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An Improved Optimization Algorithm of 3-Compartmental Model with Spill Over and Partial Volume Corrections for Dynamic FDG PET Images of Small Animal Heart In Vivo

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Abstract

The 3-Compartment model with spill-over (SP) and partial volume corrections (PV) has been widely used for noninvasive kinetic parameters study for dynamic FDG PET images of small animal heart *in vivo*. However, the approach still suffers from the estimation uncertainty or slow convergence caused by the commonly used optimization algorithms. The aim of the study was to develop an improved optimization algorithm with better estimation performance. Femoral artery blood samples, image derived input functions (IDIFs) from heart ventricles and myocardial time-activity curves (TACs) were derived from sixteen C57BL/6 mice data obtained from the UCLA Mouse Quantitation Program. Parametric equations of the average myocardium and the blood pool TACs with SP and PV corrections in a 3-compartment tracer kinetic model were formulated. A hybrid method integrating Artificial Immune System (AIS) and Interior-Reflective Newton (IRN) method were developed to solve the equations. Two penalty functions and one late time point tail vein blood sample were used to constrain the objective function. The estimation accuracy of the method was validated by comparing results with experimental values using the errors in the areas under the curves (AUC) of model corrected input function (MCIF) and the 18F-FDG influx constant K_i . Moreover, the elapsed time was used to measure the convergence speed. The overall AUC error of MCIF for 16 mice averaged $-1.4 \pm 8.2\%$, with correlation coefficients of 0.9706. Similar result can be seen in overall K_i error percentage, which was $0.4 \pm 5.8\%$ with correlation coefficient of 0.9912. The t-test P value for both showed no significant difference. The mean and standard deviation of MCIF AUC and K_i percentage errors have lower values compared to the previously published methods. The computation time of the hybrid method is also several fold lower than using just stochastic algorithm. The proposed method significantly improved the model estimation performance in terms of the accuracy of the MCIF and K_i , as well as the convergence speed.

Keywords

dynamic FDG PET; optimization algorithms; model corrected input function; FDG influx constant

1. Introduction

Non-invasive imaging in small animals using Dynamic Positron Emission Tomography (DPET) to quantify metabolism has become especially important for functional research, due to the small size of blood vessels, limited blood volume and also the risk of blood loss to perturb the physiological experimental outcome in invasive studies. Analysis of DPET images entails compartment modeling to acquire the image-derived input function (IDIF), and then estimate kinetic rate constants or physiological parameters. However, in small animal imaging, hearts and arteries are small compared to the intrinsic resolution of the PET scanner. As a result, IDIF is susceptible to severe partial volume (PV) averaging and spill-over (SP) contamination from the surrounding myocardium tissue to blood pool (BP) and vice versa. Also, cardiac and respiratory motion can cause further image blur. To avoid these problems, the method accounting for SP and PV effects via a physiologic mathematical model with 15 or more parameters to estimate a model-corrected input function (MCIF) and FDG influx constant was developed (Fang and Muzic 2008, Zhong and Kundu 2013). The unknown parameters in the model have to be varied by an optimization routine, also denoted as parameter estimation, to obtain the best fit between experimental and model computed data. The accuracy of the estimation determines the correctness of the physiological parameters of the subject under investigation, which makes parameter estimation as one of the most critical factor for the applicability of the non-invasive DPET imaging. Multi-parameter estimation of dynamic models is challenging due to the occurrence of multiple optima, i.e. multiple basins with equal or close value, in the objective function. There have been a number of methods proposed for the problem which can be categorized generally into three approaches: deterministic, stochastic and hybrid optimization algorithms (Raue *et al* 2013).

Deterministic optimization algorithms take steps that successively decrease the value of the objective function beginning from an initial guess for the parameter values (Raue *et al* 2013). In the category, Levenberg–Marquardt algorithm (Feng *et al* 1997) and Interior-reflective Newton (IRN) method are widely used in the compartmental model optimization (Muzic and Cornelius 2001, Huang *et al* 2005, Ferl *et al* 2007, Fang and Muzic 2008, Zhong and Kundu 2013), due to the capability of finding the regional minimum of a function efficiently with proper constraint. However, the sensitivity from the initial guess values and boundary of the method, which are selected by trial and error or individual experience, may prompt the uncertainty of the result (Feng *et al* 1993). Improper initial assumption on parameter values of a deterministic optimization algorithm may converge to a local rather than global optimum.

Stochastic optimization algorithms apply sophisticated heuristics that randomly sample parameter space to evaluate the objective function, hence they are less likely to converge to a local optimum. Genetic algorithms (GAs), simulated annealing (SA), particle swarm optimization (PSO), and artificial immune system (AIS) are most widely used stochastic algorithms for solving kinetic models optimization problems. GAs are popular stochastic global optimization approaches, unfortunately GAs have two disadvantages—the lack of a local search ability and premature convergence (Tazawa *et al* 1996). SA algorithms to optimize kinetic models were proposed by Wong *et al* (2002). However, due to the

randomness of Monte Carlo, the SA algorithms cannot be guaranteed to reach a global optimum without unlimited resource (Xu 2002). In addition, PSO method was applied to estimate the FDOPA kinetic model in Parkinson's disease diagnosis (Huang *et al* 2012). Nevertheless, PSO doesn't have crossover/mutation procedures and hence it tends to converge prematurely at the local minima (Yap *et al* 2011, 2012). Liu *et al* (2016) employed the AIS to conduct the parameter optimization for simultaneous estimation (SIME) of tracer kinetic model (TKM). In this study though the artificial immune method was found to have the superior global search capability, the rate of convergence for AIS in finding the global minima is rather slow, as reported as well by Yap *et al* (2011). In addition, Liu *et al* (2016) used six blood samples to fit the input function with 4 parameters and the method was not validated with the noisy IDIF. Under circumstance of noisy data, the cost function is usually ill-conditioned and is likely to get stuck in the local minimum nearest to the initial estimate, or in the worst case, the algorithm does not converge (Yaqub *et al* 2006). Furthermore, none of the aforementioned methods have been validated in model estimation with SP and PV corrections.

Hybrid optimization algorithms use a combination of both strategies. First, promising candidate sets of parameter values are generated using a stochastic strategy. The candidate sets are then further improved by a deterministic strategy which is the computationally most efficient approach (Raue *et al* 2013). The hybrid algorithm is reported for scatter search (Rodriguez-Fernandez *et al* 2006, Egea *et al* 2007), however, there has been no study of hybrid optimization applied to compartmental model optimization with SP and PV corrections for small animal studies yet.

The aim of this investigation was to develop and validate a hybrid optimization method that integrates the global search capability of stochastic algorithm together with the faster convergent speed of deterministic algorithm. The proposed stochastic and deterministic algorithms are Artificial Immune System (AIS) and Interior-reflective Newton (IRN) respectively. The improved method was applied to optimize a 3-compartment kinetic model which simultaneously corrects for SP and partial volume PV effects for both left ventricular blood pool (LVBP) and the myocardium from dynamic FDG PET data of mouse heart *in vivo* obtained from the UCLA Mouse Quantitation Program. The performance of our method was validated by comparing the estimated model corrected input function (MCIF) with the input function measured by arterial blood sampling in mice. Further validation included computing errors in the AUC of MCIF and errors in the 18F-FDG influx constant, K_i , of myocardium.

2. Materials and Methods

2.1 Mouse Imaging Studies

Our hybrid algorithm was validated using mouse data shared on the internet from UCLA Mouse Quantitation Program. Sixteen C57BL/6 male mice weighing 22–36 g were anesthetized with 1.5%–2% isoflurane in oxygen. 9–37 MBq 18F-FDG were bolus-injected in the tail vein and 5–22 blood concentrations were measured using femoral artery blood samples. Image data were reconstructed using filtered back projection algorithm with CT-based attenuation correction (Huang *et al* 2006).

2.2 The Objective Function for Optimization

Following the 3-compartment kinetic model in (Zhong and Kundu 2013), the differential equations for FDG kinetics can be written as:

$$\frac{dC_e}{dt} = K_1 C_a(t) - (k_2 + k_3) C_e(t) + k_4 C_m(t) \quad (1)$$

$$\frac{dC_m}{dt} = k_3 C_e(t) - k_4 C_m(t) \quad (2)$$

$C_a(t)$ is the FDG concentration in the vascular space (compartment 1), $C_e(t)$ is the concentration of FDG in the interstitial and cellular spaces (compartment 2) and $C_m(t)$ is the FDG concentration within the cell of the phosphorylated FDG-6-Phosphate (compartment 3). For our studies we have assumed that FDG concentrations in plasma and blood are equal. K_1 and k_2 are the forward and reverse rate constants respectively between the first 2 compartments. k_3 and k_4 are the rates of phosphorylation and de-phosphorylation between compartments 2 and 3. $C_e(t)$ and $C_m(t)$ can be solved in terms of $C_a(t)$ and the rate constants, K_1 - k_4 , (Zhong and Kundu 2013) :

$$C_T(t) = \frac{K_1}{a_1 - a_2} \left[(k_3 + k_4 - a_1) e^{-a_1 t} + (a_2 - k_3 - k_4) e^{-a_2 t} \right] \otimes C_a(t) \quad (3)$$

where

$$a_{2,1} = \left(\frac{1}{2} \right) (k_2 + k_3 + k_4 \pm \sqrt{(k_2 + k_3 - k_4)^2 - 4k_2 k_4}) \quad (4)$$

and

$$C_T(t) = C_e(t) + C_m(t) \quad (5)$$

is the net myocardium tissue concentration. Assuming the rate of de-phosphorylation, $k_4 = 0$, the net myocardial FDG influx constant, K_i , can be written as:

$$K_i = \frac{(K_1 k_3)}{k_2 + k_3} \quad (6)$$

Due to SP and PV effects, the model equation for an image-derived time activity curve from the blood pool can be written in terms of fraction of the tissue concentration in the blood compartment and partial recovery of radioactivity concentration from the blood as:

$$Model_{IDIF,i} = \frac{\int_{t_b^i}^{t_e^i} [S_{mb}C_T(t) + r_bC_a(t)]dt}{t_e^i - t_b^i} \quad (7)$$

Similarly, the myocardium tissue of the model equation is:

$$Model_{myo,i} = \frac{\int_{t_b^i}^{t_e^i} [r_mC_T(t) + S_{bm}C_a(t)]dt}{t_e^i - t_b^i} \quad (8)$$

where, r_m , r_b are the recovery coefficients for the myocardium and blood pool respectively. S_{mb} , S_{bm} are the SP coefficients from the blood pool to the myocardium and vice versa respectively. Prior work (Fang and Muzic 2008) and work from our lab (Zhong and Kundu 2013) have demonstrated that the vascular fraction can be safely accommodated in S_{bm} and r_m parameters. This formalism is more applicable since we are writing down a parametric formulation of the blood TAC and the tissue TAC with SP and PV corrections and optimizing the cost function by comparing to the experimental PET data. t_e^i and t_b^i are the beginning and end times respectively for frame in a dynamic PET scan. The model equation for the blood input function can be written as (Feng *et al* 1993):

$$C_a(t) = (A_1(t - \tau) - A_2 - A_3)e^{L_1(t - \tau)} + A_2e^{L_2(t - \tau)} + A_3e^{L_3(t - \tau)} \quad (9)$$

where, each of the terms determines the amplitude, shape and wash-out of the tracer over time. equation (9) above is a widely used parametric formulation of the input function (Fang and Muzic 2008; Zhong and Kundu 2013). This equation has the capability to model the peak value high enough to cover the problem studied, as illustrated in figure 3. Because of the involvement of the 4 SP and PV factors, the parameters in $C_T(t)$ and $C_a(t)$ influence each other, which imposes extra challenge on the optimization algorithm

The rationale of the optimization process of kinetic compartment model is to determine a combination of parameters in (1–9), that makes the model equations $Model_{IDIF,i}$ and $Model_{myo,i}$ be best fitted to the blood (PET_{IDIF}) and tissue (PET_{myo}) time-activity curves (TAC) respectively. Since the ordinary least square (OLS) yields better result in terms of precision and bias (Muzic and Christian 2006), the major part of the objective function regarding model and TAC fitting is indicated below:

$$O_1(p) = \sum_{i=1}^n \left[\left(Model_{IDIF,i} - PET_{IDIF,i} \right)^2 + \left(Model_{myo,i} - PET_{myo,i} \right)^2 \right] \quad (10)$$

where,

$$p = [k_1, k_2, k_3, k_4, S_{mb}, r_b, r_m, S_{bm}, A_1, A_2, A_3, L_1, L_2, L_3, t] \quad (11)$$

After the injection of the tracer, the concentration in the vascular space reaches peak value rapidly, as illustrated in figure 1. It also shows that though the sampling intervals on horizontal axis are nearly the equally spaced before 0.2 minute, majority of the sampling points are located below 20 MBq/mL on vertical axis, or the points around the peak are sparsely distributed in vertical direction. When computing the residual fitting error using (10), curve sections located within sections of dense PET IDIF points gain priority to obtain better model curve fitting. For example in figure 1, if the model curve that is biased vertically away from points cluster with tracer concentration below 15 MBq/mL, the total residual fitting error will be accumulated by multiple points. On the contrary, there are only 2 points around the peak and when the residual fitting error of the two points are smaller than the accumulated error of points below 15 MBq/mL and before 0.2 minutes, the optimization routine would rather choose a set of model parameters to fit the points cluster best, as the model curve shown in figure 1. Therefore, in order to reduce the fitting discrepancy around peak induced by the sparse distribution in vertical direction, a penalty function is introduced as,

$$O_2(p) = w_p \left[\left(ModelPeak_{IDIF} - PETPeak_{IDIF} \right)^2 + \left(ModelPeak_{myo} - PETPeak_{myo} \right)^2 \right] \quad (12)$$

where $PETPeak_{IDIF}$ and $PETPeak_{myo}$ are maximal value of the blood and tissue TACs before time 1 minute, $ModelPeak_{IDIF}$ and $ModelPeak_{myo}$ are the peak values of model calculated blood and tissue TACs before time 1 minute, respectively. w_p is the weighting factor and can be adjusted incrementally from 0 until the model curve peak approaches but not exceeds the PET IDIF peak. The tuning process is conducted for a couple of times by visual inspection on the preliminary fitting result. In our study, w_p was obtained from 1 mouse and applicable to rest of the mice.

Furthermore, the area under curve of PET and model derived curve were also utilized as a penalty function:

$$O_3(p) = w_{auc} \left[\left(AUC_{IDIF,model} - AUC_{IDIF,PET} \right)^2 + \left(AUC_{myo,model} - AUC_{myo,PET} \right)^2 \right] \quad (13)$$

$AUC_{IDIF,model}$, $AUC_{IDIF,PET}$, $AUC_{myo,model}$ and $AUC_{myo,PET}$ are the area under curves of blood model, blood PET, tissue model and tissue PET respectively. Since $O_1(p)$, $O_2(p)$ and

$O_4(p)$ have dimension of $(\text{MBq/ml})^2$ while $O_3(p)$ has the dimension of $(\text{MBq.min/ml})^2$, a mathematical weight w_{auc} is introduced to make the unit of measure consistent and given by:

$$w_{auc} = 1\text{min}^{-2} \quad (14)$$

This penalty function $O_3(p)$ was only applied during the latter half of the computation iterations. The reason is that during the early half iterations, there exists a big bias in the curve fitting of both blood and myocardium, thus the objective function of the AUC calculated by (13) would play the major role in the total residual fitting error. This would lead to an optimized result in the best interest of the AUC instead of individual curve fitting, the two of which aren't always consistent. However, in the latter half of the iterations, the bias in the curve fitting is significantly minor and hence allows the AUC to be introduced to further improve the curve fitting. It should however be noted that the above process is enabled by AIS's capability of learning, memory and evolution.

In addition, one late time point blood sample obtained from the tail-vein was applied as a physiological constraint for faster convergence and also for noisy data:

$$O_4(p) = (C_a(t_s) - b)^2 \quad (15)$$

where b is the blood sample activity concentration and t_s is the sampling time.

The final objective function was thus written as:

$$O(p) = O_1(p) + O_2(p) + O_3(p) + O_4(p) \quad (16)$$

2.3 The Hybrid Optimization Algorithm

An AIS and IRN method using Matlab function 'fmincon' were used as a hybrid method to solve the parametric equations. Comparing to other stochastic algorithms in the context of optimization of kinetic models, AIS has the best global search performance as mentioned earlier. The function 'fmincon' was used in order to compensate for the relative slow convergent rate of AIS.

AIS algorithm is a class of computing routine to solve complex mathematical problems, with the nature of learning, memory and feature extraction. It belongs to the sub-field of artificial intelligence and has emerged during the last decade, starting from negative selection algorithm by Forrest et al., immune network algorithm by Ishida and the clonal selection algorithm by Castro and Zuben (Dasgupta *et al* 2011).

A biological immune system is to protect the body from infectious foreign molecules as bacteria and viruses, known as pathogens as example. Molecules recognized by immune system is named antigen. Upon detection of an antigen, the best match B cell in the immune system will be provoked and cloned. Some of the cloned B cell acts as antibodies secretors

while others as memory cells. The cloned cells are subject to mutation rate which is proportional to their affinity to the antigen. Antibodies play a key role in the immune response, since they are capable of adhering to the antigens, in order to neutralize and eliminate them. These cloning and mutation processes are collectively called as the clonal selection principle (L.N.D. Castro and Zuben 2000). Simulating the biological immune process, the AIS algorithm is a novel approach to solving complex computational problems. From a computational perspective, antibody corresponds to the parameter vector of the 3 compartmental model equation. A group of antibodies is called population, which are candidate solutions to a given optimization problem. Every iteration of the algorithm is a generation, among which the population will experience a biology-like process of selection, recombination, and mutation reproduction. Following the biological principle of survival of the fittest, fitness (or affinity) indicating the goodness of the resulting solutions of each generation, is evaluated to determine which solutions will be maintained into the next generation. A predefined number of generations of simulated process was used as termination criteria.

An embodiment of AIS was implemented according to the classic clonal selection algorithms (CLONALG) framework proposed by L.N.D. Castro and Zuben (2000), which was then built into the proposed hybrid algorithm together with the 'fmincon'. The flow chart of the hybrid algorithm is shown in figure 2.

At the beginning, the dynamic PET image data was loaded and regions of interest (ROI) in the image corresponding to the left ventricle blood pool and the myocardium were drawn manually on transverse slices in the last frame of the dynamic data. The TACs for the whole scan were then generated as input of the algorithm to estimate the model parameters. Then the model parameters, as shown in (11) were encoded as the antibody. A population of antibodies was selected as 300 in size and a random value generated and assigned to each of the antibodies. The antibodies were then applied in turn to the objective function in (16) to calculate the residual sum of squares (RSS) value, which is regarded as fitness of the antibody. Then if the smallest fitness value out of the 300 was less than predefined threshold value V_0 (figure 2), the Matlab function 'fmincon' was introduced for further optimization. The reason for this condition was to prevent the failure of convergence of 'fmincon' when the initial setting is biased beyond convergence range. Herein, only one of the antibody was chosen randomly from the population to be optimized by IRN method in order to avoid the lengthy computation time introduced by 'fmincon'. Moreover, the random selection of the antibody to be optimized is a critical step to maintain the global convergence of the proposed hybrid algorithm. In this step, the selected antibody was applied as the initial value of 'fmincon'. When the calculated residual error (the fitness) by 'fmincon' was smaller than the residual error obtained using the selected antibody (parameters of equation (11)), the new parameters achieved by fmincon optimization will replace the values in the selected antibody. After this step, if the termination condition was met, the optimization process would be completed. Otherwise, further processing would calculate the excellence Exc_i based on the fitness Fit_i and the concentration Con_i as expressed below,

$$Exc_i = \rho Fit_i + (1 - \rho) Con_i \quad (17)$$

where i is the index of the antibody, ρ is the weighting factor and Con_i is defined as,

$$Con_i = \frac{m}{N} \quad (18)$$

where N represents the total number of antibody population and m denotes the number of antibodies having an Euclidean distance to the i_{th} antibody less than a threshold. Antibody with lower excellence was suppressed, which is an effective measure to preserve diversity in the solution. Following step 7 (see flow chart, figure 2), the clonal selection procedure selected 10 antibodies with higher fitness and another 10 with higher excellence as parent generation, and then clone, selection, and crossover and mutation algorithm (Liu *et al* 2009) applied to the remaining antibodies in order to generate offspring antibodies. Due to the nature of clone and reproduction of AIS algorithm, the feature of better antibody was inherited and propagated to next generations. After all the antibodies of the next generation were produced, a new iteration of the computation was performed until the termination condition was met.

2.4 Boundary Determination and Physical Constraint

The initial values of 'fmincon' was generated and provided automatically by the hybrid algorithm. However, the searching bound of the parameters still needs to be constrained within a specified range in order to reduce the fitting time and achieve a physiologically acceptable value, as shown in table 1.

$K_1 - k_4$ are compartmental model rate constants, which denotes the fraction of the total tracer that will leave the compartment per unit time. In this regard, the maximal value is 100% and minimal value is 0% so that the upper bounds of $K_1 - k_4$ were reasonable to be 1. This upper limit is based on previous studies and prior experience from metabolic studies in mice from our lab (Zhong *et al* 2013, Zhong and Kundu 2013). Considering that the FDG de-phosphorylation is close to zero, the upper bound of k_4 was set to be $1e-4$. r_b , r_m , S_{mb} , S_{bm} are 4 mixing coefficients ranging between 0 to 1. The upper bound of r_m was set to 0.04 as a mathematical constraint. Since there is blood activity in the tissue at the early time points, the tissue TAC is due to blood TAC, however since the spill-over is a function of time, the drop in blood TAC over 60 minutes will have no contribution to the tissue TAC at the late time points. The measured myocardial FDG influx constant, K_i , was used as a constraint to adjust the upper limit of the recovery coefficient for the myocardium, r_m , found to be the most sensitive mathematical factor affecting K_i . A_1 , A_2 , A_3 , L_1 , L_2 , L_3 , τ are parameters to determine the MCIF (Feng *et al* 1993). The combination of bounds should satisfy the minimal and maximal range of the MCIF curve in order to provide the possibility for the hybrid algorithm to search the best fitting of the objective function. Regarding the minimal limit, the theoretical minimal value can be met when A_1 , A_2 , A_3 are all set to 0. For the maximal range, the peak value of the MCIF based on the injection dose for mice and

its total blood volume, is normally under 50 MBq/mL (Mu *et al* 2013). As shown in figure 3, a combination of the parameters A_1 , A_2 , A_3 , L_1 , L_2 , $L_3\tau$, with values within the range shown in table 1, can result in a MCIF with a peak value 80 MBq/mL, indicating that the selected bounds can cover this maximal peak of MCIF for mice.

2.5 Computation Environments and Result Validation

The programming environment was in MATLAB 2014b (Math works Inc, Natick, MA), running on ThinkPad S5-S50 laptop. The estimation performance was first evaluated qualitatively by visual inspection of the fitting plot between PET IDIF and model input function, as well as PET myocardium TAC and model myocardium TAC, respectively. The MCIF and blood sample fitting plot were also inspected. Furthermore, following Fang and Muzic (2008), the direct and indirect methods were used to evaluate the performance of the proposed algorithm quantitatively. The AUC error of the input function was used as the direct method whereas the kinetic influx constant Ki error was regarded as indirect method. Specifically, AUC error expressed as $(AUC_{est} - AUC_{mea}) / AUC_{mea} \times 100\%$, where AUC_{est} and AUC_{mea} denotes AUC calculated using MCIF and gold standard blood samples, respectively. Similarly, Ki error was calculated as $(Ki_{est} - Ki_{mea}) / Ki_{mea} \times 100\%$. Ki values were obtained using gold standard blood samples (Ki_{mea}) and MCIF (Ki_{est}). The Ki_{mea} values were referred to the Ki calculated using blood samples in Mu *et al* (2013) for the same mice study number. The percent errors were reported as mean and standard deviation (SD). Moreover, the correlation coefficients between measured and estimated results were also determined. A student t test with a P value < 0.05 was used to detect the significant difference.

3. Results

Figure 4 shows a representative plot of the estimated result obtained using the proposed method. Figure 4(a) shows the measured gold-standard blood sample input function versus MCIF. Since the blood samples were taken from the femoral artery, there were delay and dispersion effects compared to MCIF derived from IDIF obtained from the left ventricle at the peak and within first 9 minutes of the dynamic data (Wu *et al* 2007, Mu *et al* 2013). However, after 9 minutes the blood samples and the MCIF showed good agreement. Figure 4(c) are the model blood (solid line) and model myocardium (dashed line) time activity with the PET IDIF (triangle) and PET myocardium TAC (circle). Figure 4(c) demonstrates that the model output fits the IDIF and myocardium data very well.

Penalty functions are introduced as extra constraints to improve the optimization performance of the objective function. The representative effect of the constraint $O_2(p)$ is shown in figure 5(a), indicating that the model blood curve fits the IDIF better when $O_2(p)$ is used. In addition, figure 5(b) shows that the Ki error remains unchanged until the $O_3(p)$ is put into function at computation iteration 100.

Comparison of AUC and Ki estimated error from measured and estimated input functions are summarized in table 2. The overall AUC error of 16 mice averaged $-1.4 \pm 8.2\%$, with correlation coefficients of 0.9706, as shown in figure 6(a). The t-test revealed a P value equal

to 0.3188, indicating no statistically significant difference. The AUC error has a lower mean and standard deviation values as compared to the values ($-1.7\pm 21.0\%$) reported in Fang and Muzic (2008). The overall Ki error percentage of the proposed method was $0.4\pm 5.8\%$ with correlation coefficient of 0.9912, as illustrated in figure 6(b). The t-test P value equals 0.6950 showing no significant difference. The overall Ki error percentage has lower mean and standard deviation value compared to the value of $-1.7\pm 21.8\%$ reported in Fang and Muzic (2008) and $4.9\pm 9.8\%$ in Mu *et al* (2013). The standard deviation of the Ki error percentage achieved by the proposed method was also lower than that of 20% in Zhong and Kundu (2013). By the direct and indirect comparison of both the AUC and Ki error, the proposed method demonstrates less bias in estimation than previous studies.

In order to validate the effect of the Matlab function 'fmincon' in the hybrid algorithm relative to the sole stochastic algorithm, a comparison was conducted as shown in table 3. When 'fmincon' was introduced in the hybrid algorithm, the iteration of the computation was 200; whereas, when 'fmincon' was disabled the number of iterations was set to 1000. The result indicates that even with bigger iteration number and longer computing time, both the Ki and AUC have dramatically larger mean and SD error, which are far from acceptance. Therefore, it is obvious that the 'fmincon' plays an important role in compensating for the slow convergent rate of the stochastic AIS algorithm.

It is noteworthy to point out that since this study aims to validate the proposed method in comparison to the published work of Fang and Muzic (2008) and Mu *et al* (2013), who used the same mice data (UCLA mouse quantitation program), we follow similar common metrics and hence did not report individual fitted parameters and the kinetic model parameters for each mouse.

4. Discussion

It is well known that the non-invasive method is critical for small animal dynamic PET studies, in which the compartmental model and its optimization play a key role in the accuracy of the achieved physiological values. However, due to the SP and PV contamination limited by scanner resolution and small animal organ size, quantitation is still challenging. Compartment model with SP and PV correction significantly improves the accuracy of the physiological parameter estimation from the dynamic PET images of small animal and leads to a realistic applicability of the compartment model for small animal non-invasive studies (Fang and Muzic 2008, Zhong and Kundu 2013). Nevertheless, the optimization method used in the above study were based on Interior-reflective Newton method, or matlab function 'fmincon', which is susceptible to the even minor change of the initial and bound values. Normally it will take much more effort to tune the initial and bounds value subjectively before a relatively minimal residual error of the cost function was met. The initial setting based on experience or limited attempt prompts the uncertainty of the physiological parameters estimated by the compartment model. Consequently, our study further attempts to remove the uncertainty caused by the initial setting of model parameters by using artificial immune algorithm with learning and memory capability. Different from the normal artificial immune algorithm, the 'fmincon' was introduced in a prescribed way in order to ensure the convergence of the final hybrid algorithm.

The Matlab function ‘fmincon’ is an effective and widely used tool in PET tracer kinetic model optimization, however the optimization result relies too much on the initial guess values and bounds. Therefore, the hybrid method was proposed herein to employ stochastic procedure to generate initial values and bound for ‘fmincon’ in order to attempt a higher chance to search the global optimum. However, the ‘fmincon’ might fail to converge and get stuck when an improper initial guess as provided by the stochastic procedure. Hence, in this study the ‘fmincon’ is introduced only when the fitting error is small enough as conducted by step 4 in the flow chart of figure 2, ensuring the convergence of the hybrid method using ‘fmincon’. Nevertheless, the use of any stochastic algorithm would not work for our case where 15 parameters need to be optimized. For example, using simply a Monte Carlo algorithm to generate random initial guess values for ‘fmincon’, we observed that the convergent speed of the method was too slow. We used an 8-core server to run the code but even after 3 days the residual fitting error was still far beyond acceptable range (data not shown). As shown in previously published studies (Tazawa *et al* 1996, Wong *et al* 2002, Xu 2002, Huang *et al* 2012, Yap *et al* 2011, 2012, Liu *et al* 2016), AIS has the best global search capability among the stochastic algorithms dealing with kinetic models optimization problems. Hence we chose the AIS as the stochastic procedure for our hybrid method. AIS has clonal selection procedure corresponding to step 8 of figure 2 that facilitates to generate better initial guess values from the best candidates of previous iterations, just as the biological gene inheritance. The mutation and crossover procedure of the AIS algorithm prevents early premature of the global optimum search. Moreover, with the near-optimum initial guess provided by AIS, ‘fmincon’ converges rapidly and calculates an even better candidate for AIS clonal selection algorithm. This process iterates until a predefined fitting error is met. Thus, without the AIS’s intelligence of learning and memory, it is impossible to achieve the global optimum. During the process, the ‘fmincon’ helps to accelerate the convergence, as shown in the table 3.

Considering the noisy feature of the TAC of IDIF and TAC myocardium, extra constraints were introduced into the objective function in order to increase the fitting performance between model curves and TAC generated by dynamic PET images. AUC difference of blood and myocardium turn out to be an effective solution to balance the overall residual error in the latter half of the computational iterations when the residual error is in the algorithm convergence-acceptable range. The fitting error around the peak value was also boosted by a factor in order to balance the fitting curve with dense distribution in vertical direction. In addition, 1 late time tail vein blood was applied in our study, which is easy to collect and is very similar to the arterial blood sample at this time point (Raue *et al* 2013). It is especially necessary when the TACs from the dynamic PET images are noisy.

The true performance of our method in this work was validated when comparing with prior work including Muzic and Cornelius (2001), Huang *et al* (2005), (Fang and Muzic 2008), Mu *et al* (2013) and Zhong and Kundu (2013) that used ‘fmincon’ as an optimization tool. Our hybrid method, validated in n=16 mice data, removed the uncertainty caused by initial guess values and at the same time yielded more accurate physiological parameters (Ki) and curve fitting (AUC), as described in the Results section. The result of the validation shows several fold improvement in terms of accuracy of MCIF and Ki, comparing to the methods using the deterministic algorithms (Fang and Muzic 2008, Mu *et al* 2013, Zhong and Kundu 2013). In

addition, as shown in table 3 the performance of the hybrid method was also significant in comparison to the normal artificial immune algorithm (Liu *et al* 2016) in terms of convergence speed.

The data for the mice used in this study (from the UCLA Mouse Quantitation Program) weighed ~22–36 g, which has smaller heart size and therefore more SP and PV noise, to validate our method under the worst noise situation. For bigger animals, like rats with bigger hearts, the noise will be smaller when other conditions are kept the same. Less SP and PV contamination yields smaller peak discrepancy and hence better model curve fitting. Although the hybrid method is developed and validated using 18F-FDG mice data, the methodology should be applicable to rat and other PET tracers, scanners or image reconstruction methods as well. However, the parameters of the algorithm like population number, weighting factor, etc., should be adjusted accordingly.

5. Conclusion

A hybrid method using AIS and IRN was developed for the first time to remove the uncertainty caused by initial guess values and bounds in a compartment model as well as to improve the global search performance, which at the same time reduced the convergence iteration times significantly compared to normal AIS. The AIS and IRN compensates each other to achieve an optimum between the global search capability and convergent rate. The result indicated that the suggested method could yield a much more accurate estimation of MCIF and K_i with less computing iterations. The developed method can be applied to reliable estimation of kinetic parameters and blood input function (MCIF) with PV and SP corrections in a 3-compartment tracer kinetic model from dynamic FDG PET images of rodent heart *in vivo*.

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Figure1. Illustration of representative PET data distribution around the peak and typical model fitting curve with bias. It also shows that the circles with dense distribution has better model curve fitting.

Figure 2.

Flow chart of the proposed hybrid method including Artificial Immune System and Interior Reflective Newton algorithms. Steps 4–6 indicate the improved algorithm with ‘fmincon’, using initial values optimized by AIS, which removed the uncertainty of ‘fmincon’ and enhanced the convergence performance of normal AIS.

Figure 3. Representative plot of MCIF upper limit for a combination of the parameters A_1 , A_2 , A_3 , L_1 , L_2 , L_3 , τ with values within the range indicated in Table 1. This results in a MCIF with a peak value 80 MBq/mL, indicating the selected bounds can cover the maximal peak of MCIF based on the injected dose for mice.

Figure 4.

Representative plot of estimated result. (a) Measured blood samples (circles with dash line) and estimated input (solid line) for the first 9 minutes. (b) Measured blood samples (circles) and estimated input (solid line) for the entire scan duration. (c) The PET image derived and model estimated time activity curves of blood and myocardium.

Figure 5.

Representative plots showing the effects of constraints. (a) Peak fitting accuracies of model blood with constraint $O_2(p)$ (solid line) and without constraint $O_2(p)$ (dotted line). (b) Ki error drop at iteration 100 when $O_3(p)$ is introduced.

Figure 6.

(a) Correlation plot of the AUCs of gold standard input function (IF) versus the estimated IF ($r = 0.9706$). (b) Correlation plot of the Ki using gold standard IF versus Ki using estimated IF ($r = 0.9912$)

Table 1

Bounds for parameters used in the optimization

Para	<i>K1</i>	<i>k2</i>	<i>k3</i>	<i>k4</i>	<i>Smb</i>	<i>rb</i>	<i>rm</i>	<i>Sbm</i>	<i>A1</i>	<i>A2</i>	<i>A3</i>	<i>L1</i>	<i>L2</i>	<i>L3</i>	τ
Upper	1	1	1	0.001	1.0	1.0	0.04	1.0	20000	1000	1000	0	0	0	2
Lower	0	0	0	0	0	0.0	0	0	0	0	0	-10	-10	-10	0

Table 2

Comparison of AUC and Ki estimates from measured and estimated input functions (n=16)

Statistics	<i>AUC</i> *	<i>Ki</i> *
Error (%)	-1.4±8.2	0.4±5.8
Corr. Coefficient	0.9706	0.9912
T test P value	0.3188	0.6950

* Error of AUC and Ki are expressed as mean±SD

Correlation coefficient(Corr.coefficient) and P values are calculated from the *Ki* and *AUC* pairs

Table 3

Effect of the 'fmincon' function in the hybrid algorithm

Statistics	<i>AUC</i> error (%) [*]	<i>Ki</i> error (%) [*]	Elapsed time (s) [*]
'fmincon' ON	-1.4±8.2	0.4±5.8	327.7±51.5
'fmincon' OFF	5.7±88.9	28.6±139.8	1819.9±658.9

^{*} Error of AUC and Ki are expressed as mean±SD