Modeling Transit Compartments with Multiple Doses in Phoenix NLME

Michael R. Dunlavey, Robert H. Leary

Certara/Pharsight® Corporation

Objective

Savic et al. [1] give a closed-form computation to model absorptive delay through multiple transit compartments, where the number of compartments is a parameter to be estimated. It works for single delta-function inputs sufficiently separated in time. It is desirable to model such absorption in a way that easily handles arbitrary dosing sequences and steady-state determination.

Methods

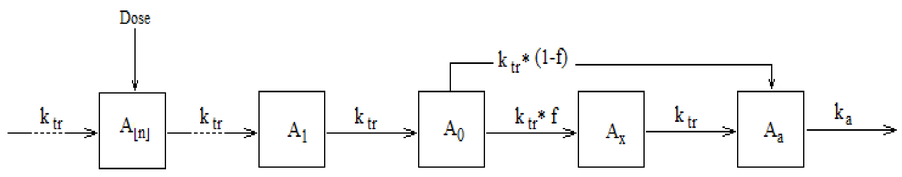
It is typical to model absorption delay by a simple time lag, but a useful alternative is to model the delay as a sequence of transit compartments terminating in an absorption compartment. Following Savic et al. [1], a closed form expression for the flow rate into the absorption compartment is given by:

$$\frac{dA_a}{dt} = Dose\ F\ k_{tr}\ \frac{(k_{tr}\ t)^n}{\Gamma(n+1)}\ e^{-k_{tr}\ t} \qquad (1)$$

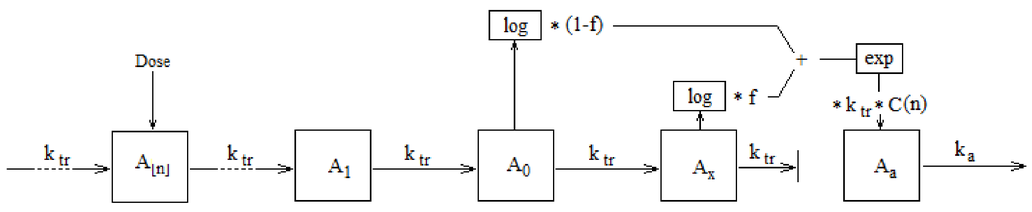
Where k_{tr} is given in terms of the number of transit stages *n*, and the mean transit time *mtt*:

$$k_{tr} = \frac{n+1}{mtt} \qquad (2)$$

This formulation has the advantage that *n* can vary between individuals, and it need not be an integer. However, it has a difficulty that it cannot be used easily with multiple doses unless they are separated by a washout interval. An alternative is to use a sequence of compartments modeled with differential equations, and deliver the dose to an upstream compartment chosen by *n*. If *n* is not an integer, an approximation is to linearly interpolate between the final two transit compartments, as in this diagram, where A_x is an extra compartment:



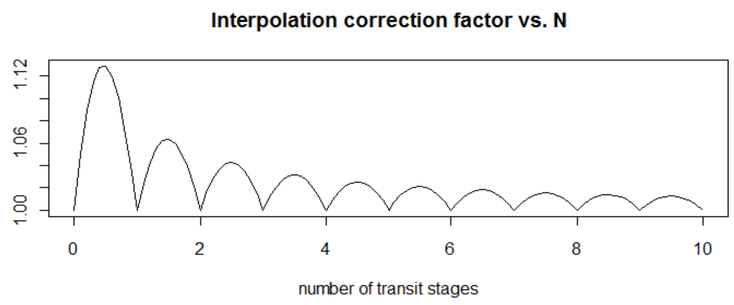
and where $f = n - \lfloor n \rfloor$, and doses are delivered to compartment $A_{\lfloor n \rfloor}$. However, it is not particularly accurate for non-integer *n* because it is piecewise linear w.r.t. *n* and equation (1) is a smooth curve. An alternative is to perform logarithmic interpolation as in this diagram:



Logarithmic interpolation has smaller errors than linear interpolation. Furthermore, the errors are proportional, not a function of time, and they can be exactly corrected by the following function:

$$C(n) = \frac{\Gamma(\lfloor n \rfloor + 1)}{\Gamma(n+1)} (\lfloor n \rfloor + 1)^f$$

whose graph is as follows:



This scheme has been incorporated in the Phoenix Modeling Language (PML) as a statement. The fragments below illustrate a first-order model with time-lag and a corresponding transit compartment model:

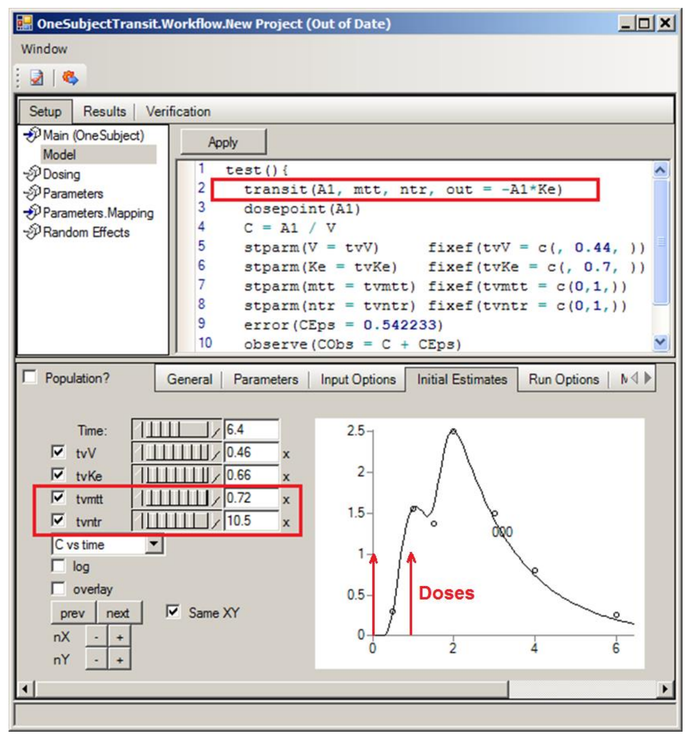
Simple tlag model:

```
deriv( Aa = -Aa*Ka)
dosepoint( Aa, tlag = mtt )
deriv( A1 = Aa*Ka - A1*Ke )
```

Transit compartment model:

```
transit( Aa, mtt, n, out = -Aa*Ka )
dosepoint( Aa )
deriv( A1 = Aa*Ka - A1*Ke )
```

In both models, the lag time and mean transit time are represented by *mtt*. In the transit model there is an additional parameter *n*, where *maxn* > *n* ≥ *0*, representing the number of transitions minus one. (*maxn* can be specified by an optional argument, default 50.) *n* functions as a sigmoidicity parameter, analogous to the Hill parameter in a sigmoid Emax model. A simple example is shown below.



Discussion

The advantage of the interpolated transit model is that it can handle arbitrary dosing sequences, including steady-state. A disadvantage is that the size of *n* is limited, because it effectively creates a vector differential equation of size *maxn*, creating a performance cost.

References

[1] R. M. Savic, D. M. Jonker, T. Kerbusch, M. O. Karlsson, “Implementation of a transit compartmental model for describing drug absorption in pharmacokinetic studies”, J. of Pharmacokinetics and Pharmacodynamics (2007) 34:711-726

Contact

Michael R. Dunlavey, PhD, Certara/Pharsight Corporation,
Ph: +1 781.449.2719, Email: Mike.Dunlavey@Certara.com