Implementation of distributed delays for absorption delays and delayed drug response

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Background

- Transit compartment models, described by system of ordinary differential equations, have been widely used to describe delayed outcomes in pharmacokinetics (PK) and pharmacodynamics (PD) studies. Even though the transit compartment model approach can capture a variety of data quite well, it suffers a number of disadvantages.
  - It requires manually finding a proper value for the number of compartments. Hence, it is time-consuming, and is also difficult, if not impossible, to do population analysis. This is especially true in the case where the number of compartments may vary among individuals.
  - It may require a large number of differential equations to fit the data, and hence it may become inconvenient.
  - It may not adequately describe some complex features such as double/multiple-peak phenomenon after oral administration.
- The distributed delay approach provides an alternative way to model delayed outcomes, and does not suffer these disadvantages [1]. It involves convolution of the signal to be delayed (S) and the probability density function (g) of the delay time, $\int_0^{+\infty} S(t-\tau)g(\tau)d\tau$.
- The distributed delay approach incorporates a wide variety of PK/PD models as special cases including transit compartment models, typical absorption models (either zero-order or first-order absorption), and a number of atypical (or irregular) absorption models [1]. Specifically, transit compartment models are based on the assumption that the delay time is Erlang distributed with shape and rate parameters respectively determining the number of transit compartments and the transition rate between the compartments.

Objectives

- To demonstrate how to implement distributed delays in Phoenix modeling language (PML) for modeling absorption delays and delayed drug response.

Methods

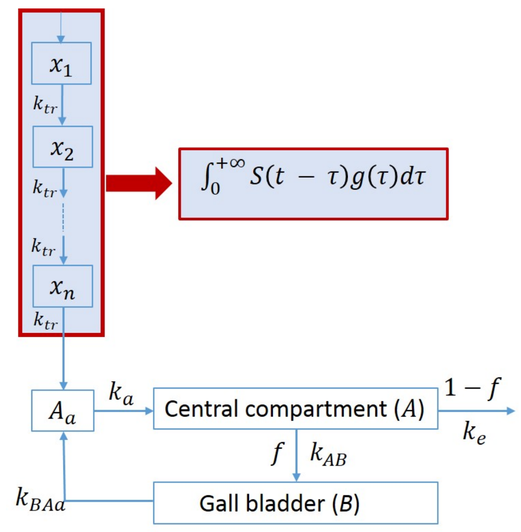
- The discrete `delay` function in PML has been extended to incorporate distributed delays for the common case of a gamma distribution (which allows for non-integer shape parameter, and has exponential and Erlang distributions as special cases). The syntax for the distributed delay function is given in Table 1, and it has the following features/capabilities.
  - There is no restriction on the number of distributed delay functions put in a model. However, it should be used sparingly to avoid performance issue.
  - The distributed delay function can be put on the right-hand side of a differential equation, and hence can be used to numerically solve a differential equation with gamma distributed delays.
  - Both the mean and shape parameter for the gamma distribution can be estimated.
- However, the signal to be delayed, S, in the `delay` function cannot contain dosing information. Hence, it cannot be used to model absorption delays. To achieve this, a compartment-modeling statement, `delayInfCpt`, was added to the PML (see Table 1 for its syntax).

	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 1: Syntax for the distributed `delay` function and `delayInfCpt` statement. It is worth noting that, for the gamma distribution, its mean is the ratio of the shape parameter to the rate parameter. In addition, "ShapeParameterMinusOne" for the `delayInfCpt` is to prevent the shape parameter from going less than one, which gets into singularities with the gamma distribution.

Results

Examples of demonstrating how to use the `delayInfCpt` statement and the distributed `delay` function to model delayed outcomes are based on the studies in [2, 3], where transit compartment models were used respectively to describe absorption delay of sorafenib exhibiting enterohepatic circulation and to model delayed production of platelet following dosing with feedback mechanism. Instead of manually finding a proper value for the number of compartments as in [2, 3], we generalized these models using the distributed delay approach (see Figures 1 and 2) with the delay time assumed to be gamma distributed to automatically determine this (through estimating the shape parameter value).



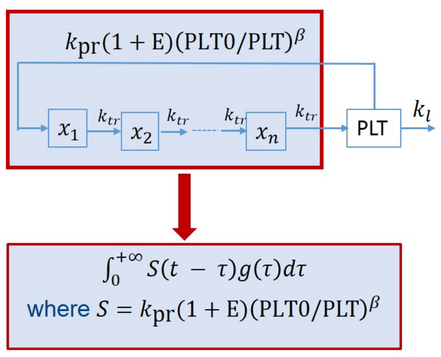

```
# absorption compartment
delayInfCpt(Aa, MeanDelayTime, ShapeParamMinusOne
            , out = - ka * Aa  + kBAa * B
           )

dosepoint(Aa)

# central compartment
deriv(A = ka * Aa - ke * (1 - f) * A
          - kAB * f * A
      )

# gall bladder compartment
deriv(B = kAB * f * A - kBAa * B)
```

Figure 1: (left panel): flow chart of original model [2] for describing absorption delay of sorafenib exhibiting enterohepatic circulation as well as the flow chart of the modified model using the distributed delay approach with $S(t)$ denoting the rate of drug administered at time t; (right panel): snapshot of PML codes using the `delayInfCpt` statement.




```
# drug effect  (described by a sigmoid Emax model)
E = Emax * C^h/(C^h + EC50^h)

# rate for production of platelet precursors
S = KPR * (1 + E) * (PLT0/PLT)^beta

# Compartment for platelet (PLT)
delayedS = delay(S, MeanDelayTime, shape = ShapeParam, hist = KPR)
deriv(PLT = delayedS - (PLT * KL))

# initial condition
sequence{PLT = PLT0}
```

Figure 2: (left panel): flow chart of original model [3] for modeling delayed production of platelet following lusutrombopag dosing with feedback mechanism as well as the flow chart of the modified model using the distributed delay approach; (right panel): snapshot of PML codes using the distributed `delay` function.

With this approach, we successfully obtained the value of shape parameter. In addition, all standard diagnostic plots and visual predictive checks were excellent.

Conclusions

Compared to transit compartment models, the distributed delay function or statement in PML provides a more powerful and flexible way to model delayed outcomes.

- It allows the shape parameter to be estimated. 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.
- Users only need to write one simple function/statement instead of a large number of differential equations.
- It allows for non-integer shape parameter and hence may capture dynamics better.

References

[1] Hu S, Feng K, Leary R and Dunlavey M (2015) A distributed delay approach for modeling delayed outcomes in pharmacokinetics and pharmacodynamics studies. ACOP6, T-39.

[2] Jain L, Woo S, Gardner ER, Dahut WL, Kohn EC, Kummar S, Mould DR, Giaccone G, Yarchoan R, Venitz J, Figg WD (2011) Population pharmacokinetic analysis of sorafenib in patients with solid tumours. Br J Clin Pharmacol 72:294–305.

[3] Katsube T, Ishibashi T, Kano T, Wajima T (2016) Population pharmacokinetic and pharmacodynamic modeling of lusutrombopag, a newly developed oral thrombopoietin receptor agonist, in healthy subjects. Clin Pharmacokinet 55:1423–1433.