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Note

Using three-, four-, and *n*-compartment closed models to estimate glomerular filtration rate during and after a constant rate intravenous infusion

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Abstract

The two-compartment open model is currently used to assess the glomerular filtration rate (GFR) after a single intravenous injection or a constant rate intravenous infusion. This model needs multiple blood samples from a patient, thus numerous limited sampling models have been so far developed to reduce the number of blood samples. In the present study, the three-, four- and *n*-compartment closed models have been developed to assess GFR after and during a constant rate intravenous infusion, which include the renal and all possible non-renal elimination pathways. Although more non-renal elimination compartments were included in the modelling, the results show it only leads to the increase in the similar analytical solutions for these compartments and the analytical solution for the blood compartment is the same as that in the two-compartment open model. Theoretically, the developed models can be used to assess GFR with a single blood sample at any sampling time with several urine samples.

Keywords: Compartmental model; Glomerular filtration rate; Kidney function; Limited sampling strategy

1. Introduction

The assessment of glomerular filtration rate (GFR) is particularly important in clinical settings. One of the methodologies to assess GFR involves the use of pharmacokinetic methods i.e. the two-compartment open model after a single intravenous injection or a constant rate intravenous infusion [1]. For example, after a constant rate intravenous infusion, multiple blood samples are taken from the patient and fitted using the equation

$$C(T) = \frac{D(\alpha - k_{21})}{\tau\alpha(\alpha-\beta)V}(1-e^{-\alpha\tau})e^{-\alpha T} - \frac{D(\beta - k_{21})}{\tau\beta(\alpha-\beta)V}(1-e^{-\beta\tau})e^{-\beta T} \quad (1)$$

where $C(T)$ is the blood tracer concentration at different sampling times after infusion, τ is the duration of infusion, T is the time after infusion, D is the infusion dose, α, β and k_{21} are pharmacokinetic parameters and V is the volume of distribution. After having obtained these parameters, GFR can be calculated using various equations, e.g.

$$GFR = \frac{injected\ dose \times \alpha \times \beta}{B \times \alpha + A \times \beta}\ \left(ml\ \min^{-1}\right)$$

[2] and $GFR = A \times \ln C(t) + B$ [3].

Because the pharmacokinetic model requires multiple blood samples, which can be inconvenient in clinical settings, numerous limited sampling strategies have been developed to reduce the number of samples [3–5]. The blood samples in limited sampling strategies are obtained at various specific sampling times, therefore one finds different limited sampling strategies to follow and conflicting results from the various comparisons [6,7].

If the tracer in the eliminated urine can be sampled to estimate some of the pharmacokinetic parameters, the num-

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ber of blood samples can theoretically be reduced [8]. In order to use the samples from urine, the urine compartment needs to be incorporated into the two-compartment open model, thus making a three-compartment closed model (Fig. 1).

Due to the fact that numerous tracers used in the assessment of GFR are eliminated to varying degrees via the non-renal elimination pathway [9], which is not modelled in the two-compartment open model (Fig. 1), the current two-compartment open model is ideally suited in the case where the tracers are exclusively eliminated via the kidneys i.e. the plasma clearance is equal to the renal clearance. In order to model renal and non-renal elimination pathways separately, both renal and non-renal elimination compartments need to be incorporated into the two-compartment open model, which makes a four-compartment closed model (Fig. 2).

If the tracers can be eliminated via several non-renal elimination pathways, more non-renal elimination compartments need to be incorporated into the modelling, which leads to a *n*-compartment closed model (Fig. 2).

In the present study, we deduce the equations to estimate some of the pharmacokinetic parameters in the three-, four- and *n*-compartment closed model during, and after, a constant rate intravenous infusion using the tracer samples from urine, and demonstrate these equations to have similar forms for all these models no matter how many non-renal elimination pathways are involved.

2. Theoretical development

2.1. Three-, four-, and n-compartment closed models

When incorporating different elimination compartments into the two-compartment open model (Figs. 1 and 2), the analytical solutions for all the elimination compartments have similar forms (Appendix). Since the volume of eliminated urine changes over time and the eliminated tracer is accumulated over time, one can use only the amount of accumulated tracer to estimate parts of the pharmacokinetic parameters. The amount of accumulated tracer in the eliminated urine compartment after a constant rate intravenous infusion has the same analytical solution for three-, four- and *n*-compartment closed models (Appendix A):

$$x_3(T) = \frac{Dk_{13}}{\tau}\left[\frac{k_{21}\tau}{\alpha\beta} + \frac{\alpha - k_{21}}{\alpha^2(\alpha-\beta)}\left(e^{-\alpha\tau} - 1\right)\right.$$
$$\left. e^{\alpha T} - \frac{\beta - k_{21}}{\beta^2(\alpha-\beta)}\left(e^{-\beta\tau} - 1\right)e^{-\beta T}\right] \quad (2)$$

where $\alpha + \beta = k_{12} + k_{13} + k_{21}$ and $\alpha\beta = k_{21}k_{13}$ for the three-compartment closed model, $\alpha + \beta = k_{12} + k_{13} + k_{14} + k_{21}$ and $\alpha\beta = k_{21}(k_{13} + k_{14})$ for the four-compartment closed model, $\alpha + \beta = k_{12} + k_{13} + .. + k_{1n} + k_{21}$ and $\alpha\beta = k_{21}(k_{13} + .. + k_{1n})$ for the *n*-compartment closed model.

The equations deduced for the three-, four- and *n*-compartment closed models suggest that (i) the increase in the non-renal elimination pathways does not lead to the change in the analytical solution for the description of blood tracer concentrations, (ii) all elimination compartments have similar analytical solutions and (iii) the increase in the non-renal elimination pathways only leads to a fraction of the existing elimination pathway.

Eq. (2). describes the accumulated amount of tracer in urine after infusion, thus one has no need to measure the volume of urine per minute as used in other methods [4] one only needs to measure the amounts of the eliminated tracer in urine and the volume of urine at different intervals.

2.2. Calculation

Two methods can be used to estimate the pharmacokinetic parameters in all of the above compartmental models to further determine GFR.

(i) One can use Eqs. (1) and (2) together with the appropriate computer software, e.g. PCNONLIN, to simultaneously fit a blood drug concentration and several accumulated amounts of eliminated tracer in urine after infusion and

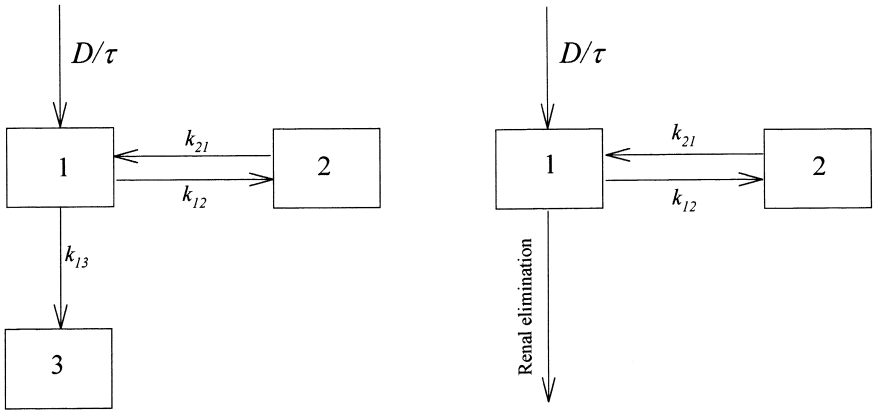

Fig. 1. The three-compartment closed model (left) and two-compartment open model (right) with a constant rate intravenous infusion.

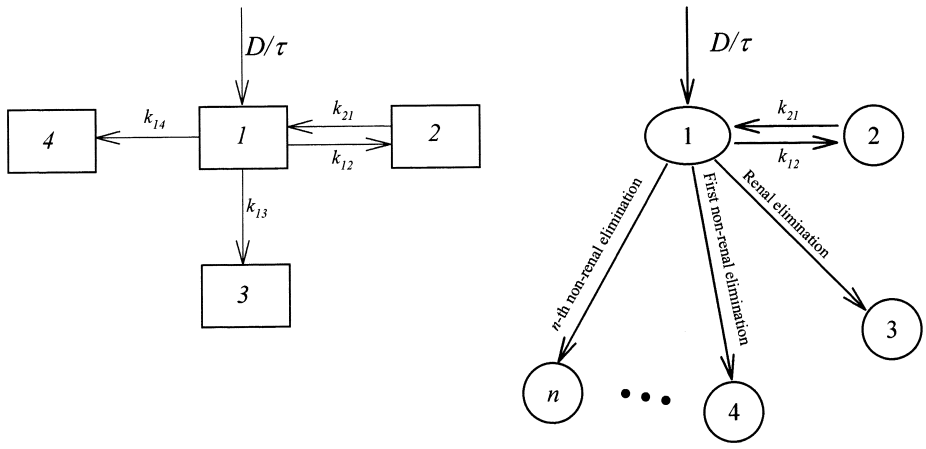

Fig. 2. The four- and *n*-compartment closed models with a constant rate intravenous infusion.

obtain α, β, k_{21}, k_{13}, and V. A similar method has been documented in the one-compartment model after a single intravenous injection [10].

(ii) One can use Eq. (2) to fit several accumulated amounts of eliminated tracer in urine after infusion to obtain α, β, k_{21} and k_{13}, then put the obtained pharmacokinetic parameters into Eq. (1) to determine V with one blood sample.

There are five and four parameters in the first and second methods, respectively. Since the number of degrees of freedom (difference between the number of data and the number of model parameters) should be larger than, or equal to, one, one needs about five accumulated amounts of the eliminated tracer in urine and one blood tracer concentration, which is possible because the elimination of tracers usually takes several hours. When considering the amount of the eliminated tracer to be zero in urine at the beginning of administration, one only needs four accumulated amounts of the eliminated tracer with the zero time in the fitting. But this approach is suitable only during infusion (Appendix), because the time is separately determined after infusion.

Table 1

Blood furbenifillin concentrations and accumulated amounts of furbenifillin in urine after infusion

Time after infusion (h)	Blood furbenifillin concentration (unit l^{-1})	Time after infusion (h)	Accumulated amount of furbenifillin (units)
0	305300	4	1142742
0.25	291435	6	1304214
0.5	279452	8	1456454
1	230648	10	1544280
1.5	223406	12	1706354
2	208045	16	1814113
3	190892	20	1939799
4	187056	26	1973244
6	160347	32	1981354

3. Example and discussion

Due to the fact no clinical data are available to the author, the present study is mainly a theoretical study. However, the data in an experimental animal were used to show the potential use of the developed models. Table 1 shows the amounts of eliminated furbenifillin in urine and blood furbenifillin concentrations after 4 h, 200 0000 units constant rate, intravenous infusion in a dog (the experiment was approved by the local Animal Care Committee). By means of any above method with any blood concentration, the estimated pharmacokinetic parameters are about $k_{21} = 0.104\ h^{-1}$, $\alpha = 0.171\ h^{-1}$, $\beta = 0.082\ h^{-1}$ and $V = 5l$. Thus one can further calculate GFR.

The example shows that the devolved models can estimate GFR with only one blood sample at any sampling time, and five amounts of the eliminated tracer in urine at any five sampling times after infusion. These models do not require a specific blood sampling time and measurement of volume of urine per minute. If the bladder cumulative method is used to determine the amounts of the eliminated tracer in the bladder [4], these models require only one blood sample without the collection of urine.

In the past, the open compartmental model received great attention, all the parameters in a compartmental model are estimated by fitting blood drug concentrations. However, if one needs to reduce the blood samples, the use of the closed compartmental model is an alternative method, because several pharmacokinetic parameters can be estimated in the compartment outside of the body.

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Appendix A

The finding of analytical solutions for the differential equations for the three-, four-, and *n*-compartment closed models during and after a constant rate intravenous infusion.

The three-, four- and *n*-compartment closed models with a constant rate intravenous infusion have the following systems of differential equations:

$$\begin{aligned}
&\frac{dx_1(t)}{dt} = -(k_{12}+k_{13})x_1(t) + k_{21}x_2(t) + \frac{D}{\tau}\left[u(t)-u(t-\tau)\right]\\
&\frac{dx_2(t)}{dt} = k_{12}x_1(t) - k_{21}x_2(t)\\
&\frac{dx_3(t)}{dt} = k_{13}x_1(t)
\end{aligned} \tag{1}$$

$$\begin{aligned}
&\frac{dx_1(t)}{dt} = -(k_{12}+k_{13}+k_{14})x_1(t) + k_{21}x_2(t) + \frac{D}{\tau}\left[u(t)-u(t-\tau)\right]\\
&\frac{dx_2(t)}{dt} = k_{12}x_1(t) - k_{21}x_2(t)\\
&\frac{dx_3(t)}{dt} = k_{13}x_1(t)\\
&\frac{dx_4(t)}{dt} = k_{14}x_1(t)
\end{aligned} \tag{2}$$

$$\begin{aligned}
&\frac{dx_1(t)}{dt} = -\left(k_{12}+k_{13}+k_{14}+\ \ldots\ +k_{1n}\right)x_1(t) + k_{21}x_2(t) + \frac{D}{\tau}\left[u(t)-u(t-\tau)\right]\\
&\frac{dx_2(t)}{dt} = k_{12}x_1(t) - k_{21}x_2(t)\\
&\frac{dx_3(t)}{dt} = k_{13}x_1(t)\\
&\frac{dx_4(t)}{dt} = k_{14}x_1(t)\\
&\ldots\\
&\frac{dx_n(t)}{dt} = k_{1n}x_1(t)
\end{aligned} \tag{3}$$

where t is the time during infusion, $u(t)$ and $u(t-\tau)$ are unit functions, $x_i(t)$ is the amount of the tracer in the i-th compartment, k_{ij} is the transfer rate from the i-th compartment to the j-th compartment, the initial conditions are $x_i(0) = 0$ ($i = 0, 1,.. n$).

All the elimination compartments have similar forms of differential equations, they should therefore have similar forms of analytical solutions. As no analytical solutions for these compartmental models have been documented, we used the Laplace transform, partial fraction expansion and inverse Laplace transform to solve these systems of differential equations and found the completely analytical solutions for the three-, four- and *n*-compartments during infusion as follows:

$$\begin{aligned}
x_1(t) &= \frac{D}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[1-u(t-\tau)\right] - \frac{\alpha-k_{21}}{\alpha(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right] + \frac{\beta-k_{21}}{\beta(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}\\
x_2(t) &= \frac{Dk_{12}}{\tau}\left\{\frac{1}{\alpha\beta}\left[1-u(t-\tau)\right] + \frac{1}{\alpha(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right] - \frac{1}{\beta(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}\\
x_3(t) &= \frac{Dk_{13}}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[t-(t-\tau)u(t-\tau)\right] + \frac{\alpha\beta-(\alpha+\beta)k_{21}}{\alpha^2\beta^2}\left[1-u(t-\tau)\right] + \frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right] + \frac{k_{21}-\beta}{\beta^2(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}
\end{aligned} \tag{4}$$

$$\begin{aligned}
x_1(t) &= \frac{D}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[1-u(t-\tau)\right] - \frac{\alpha-k_{21}}{\alpha(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right] + \frac{\beta-k_{21}}{\beta(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}\\
x_2(t) &= \frac{Dk_{12}}{\tau}\left\{\frac{1}{\alpha\beta}\left[1-u(t-\tau)\right] + \frac{1}{\alpha(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right] - \frac{1}{\beta(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}\\
x_3(t) &= \frac{Dk_{13}}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[t-(t-\tau)u(t-\tau)\right] + \frac{\alpha\beta-(\alpha+\beta)k_{21}}{\alpha^2\beta^2}\left[1-u(t-\tau)\right] + \frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right] + \frac{k_{21}-\beta}{\beta^2(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}\\
x_4(t) &= \frac{Dk_{14}}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[t-(t-\tau)u(t-\tau)\right] + \frac{\alpha\beta-(\alpha+\beta)k_{21}}{\alpha^2\beta^2}\left[1-u(t-\tau)\right] + \frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right] + \frac{k_{21}-\beta}{\beta^2(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}
\end{aligned} \tag{5}$$

$$x_1(t)=\frac{D}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[1-u(t-\tau)\right]-\frac{\alpha-k_{21}}{\alpha(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right]+\frac{\beta-k_{21}}{\beta(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}$$

$$x_2(t)=\frac{Dk_{12}}{\tau}\left\{\frac{1}{\alpha\beta}\left[1-u(t-\tau)\right]+\frac{1}{\alpha(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right]-\frac{1}{\beta(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}$$

$$x_3(t)=\frac{Dk_{13}}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[t-(t-\tau)u(t-\tau)\right]+\frac{\alpha\beta-(\alpha+\beta)k_{21}}{\alpha^2\beta^2}\left[1-u(t-\tau)\right]+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right]+\frac{k_{21}-\beta}{\beta^2(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}$$

$$x_4(t)=\frac{Dk_{14}}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[t-(t-\tau)u(t-\tau)\right]+\frac{\alpha\beta-(\alpha+\beta)k_{21}}{\alpha^2\beta^2}\left[1-u(t-\tau)\right]+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right]+\frac{k_{21}-\beta}{\beta^2(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\}$$

…

$$x_n(t)=\frac{Dk_{1n}}{\tau}\left\{\frac{k_{21}}{\alpha\beta}\left[t-(t-\tau)u(t-\tau)\right]+\frac{\alpha\beta-(\alpha+\beta)k_{21}}{\alpha^2\beta^2}\left[1-u(t-\tau)\right]+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left[e^{-\alpha t}-e^{-\alpha(t-\tau)}u(t-\tau)\right]+\frac{k_{21}-\beta}{\beta^2(\alpha-\beta)}\left[e^{-\beta t}-e^{-\beta(t-\tau)}u(t-\tau)\right]\right\} \tag{6}$$

and after infusion as follows:

$$x_1(T)=\frac{D}{\tau}\left[\frac{k_{21}-\alpha}{\alpha(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{k_{21}-\beta}{\beta(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right]$$

$$x_2(T)=\frac{Dk_{12}}{\tau}\left[\frac{e^{-\alpha T}}{\alpha(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)-\frac{e^{-\beta T}}{\beta(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)\right]$$

$$x_3(T)=\frac{Dk_{13}}{\tau}\left[\frac{k_{21}\tau}{\alpha\beta}+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{\beta-k_{21}}{\beta^2(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right] \tag{7}$$

$$x_1(T)=\frac{D}{\tau}\left[\frac{k_{21}-\alpha}{\alpha(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{k_{21}-\beta}{\beta(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right]$$

$$x_2(T)=\frac{Dk_{12}}{\tau}\left[\frac{e^{-\alpha T}}{\alpha(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)-\frac{e^{-\beta T}}{\beta(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)\right]$$

$$x_3(T)=\frac{Dk_{13}}{\tau}\left[\frac{k_{21}\tau}{\alpha\beta}+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{\beta-k_{21}}{\beta^2(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right]$$

$$x_4(T)=\frac{Dk_{14}}{\tau}\left[\frac{k_{21}\tau}{\alpha\beta}+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{\beta-k_{21}}{\beta^2(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right] \tag{8}$$

$$x_1(T)=\frac{D}{\tau}\left[\frac{k_{21}-\alpha}{\alpha(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{k_{21}-\beta}{\beta(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right]$$

$$x_2(T)=\frac{Dk_{12}}{\tau}\left[\frac{e^{-\alpha T}}{\alpha(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)-\frac{e^{-\beta T}}{\beta(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)\right]$$

$$x_3(T)=\frac{Dk_{13}}{\tau}\left[\frac{k_{21}\tau}{\alpha\beta}+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{\beta-k_{21}}{\beta^2(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right]$$

$$x_4(T)=\frac{Dk_{14}}{\tau}\left[\frac{k_{21}\tau}{\alpha\beta}+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{\beta-k_{21}}{\beta^2(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right]$$

…

$$x_n(T)=\frac{Dk_{1n}}{\tau}\left[\frac{k_{21}\tau}{\alpha\beta}+\frac{\alpha-k_{21}}{\alpha^2(\alpha-\beta)}\left(e^{-\alpha\tau}-1\right)e^{-\alpha T}-\frac{\beta-k_{21}}{\beta^2(\alpha-\beta)}\left(e^{-\beta\tau}-1\right)e^{-\beta T}\right] \tag{9}$$

Clearly, all the elimination compartments have similar forms of analytical solutions.