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

Shuhua Hu, Kevin Feng, Bob Leary, Mike Dunlavey

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 $k_{\text{in}}$ 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

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

which can be equivalently written as

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

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

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

with

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

Here $N_s$ denotes the number of signals, $k_{\text{in},j}$ 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.
- $t_{\text{dose},i}$ or $t_{\text{dose},ji}$: dosing time point.
- $t_{\text{lag},j}$: lag time.

### Theoretical Results

Impulsive flows with general delays

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

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

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, $k_{\text{in},j} = \sum_{i=1}^{m_j} D_{ji} \delta(t - t_{\text{dose},ji})$, $i = 1, 2, \ldots, m_j$, $j = 1, 2, \ldots, N_s$). In this case, (1) reduces to

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

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

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

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

- 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., $k_{\text{in}}$ 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

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

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.

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Erlang distributed delays with general $k_{\text{in}}$

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

$$\begin{aligned} \dot{x}_1(t) &= k k_{\text{in}}(t) - k x_1(t), \\ \dot{x}_i(t) &= k x_{i-1}(t) - k x_i(t), \quad i = 2, 3, \ldots, n \end{aligned} \tag{5}$$

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

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

$$\begin{aligned} \dot{x}_1(t) &= -k x_1(t), \\ \dot{x}_i(t) &= k x_{i-1}(t) - k x_i(t), \quad i = 2, 3, \ldots, n, \\ x_1(0) &= kD, \; x_i(0) = 0, \; i = 2, 3, \ldots, n. \end{aligned} \tag{6}$$

  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 $k_{\text{in}}$, 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 $k_{\text{in}}$ 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 $k_{\text{in}}$ 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 $t_{\text{lag}}$ 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]).

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### 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® NLME™ (Pharsight/Certara).

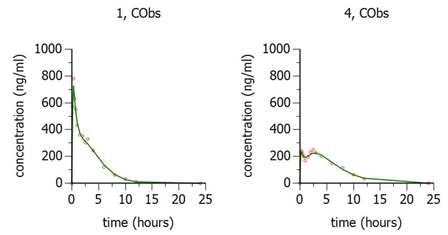


Figure 1: Model fitting results for two individuals, where red circle denotes observations and green solid line represents predicated model solution.

## 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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