

# A Distributed Delay Approach for Modeling Delayed Outcomes in Pharmacokinetics and Pharmacodynamics Studies

Shuhua Hu, Kevin Feng, Bob Leary, Mike Dunlavy

Certara/Pharsight, Cary, NC, 27518

## Introduction

- Transit compartment models described by systems of ordinary differential equations (ODEs) have been widely used in the pharmacokinetics and pharmacodynamics studies to describe delayed outcomes.
  - One of the obvious disadvantages of this type of models is that it may require a large number of differential equations to fit the data.
  - In addition, one needs to manually find a proper value for the number of compartments.
  - It is also not adequate to describe some complex features such as double/multiple-peak phenomenon after oral administration.
- We propose to use a distributed delay approach to model delayed outcomes that does not suffer these disadvantages, and this approach is conceptually similar to red cell lifespan models [3] with each individual assumed to have its own lifespan.

## Objective

To demonstrate that the distributed delay approach is general enough to incorporate a wide array of models as special cases including transit compartment models, typical absorption models, and models for describing atypical absorption profiles such as double/multiple-peak phenomenon after oral administration in pharmacokinetics.

## Methods

Let  $k_{in}$  denote the inflow of a signal to a terminating compartment, and  $\mathcal{T}$  be a random variable representing the delay time with probability density function (PDF)  $G$ . Then the delayed signal is given by

$$\mathcal{S}(t) = \int_0^\infty G(\tau)k_{in}(t - \tau)d\tau, \quad (1)$$

which can be equivalently written as

$$\mathcal{S}(t) = \int_{-\infty}^t G(t - s)k_{in}(s)ds.$$

More generally, for the case where multiple signals flow into a terminating compartment, the delayed signals can be expressed as follows:

$$\mathcal{S}(t) = \sum_{j=1}^{N_s} \mathcal{S}_j(t) \quad (2)$$

with

$$\mathcal{S}_j(t) = \int_0^\infty G_j(\tau)k_{in,j}(t - \tau)d\tau.$$

Here  $N_s$  denotes the number of signals,  $k_{in,j}$  denotes the inflow of the  $j$ th signal to the terminating compartment, and  $G_j$  is the PDF of the delayed time  $\mathcal{T}_j$  for the  $j$ th signal.

- If delay times arise from PK absorption phase, then  $\mathcal{S}$  is the input function feeding into the central compartment.
- If delay time are due to the distributional delay for PK/PD link, then  $\mathcal{S}$  is the input function feeding into a hypothetical effect compartment.
- If delay times are for the observed drug effect, then  $\mathcal{S}$  is the delayed drug effect.

## Results

### Notations

- $\delta$ : Dirac delta (or impulse) function.
- $\Gamma(t; k, \nu)$ : PDF of a gamma distribution with rate  $k$  and shape parameter  $\nu$ ;
  - if  $\nu$  is a positive integer, then it is the PDF of an Erlang distribution;
  - if  $\nu = 1$ , then it is the PDF of an exponential distribution.
- $D_i$  or  $D_{ji}$ : dose administered.
- $t_{dose,i}$  or  $t_{dose,ji}$ : dosing time point.
- $t_{lag,j}$ : lag time.

### Theoretical Results

#### Impulsive flows with general delays

Consider the single-pathway scenario (1) with multiple bolus (impulsive) dosing events (i.e.,  $k_{in} = \sum_{i=1}^m D_i \delta(t - t_{dose,i})$  with  $m$  being the number of dosing events). For this case, (1) reduces to

$$\mathcal{S}(t) = \sum_{i=1}^m D_i G(t - t_{dose,i}), \quad (3)$$

which is the input function feeding into the central compartment considered in [6] and [7] with a gamma distributed delay (that is,  $G$  is the PDF of a gamma distribution).

Consider the multiple-pathway scenario (2) with multiple bolus dosing events for each pathway (i.e.,  $k_{in,j} = \sum_{i=1}^{m_j} D_{ji} \delta(t - t_{dose,ji})$ ,  $i = 1, 2, \dots, m_j$ ,  $j = 1, 2, \dots, N_s$ ). In this case, (1) reduces to

$$\mathcal{S}(t) = \sum_{j=1}^{N_s} \sum_{i=1}^{m_j} D_{ji} G_j(t - t_{dose,ji}). \quad (4)$$

#### Point distributed (or discrete) delays with general $k_{in}$

Consider the case where  $G$  is a linear combination of Dirac delta functions and is given by  $G(t) = \sum_{j=1}^m \omega_j \delta(t - t_{lag,j})$ ,  $\omega_j \geq 0$  and  $\sum_{j=1}^m \omega_j = 1$ . We found that for this case (1) reduces to

$$\mathcal{S}(t) = \sum_{j=1}^m \omega_j k_{in}(t - t_{lag,j})$$

- For a special case with a pointed distributed delay at 0 (i.e., no lag time and  $G(t) = \delta(t)$ ) and constant infusion (i.e.,  $k_{in}$  is a positive constant for a duration of time and then zero afterwards), the resulting  $\mathcal{S}$  is the input function feeding into the central compartment for the zero-order absorption model.

### Reducibility of a Delayed Signal into a System of ODEs

If we make additional assumption on the form of  $G$ , then one can reduce (1) into a system of ODEs by using the so-called *linear chain trick* [1]. Specifically, a necessary and sufficient condition for the reducibility of (1) to a system of ODEs is that  $G$  is a linear combination of functions

$$\exp(\xi t), \quad t \exp(\xi t), \quad \dots, \quad t^m \exp(\xi t)$$

with  $m$  being a positive integer and  $\xi$  being a complex number. Examples of such  $G$ : PDF of an Erlang distribution, PDF of a mixture of Erlang distributions.

#### Erlang distributed delays with general $k_{in}$

Consider the single-pathway scenario (1) with an Erlang distributed delay (i.e.,  $G(t) = \Gamma(t; k, n)$ ,  $n$  is a positive integer). For this case, (1) reduces to a transit compartment model

$$\dot{x}_1(t) = k k_{in}(t) - k x_1(t), \quad (5)$$

$$\dot{x}_i(t) = k x_{i-1}(t) - k x_i(t), \quad i = 2, 3, \dots, n$$

with output  $x_n = \mathcal{S}$ . If we assume that  $k_{in}(t) = 0$  for  $t < 0$ , then the initial condition for (5) is  $x_i(0) = 0$ ,  $i = 1, 2, \dots, n$ .

- If  $k_{in}(t) = D \delta(t)$ , then (5) has zero initial conditions and it is equivalent to

$$\dot{x}_1(t) = -k x_1(t),$$

$$\dot{x}_i(t) = k x_{i-1}(t) - k x_i(t), \quad i = 2, 3, \dots, n, \quad (6)$$

$$x_1(0) = kD, \quad x_i(0) = 0, \quad i = 2, 3, \dots, n.$$

Note: (6) is a special case of (3) with an Erlang distributed delay and single bolus dose at time 0; and (6) with  $n = 1$  is the absorption compartment for the first-order absorption model.

- For a single compartment and unknown  $k_{in}$ , the resulting  $\mathcal{S}$  is the input function considered in [2] feeding into the central compartment for the variability of absorption approach used to model the double-peak phenomenon after oral administration.
- If  $k_{in}$  is the solution of an Emax model, then the resulting  $\mathcal{S}$  is the delayed drug effect (e.g., a transit compartment model with 4 compartments was considered in [4, 8]).
- If  $k_{in}$  denotes the solution of an indirect response model, then the resulting  $\mathcal{S}$  is the delayed indirect response (e.g., see [3]).

Consider the multiple-pathway scenario (2) with an Erlang distributed delay for each pathway. For this case, each of  $\mathcal{S}_j$ 's is the output of some transit compartment model, and hence  $\mathcal{S}$  is the sum of the outputs of all these transit compartment models.

- For a special two-pathway case with a single bolus dosing event at time 0 for each pathway, the resulting  $\mathcal{S}$  is the input function for the parallel inputs approach [2] to model the double-peak phenomenon (Note: this is also a special case of (4) with an Erlang distributed delay and a single bolus dosing event at time 0 for each pathway).
- For a two-pathway case with exponential distributed delays and bolus dosing at time 0 for one pathway and bolus dosing at time  $t_{lag}$  for the other one, the resulting  $\mathcal{S}$  is the input function for modeling two parallel first-order absorption processes [5] (Note: this is also a special case of (4) with exponential distributed delay and single bolus dosing for each pathway).

#### Mixture of discrete delays and Erlang Distributed Delays

- For a two-pathway case with an exponential distributed delay and bolus dosing at time 0 for one pathway and a pointed distributed delay at 0 and a constant infusion dosing event for the other pathway, the resulting  $\mathcal{S}$  is the input function for the mixture of first-order absorption and zero-order absorption model (e.g., [5]).

## Numerical Results

- Data set [2]: consisting of plasma concentration-time profiles for 12 subjects following an oral dose of veralipride at time 0.
- The parallel inputs approach is one of the two methods used in [2] to model the double-peak feature presented in this data set. Note: It requires numerous different combination of number of compartments in each pathway to be manually tried, and hence it is very inefficient and time-consuming.
- Instead of manually identifying the number of compartments for each pathway, we estimate them along with other parameters using the input function given in (4) with single dosing event and a gamma distributed delay for each pathway. Through this approach, we obtained reasonably good fitting results for all the subjects and similar residual mean square errors as those obtained in [2]. Figure 1 illustrates model fitting results for two example individuals using FOCE in Phoenix<sup>®</sup> NLME<sup>™</sup> (Pharsight/Certara).

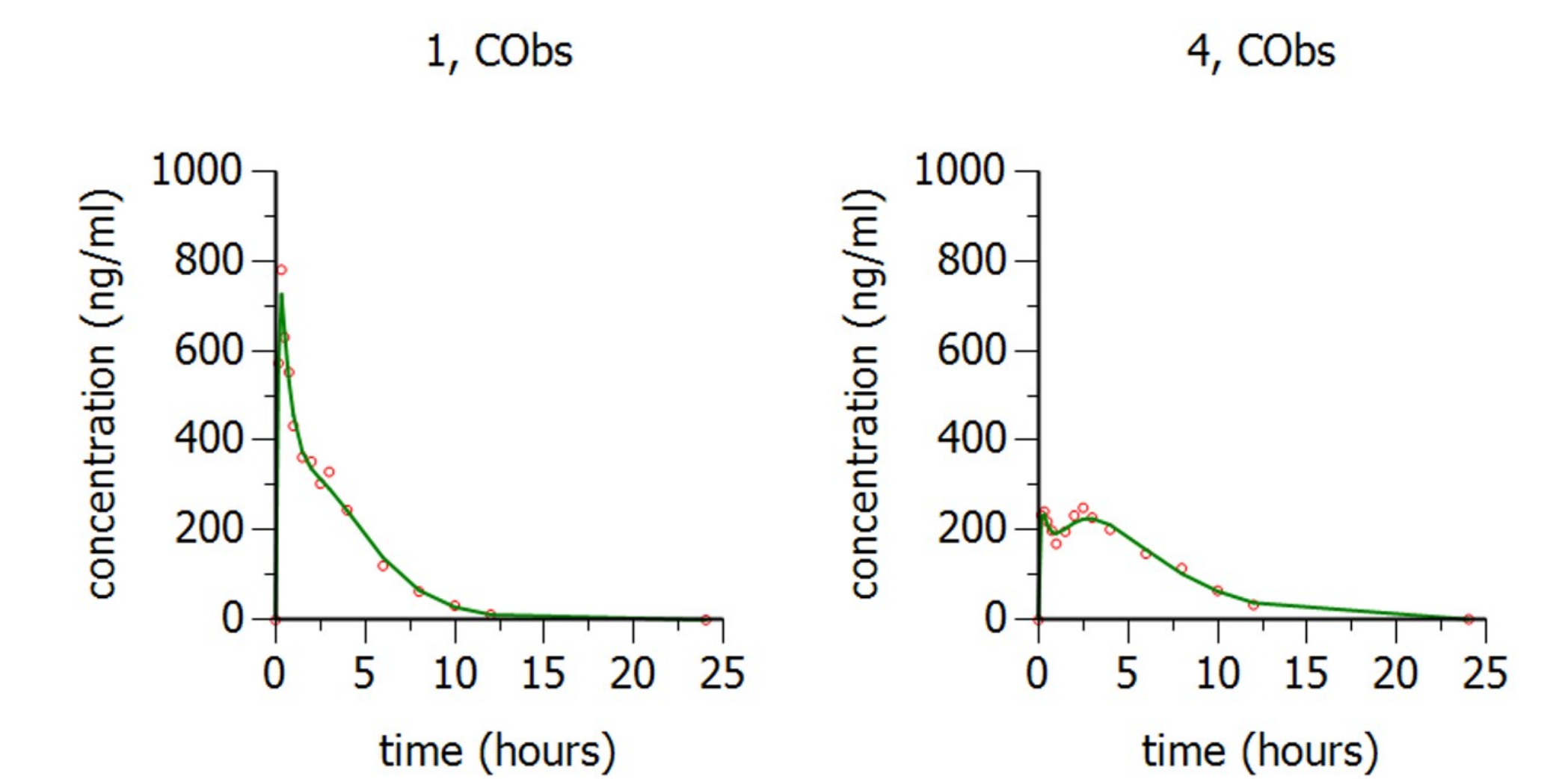


Figure 1: Model fitting results for two individuals, where red circle denotes observations and green solid line represents predicted model solution.

## Conclusions

The distributed delay approach provides a more general and flexible way to model delayed outcomes including absorption, distribution, PK/PD link, drug response etc., and hence can capture more complex features.

## References

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