Solving Semi-Delay Differential Equations in NONMEM

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Introduction and Objective

Delay differential equations (DDEs) are a growing tool to model delays (e.g. strongly delayed response) or lifespans (e.g. maturation processes in populations) in pharmacokinetics/pharmacodynamics (PKPD) [1]. In contrast to its ordinary differential equation (ODE) counterpart, a DDE describes a delay or lifespan with an explicit delay parameter T in the argument of the state. Currently, DDEs could not be directly solved in NONMEM. However, we identified a sub-class of DDEs, calling them Semi-DDEs, which often appear in PKPD modeling [1]. These Semi-DDEs could be rewritten by two systems of ODEs, one system for the time before the delay T and one for time after T. Applying the `ALAG` command and a case-by-case analysis, Semi-DDEs could be solved with NONMEM.

Delay Differential Equations:
The general form of a DDE with a single delay $T > 0$ reads

$$\frac{d}{dt}x(t) = f(t, x(t), x(t-T)), \qquad x(t) = x^0(t) \text{ for } t \le 0. \tag{1}$$

In contrast to ODEs, where $T = 0$, the mechanism f additionally depends on the delayed state $x(t-T)$ and we have an initial function $x^0(t)$ describing the past $-T \le t \le 0$ instead of an initial value at $t = 0$.

Semi-Delay Differential Equations:
We identified an important sub-class of DDEs, calling them Semi-DDEs in [1]. The general structure of a Semi-DDE with a single delay $T > 0$ reads

$$\frac{d}{dt}u(t) = g(t, u(t)), \qquad u(t) = u^0(t) \text{ for } t \le 0 \tag{2}$$
$$\frac{d}{dt}v(t) = h(t, u(t), u(t-T), v(t)), \qquad v(0) = v^0. \tag{3}$$

Here the mechanism g does not depend on v and its delayed state $u(t-T)$. However, $u(t-T)$ is used to describe the mechanism h for $v(t)$ and therefore a past for $u(t)$ is necessary. Note that $v(t)$ has no past but an initial value.

Method

General method to rewrite a Semi-DDE (2)-(3) to a system of two ODEs:
Step 1: $0 \le t \le T$
Substituting the explicitly initial function u^0 for the delayed state $u(t-T)$ gives the ODE

$$\frac{d}{dt}u(t) = g(t, u(t)), \qquad u(0) = u^0(0) \tag{4}$$
$$\frac{d}{dt}v(t) = h(t, u(t), u^0(t-T), v(t)), \qquad v(0) = v^0 \tag{5}$$
$$\frac{d}{dt}z(t) = 0, \qquad u(0) = u^0(0) \tag{6}$$

where Eq. (6) is a place holder for the upcoming delayed version of Eq. (4).
Step 2: $t \ge T$
Duplicate Eq. (4), where z now describes the state of u before $t-T$ time units, i.e. $z(t) = u(t-T)$. We denote by (u^T, v^T) the value of $u(t)$ and $v(t)$ at time point T. Then the second ODE reads

$$\frac{d}{dt}u(t) = g(t, u(t)), \qquad u(T) = u^T \tag{7}$$
$$\frac{d}{dt}v(t) = h(t, u(t), z(t), v(t)), \qquad v(T) = v^T \tag{8}$$
$$\frac{d}{dt}z(t) = g(t-T, z(t)), \qquad z(T) = u^0(0). \tag{9}$$

Note that there are no more delayed states in the right hand side of Eqs. (7)-(9).

References:
[1] Koch G, Krzyzanski W, Perez-Ruixo JJ, Schropp J (2014) Modeling of delays in PKPD - Classical approaches and a tutorial for delay differential equations. JPKPD (accepted)

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Application / Results

In CIA mice increased GM-CSF $G(t)$ is inhibited by a drug $c(t)$. A total arthritic score (TAS) $R_1(t)$, an overall description of inflammation $I(t)$ and bone destruction $D(t)$, and a pure bone destruction score (AKS) $R_2(t)$ were measured. The visibility of bone destruction is strongly delayed due to first signs of inflammation. This delay is described by an explicit delay parameter $T > 0$. Further it is assumed, that cytokine overproduction starts earlier before the mouse visibly develops inflammation, modeled by an initial function.

The **rheumatoid arthritis (RA) model in DDE formulation** [1] reads

$$\frac{d}{dt}c(t) = -k_{el}c(t) \qquad c(0) = \frac{dose}{V} \tag{10}$$
$$\frac{d}{dt}G(t) = k_3 - \frac{k_1}{k_2}(1-\exp(-k_2 t))\,G(t) - \frac{E_{max}c(t)}{EC_{50}+c(t)}G(t),$$
$$G(t) = a\exp(bt) \text{ for } -T \le t \le 0 \tag{11}$$
$$\frac{d}{dt}I(t) = k_4 G(t) - k_4 G(t-T), \qquad I(0) = I_0 \tag{12}$$
$$\frac{d}{dt}D(t) = k_4 G(t-T) - k_5 D(t), \qquad D(0) = 0 \tag{13}$$

where $R_1(t) = I(t) + D(t)$ is the TAS and $R_2(t) = D(t)$ the AKS.

NONMEM implementation of the ODE formulation of Eqs. (10)-(13):

```
$DES
c = A(1)/V
cdel = A(2)/V
eff = (Emax*c)/(EC50+c)
effdel = (Emax*cdel)/(EC50+cdel)
DADT(1) = -kel*A(1)
DADT(2) = -kel*A(2)
DADT(3) = k3 - eff*A(3) - (k1/k2)*(1-exp(-k2*t))*A(3)
if (t .LE. Tlag) then
    DADT(4) = k4*A(3) - k4*aa*exp(bb*(t-Tlag))
    DADT(5) = k4*aa*exp(bb*(t-Tlag)) - k5*A(5)
    DADT(6) = 0
else
    DADT(4) = k4*A(3) - k4*A(6)
    DADT(5) = k4*A(6) - k5*A(5)
    DADT(6) = k3 - effdel*A(6)
              - (k1/k2)*(1-exp(-k2*(t-Tlag)))*A(6)
endif
```

where `Tlag` = T, `aa` = a and `bb` = b.

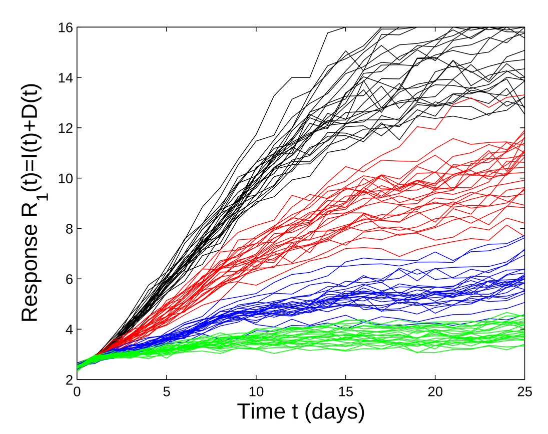
Remark: For $0 \le t \le T$ the delay appears in the substituted initial function. For $t > T$ the delay is in the PK. Therefore, the `ALAG` command which delays the dosing time by T time units is used.

Data for control (black) and three dosing groups (0.1 mg/kg (red), 0.5 mg/kg (blue) and 2.5 mg/kg (green)), each consisting of 25 individuals, was simulated with the DDE Eqs. (11)-(13) in `MATLAB`. PK profiles were equal for all individuals. The parameter k_4 (production rate of inflammation driven by GM-CSF), E_{max} (maximal effect of the drug) and T (delay until onset of bone destruction) have log-normal distributed BSV. A proportional error model was applied. Data was refitted with the presented NONMEM implementation.

	k_1	k_2	k_4	k_5	E_{max}	EC_{50}	T	I_0	$\omega^2_{k_4}$	$\omega^2_{E_{max}}$	ω^2_T	ε
Original	0.75	1.2	0.1	0.15	10	1	10	2.5	0.01	0.04	0.04	0.025
Estimate	0.746	1.19	0.100	0.143	10.2	1.02	9.92	2.49	0.009	0.037	0.039	0.018

Fixed parameter $k_{el} = 0.25$, $V = 1$, $k_3 = 5$, $a = 1$ and $b = 0.5$. Covariance step failed.

Response $R_1(t) = I(t) + D(t)$



Response $R_2(t) = D(t)$