Short Communication

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Nonlinear fitting of multi-compartmental data using Hooke and Jeeves direct search method

Abstract: Compartmental modelling refers to modelling the transport of substances in a system consisting of multiple compartments, which is characterized by the transfer rates among the relevant compartments. In a generalized compartmental system, recycling of substances among the compartments is allowed. Compartmental modelling is a generic technique which is needed in many branches of applied physics. The most challenging task is to determine the transfer rates. The present work described the use of the Hooke and Jeeves (HJ) derivative free direct search method in determining the transfer rates to construct a multi-compartmental model with recycling among the compartments. The use of a direct search method ensures the applicability of the model to functions which are not continuous or differentiable. The present model was successfully validated using previously reported experimental data for distribution of trace elements in four compartments in an animal.

Keywords: compartmental modelling, Hooke and Jeeves method, numerical analysis, nonlinear fitting, derivative free method

1 Introduction

Compartmental modelling is a generic technique which is needed in many branches of applied physics ranging from medical physics [1] to environmental physics [2], etc. As an example used here to provide background information, in medical physics, analyses on the transfer of drugs among different organs in the human body are required. Compartmental models are being widely used in biokinetic applications. Previously, Upton [3] discussed the two-compartment recirculatory pharmacokinetic model which consisted of the lungs and the remainder of the body. Similarly, Petráš and Magin [4] developed a two-compartment model for drug uptake by the gut and the target tissue. Sharma et al. [5] developed a multi-compartment model for radon contamination in the human body. In another work, Garcia et al. [6,7] developed a statistical method for multiple-compartment biokinetical models, where the least-squares technique was employed to determine the flow parameters from experimentally available curves of concertation versus time. From experimental studies, the drug concentrations in various organs are obtained as a function of time. In compartmental modelling, these organs are modeled as multiple compartments, and the rate of change in the drug concentration in a particular compartment is related to the rates of change in the drug concentrations in all other relevant compartments through linear differential equations [8,9]. More specifically, the temporal change in the drug concentration in each compartment is controlled by the respective parameters: (1) uptake and excretion rates, (2) initial drug concentration, (3) compartment volume, and (4) transfer rates among the relevant compartments. The task of compartmental modelling is to determine these parameters based on experimental data. Notably, a most challenging task is to determine the transfer rates, particularly in a generalized compartmental system where recycling of drugs among the compartments is allowed. The present work described the use of the Hooke and Jeeves (HJ) derivative free direct search method [10] in determining the transfer rates to construct a multi-compartmental model with recycling among the compartments. The use of a direct search method ensures the applicability of the model to functions which are not continuous or differentiable.

2 Materials and methods

The HJ method mainly involves two steps, namely, (1) exploratory search and (2) pattern move. The HJ method

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perturbs the current point (which is initially the guessed transfer rates) by a small amount in each variable direction (determined by the number of compartments in the system and the presence or absence of recycling among the compartments) and checks whether the value of the objective function [which in the present case is the sum of absolute values of (experimental value – fitted value)/ (fitted value)] improves or worsens. More information on the well-established HJ method can be found in refs. [11,12] and references therein. Remarkably, the method does not necessitate very precise starting points (i.e., guessed values) and complex Jacobian matrices (as it is derivative free) [13]. Furthermore, it is much more user-friendly since the users need to control fewer parameters (only the step size, tolerance, and maximum iterations) and the accuracy and convergence of the present method have been found to be phenomenal [12]. The overall computational speed of this method is another advantage that stands out when compared to other methods.

The general outline of our developed algorithm is shown below:
1. Initialize variables.
2. Read number of compartments (N).
3. Dynamically allocate arrays based on N.
4. Read the input data into arrays; volume ($\boldsymbol{V}$), excretion ($\boldsymbol{\xi}$), uptake ($\boldsymbol{P}$), initial concentrations ($\boldsymbol{X_0}$), guessed transfer rates ($\boldsymbol{R_i}$).
5. Read the time (t).
6. Get step size factor (ρ), tolerance (δ), maximum iterations ($iter$).
7. Call Hooke–Jeeves function.
   (a) Calculate concentration vector $\boldsymbol{x_t}$.
   (b) Calculate sum of absolute values of (experimental value $\boldsymbol{x_{tE}}$ – fitted value $\boldsymbol{x_t}$)/(fitted value $\boldsymbol{x_t}$)
   (c) Determine new transfer rates ($\boldsymbol{R}$) based on the accepted exploratory search and pattern move.
   (d) Check tolerance and iteration and, if reached, terminate.
8. If $t > t_n$ (total number of time points), terminate; if not, ($t = t + 1$) then go to step 5.
9. Determine mean and standard deviation of the transfer rates ($\boldsymbol{R}$).
10. Report the final transfer rates ($\boldsymbol{R}$) and associated errors.

The user needs to input the required parameters such as volume, uptake, initial concentration, and the initial guessed transfer rates. Our model used in the present work was developed with the FORTRAN90 programming language. This model was highly flexible and faster in terms of computational speed and convergence, thanks to the derivate free method and also the FORTRAN90 programming language. While derivative free methods use function values, derivative-based methods involve differentiation of the objective functions. When compared to derivative-based methods, derivative free methods have a major advantage in that they can have applications in a wide variety of mathematical problems, e.g., when the objective function is unknown (i.e., black box functions), when determination of derivatives would be impractical, when the objective function has stochastic noise that may lead to inaccurate finite differencing, or when it is computationally expensive to evaluate large dimensional gradient of a system [14]. However, some previously published works found that derivative-based methods provided a better estimate of the objective function, and the computational time needed by derivative-based methods was shorter [15]. We refer interested readers to ref. [16] and references therein for a more detailed comparison between the pros and cons of derivative-based and derivative free methods for different applications. We refer interested readers to the supplementary materials associated with the present paper for more information on our numerical model and its benchmarking.

3 Results and discussion

Our model was tested using previously reported experimental data [2] for distribution of trace elements in four compartments in an animal, namely, (a) blood, (b) muscle, (c) fat, and (d) lung tissue. In that study [2], there was uptake of trace elements only during the first 60 days, and the diet was switched back to contamination-free diet afterwards. The temporal changes of trace-element concentrations were reported. Fits obtained using the present model as well as those obtained in ref. [2] are presented in Figure 1 for comparison. Good agreement is observed between our fits and the experimental data, which demonstrates the feasibility of using the HJ method in multi-compartmental modelling. The model searches for the best transfer rates through minimizing the sum of absolute values of (experimental value – fitted value)/(fitted value) and does not necessitate very precise guessed initial transfer rates. The entire fitting process is carried out automatically, with minimal human interaction and point correction. We plan to develop a graphical user interface program in future which will be available to the research community for multi-compartmental modelling and analysis.
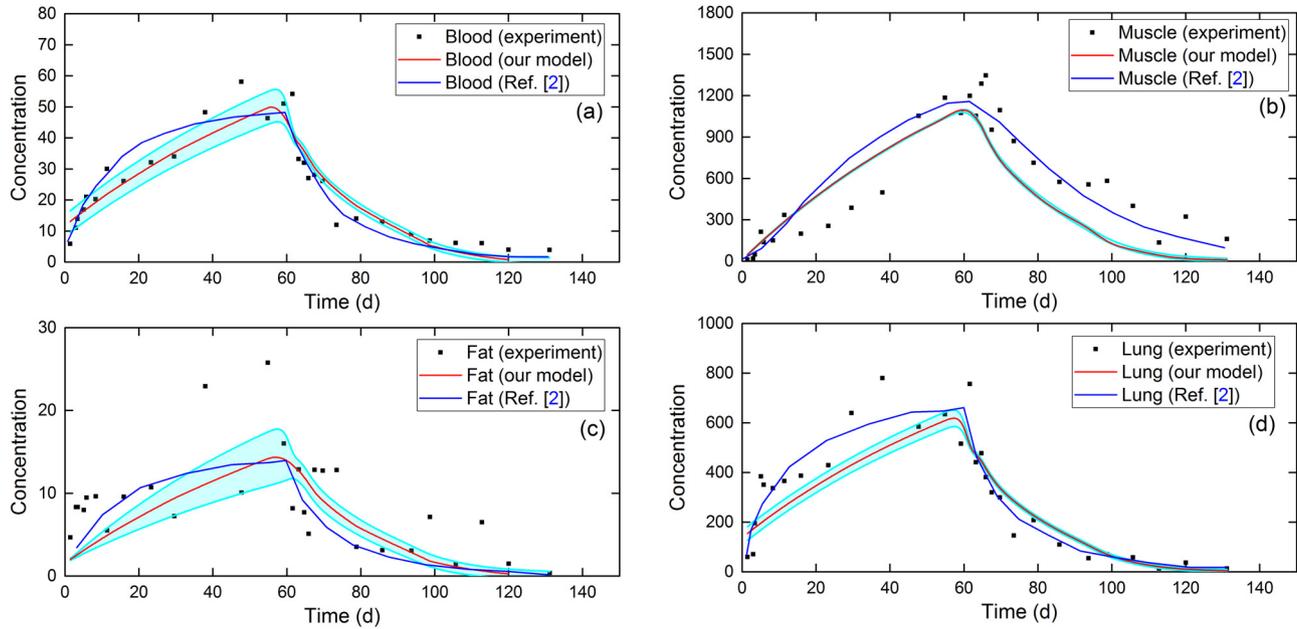
Figure 1: Validation of our present model using previously reported experimental data [2] (black squares) for distribution of trace elements in four compartments in an animal, namely, (a) blood, (b) muscle, (c) fat, and (d) lung tissue. There was uptake of trace elements only during the first 60 days. Fits obtained using the present model (red curve) as well as those obtained in ref. [2] (blue curve) are presented. Statistical variations for our fits are shown as cyan shades.

4 Conclusion

Our present model was found capable of fitting multi-compartmental data using the direct search algorithm (i.e., HJ method). The employment of direct search HJ method in the present work was the main innovative step in the present work when compared to previous works [6,7]. In addition, the present model allows users to control all the required parameters to fine-tune the fitting of experimental results; this is useful to achieve the best possible fit. The implementation of derivative free method would enable us to further develop this into a versatile computer program that can be used in a variety of applications even when the objective function is unknown. Therefore, in the future we aim to further develop this into a graphical user interface program that would be useful in multi-compartmental modelling and analysis in a variety of applications.

Conflict of interest: Kwan Ngok Yu is an Editor in Open Physics journal but was not involved in the peer review process.

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Supplementary material

1 Supplementary material

The rate of change of the concentration x_i in a particular compartment i is described using the first-order differential equation as

$$\frac{dx_i}{dt} = \sum_{\substack{j=1 \\ j \neq i}}^{N} r_{ji}x_i - x_i \sum_{\substack{j=1 \\ j \neq i}}^{N} r_{ij} \qquad (S1)$$

where N is the number of compartments in the modelled system, and r_{ij} is the set of transfer rates.

Here we assumed that compartment i is being fed from the outside with a constant rate P_i and releases its content through excretion with the rate $\xi_i x_i$, given ξ_i and x_i are constant and concentration, respectively. The temporal variation in the number of molecules (M_i) in compartment i can be shown as;

$$\frac{dM_i}{dt} = P_i + \sum_{\substack{j=1 \\ j \neq i}}^{N} r_{ji}x_j - x_i \left(\sum_{\substack{j=1 \\ j \neq i}}^{N} r_{ij} \right) - \xi_i x_i \qquad (S2)$$

where the unit of ξ_i could be presented in liters per day or kilogram per day depending on the unit that was used for the concentration x_i.

Considering the relation between the number of molecules (M_i), volume (V_i) and concentration (x_i) in compartment i, the expression would then be;

$$M_i = x_i V_i \qquad (S3)$$

Substituting equation (S3) into equation (S2) will give

$$\frac{d(V_i x_i)}{dt} = P_i + \sum_{\substack{j=1 \\ j \neq i}}^{N} r_{ji}x_j - x_i \left(\sum_{\substack{j=1 \\ j \neq i}}^{N} r_{ij} \right) - \xi_i x_i \qquad (S4)$$

In these expressions, $i \neq j$, so the diagonal elements can be defined as

$$r_{ii} = - \sum_{\substack{j=1 \\ j \neq i}}^{N} r_{ij} - \xi_i \qquad (S5)$$

which simply means replacing each diagonal element of $\mathbf{R}$ by the negative of the sum of each row elements. With equation (S5), we can rewrite equation (S4) as

$$\frac{d(V_i x_i)}{dt} = P_i + \sum_{j=1}^{N} r_{ji}x_j \qquad (S6)$$

Considering a system with multiple compartments, equation (S6) can be simply presented in the matrix form:

$$\frac{d(\mathbf{Vx})}{dt} = \mathbf{P} + \mathbf{Rx} \qquad (S7)$$

In our model, constant volume was considered, i.e., the volume of each compartment does not change with time, so we can then move volume ($\mathbf{V}$) out of the differential as

$$\mathbf{V}\frac{d(\mathbf{x})}{dt} = \mathbf{P} + \mathbf{Rx} \qquad (S8)$$

Let $\mathbf{u} = \mathbf{x} + \mathbf{R}^{-1}\mathbf{P}$, where u and $\mathbf{R}^{-1}$ are column vector and the inverse matrix of $\mathbf{R}$, respectively, so equation (S8) can be written as

$$\mathbf{V}\frac{d\mathbf{u}}{dt} = \mathbf{Ru} \qquad (S9)$$

Taking the inverse of the volume matrix ($\mathbf{V}^{-1}$), equation (S9) will become

$$\frac{d\mathbf{u}}{dt} = \mathbf{V}^{-1}\mathbf{Ru} \qquad (S10)$$

The solution to equation (S10) is

$$\mathbf{u}(t) = \exp(\mathbf{V}^{-1}\mathbf{R}t)\mathbf{u}(0) \qquad (S11)$$

Through changing the variables from the definition of $\mathbf{u}$, equation (S11) can be used to obtain the general solution for $\mathbf{x}(t)$ as;

$$\mathbf{x}(t) = [\exp(\mathbf{V}^{-1}\mathbf{R}t) - 1]\mathbf{R}^{-1}\mathbf{P} + \exp(\mathbf{V}^{-1}\mathbf{R}t)\mathbf{x}(0) \quad (S12)$$

where $\mathbf{x}(t)$ is the concentration of contaminants, $\mathbf{V}^{-1}$ is the inverse matrix of volume, $\mathbf{R}^{-1}$ is the inverse matrix of transfer rates and t is the time.

For benchmarking our model, we have used the results previously reported by Birchall and James [1], who presented a hypothetical example of a closed model with 5 compartments. In addition, their system had extreme ranges of transfer rates (see Figure S1).

The contaminant concentrations in 5 different compartments obtained by Birchall and James [1] and by our present model are compared in Table S1, which shows good agreement. Therefore, our model can adequately
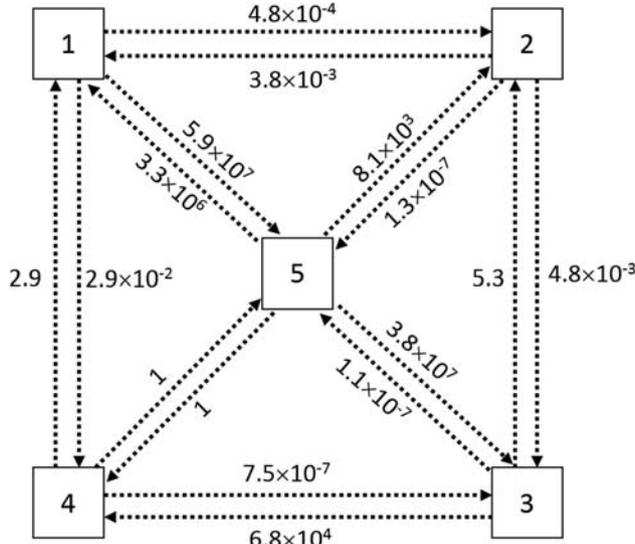
Figure S1: The 5-compartment model of Birchall and James [1] used for validation of our model.

determine the temporal changes in the concentrations of contaminant in different compartments.

Here we provide more explanation on the Hooke and Jeeves method which was initially published in 1961. The Hooke and Jeeves method has two main steps, namely, (1) exploratory search and (2) pattern move. The exploratory search will search locally for a direction to move which is also referred to as the improving direction. The pattern move is a much larger search in the direction of improving results. The Hooke and Jeeves method is a derivative free method which tries to minimize the value of a function by searching for suitable arguments. The following is the algorithm for the general Hooke and Jeeves method.

First, the perturbation step size in each of the dimensions that is present in the problem is set up. This can be accomplished through the definition of perturbation vector as;

$$P_0 = (\Delta x_1, \Delta x_2, \Delta x_3, \Delta x_4, ..., \Delta x_n) \quad (S13)$$

The perturbation step sizes are usually small. Now we can define x^0 and $f(x^0)$ as current point and objective function value, respectively. The first step which is the exploratory search will be as follows:

1. Set $x^1 = x^0$ then initialize f_{best} by copying the objective function value (i.e., $f(x^0)$) into it.
2. Loop over each variable (x_j)
   (a) Increase each element by the perturbation value as
   $$x^1 = (x_1^1, x_2^1, x_3^1, ..., x_j^1 + \Delta x_j, ..., x_n^1)$$

(b) If $f(x^1) < f_{best}$ (i.e., if it improves), set $f_{best} = f(x^1)$, use the same perturbation value, go to step 2(a) for next variables ($j = j + 1$)

(c) If $f(x^1) > f_{best}$ (i.e., if it worsens) or if $f(x^1) = f_{best}$ (i.e., no change), then set $x^1 = (x_1^1, x_2^1, x_3^1, ..., x_j^1 - \Delta x_j, ..., x_n^1)$; decrease each element by the perturbation value

(d) If improvement of $f(x^1)$ accepted compared to f_{best}; retain perturbation value and set $f_{best} = f(x^1)$. Otherwise discard by setting $x_j^1 = x_j^0$

(e) Go to step 2(a) for next variable ($j = j + 1$)

3. Calculate the improving direction vector as $x^1 - x^0$. If $x^1 - x^0 = 0$ then the exploratory search has failed.

The pattern move in the Hooke and Jeeves method uses the x^0 and x^1 which in fact has provided a better value of the objective function (f). The pattern move in the so-called improving direction (in step 3 of the algorithm shown above) will result in a new point x^2 as

$$x^2 = x^0 + a[x^1 - x^0] \quad (S14)$$

where the factor a is the so-called acceleration factor; this extends the length of the improving direction.

In our model, we have developed and implemented the Hooke and Jeeves method as a module. The main goal for this module is to perform exploratory search and pattern move to find suitable values for the transfer-rate matrix, in a way that the sum of absolute values of (experimental value – fitted value)/(fitted value) at each time point is minimized. For example, for the 4-compartment case that is shown in the main paper, the transfer-rate matrix will be 4×4 and there will be a total of 12 transfer rates that will be changed using the Hooke and Jeeves module (as the diagonal elements in the transfer-rate matrix have been replaced with the negative sum of row elements for that particular diagonal location, see equation (S5) for the mathematical representation). These 12 points will be initially supplied as guessed values by the user. The current model has another module that determines the value of the objective function by taking the transfer rates and other inputs such as experimentally measured concentration values, then calculates the absolute values of (experimental value – fitted value)/(fitted value) and then sums for all compartments present in the problem and passes the value to the Hooke and Jeeves module as the value of the objective function. The Hooke and Jeeves module then tries to minimize the

Table S1: Comparisons among contaminant concentrations in 5 different compartments obtained by Birchall and James [1] and by our present model

Time	1 (Ref. [1])	1 (our model)	2 (Ref. [1])	2 (our model)	3 (Ref. [1])	3 (our model)	4 (Ref. [1])	4 (our model)	5 (Ref. [1])	5 (our model)
10^{-8}	1.16×10^1	1.16×10^1	2.00×10^1	2.00×10^1	2.73×10^1	2.73×10^1	2.00×10^1	2.00×10^1	2.11×10^1	2.10×10^1
10^{-7}	2.79×10^{-1}	2.79×10^{-1}	2.00×10^1	2.00×10^1	5.73×10^1	5.73×10^1	2.03×10^1	2.03×10^1	2.15×10^1	2.15
10^{-6}	1.32×10^{-6}	1.34×10^{-6}	2.00×10^1	2.00×10^1	5.61×10^1	5.61×10^1	2.38×10^1	2.38×10^1	2.64×10^{-6}	2.67×10^{-6}
10^{-5}	2.74×10^{-6}	2.76×10^{-6}	2.00×10^1	2.00×10^1	3.04×10^1	3.04×10^1	4.95×10^1	4.95×10^1	5.51×10^{-6}	5.54×10^{-6}
10^{-4}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	7.15×10^{-2}	7.15×10^{-2}	7.99×10^1	7.99×10^1	8.90×10^{-6}	8.93×10^{-6}
10^{-3}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	4.59×10^{-3}	4.60×10^{-3}	8.00×10^1	8.00×10^1	8.91×10^{-6}	8.94×10^{-6}
10^{-2}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	4.59×10^{-3}	4.60×10^{-3}	8.00×10^1	8.00×10^1	8.91×10^{-6}	8.94×10^{-6}
10^{-1}	4.43×10^{-6}	4.45×10^{-6}	2.00×10^1	2.00×10^1	4.59×10^{-3}	4.60×10^{-3}	8.00×10^1	8.00×10^1	8.91×10^{-6}	8.94×10^{-6}
1	4.44×10^{-6}	4.46×10^{-6}	1.99×10^1	1.97×10^1	4.59×10^{-3}	4.62×10^{-3}	8.01×10^1	8.03×10^1	8.92×10^{-6}	8.97×10^{-6}
10^1	4.47×10^{-6}	4.59×10^{-6}	1.93×10^1	1.75×10^1	4.63×10^{-3}	4.75×10^{-3}	8.07×10^1	8.25×10^1	8.99×10^{-6}	9.22×10^{-6}
10^2	4.70×10^{-6}	5.11×10^{-6}	1.52×10^1	8.03	4.86×10^{-3}	5.29×10^{-3}	8.48×10^1	9.20×10^1	9.45×10^{-6}	1.03×10^{-5}
10^3	4.86×10^{-6}	5.22×10^{-6}	1.23×10^1	6.11	5.03×10^{-3}	5.40×10^{-3}	8.77×10^1	9.39×10^1	9.77×10^{-6}	1.05×10^{-5}
10^4	4.86×10^{-6}	5.22×10^{-6}	1.23×10^1	6.11	5.03×10^{-3}	5.40×10^{-3}	8.77×10^1	9.39×10^1	9.77×10^{-6}	1.05×10^{-5}
10^5	4.88×10^{-6}	5.22×10^{-6}	1.24×10^1	6.11	5.03×10^{-3}	5.40×10^{-3}	8.81×10^1	9.39×10^1	9.82×10^{-6}	1.05×10^{-5}
10^6	4.84×10^{-6}	5.22×10^{-6}	1.23×10^1	6.11	5.01×10^{-3}	5.40×10^{-3}	8.73×10^1	9.39×10^1	9.73×10^{-6}	1.05×10^{-5}
10^7	4.97×10^{-6}	5.22×10^{-6}	1.26×10^1	6.11	5.14×10^{-3}	5.40×10^{-3}	8.97×10^1	9.39×10^1	9.99×10^{-6}	1.05×10^{-5}
10^8	1.12×10^{-5}	5.22×10^{-6}	2.83×10^1	6.11	1.16×10^{-2}	5.40×10^{-3}	2.02×10^2	9.39×10^1	2.25×10^{-5}	1.05×10^{-5}

objective function value by changing the transfer rates. It is noted here that the objective function is in a form of a subroutine that will be called in the Hooke and Jeeves loop. The entire program was written in FORTRAN90 programming language.

Reference

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