solution by using NMS.*

Use the solution vector of PSO, denoted with $\boldsymbol{\theta}$ in n-dimensions, as an initial guess for NMS. Make the evaluations from Step 2.2 to Step 2.8 given in Section 3.1.

4. APPLICATION

In this section, two numerical examples are given to illustrate the pharmacokinetic parameters estimation procedure. The examples are about the two-compartment models. In order to evaluate the relative performances of the GA, PSO, GANMS and PSONMS for pharmacokinetic parameter estimation, the RMSE criteria is used.

Example 1. Two-compartment model

A drug, 75 mg amount, is enjected to plasma by the IV method. The concentration amounts in the plasma are obtained as in Table 1 (Ağabeyoğlu, 2009).

Table 1. Observed plasma concentrations for two-compartment model

$t\ (hr)$:	0	0.25	0.50	0.75	1	2	3	4	6	8	12	16	24
$C_p\ (mg/ml)$:	16.4	14.2	12.53	11.17	10.09	7.56	6.44	5.85	5.16	4.65	3.18	3.12	2.09

The plasma concentration-time profile is illustrated in Figure 3.

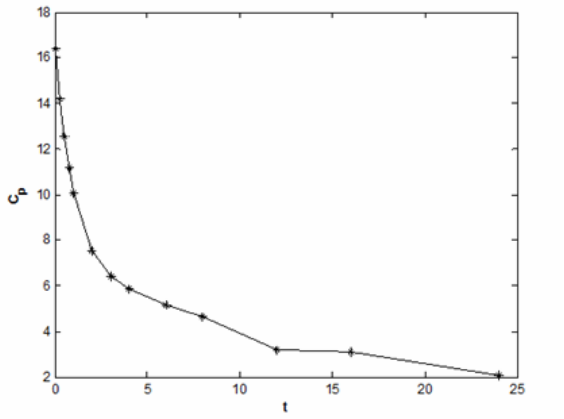

Figure 3. Drug plasma concentration-time profile for two-compartment model

The two-compartment model can be written as follows:

$$Y_i = \alpha_1 e^{-\lambda_1 t_i} + \alpha_2 e^{-\lambda_2 t_i} + \varepsilon_i, \quad i = 1, 2, ..., 13 \tag{4.1}$$

in which α_1 and α_2 are constants and λ_1 and λ_2 are absorbtion and elimination rate parameters. By using these constants and rate parameters, the pharmacokinetic parameter vector can be denoted as $\boldsymbol{\theta} = \left[\alpha_1 \ \lambda_1 \ \alpha_2 \ \lambda_2\right]$. The interval of pharmacokinetic parameters are given in Table 2.

Table 2. Interval of pharmacokinetic parameters for one-compartment model

Parameters	*Lower bounds*	*Upper bounds*
α_1	9.2	9.8
λ_1	0.9	1.2
α_2	6.9	7.2
λ_2	0	0.1

In order to analyse the two-compartment model, the transfer and elimination parameters, presented in Figure 2, are described with reparameterization by the following equations:

$$k_{21} = \frac{\alpha_1 \lambda_2 + \alpha_2 \lambda_1}{\alpha_1 + \alpha_2}, \tag{4.2}$$

$$k_{el} = \frac{\lambda_1 \lambda_2}{k_{21}}, \tag{4.3}$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{el}. \tag{4.4}$$

The objective functions can be written as according to the *RMSE* and *MAPE* criteria by following

The estimated values of parameters $\hat{\boldsymbol{\theta}} = \left[\hat{\alpha}_1 \ \hat{\lambda}_1 \ \hat{\alpha}_2 \ \hat{\lambda}_2 \right]$ are obtained as $\left[9.59 \ 1.06 \ 7.05 \ 0.0509\right]$ through stripping method (Ağabeyoğlu, 2009). Table 3 shows the tunable parameter values of the optimization algorithms.

Table 3. Tunable parameter values of the optimization algorithms

Methods	***Parameters - Values***
NMS	Reflection (ρ) - 1
	Expansion (γ) - 2
	Contraction (λ) – 0.5
	Shrinkage (η) – 0.5
	Stopping Criteria (ε) – 10^{-5}
GA	Population size (n_{pop}) - 50
	Maximum number of generation ($maxgen$) - 100
	Probability of crossover (Pr_{cr}) – 0.90
	Probability of mutation (Pr_{mut}) – 0.01
	Selection operator – Roulette wheel selection
	Crossover operator – Single point crossover
	Mutation operator – Bit flip mutation
PSO	Number of particles (N) - 50
	Maximum iteration number ($maxiter$) – 100
	Cognitive parameter (c_1) - 2
	Social parameter (c_2) - 2
	Maximum velocity of particles ($v_{\max}$) - 1
	Inertia weight (w) – 0.5+rand/2

The algorithms are coded in Matlab 7.9. By using the tunable parameter values given in Table 3, global solutions are obtained for GA and PSO. It is well known that the GA and PSO are much similar in their searching principle for global optimal. It is clear from Figure 4a-4b that the GA performs similar with PSO in terms of convergence rate for optimizing the fitness function given in Equation (2.4).

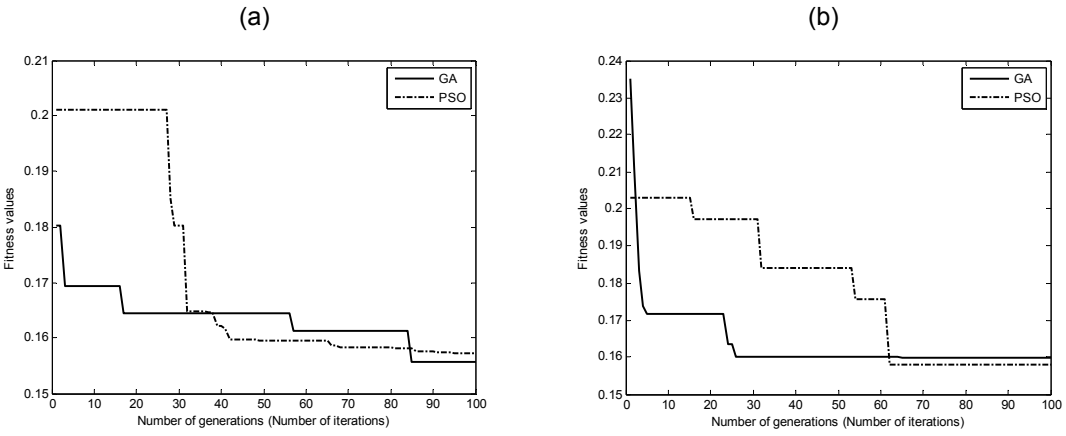

Figure 4 (a)-(b). Fitness values versus number of generation (number of iteration) for GA and PSO

And also, the experimental results for the fitness function value are presented in Table 4.

Table 4. Median (Med), Average (Ave) and Best fitness values with standart errors (SE) for GA and PSO

Methods	Med	Ave	Best	SE
GA	0.1590	0.1657	0.1547	0.0223
PSO	0.1553	0.1565	0.1542	0.0032

The results are averaged over 50 runs. The median of fitness values (Med), the average of fitness values (Ave), the best fitness values (Best) and standart errors of fitness values (SE) are reported in Table 4. According to the Table 4, GA and PSO have similar performances for obtaining the best fitness values. However, the SE value of PSO (0.0032) is lower than SE value of GA (0.0223) for over 50 runs. Figure 5 also shows that the PSO performs better than GA in terms of the consistency.

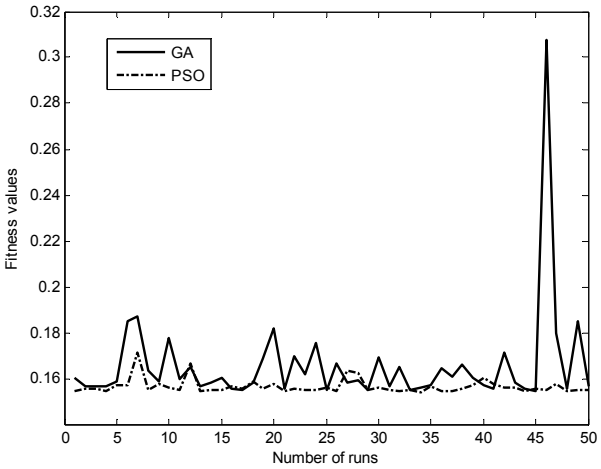

Figure 5. Fitness values versus number of runs for GA and PSO

Table 5 represents fitness values for hybrid algorithms, GANMS ans PSONMS, over 50 runs. According to the Table 5, GANMS and PSONMS are more consistent than the GA and PSO with the value of zero SE.

Table 5. Median (Med), Average (Ave) and Best fitness values with standart errors (SE) for GANMS and PSONMS

Methods	Med	Ave	Best	SE
GANMS	0.154206	0.15420571	0.15420570	7.44e-010
PSONMS	0.1542	0.1542	0.1542	0

How the hybridization effects on GA and PSO in terms of convergence rate is much more clear in Figure 6 and Figure 7. From Figure 6-7, it is easy to say that the hybrid algorithms have better consistence convergence to the best fitness value.

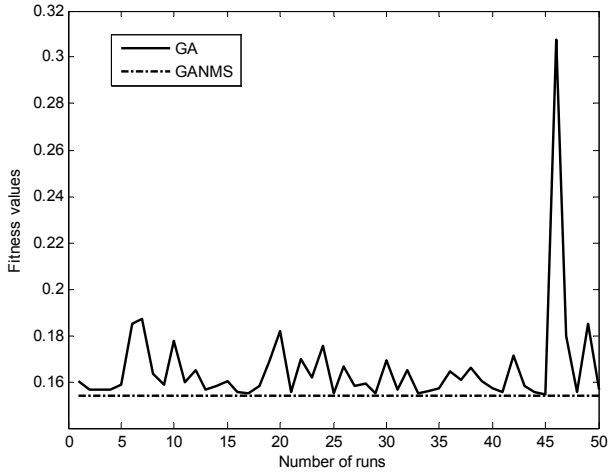

Figure 6. Fitness value versus number of runs for GA and GANMS

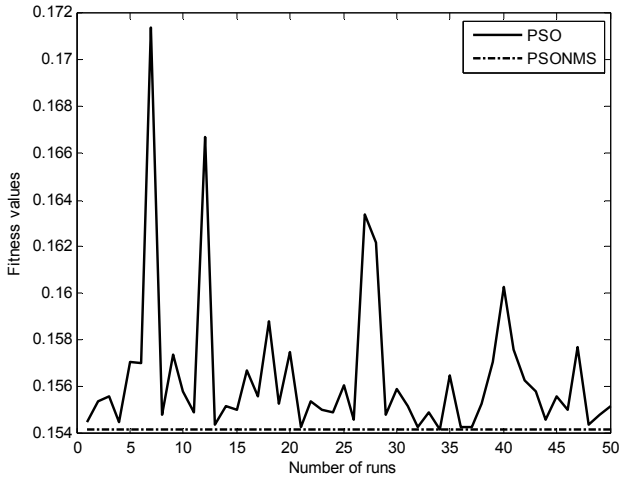

Figure 7. Fitness value versus number of runs for PSO and PSONMS

The estimates of the compartment model parameters, given in Equation (4.1), and SE values of estimated parameters, given in paranthesis, are summarized in Table 6.

Table 6. Parameter estimation results GA, GANMS, PSO and PSONMS

	GA		**GANMS**		**PSO**		**PSONMS**	
$\hat{\boldsymbol{\theta}}$	Value	SE	Value	SE	Value	SE	Value	SE
$\hat{\alpha}_1$	9.4045	0.0818	9.3994	3.421e-005	9.3875	0.0811	9.3994	0
$\hat{\lambda}_1$	0.989	0.0110	0.9937	0.889e-005	0.9956	0.0204	0.9937	0
$\hat{\alpha}_2$	6.9654	0.0687	6.9853	3.26e-005	6.9962	0.0884	6.9853	0
$\hat{\lambda}_2$	0.053	0.0027	0.0536	0.053e-005	0.0538	0.0013	0.0536	0

By comparing these results, it can be easily seen that the GANMS and PSONMS are more consistent on parameter estimates with the lowest SE values. And is it fair to say that the PSONMS is the most preferable one with better consistency.

In order to validate the results, by substituting the parameter estimates of PSONMS, a comparison between observed and predicted plasma concentration was accomplished. The results are presented in Figure 8. This comparison shows that good agreement was obtained with determination coefficient, $R^2 = 0.9988$, and $RMSE = 0.028$. In addition, the comparison of the estimation results between the Stripping method and PSONMS is presented in Figure 9. As a result from Figure 8.b, the predicted performance of the compartment model with PSONMS estimates has better accuracy than the Stripping method estimates which has larger error value, $RMSE = 0.033$.

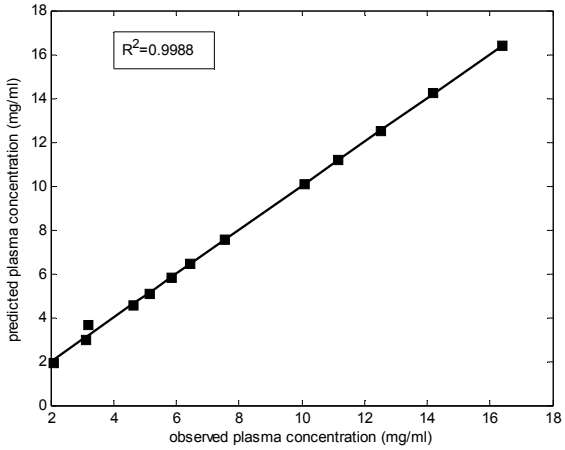

Figure 8. Comparison between observed and predicted plasma concentration for PSONMS

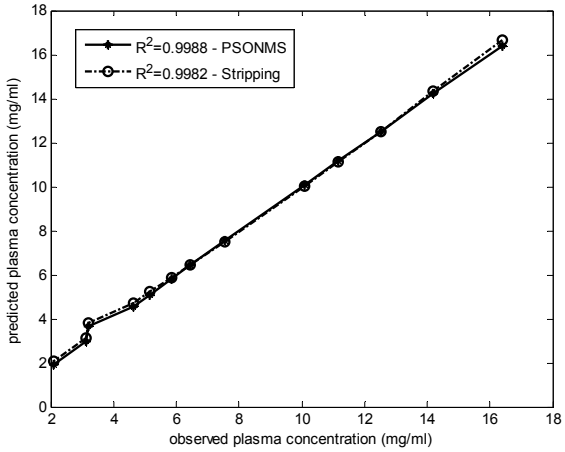

Figure 9. Comparison of predicted plasma concentration between PSONMS and Stripping method

Example 2. Two-compartment model (with three-exponential terms)

This is the example of three exponential terms from plasma level data and the two compartment open model with first order absorption. Table 7 shows the data following intramsular administration of a dose of 2 mg/kg of body weight (Wagner, 1975).

Table 7. Observed plasma concentrations for two-compartment model

t:	0	0.1	0.25	0.5	0.75	1	1.5	2	2.5	3	4	5	6	8	12	14
C_p:	0	1.47	2.82	4.02	4.63	4.93	5.02	4.77	4.38	3.98	3.20	2.55	2.03	1.28	0.509	0.321

The predicted two-compartment model, with three exponential terms, can be written as

$$\hat{Y}_i = \hat{A}_1 e^{-\hat{\alpha} t_i} + \hat{A}_2 e^{-\hat{\beta} t_i} + \hat{A}_3 e^{-\hat{k}_a t_i},\ i = 1,2,...,16 \tag{4.5}$$

in which A_1, A_2, A_3 are coefficients and α, β, k_a are rate parameters. The parameters k_{12}, k_{21} and k_{el}, used for two-compartment model as presented in Figure 2, are described with reparameterization by following equations:

$$k_{21} = \frac{A_1^* \beta k_a + A_2^* \alpha k_a + A_3^* \alpha \beta}{A_1^* (k_a - \alpha) + A_2^* (k_a - \beta)}, \tag{4.6}$$

$$k_{el} = \frac{\alpha \beta}{k_{21}}, \tag{4.7}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{el}. \tag{4.8}$$

Table 8 represents the interval of lower and upper bound of model parameters.

Table 8. Interval of pharmacokinetic parameters for two compartment model with three exponential terms

Parameters	*Lower bounds*	*Upper bounds*

A_1	−1.5	0
α	13	14
A_2	7.5	8.5
β	0	1
A_3	−7.5	−6.5
k	1	2

The estimated values of parameter vector is obtained as $\hat{\boldsymbol{\theta}} = \left[-1.02 \;\; 13.5 \;\; 8.06 \;\; 0.23 \;\; -7.03 \;\; 1.56\right]$ by stripping method for $\hat{\boldsymbol{\theta}} = \left[\, \hat{A}_1 \;\; \hat{\alpha} \;\; \hat{A}_2 \;\; \hat{\beta} \;\; \hat{A}_3 \;\; \hat{k}_a \,\right]$ (Wagner, 1975).

By using the tunable parameter values given in Table 3, the obtained parameter estimates of GA, GANMS, PSO and PSONMS are presented in Table 9. It is clear from Table 9 that the PSONMS is the most preferable parameter estimation method with the highest consistency among the others.

Table 9. Parameter estimation results GA, GANMS, PSO and PSONMS

	GA		**GANMS**		**PSO**		**PSONMS**	
$\hat{\boldsymbol{\theta}}$	Value	SE	Value	SE	Value	SE	Value	SE
$\hat{A}_1$	-0.7180	0.3251	-0.869	0.00046	-0.9254	0.1420	-0.8643	0.5285e-003
$\hat{\alpha}$	13.1183	0.333	13	0	13.0849	0.7819	13.1	0
$\hat{A}_2$	7.7321	0.3353	7.8985	0.00044	7.9748	0.3784	7.8969	0.4443e-003
$\hat{\beta}$	0.2210	0.0239	0.2263	0	0.2288	0.0109	0.2262	0.0134e-003
$\hat{A}_3$	-7.0240	0.2809	-7.0410	0.00043	7.0541	0.3158	-7.044	0.4292e-003
$\hat{k}_a$	1.7659	0.1567	1.6607	0.00022	1.6243	0.1334	1.6623	0.2296e-003

5. CONCLUSION

In this study, compartment models are considered as nonlinear response problems and these are represented as polyexponential regression models in the statistical context. Population based heuristic algorithms, GA and PSO, are hybridized with NMS and called GANMS and PSONMS, respectively. These algorithms are used to estimate the pharmacokinetic parameters for two-compartment models. Through these algorithms, pharmacokinetic parameter estimation is achieved without using any assumptions in compartment models. The flexibility of the heuristic based hybrid

algorithms makes them preferable with respect to the derivative based algorithm. The main difficulty is defining the tunable parameters of intelligence methods during the estimation process. It is seen from the results that the PSONMS gives the best estimation values of parameters with the smallest *RMSE* value. And also, the standard deviation values of the estimates show that the PSONMS can be considered as a consistent optimization tool for compartment model studies.

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