Extension of the distributed delay approach to model delayed outcomes involving loss mechanism during the delay process

Shuhua Hu

Certara, Raleigh, NC, USA 27606

Contact: Shuhua Hu

Email: Shuhua.Hu@certara.com

Background

The distributed delay approach provides an alternative and flexible way to model delayed outcomes in pharmacokinetics (PK)/pharmacodynamics (PD) studies [1].

- It involves convolution of the signal to be delayed, S, and the probability density function (PDF), g, of the delay time, $\mathcal{S}(t) = \int_0^{+\infty} g(\tau)S(t-\tau)d\tau$.
- It incorporates a variety of PK/PD models as special cases including transit compartment models, effect compartment models, typical absorption models (either zero- or first-order absorption), and a number of atypical (e.g., parallel first-order, mixed first-order and zero-order, and Weibull) absorption models.

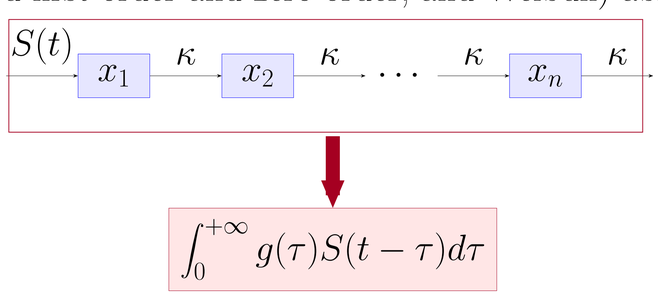

Figure: The distributed delay reduces to the transit compartment model when g is assumed to be the PDF of an Erlang distribution, which has a shape parameter (a positive integer) and a rate parameter (a positive number). Specifically, the shape parameter, n, determines the number of compartments, and the rate parameter, κ, is the transition rate. In addition, its mean, n/κ, is the so-called mean transit time.

- The gamma distributed delay model is a natural extension of the transit compartment model, and does not suffer its disadvantages.

	Syntax	Meaning
The distributed "delay" function	delay(*S*, MeanDelayTime , shape = ShapeExpression [, hist = HistExpression])	• The distributed "delay" function returns the value of $\int_0^{+\infty} S(t-\tau)g(\tau)d\tau$ • The function g is the PDF of a gamma distribution with shape parameter being "ShapeExpression" (positive) provided by the shape option and mean being "MeanDelayTime" (positive). • The hist option is used to specify the value of $S(t)$ prior to time 0; that is, $S(t) = \text{HistExpression}$, if $t < 0$.
The "delayInfCpt" statement	delayInfCpt(A, MeanDelayTime , ShapeParamMinusOne [, in = inflow] [, out = outflow])	• Conceptually, it is used to denote a compartment, A, (which can receive doses through the dosepoint statement) with all of its input delayed, including doses (if provided) and the inflow specified by the in option. The out option is used to specify any additional flow that is not delayed. • Mathematically, this statement means $\dot{A}(t) = \int_0^{+\infty} S(t-\tau)g(\tau)d\tau + \text{outflow}(t)$ Here S denotes all the input to be delayed (with $S(t) = 0$, if $t < 0$), and g is the PDF of a gamma distribution with shape parameter being "ShapeParamMinusOne + 1" ("ShapeParamMinusOne" must be non-negative) and mean being "MeanDelayTime" (positive).

Table: Syntax for the distributed `delay` function and `delayInfCpt` statement in Phoenix Modeling Language (PML). Compared to transit compartment models, the distributed delay function/statement in PML provides a more powerful and flexible way to model delayed outcomes: (1) It allows the shape parameter to be estimated instead of manually finding one. Hence, it is more efficient and less error-prone. In addition, it enables population analysis feasible in the case where the value of shape parameter may vary among individuals; (2) Users only need to write one simple function/statement instead of a large number of differential equations; (3) It allows for non-integer shape parameter and hence may capture dynamics better.

Objectives

- Note that an inherent assumption made in the distributed delay approach is that the involved mediators (e.g., drug molecules, cells) cannot leave the pool until at the end of the delay process. Hence, it cannot be applied to the case where there is a loss during this process due to degradation or emigration.
- The goal here is to demonstrate how to extend the distributed approach to model delayed outcomes involving loss mechanism during the delay process.

Methods

Assume that the loss of the involved mediators occurs at a first-order rate κ_l. Then the number of mediators at τ time ago that survive to time t is given by

$$\exp(-\kappa_l\tau)S(t-\tau)$$

Hence, the delayed outcomes is described by

$$\mathcal{S}_l(t) = \int_0^{+\infty} g(\tau)\exp(-\kappa_l\tau)S(t-\tau)d\tau.$$

Observe that if there is no loss (i.e., $\kappa_l = 0$), then the extended distributed delay reduces to the traditional one.

....

Application of the extended distributed delay approach to model delayed outcomes in PK/PD studies

- **Absorption delay**: Let $S(t)$ denote the rate of drug administered at time t, g represent the PDF of the delay time between the administration time of the drug and the time when the drug molecules reach the central compartment, and κ_l be the first-order degradation rate of the drug. Then $\mathcal{S}_l$ is the input function to the central compartment with the fraction of dose absorbed given by

$$F_a = \int_0^{+\infty} g(\tau)\exp(-\kappa_l\tau)d\tau.$$

- **Delays in viral infection**: Let $S(t)$ denote the amount of acutely infected cells at time t, g represent the PDF of the delay time from the initial infection to the viral production, and κ_l be the first-order clearance rate of the acutely infected cells. Then $\mathcal{S}_l(t)$ is the amount of cells that can produce virus at time t.

Results

Effect of the loss on the PDF of the delay time

	No loss	Loss incorporated
PDF	$g(t)$	$\frac{(\kappa+\kappa_l)^\nu}{\kappa^\nu}\exp(-\kappa_l(t))g(t)$
Mean	$\frac{\nu}{\kappa}$	$\frac{\nu}{\kappa+\kappa_l}$
Variance	$\frac{\nu}{\kappa^2}$	$\frac{\nu}{(\kappa+\kappa_l)^2}$

Table: The PDF of the delay time with loss incorporated as well as its mean and variance, where g is the PDF of a gamma distribution with shape parameter ν and rate parameter κ.

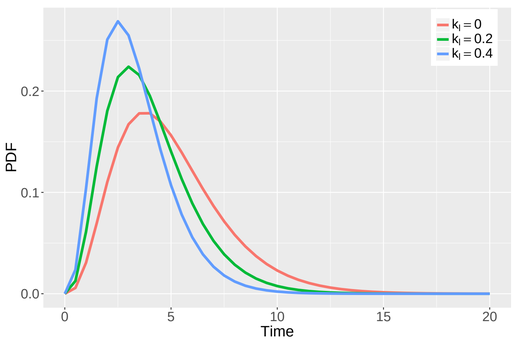

Figure: The PDF of the delay time with different loss rate, where g is the PDF of a gamma distribution with shape parameter $\nu = 4$ and rate parameter $\kappa = 0.8$.

Relationship between the extended distributed delay approach and the compartmental absorption and transit (CAT) model: If g is the PDF of an Erlang distribution with shape parameter n (a positive integer) and rate parameter κ (a positive number), then one can show that the extended distributed delay reduces to the following system of ordinary differential equations (ODEs)

$$\begin{aligned}
\dot{x}_1(t) &= \kappa S(t) - \kappa x_1(t) - \kappa_l x_1(t),\\
\dot{x}_i(t) &= \kappa x_{i-1}(t) - \kappa x_i(t) - \kappa_l x_i(t), \quad i = 2,3,\ldots,n,\\
x_i(0) &= x_i^0,\ i = 1,2,\ldots,n
\end{aligned}$$

with $\mathcal{S}_l = x_n$ and $x_i^0 = \int_{-\infty}^0 \frac{\kappa^i(-s)^{i-1}}{(i-1)!}\exp((\kappa+\kappa_l)s)S(s)ds, \quad i = 1,2,\ldots,n.$

- The above system of ODEs with seven compartments and κ_l representing the absorption rate is the compartmental absorption and transit (CAT) model [2].

Conclusions

- The extended distributed delay approach provides a more general and realistic description of the delay process, and hence may capture more complex features than the traditional one.
- The loss in the delay process may have a significant effect on the mean delay time as well as its variance, and hence should be appropriately considered.

References

[1] Hu S, Dunlavey M, Guzy S, and Nathan T, A distributed delay approach for modeling delayed outcomes in pharmacokinetics and pharmacodynamics studies, *J Pharmacokinet Pharmacodyn* (2018) 45:285–308. https://doi.org/10.1007/s10928-018-9570-4.

[2] Yu LX, Lipka E, Crison JR, and Amidon GL, Transport approaches to the biopharmaceutical design of oral drug delivery systems: prediction of intestinal absorption, *Adv Drug Deliv Rev* (1996) 19:359–376.