PKconverter: pharmacokinetic parameter converter with Shiny App

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1 Compartmental model

In the pharmacometrics area, a basic type of model is the compartmental model that is categorized by the number of compartments needed to describe the drug's absorption, distribution, metabolism, and excretion in the body. There are one-compartmental, two-compartmental, and multi-compartmental models. We usually use up to three-compartmental model. These models are used to predict the time course of drug concentrations in the body. The one compartmental model is

$$\begin{aligned} C_t &= C_0 e^{-K_{10} t} && (1) \\ &= A e^{-\alpha t} && (2) \end{aligned}$$

where C_t is the drug concentration at time t, C_0 is the initial concentration, and K_{10} is the elimination rate. (2) is the general form of one compartmental model. A is called the true coefficient and α is called as the exponents. These two parameters have functional relation with various pharmacokinetic parameters - $V1$, $CL1$, K_{10}, $t_{1/2\alpha}$, etc.

$$\begin{aligned} V1 &= \frac{1}{A} \\ CL1 &= \frac{\alpha}{A} \\ K_{10} &= \alpha \\ t_{1/2,\alpha} &= log(2)/\alpha \\ V_{dss} &= V1 = \frac{1}{A} \\ F.A &= A \cdot V1 = 1 \end{aligned}$$

For example, one compartmental intravenous (IV) bolus model can be represented in these three ways:

$$\begin{aligned} C_t &= \frac{Dose}{V1} e^{-K_{10} \cdot t} && (3) \\ &= \frac{Dose \cdot K_{10}}{CL1} e^{-K_{10} \cdot t} && (4) \\ &= \frac{Dose}{V1} e^{-\frac{CL1}{V1} \cdot t}, && (5) \end{aligned}$$

where $CL1$ is the clearance, $V1$ is the volume of distribution, and K_{10} is the elimination rate constant. Because the pharmacokinetic parameters - $V1$, $CL1$ and K_{10} - have the functional relation, $CL1 = V1 \cdot K_{10}$, the model equation can be represented by various form with only two pharmacokinetic parameters and we can find the other parameters after fitting one of three equations. If we estimate $V1$ and K_{10} from the model (3), we can calculate the other pharmacokinetic parameters with the following equations:

$$\begin{aligned} CL1 &= V1 \cdot K_{10}, \\ \alpha &= K_{10}, \\ t_{1/2,\alpha} &= log(2)/\alpha, \\ A &= \frac{1}{V1}, \\ Fractional \quad A &= A \cdot V1. && (6) \end{aligned}$$

The general form of the two compartmental model is

$$C_t = Ae^{-\alpha t} + Be^{-\beta t}, \tag{7}$$

where A or B is used for C_0 in the one compartmental model, and α or β are used for the elimination rate. With these four parameter estimates, we can calculate the whole parameters - 12 more parameters - with the following equations:

$$\begin{aligned} K_{21} &= \frac{A\alpha + B\beta}{A+B}, \qquad K_{10} = \frac{\alpha\beta}{K_{21}}, \qquad K_{12} = \alpha + \beta - K_{21} - \frac{\alpha\beta}{K_{21}}, \\ V1 &= \frac{1}{A+B}, \qquad V2 =, \frac{V1}{K_{21}} \left(\alpha + \beta - K_{21} - \frac{\alpha\beta}{K_{21}} \right), \qquad V_{dss} = V1 + V2 \\ CL1 &= V1 \cdot K_{10}, \qquad CL2 = V2 \cdot K_{12}, \\ t_{1/2,\alpha} &= log(2)/\alpha, \qquad t_{1/2,\beta} = log(2)/\beta, \\ F.A &= A \cdot V1, \qquad F.B = B \cdot V1. \end{aligned}$$

We can define similar relations in the three compartmental model.

Shiner (1999) provided “Convert.xls” file from the web site www.nonmemcourse.com. He uses 5 different spreadsheets and each spreadsheet has different input parameters and calculate the other pharmacokinetic parameters from one to three compartment model. Table 1 summarized important pharmacokinetic parameters in each compartment model and table 2 summarized input parameters for each compartment model in each spreadsheet.

Table 1: Important pharmacokinetic parameters in each compartment model

Type	one comp	two comp	three comp
Volume of distribution	$V1$	$V1$, $V2$	$V1$, $V2$, $V3$
Vdss	V_{dss}	V_{dss}	V_{dss}
Clearance	$CL1$	$CL1$, $CL2$	$CL1$, $CL2$, $CL3$
Rate constant	K_{10}	K_{10}, K_{12}, K_{21}	K_{10}, K_{12}, K_{21}, K_{13}, K_{31}
Half-lives	$t_{1/2,\alpha}$	$t_{1/2,\alpha}$, $t_{1/2,\beta}$	$t_{1/2,\alpha}$, $t_{1/2,\beta}$, $t_{1/2,\gamma}$
True coef.	A	A, B	A, B, C
Fractional coef.	$F.A$	$F.A$, $F.B$	$F.A$, $F.B$, $F.C$
Exponents	α	α, β	α, β, γ

Table 2: Summary of input parameters and function names in each compartment in each model

Model	comp	input	function name
1	1	$V1$, $CL1$	`OneComp_Volume_Clearance`
	2	$V1$, $V2$, $CL1$, $CL2$	`TwoComp_Volume_Clearance`
	3	$V1$, $V2$, $V3$, $CL1$, $CL2$, $CL3$	`ThreeComp_Volume_Clearance`
2	1	$V1$, K_{10}	`OneComp_Volume_RateConstant`
	2	$V1$, K_{10}, K_{12}, K_{21}	`TwoComp_Volume_RateConstant`
	3	$V1$, K_{10}, K_{12}, K_{21}, K_{13}, K_{31}	`ThreeComp_Volume_RateConstant`
3	1	$CL1$, $t_{1/2,\alpha}$	`OneComp_Volume_Clearance_HalfLife`
	2	$V1$, $CL1$, $t_{1/2,\alpha}$, $t_{1/2,\beta}$	`TwoComp_Volume_Clearance_HalfLife`
	3	$V1$, $CL1$, $t_{1/2,\alpha}$, $t_{1/2,\beta}$, $t_{1/2,\gamma}$, V_{dss}	`ThreeComp_Volume_Clearance_HalfLife`
4	1	A, α	`OneComp_Coefficient_Exponent`
	2	A, B, α, β	`TwoComp_Coefficient_Exponent`
	3	A, B, C, α, β, γ	`ThreeComp_Coefficient_Exponent`
5	1	$V1$, α	`OneComp_Volume_Exponent`
	2	$V1$, K_{21}, α, β	`TwoComp_Volume_Exponent`
	3	$V1$, K_{21}, K_{31}, α, β, γ	`ThreeComp_Volume_Exponent`

1.1 Delta method

In the pharmacometric area, we find the MLEs of the pharmacokinetic parameters with NONMEM or other softwares. Most softwares to find the estimates of the PK parameter are based on the maximum likelihood theory. Therefore we can get the MLE's of the PK parameters. Let θ be the PK parameter and $\hat{\theta}$ be the MLE of θ. Then,

$$\sqrt{n}(\hat{\theta} - \theta) \sim N(0, Var(\hat{\theta})) \tag{8}$$

by the properties of MLE. In our situation, we have to calculate the other PK parameters that are the functions of MLE's. Let $f(\theta)$ be the other PK parameters. Then, the estimate of $f(\theta)$ is $\hat{f(\theta)} = f(\hat{\theta})$ and $zVar(\hat{f(\theta)}) = f'(\theta)^2 Var(\hat{\theta})$, by delta method. If the dimension of θ, q, is greater than 1,

$$Var(\hat{f(\theta)}) = G(\theta)^T Var(\hat{\theta}) G(\theta), \tag{9}$$

where $G(\theta) = \frac{\partial f(\theta)}{\partial \theta^T}$, q-dimensional vector.

In this package, we use this delta method to calculate the approximate standard error of estimates of the other pharmacokinetic parameters.

2 Population parameter convert

We provide five different models with known parameters. There are three kinds of compartment model in each model. In the following subsection, we summarise the functional relation between input and output parameters of each model. We provide functions to calculate pharmacokinetic parameters with the approximated standard errors and a shiny app for each model. Table 2 shows input parameters and R function names for each model.

2.1 Model1: Volumes and Clearances

2.1.1 One-compartmental model

* Input parameters: $V1, CL1$

$$\begin{aligned}
V_{dss} &= V1, \\
A &= \frac{1}{V1}, \\
\alpha &= \frac{CL1}{V1}, \\
T_{1/2,\alpha} &= \frac{\log 2}{K_{10}} = \log 2 \cdot \frac{V1}{CL1}, \\
K_{10} &= \frac{CL1}{V1}, \\
FractionalA &= A \cdot V1 = 1.
\end{aligned}$$

2.1.2 Two-compartmental model

* Input parameters: $V1, V2, CL1, CL2$

$$\begin{aligned}
V_{dss} &= V1 + V2, \\
K_{10} &= \frac{CL1}{V1}, \qquad K_{12} = \frac{CL2}{V1}, \qquad K_{21} = \frac{CL2}{V2}, \\
a_0 &= \frac{CL1}{V1} \cdot K_{21}, \qquad a_1 = -(\frac{CL1}{V1} + \frac{CL2}{V1} + \frac{CL2}{V2}), \\
\alpha &= \frac{-a_1 + \sqrt{{a_1}^2 - 4a_0}}{2}, \qquad \beta = \frac{-a_1 - \sqrt{{a_1}^2 - 4a_0}}{2}, \\
A &= \frac{\frac{CL2}{V2} - \alpha}{(\beta - \alpha)V1}, \qquad B = \frac{\frac{CL2}{V2} - \beta}{(\alpha - \beta)V1}, \\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}, \qquad t_{1/2,\beta} = \frac{\log 2}{\beta}.
\end{aligned}$$

2.1.3 Three-compartmental model

* Input parameters: $V1, V2, V3, CL1, CL2, CL3$

$$\begin{aligned}
V_{dss} &= V1 + V2 + V3, \\
K_{10} &= \frac{CL1}{V1}, \qquad K_{12} = \frac{CL2}{V1}, \qquad K_{13} = \frac{CL3}{V1}, \qquad K_{21} = \frac{CL2}{V2}, \qquad K_{31} = \frac{CL3}{V2}, \\
A &= \frac{(K_{21} - \alpha)(K_{31} - \alpha)}{V1(\alpha - \beta)(\alpha - \gamma)}, \qquad B = \frac{(K_{21} - \beta)(K_{31} - \beta)}{V1(\beta - \alpha)(\beta - \gamma)}, \qquad C = \frac{(K_{21} - \gamma)(K_{31} - \gamma)}{V1(\gamma - \alpha)(\gamma - \beta)}, \\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}, \qquad t_{1/2,\beta} = \frac{\log 2}{\beta}, \qquad t_{1/2,\gamma} = \frac{\log 2}{\gamma}.
\end{aligned}$$

α, β, and γ are determined by size order of $root_1$, $root_2$, and $root_3$ from the largest to smallest.

$$
\begin{aligned}
root_1 &= -r_2\cos(\phi) + \frac{a_2}{3}, \qquad root_2 = -r_2\cos(\phi + \frac{2\pi}{3}) + \frac{a_2}{3}, \\
root_3 &= -r_2\cos(\phi + \frac{4\pi}{3}) + \frac{a_2}{3}, \\
a_0 &= K_{10}\cdot K_{21}\cdot K_{31}, \\
a_1 &= K_{10}\cdot K_{31} + K_{21}\cdot K_{31} + K_{21}\cdot K_{13} + K_{10}\cdot K_{21} + K_{31}\cdot K_{12}, \\
a_2 &= K_{10} + K_{12} + K_{13} + K_{21} + K_{31}, \\
p &= a_1 - \frac{{a_2}^2}{3}, \qquad q = \frac{2{a_2}^2}{27} - \frac{a_1\cdot a_2}{3} - a_0, \qquad \phi = \frac{1}{3}\arccos\left(-\frac{q}{2r_1}\right), \\
r_1 &= \sqrt{-\frac{p^2}{27}}, \qquad r_2 = 2\exp\left(\frac{\log(r_1)}{3}\right).
\end{aligned}
\tag{10}
$$

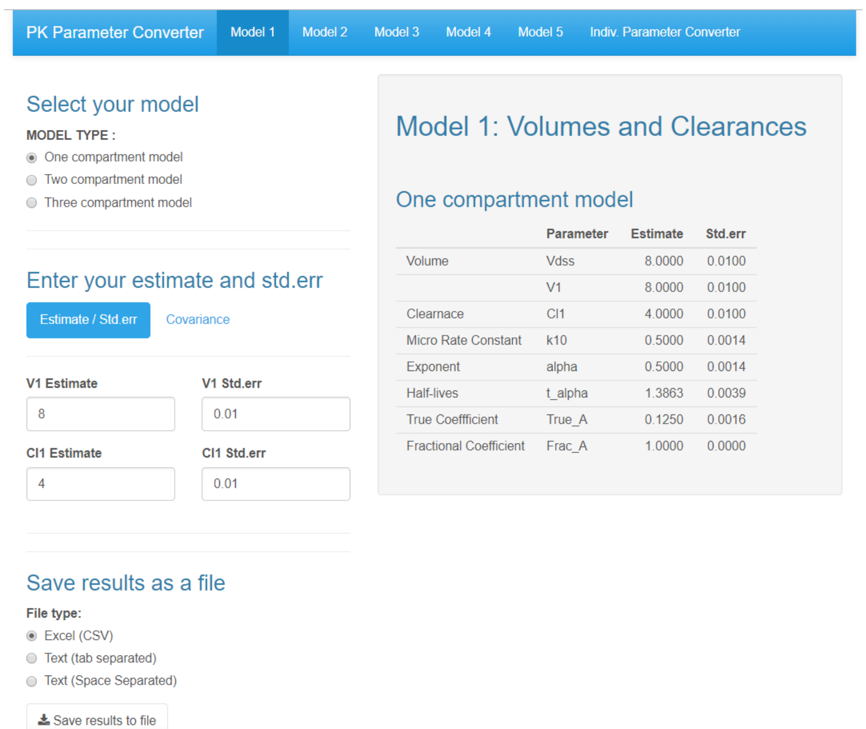

Figure 1: Main GUI of Shiny App for Pharmacokinetic Parameter Converter-Model 1.

2.2 Model 2: V1 and Rate constants

2.2.1 One-compartmental model

* Input parameters: $V1, K_{10}$

$$\begin{aligned}
V_{dss} &= V1, \\
CL1 &= V1 \cdot K_{10}, \\
A &= \frac{1}{V1}, \\
\alpha &= K_{10}, \\
t_{1/2,\alpha} &= \frac{\log 2}{K_{10}}.
\end{aligned}$$

2.2.2 Two-compartmental model

* Input parameters: $V1, K_{10}, K_{12}, K_{21}$

$$\begin{aligned}
V_2 &= \frac{V_1 \cdot K_{12}}{K_{21}}, \qquad V_{dss} = V1 + V2, \\
CL1 &= V1 \cdot K_{10}, \qquad CL2 = V1 \cdot K_{12}, \\
A &= \frac{1}{V1}\left(\frac{K_{21} - \frac{1}{2}\left((K_{10}+K_{12}+K_{21}) + \sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}\right)}{-\sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}}\right), \\
B &= \frac{1}{V1}\left(\frac{K_{21} - \frac{1}{2}\left((K_{10}+K_{12}+K_{21}) - \sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}\right)}{-\sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}}\right), \\
\alpha &= \frac{1}{2}\left((K_{10}+K_{12}+K_{21}) + \sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}\right), \\
\beta &= \frac{1}{2}\left((K_{10}+K_{12}+K_{21}) - \sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}\right), \\
t_{1/2,\alpha} &= \frac{\log 2}{\left((K_{10}+K_{12}+K_{21}) + \sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}\right)}, \\
t_{1/2,\beta} &= \frac{\log 2}{\left((K_{10}+K_{12}+K_{21}) - \sqrt{(K_{10}+K_{12}+K_{21})^2 - 4K_{10}K_{21}}\right)}.
\end{aligned}$$

2.2.3 Three-compartmental model

* Input parameters: $V1, K_{10}, K_{12}, K_{21}, K_{13}, K_{31}$

$$
\begin{aligned}
V_2 &= \frac{V_1 \cdot K_{12}}{K_{21}}, \qquad V_3 = \frac{V_1 \cdot K_{13}}{K_{31}}, \qquad V_{dss} = V1 + V2 + V3, \\
CL1 &= V1 \cdot K_{10}, \qquad CL2 = V1 \cdot K_{12}, \qquad CL3 = V1 \cdot K_{13}, \\
A &= \frac{(K_{21} - \alpha)(K_{31} - \alpha)}{V1(\alpha - \beta)(\alpha - \gamma)}, \qquad B = \frac{(K_{21} - \beta)(K_{31} - \beta)}{V1(\beta - \alpha)(\beta - \gamma)}, \\
C &= \frac{(K_{21} - \gamma(K_{31} - \gamma)}{V1(\gamma - \alpha)(\gamma - \beta)}, \\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}, \qquad t_{1/2,\beta} = \frac{\log 2}{\beta}, \qquad t_{1/2,\gamma} = \frac{\log 2}{\gamma}.
\end{aligned}
$$

α, β and γ are determined by equation (10).

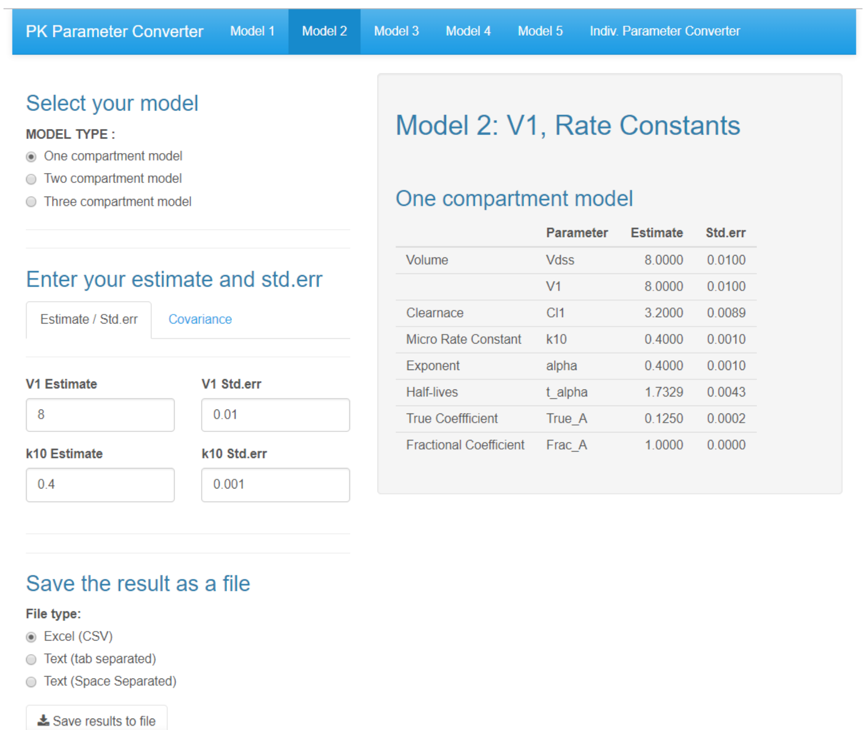

Figure 2: Main GUI of Shiny App for Pharmacokinetic Parameter Converter-Model 2.

2.3 Model 3: V1, Vdss, CL1 and Half-lives

2.3.1 One-compartmental model

* Input parameters: $CL1, t_{1/2,\alpha}$

$$\begin{aligned}
\alpha &= \frac{\log 2}{t_{1/2,\alpha}}, \\
V1 &= \frac{CL1 \cdot t_{1/2,\alpha}}{\log 2}, \qquad V_{dss} = V1, \\
K_{10} &= \frac{\log 2}{t_{1/2,\alpha}}, \\
A &= \frac{1}{V1}.
\end{aligned}$$

2.3.2 Two-compartmental model

* Input parameters: $V1, CL1, t_{1/2,\alpha}, t_{1/2,\beta}$

$$\begin{aligned}
\alpha &= \frac{\log 2}{t_{1/2,\alpha}}, \qquad \beta = \frac{\log 2}{t_{1/2,\beta}}, \\
V2 &= V1 \times \frac{K_{12}}{K_{21}}, \qquad V_{dss} = V1 + V2, \\
CL2 &= V1\left(\frac{\log 2}{t_{1/2,\alpha}} + \frac{\log 2}{t_{1/2,\beta}} - \frac{CL1}{V1}\left(\frac{(\log 2)^2}{t_{1/2,\alpha}t_{1/2,\beta}} + 1\right)\right), \\
K_{10} &= \frac{CL1}{V1}, \qquad K_{12} = \frac{\log 2}{t_{1/2,\alpha}} + \frac{\log 2}{t_{1/2,\beta}} - \frac{CL1}{V1}\left(\frac{(\log 2)^2}{t_{1/2,\alpha}t_{1/2,\beta}} + 1\right), \\
K_{21} &= \frac{(\log 2)^2}{t_{1/2,\alpha}t_{1/2,\beta}}\frac{CL1}{V1}, \\
A &= \left(\frac{\frac{(\log 2)^2}{t_{1/2,\alpha}t_{1/2,\beta}}\frac{CL1}{V1} - \frac{\log 2}{t_{1/2,\alpha}}}{\frac{\log 2}{t_{1/2,\alpha}} - \frac{\log 2}{t_{1/2,\beta}}}\right)\frac{1}{V1}, \qquad B = \left(\frac{\frac{(\log 2)^2}{t_{1/2,\alpha}t_{1/2,\beta}}\frac{CL1}{V1} - \frac{\log 2}{t_{1/2,\beta}}}{\frac{\log 2}{t_{1/2,\alpha}} - \frac{\log 2}{t_{1/2,\beta}}}\right)\frac{1}{V1}.
\end{aligned}$$

2.3.3 Three-compartmental model

* Input parameters: $V1, V_{dss}, CL1, t_{1/2,\alpha}, t_{1/2,\beta}, t_{1/2,\gamma}$

$$
\begin{aligned}
\alpha &= \frac{\log 2}{t_{1/2,\alpha}}, \qquad \beta = \frac{\log 2}{t_{1/2,\beta}}, \qquad \gamma = \frac{\log 2}{t_{1/2,\gamma}}, \\
V2 &= V1 \times \frac{K_{12}}{K_{21}}, \qquad V3 = V1 \times \frac{K_{13}}{K_{31}}, \qquad V_{dss} = V1 + V2 + V3, \\
CL2 &= V1 \times K_{12}\ , \qquad CL3 = V1 \times K_{13}, \\
K_{10} &= \frac{CL1}{V1}, \qquad K_{21} = \frac{f + root}{2}, \qquad K_{31} = \frac{f - root}{2}, \\
g_0 &= \frac{\alpha\beta\gamma}{K_{10}}, \qquad g_1 = \frac{V2 + V3}{V1 \times g_0}, \qquad f = \frac{\alpha \cdot \beta + \alpha \cdot \gamma + \beta \cdot \gamma - g_1 - g_0}{K_{10}}, \\
root &= \sqrt{f^2 - 4 \cdot g_0}, \qquad h = \left(\frac{V_{dss}}{V1} - 1\right) \times g_0, \\
K_{13} &= \frac{h - (\alpha + \beta + \gamma - K_{10} - K_{21} - K_{31}) \times K_{31}}{K_{21} - K_{31}}, \qquad K_{12} = \alpha + \beta + \gamma - K_{10} - K_{21} - K_{31} - K_{13}, \\
A &= \frac{(K_{21} - \alpha)(K_{31} - \alpha)}{V1(\alpha - \beta)(\alpha - \gamma)}, \qquad B = \frac{(K_{21} - \beta)(K_{31} - \beta)}{V1(\beta - \alpha)(\beta - \gamma)}, \\
C &= \frac{(K_{21} - \gamma(K_{31} - \gamma)}{V1(\gamma - \alpha)(\gamma - \beta)}.
\end{aligned}
$$

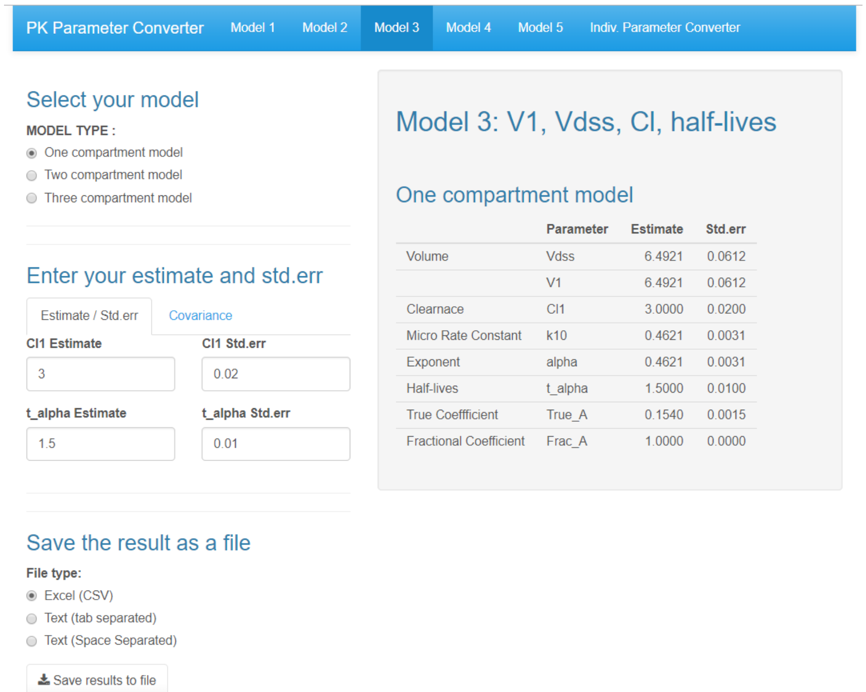

Figure 3: Main GUI of Shiny App for Pharmacokinetic Parameter Converter-Model 3.

2.4 Model 4: Coefficients and Exponents

2.4.1 One-compartmental model

* Input parameters: A, α

$$
\begin{aligned}
V1 &= \frac{1}{A} \\
V_{dss} &= \frac{1}{A} \\
CL1 &= \frac{\alpha}{A} \\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha} \\
K_{01} &= \alpha
\end{aligned}
$$

2.4.2 Two-compartmental model

* Input parameters: A, B, α, β

$$
\begin{aligned}
K_{01} &= \frac{\alpha\beta(A+B)}{A\beta+B\alpha}, \qquad K_{12} = \alpha+\beta-\frac{A\beta+B\alpha}{A+B}-\frac{\alpha\beta(A+B)}{A\beta+B\alpha}, \qquad K_{21} = \frac{A\beta+B\alpha}{A+B},\\
V1 &= \frac{1}{A+B}, \qquad V2 = \frac{K_{12}}{K_{21}(A+B)}, \qquad V_{dss} = V1+V2,\\
CL1 &= \frac{\alpha\beta}{A\beta+B\alpha}, \qquad CL2 = \frac{1}{A+B}\left(\alpha+\beta-\frac{A\beta+B\alpha}{A+B}-\frac{\alpha\beta(A+B)}{A\beta+B\alpha}\right),\\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}, \qquad t_{1/2,\beta} = \frac{\log 2}{\beta}.
\end{aligned}
$$

2.4.3 Three-compartmental model

* Input parameters: $A, B, C, \alpha, \beta, \gamma$

$$
\begin{aligned}
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}, \qquad t_{1/2,\beta} = \frac{\log 2}{\beta}, \qquad t_{1/2,\gamma} = \frac{\log 2}{\gamma}\\
b_{temp} &= -\left(\frac{\alpha C+\alpha B+\gamma A+\gamma B+\beta A+\beta C}{A+B+C}\right), \qquad c_{temp} = \frac{\alpha\beta C+\alpha\gamma B+\beta\gamma A}{A+B+C},\\
K_{21} &= \frac{1}{2}\left(-b_{temp}+\sqrt{{b_{temp}}^2-4c_{temp}}\right), \qquad K_{31} = \frac{1}{2}\left(-b_{temp}-\sqrt{{b_{temp}}^2-4c_{temp}}\right),\\
K_{10} &= \frac{\alpha\beta\gamma}{K_{21}K_{31}}, \qquad K_{12} = \frac{(\beta\gamma+\alpha\beta+\alpha\gamma)-K_{21}(\alpha+\beta+\gamma)-K_{10}K_{31}+{K_{21}}^2}{K_{31}-K_{21}},\\
K_{13} &= \alpha+\beta+\gamma-(K_{10}+K_{12}+K_{21}+K_{31}),\\
V1 &= \frac{1}{A+B+C}, \qquad V2 = V1\times\frac{K_{12}}{K_{21}}, \qquad V3 = V1\times\frac{K_{13}}{K_{31}},\\
V_{dss} &= V1+V2+V3,\\
CL1 &= V1\times K_{10}, \qquad CL2 = V1\times K_{12}, \qquad CL3 = V1\times K_{13}.
\end{aligned}
\tag{11}
$$

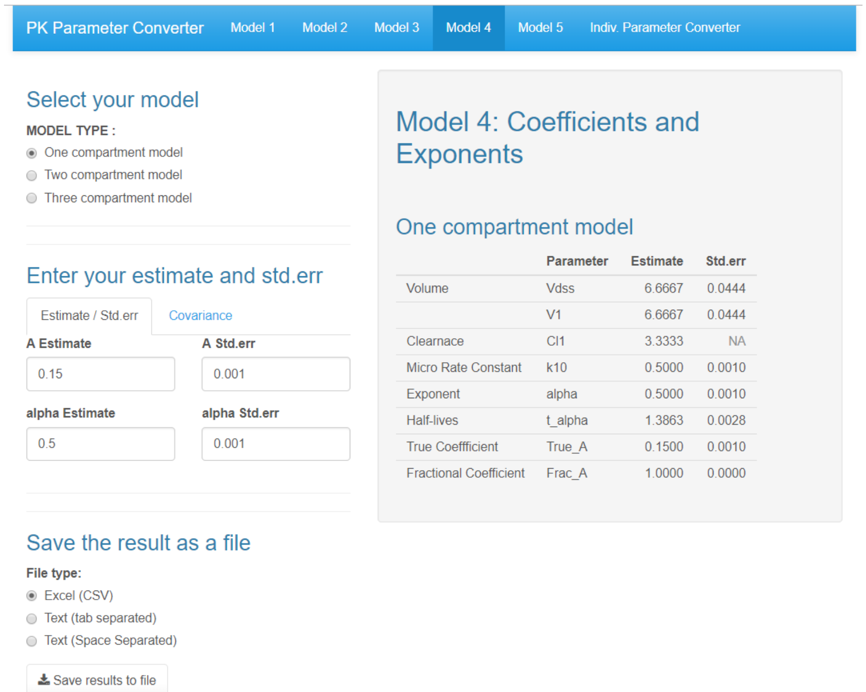

Figure 4: Main GUI of Shiny App for Pharmacokinetic Parameter Converter-Model 4.

2.5 Model 5: V1, Exponents, K_{21}, and K_{31}

2.5.1 One-compartmental model

* Input parameters: $V1, \alpha$

$$
\begin{aligned}
V_{dss} &= V1, \\
K_{01} &= \alpha, \\
CL1 &= V1 \times \alpha, \\
A &= \frac{1}{V1}, \\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}.
\end{aligned}
$$

2.5.2 Two-compartmental model

* Input parameters: $V1, K_{21}, \alpha, \beta$

$$
\begin{aligned}
V2 &= \frac{V1}{K_{21}}\left(\alpha+\beta-K_{21}-\frac{\alpha\beta}{K_{21}}\right), \qquad V_{dss}=V1+\frac{V1}{K_{21}}\left(\alpha+\beta-K_{21}-\frac{\alpha\beta}{K_{21}}\right),\\
CL1 &= V1\times K_{10}, \qquad CL2=V1\times K_{12},\\
A &= \frac{K_{21}-\alpha}{\beta-\alpha}\times\frac{1}{V1}, \qquad B=\frac{K_{21}-\beta}{\alpha-\beta}\times\frac{1}{V1},\\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}, \qquad t_{1/2,\beta}=\frac{\log 2}{\beta},\\
K_{01} &= \frac{\alpha\beta}{K_{21}}, \qquad K_{12}=\alpha+\beta-K_{21}-\frac{\alpha\beta}{K_{21}}.
\end{aligned}
$$

2.5.3 Three-compartmental model

* Input parameters: $V1, K_{21}, K_{31}, \alpha, \beta, \gamma$

$$
\begin{aligned}
V2 &= \frac{V1\times K_{12}}{K_{21}}, \qquad V3=\frac{V1\times K_{13}}{K_{31}}, \qquad V_{dss}=V1+V2+V3,\\
K_{01} &= \frac{\alpha\beta\gamma}{K_{21}K_{31}}, \qquad K_{12}=\frac{(\beta\gamma+\alpha\beta+\alpha\gamma)-K_{21}(\alpha+\beta+\gamma)-\frac{\alpha\beta\gamma}{K_{21}}+{K_{21}}^2}{K_{31}-K_{21}},\\
K_{13} &= \alpha+\beta+\gamma-(K_{10}+K_{12}+K_{21}+K_{31}),\\
CL1 &= V1\times K_{10}, \qquad CL2=V1\times K_{12}, \qquad CL3=V1\times K_{13},\\
A &= \frac{(K_{21}-\alpha)(K_{31}-\alpha)}{V1(\alpha-\beta)(\alpha-\gamma)}, \qquad B=\frac{(K_{21}-\beta)(K_{31}-\beta)}{V1(\beta-\alpha)(\beta-\gamma)}, \qquad C=\frac{(K_{21}-\gamma)(K_{31}-\gamma)}{V1(\gamma-\alpha)(\gamma-\beta)},\\
t_{1/2,\alpha} &= \frac{\log 2}{\alpha}, \qquad t_{1/2,\beta}=\frac{\log 2}{\beta}, \qquad t_{1/2,\gamma}=\frac{\log 2}{\gamma}.
\end{aligned}
\tag{12}
$$

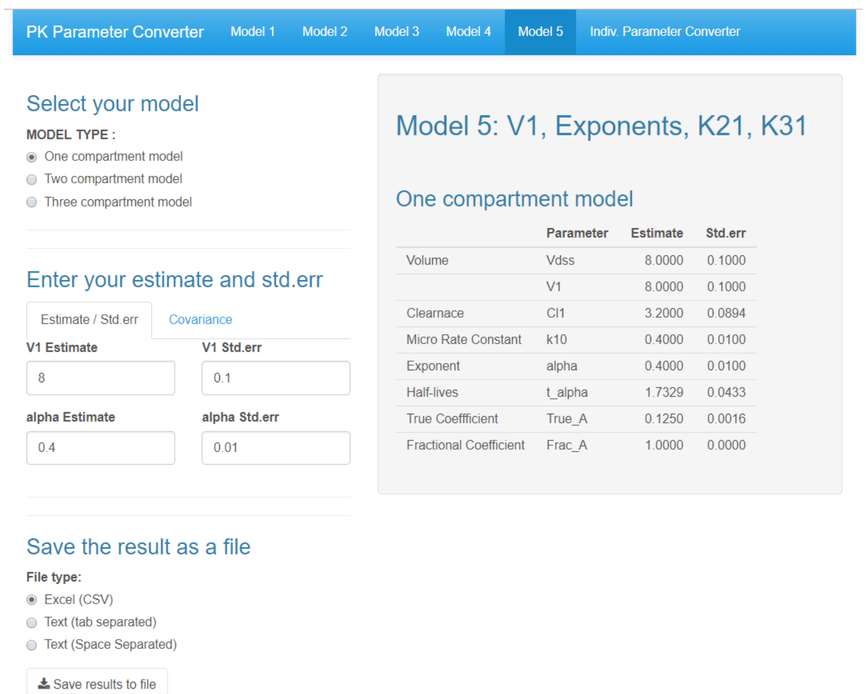

Figure 5: Main GUI of Shiny App for Pharmacokinetic Parameter Converter-Model 5.