DDEXPAND Interface for Coding Delay Differential Equations Based Models in NONMEM

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Objectives

Models using delay differential equations (DDEs) can be coded as ordinary differential equations (ODEs) with the method of steps. A drawback of method of steps is the large number of ODEs and delays making the DDE model implementation strenuous to code. DDEXAPND is a program that uses the method of steps to expand the base ODE's to include their time-delayed ODE's, and generate a NONMEM control stream for the DDE model.

Features

- DDEXPAND is a utility program that expands an NM-TRAN-template control stream to form a functional NMTRAN control stream to be run by NONMEM.
- DDEXAPAND requires for input a template text file (*.dde) with base model equations and a regular NONMEM data file (*.csv).
- The program outputs a text file (*.ctl) with a NMTRAN control stream and a modified data file (*.csv).
- DDEs are implemented in the *.dde file using the NMTRAN syntax for ODEs with additional structures accounting for delays of model states and their past conditions.

Demonstrations

- Introduction to the Method of Steps
- DDEXPAND basics
- Rheumatoid arthritis development in collagen-induced arthritic mice
- Influenza A virus infection in humans
- Lifespan indirect response model with precursor pool
- Erythropoietin stimulation of RBCs

Installation

- DDEXPAND source files consist of two FORTRAN files ddexpand.f90 and finedata.f90 which need to be compiled in a working directory containing NMTRAN control steam and data file to be run by NONMEM.
- DDEXPAND is an executable file that runs under DOS command window.

Conclusions

- DDE based models can be implemented in NONMEM using the method of steps.
- DDEXPAND provides a convenient tool for propagating and coding DDEs in NONMEM.
- DDEXPAND solutions of DDE models are equally accurate as solutions obtained by standard DDE solvers.

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Introduction to Methods of Steps

Wojciech Krzyzanski, PhD
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Objective

- Explain how MOS works using a simple DDE example.
- Implement MOS in NONMEM

General Form of DDE System

$$\frac{dx}{dt} = f(t, x(t), x(t-T_1), x(t-T_2), \ldots, x(t-T_p)) \qquad \text{for } t > 0$$

$x(t) = \varphi(t)$, for $t \le 0$

$x(t)$ = vector of states at time t.
$T_1, \ldots, T_p$ = delay times.
$\varphi(t)$ = vector valued function describing the states in the past.

The rate of change of x depends not only on the current value x(t), but also on the system states before times T_1, …, T_p: $x(t-T_1), \ldots, x(t-T_p)$.

Methods of Steps: Example

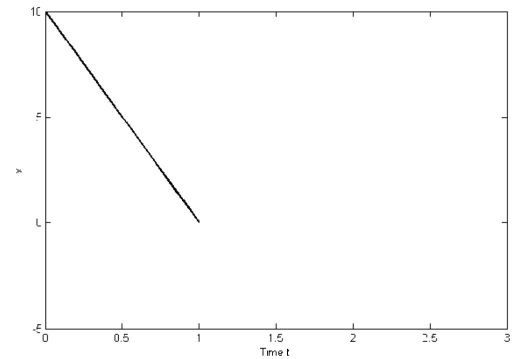
DDE: $$\frac{dx}{dt} = -x(t-1) \quad \text{for } 0 < t \qquad x(t) = 10 \quad \text{for } t \le 0$$

1st step: Find solution for **0< t <1**:

$0 < t < 1 \Rightarrow -1 < t-1 < 0 \Rightarrow x(t-1) = 10$

$$\frac{dx}{dt} = -10$$

$$x(t) = 10 - 10t$$

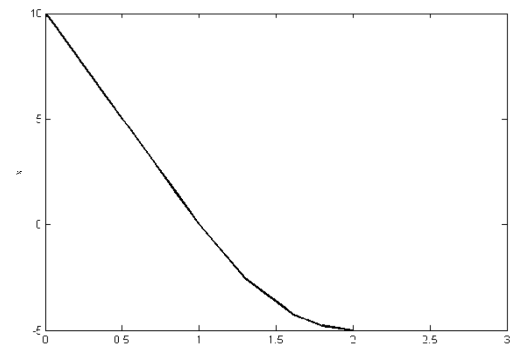


2nd step: Find solution for **1< t <2**:

$1 < t < 2 \Rightarrow 0 < t-1 < 1 \Rightarrow x(t-1) = 10 - 10(t-1)$

$$\frac{dx}{dt} = -(10 - 10(t-1))$$

$$x(t) = -10(t-1) + 5(t-1)^2$$

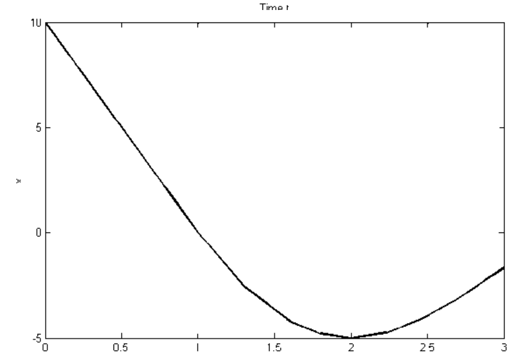


3rd step: Find solution for **2 < t <3**:

$1 < t < 2 \Rightarrow 1 < t-1 < 2 \Rightarrow x(t-1) = -10(t-2) + 5(t-2)^2$

$$\frac{dx}{dt} = -(-10(t-2) + 5(t-2)^2)$$

$$x(t) = -5 + 5(t-2)^2 - \frac{5}{3}(t-1)^3$$



Method of Steps

- **If for a time interval $t_i < t < t_{i+1}$ ("a step") the delay t_{i+1}- T is less than t_i, then delayed state y(t-T) defined by its values for times less than t_i, which makes y(t-T) a "known" variable.**

- **If all delayed variables become "known" over the time interval $t_i < t < t_{i+1}$, then for this time interval the system does not have unknown delay variables and becomes an ODE system.**

- **Methods of steps transforms a system of DDEs into a system of ODEs.**

Driver RD. Ordinary and Delay Differential Equations. New York, Springer-Verlag, 1977.

MOS: Numerical Implementation

$$\frac{dx}{dt} = -x(t-1) \quad \text{for } 0 < t \qquad x(t) = 10 \quad \text{for } t \le 0$$

To find a solution for **0< t <3**: $y_1(t)=x(t)$, $y_2(t)=x(t-1)$

$$\frac{dy_1}{dt} = -y_2(t)$$

$$\frac{dy_2}{dt} = \begin{cases} 0, & t \le 1 \\ -x(t-2), & t > 1 \end{cases}$$

Since $t-2 > 0$ for some t, we need to calculate x(t-2): $y_3(t)=x(t-2)$

$$\frac{dy_2}{dt} = \begin{cases} 0, & t \le 1 \\ -y_3(t), & t > 1 \end{cases}$$

$$\frac{dy_3}{dt} = \begin{cases} 0, & t \le 2 \\ -x(t-3), & t > 2 \end{cases}$$

Since $t-3 < 0$ for all $0 < t < 3$: $x(t-3) = 10$ and

$$\frac{dy_3}{dt} = \begin{cases} 0, & t \le 2 \\ -10, & t > 2 \end{cases}$$

Initial conditions: $y_1(0)= 10$, $y_2(0) = 10$, $y_3(0) = 10$

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NM-TRAN Control Stream

```
$PK
K=THETA(1)*EXP(ETA(1))
TAU=THETA(2)
A0=THETA(3)

; Initial conditions
A_0(1)=A0
A_0(2)=A0
A_0(3)=A0

$DES
;ODE for 0<T<3*TAU
DADT(1)=-K*A(2)

DTAU_1=0.0
IF(T>=TAU) DTAU_1=1.0

DADT(2)=DTAU_1*(-K*A(3))

DTAU_2=0.0
IF(T>=2*TAU) DTAU_2=1.0

DADT(3)=DTAU_2*(-K*A0)


$ERROR
```

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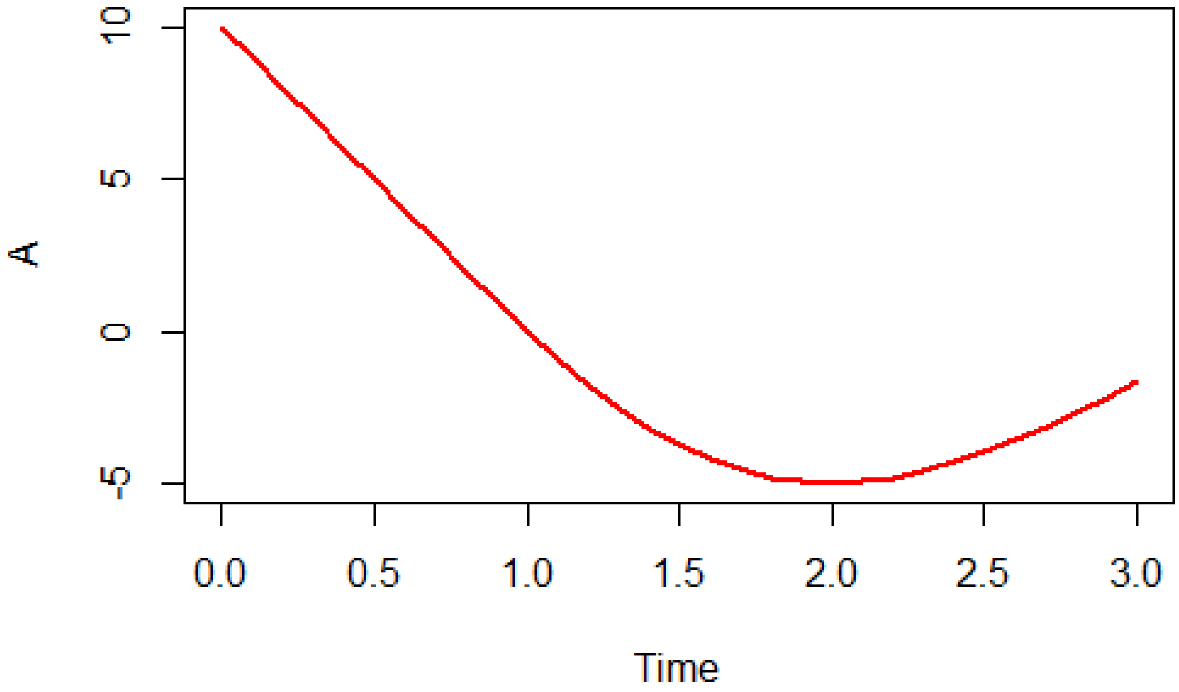
Results



Lifespan Indirect Response Model with Precursor Pool DDEXPAND

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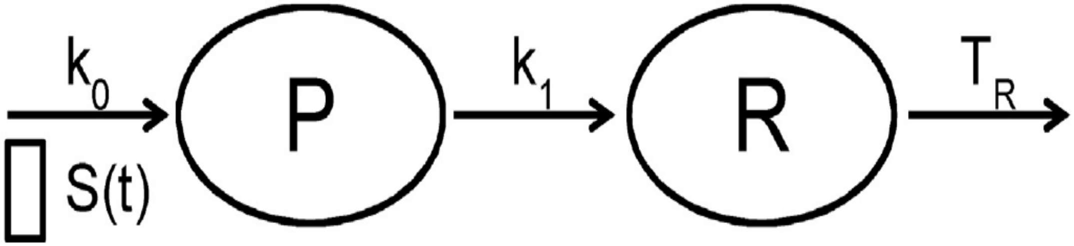
Objective

- Implement in NM lifespan indirect response model with a precursor (LIPDR) using the method of steps.
- Fit PDLIDR model to simulated responses for N=125 subjects in five dose groups and compare the parameter estimates with their original values.

PDLIDR Model



$$\frac{dA}{dt} = -k_{el}A$$

$$\frac{dP}{dt} = k_0 S(t) - k_1 P \qquad P(t) = \frac{k_0}{k_1} \qquad t \le 0$$

$$\frac{dR}{dt} = k_1 P - k_1 P(t - T_R) \qquad R(t) = k_0 T_R \qquad t \le 0$$

$$S(t) = 1 + \frac{S_{max} C(t)}{SC_{50} + C(t)} \qquad C = A/V$$

Bauer and Krzyzanski, Computer Methods and Programs in Biomedicine. 111:715–734 (2013)

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Simulated Data

Inter individual variability model

$$\theta_i = \theta e^{\eta i}$$

Inter individual variability model

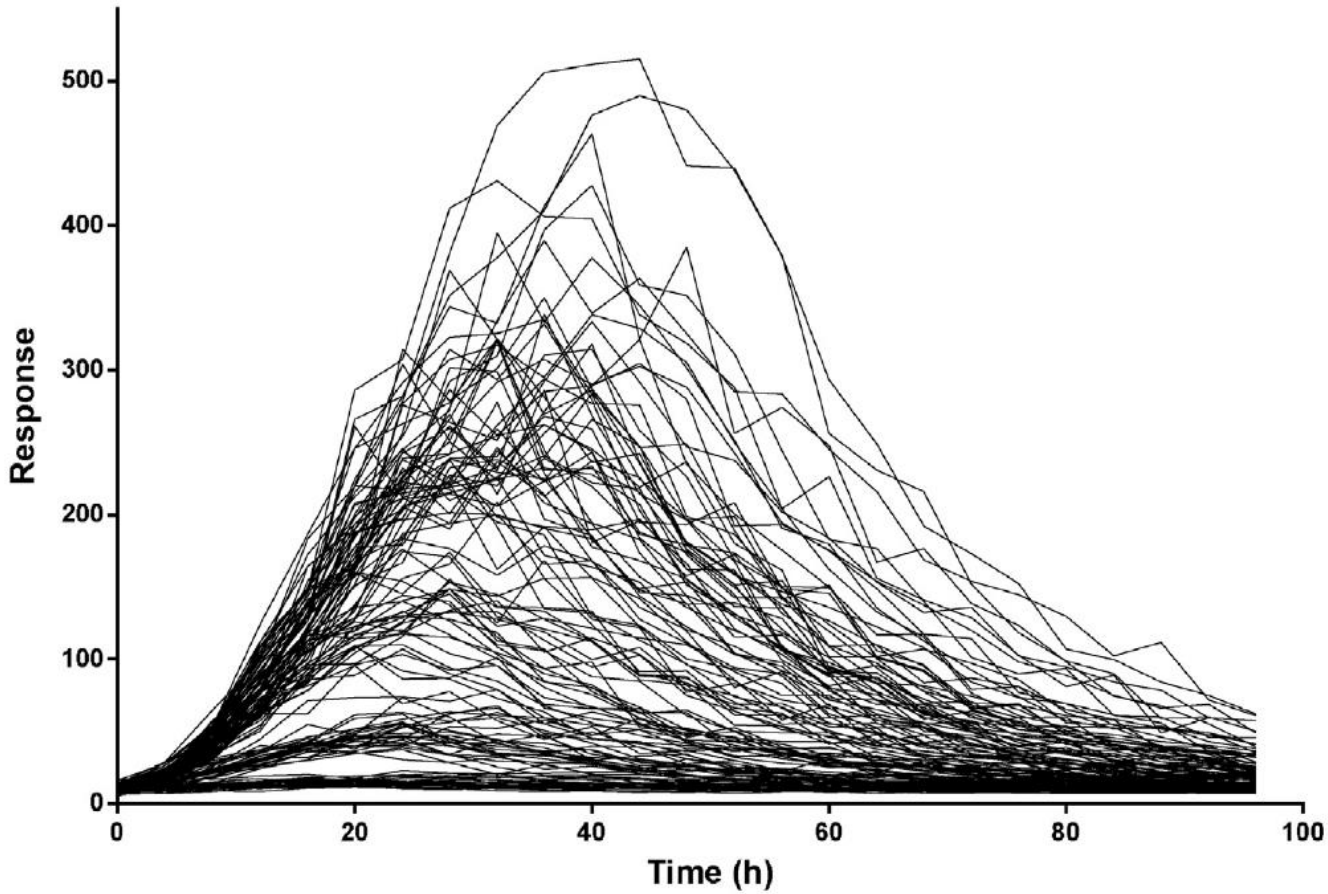
$$\log(Y_{ij}) = \log(R_i(t_j)) + \varepsilon_{ij}$$

- N =125 subjects divided evenly into 5 IV dosing groups at doses 0.1, 1, 10, 100 and 100 units.
- Data points were simulated at 25 evenly distributed time points from 0-96 h.
- Simulations were performed in MATLAB.

Parameters	True values
T_R	20
k_0	0.5
k_1	0.05
SC_{50}	1
S_{max}	50
k_{el}	0.25
V	1
ω^2_{TR}	0.04
ω^2_{k1}	0.04
ω^2_{k0}	0
ω^2_{SC50}	0
ω^2_{SMAX}	0
σ	0.1

Bauer and Krzyzanski, Computer Methods and Programs in Biomedicine. 111:715–734 (2013)

Individual Response Time Courses



Individual plots described by the lifespan indirect response model with a precursor

Bauer and Krzyzanski, Computer Methods and Programs in Biomedicine. 111:715–734 (2013)

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Install ddexpand and finedata

```
c:\DDEXPAND\PDLIDR>ifort ddexpand.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

Copyright (C) 1985-2010 Intel Corporation.  All rights reserved.

Microsoft (R) Incremental Linker Version 9.00.21022.08
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-out:ddexpand.exe
-subsystem:console
ddexpand.obj

c:\DDEXPAND\PDLIDR>ifort finedata.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

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-out:finedata.exe
-subsystem:console
finedata.obj
```

ddexpand and finedata should be installed in a working directory where pre-control stream and data files are.

Pre-control Stream

```
$PROBLEM PDLIDR
;TAU1=5.0
;TSTOP=96.0
$INPUT ID AMT TIME DV EVID  CMT
$DATA C:\DDEXPAND\PDLIDR\PDLIDR.csv IGNORE=C
$SUBROUTINES ADVAN13 TOL=12
$MODEL NCOMPARTMENTS=3
```

Lower bound for model delay

Last time point

Pre-control Stream

```
$PK
KEL=THETA(1)
V=THETA(2)
K0=THETA(3)*EXP(ETA(1))
K1=THETA(4)*EXP(ETA(2))
SMAX=THETA(5)*EXP(ETA(3))
SC50=THETA(6)*EXP(ETA(4))
;  TAUy
TAU1=THETA(7)*EXP(ETA(5))
; Initial conditions
A_0(1)=0
A_0(2)=K0/K1
A_0(3)=K0*TAU1

$DES
; AD_x_y is the State value of A(x) delayed for time TAUy.
; AP_x_y is the State value of A(x) in the past, for time delay
TAUy.
AP_2_1=K0/K1
;BASE EQUATIONS
CC=A(1)/V
DADT(1)=-KEL*A(1)
DADT(2)=K0*(1+SMAX*CC/(SC50+CC))-K1*A(2)
DADT(3)=K1*A(2)-K1*AD_2_1
```

Definition of model delay (TAU1=THETA(7)*EXP(ETA(5)))

Definition of past (AP_2_1=K0/K1)

Model equations (CC … DADT(3))

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Run ddexpand

Pre-control stream

NM-TRAN control stream

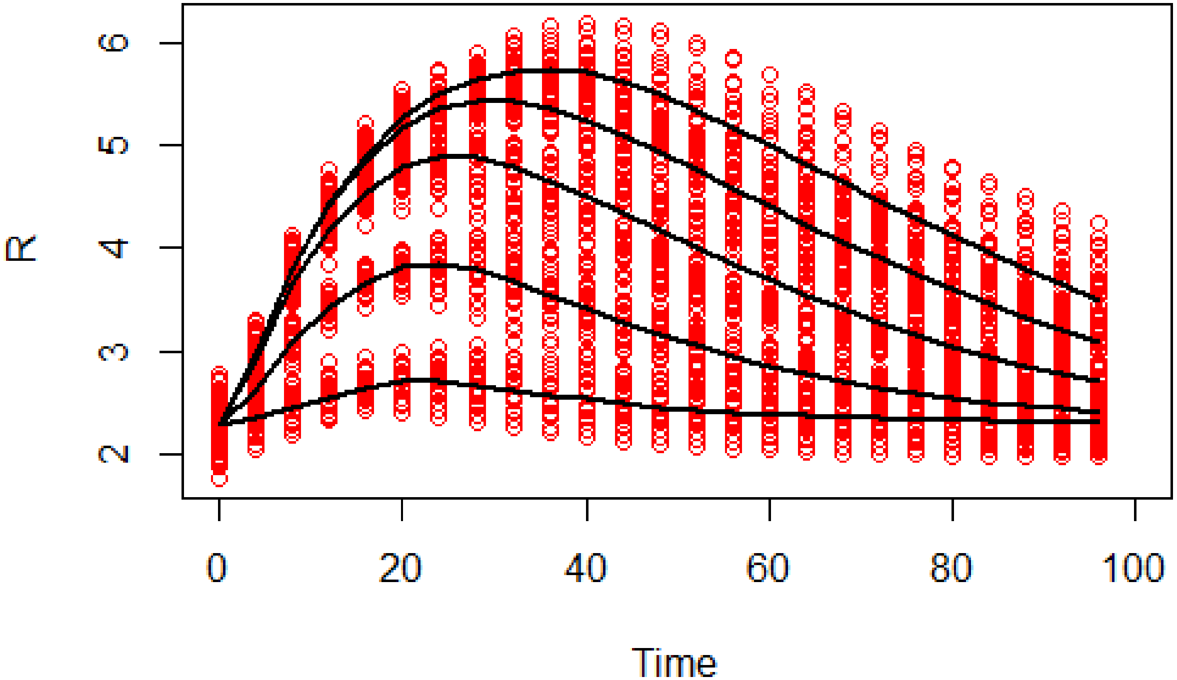
```
c:\DDEXPAND\PDLIDR>ddexpand pdlidr.dde pdlidr.ctl
 finedata file is fine.ftl
 executing: finedata fine.ftl
 PROBLEM              1 : FILE C:\DDEXPAND\PDLIDR\PDLIDR_dde.csv
```

NM data set

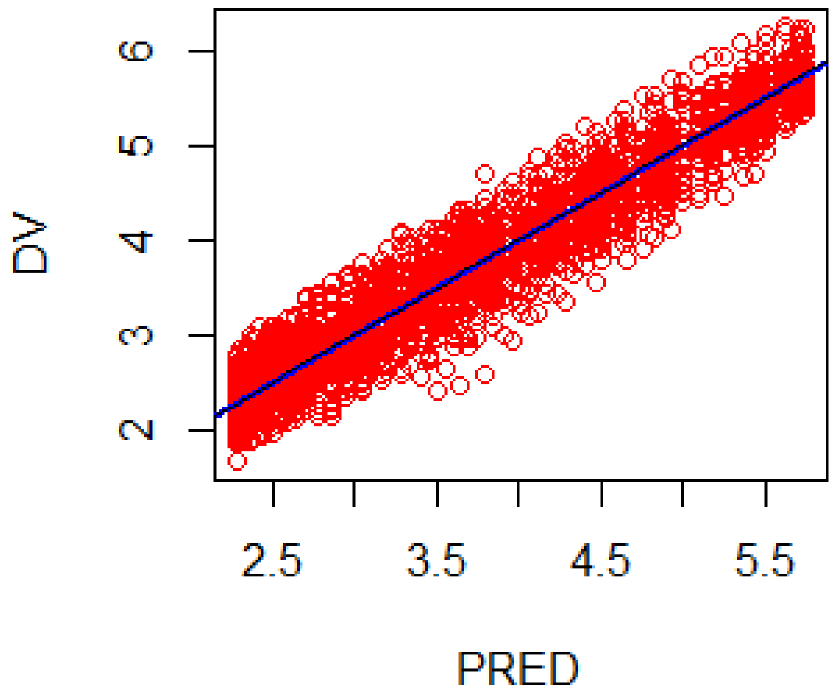
Run NM-TRAN Control Stream

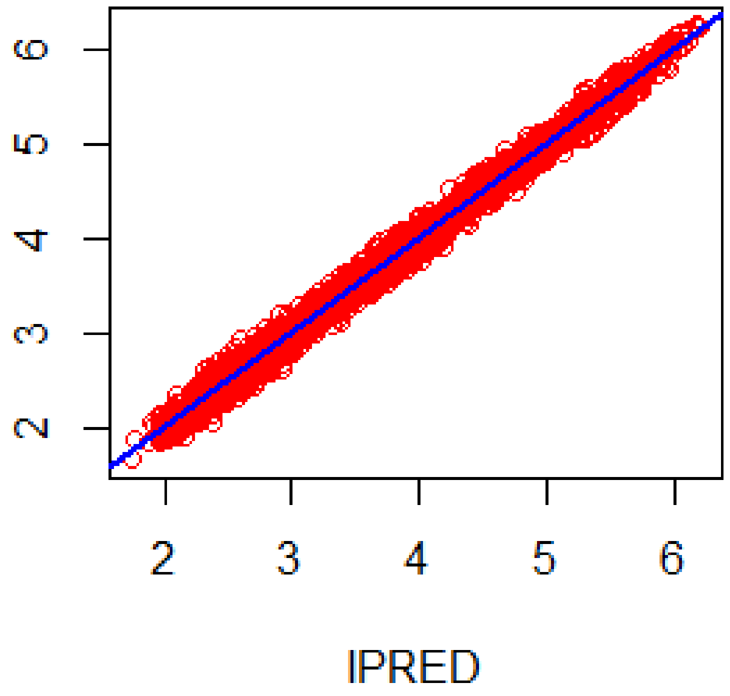
```
c:\nm730\run>nmfe73 c:\ddexpand\pdlidr\pdlidr.ctl c:\ddexpand\pdlidr\pdlidr.out
Starting NMTRAN

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM    1

 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

 (WARNING  3) THERE MAY BE AN ERROR IN THE ABBREVIATED CODE. THE FOLLOWING
 ONE OR MORE RANDOM VARIABLES ARE DEFINED WITH "IF" STATEMENTS THAT DO NOT
 PROVIDE DEFINITIONS FOR BOTH THE "THEN" AND "ELSE" CASES. IF ALL
 CONDITIONS FAIL, THE VALUES OF THESE VARIABLES WILL BE ZERO.

   IPRED Y

        1 file(s) copied.
Recompiling certain components.
starting wait
```

PRED vs. TIME



Observed vs Predicted





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Parameter Estimates

Parameter	Estimate	SE
KEL	0.25	FIX
V	1.0	FIX
K0	0.49	0.00558
K1	0.0498	0.000919
SMAX	51.3	0.909
SC50	1.04	0.0404
TR	20.1	0.446
ω_{K0}^2	0	FIX
ω_{K1}^2	0.034	0.005
ω_{SMAX}^2	0	FIX
ω_{SC50}^2	0	FIX
ω_{TR}^2	0.0447	0.00522
σ^2	0.0979	0.000251

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Collagen-Induced Arthritis Mouse Model for Rheumatoid Arthritis DDEXPAND

Wojciech Krzyzanski, PhD

Bob Bauer, PhD

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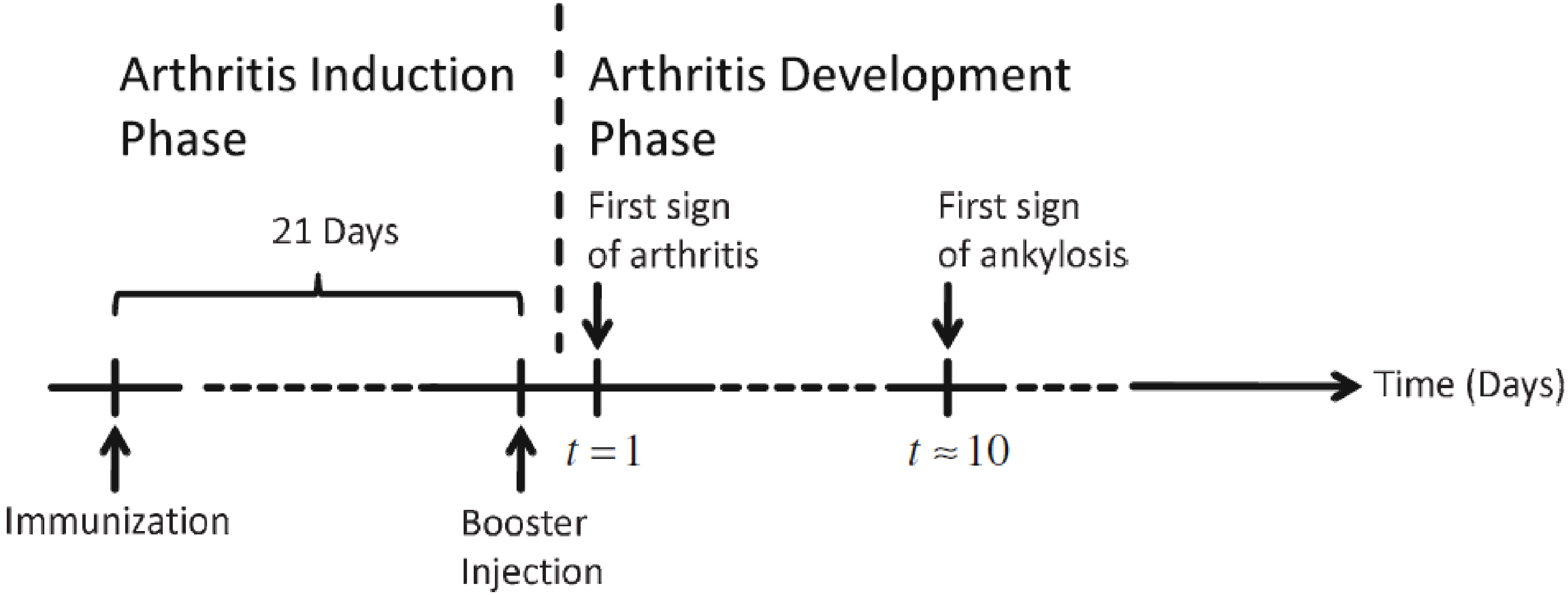
Objective

- Implement in NM CIA model for RA in mouse using the method of steps.
- Simulate Total Arthritic Sore and Alkylosis Score time courses following bolus administration of placebo, 1, 10, and 100 mg/kg of anti-GM-CSF antibody.

Collagen-Induced Arthritis Mouse Model for Rheumatoid Arthritis



The CIA mouse model consists of two phases, the induction phase followed by the arthritis development phase. In the induction phase an initial immunization with collagen takes place and after 21 days a booster injection is administered. The begin of the arthritis development phase is the day of disease onset when first signs of arthritis are detected. At this time the disease development phase begins.

Koch et al., JPKPD 39:55 (2012).

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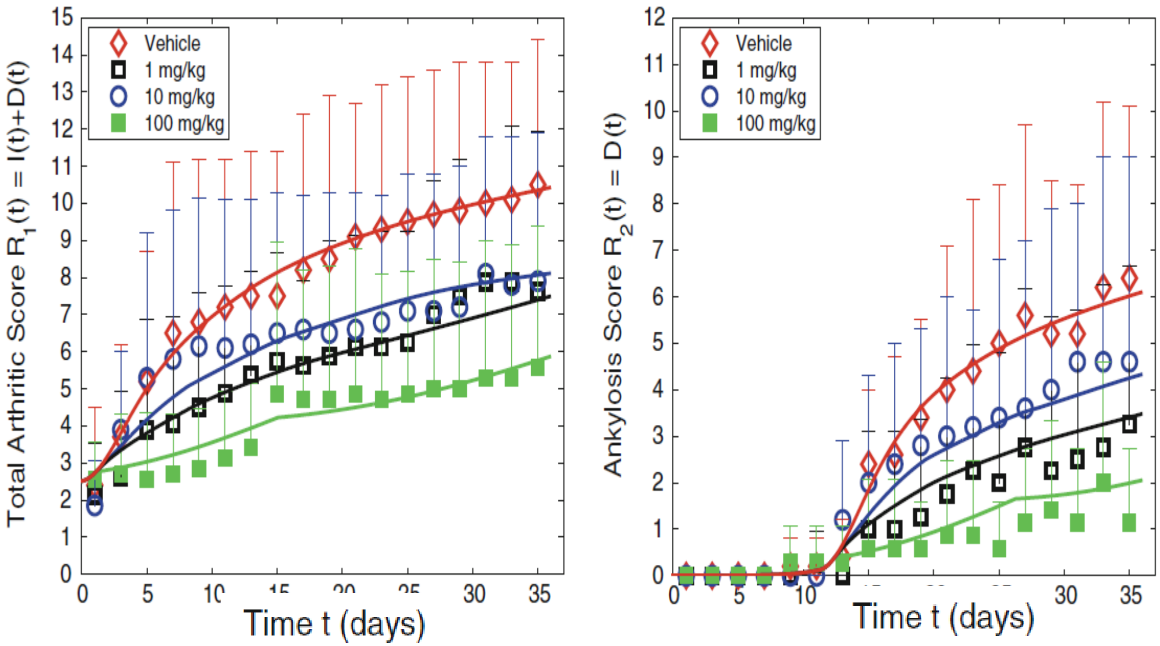
Collagen-Induced Arthritis Mouse Model for Rheumatoid Arthritis



Time courses of TAS and AKS (mean and SD) following multiple administration of 22E9 at specified doses: symbols (observed), lines (model predicted).

- **CIA was induced in DBA/1 mice by immunization with collagen.**
- **After 21 days a dose of GM-CSF neutralizing antibody 22E9 is injected IV into mice (t = 0, 7, 14 days).**
- **Total arthritic score (TAS) (0-4) and ankylosis score (AKS) (0-2) is assigned to each animal ever other day for 35 days.**

Koch et al., JPKPD 39:55 (2012).

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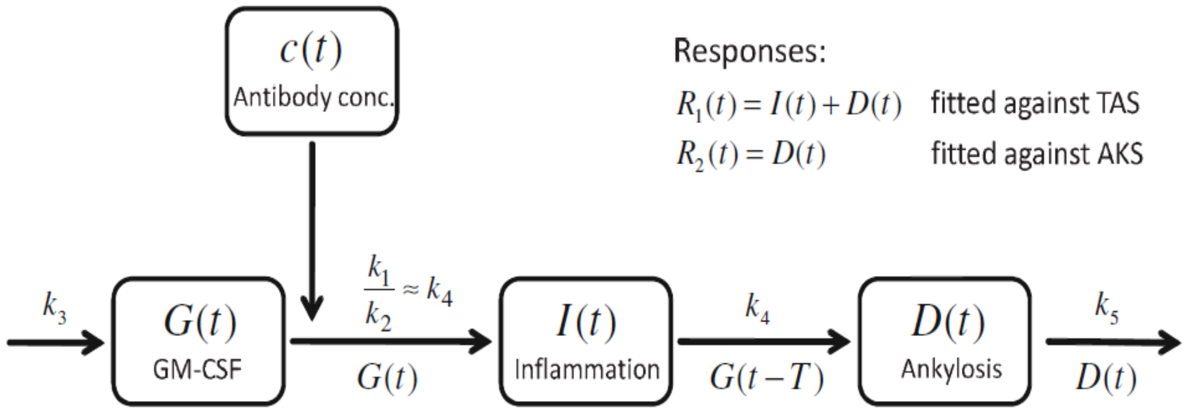
PKPD Model of CIA in Mice

T = Delay before development of ankylosis.



$$\frac{d}{dt}G(t) = k_3 - e(c(t))G(t) - \frac{k_1}{k_2}(1 - \exp(-k_2 t))G(t) \qquad G(t) = a\exp(bt) \quad \text{for } t \le 0$$

$$\frac{d}{dt}I(t) = k_4 G(t) - k_4 G(t - T) \qquad I(0) = I_0$$

$$\frac{d}{dt}D(t) = k_4 G(t - T) - k_5 D(t) \qquad D(0) = 0$$

where

$$e(c(t)) = \frac{E_{max} c(t)}{EC_{50} + c(t)}$$

Koch et al., JPKPD 39:55 (2012).

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Model Parameters

Physiological constants	Explanation	Value (CV %)
Cl (L h^{-1} kg^{-1})	Clearance	0.0004 (3.8)
Cl_d (L h^{-1} kg^{-1})	Intercompartmental distribution	0.0029 (10.5)
V_1 (L kg^{-1})	Volume of distribution (blood compartment)	0.0265 (1.3)
V_2 (L kg^{-1})	Volume of distribution (peripheral compartment)	0.0270 (9.9)

Parameter	Explanation	Experiment B Value (CV%)
k_1	Outflow GM-CSF	0.456 (42)
k_2	Outflow GM-CSF	0.169 (25)
k_3^+	Inflow GM-CSF	5
k_4	Inflow/outflow inflammation; inflow ankylosis	0.185 (30)
k_5	Outflow ankylosis	0.031 (21)
σ_1	Effect term parameter	0.328 (41)
σ_2	Effect term parameter	0.328 (25)
σ_3	Effect term parameter	0.025 (35)
T	Delay ankylosis	10.6 (4.3)
I_0	Initial value inflammation	2.83 (8.5)
a^+	Initial function parameter GM-CSF	1
b^+	Initial function parameter GM-CSF	0.5

Koch et al., JPKPD 39:55 (2012).

Install ddexpand and finedata

```
c:\DDEXPAND\RA>ifort ddexpand.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

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-out:ddexpand.exe
-subsystem:console
ddexpand.obj

c:\DDEXPAND\RA>ifort finedata.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

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-out:finedata.exe
-subsystem:console
finedata.obj
```

ddexpand and finedata should be installed in a working directory where pre-control stream and data files are.

Pre-control Stream

```
$PROBLEM RA
;TAU1=10.0
;TSTOP=25.0
$INPUT ID TIME    AMT     RATE    CMT    EVID MDV   DV
$DATA C:\DDEXPAND\RA\RA.csv IGNORE=C
$SUBROUTINES ADVAN13 TOL=12
$MODEL NCOMPARTMENTS=5

$PK
CL=THETA(1)+ETA(1)
V1=THETA(2)+ETA(2)
CLD=THETA(3)+ETA(3)
V2=THETA(4)+ETA(4)
K1=THETA(5)+ETA(5)
K2=THETA(6)+ETA(6)
K4=THETA(7)+ETA(7)
K5=THETA(8)+ETA(8)
SIG1=THETA(9)+ETA(9)
SIG2=THETA(10)+ETA(10)
SIG3=THETA(11)+ETA(11)
I0=THETA(13)+ETA(13)
TT=THETA(12)+ETA(12)
I0=THETA(13)+ETA(13)

;  TAUy
TAU1=TT
```

Lower bound for model delay (→ ;TAU1=10.0)

End time for simulation or last time point (→ ;TSTOP=25.0)

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Pre-control Stream

```
K10=CL/V1
K12=CLD/V1
K21=CLD/V2
K3=5.0
AA=1.0
BB=0.5
; Initial conditions
A_0(1)=AA
A_0(2)=I0

$DES
; AD_x_y is the State value of A(x) delayed for time TAUy.
; AP_x_y is the State value of A(x) in the past, for time delay
TAUy.

;PAST
AP_1_1=AA*EXP(BB*T)

;BASE EQUATIONS
CC=A(4)/V1
EFFECT=CC*(SIG1*EXP(-SIG2*CC)+SIG3)

DADT(1)=K3-EFFECT*A(1) - K1/K2* &
(1.0-EXP(-K2*T))*A(1)
DADT(2)=K4*A(1)-K4*AD_1_1
DADT(3)=K4*AD_1_1-K5*A(3)
DADT(4)=-K10*A(4)-K12*A(4)+K21*A(5)
DADT(5)=K12*A(4)-K21*A(5)

$ERROR
```

← Definition of past

Model equations

Run ddexpand

Pre-control stream

NM-TRAN control stream

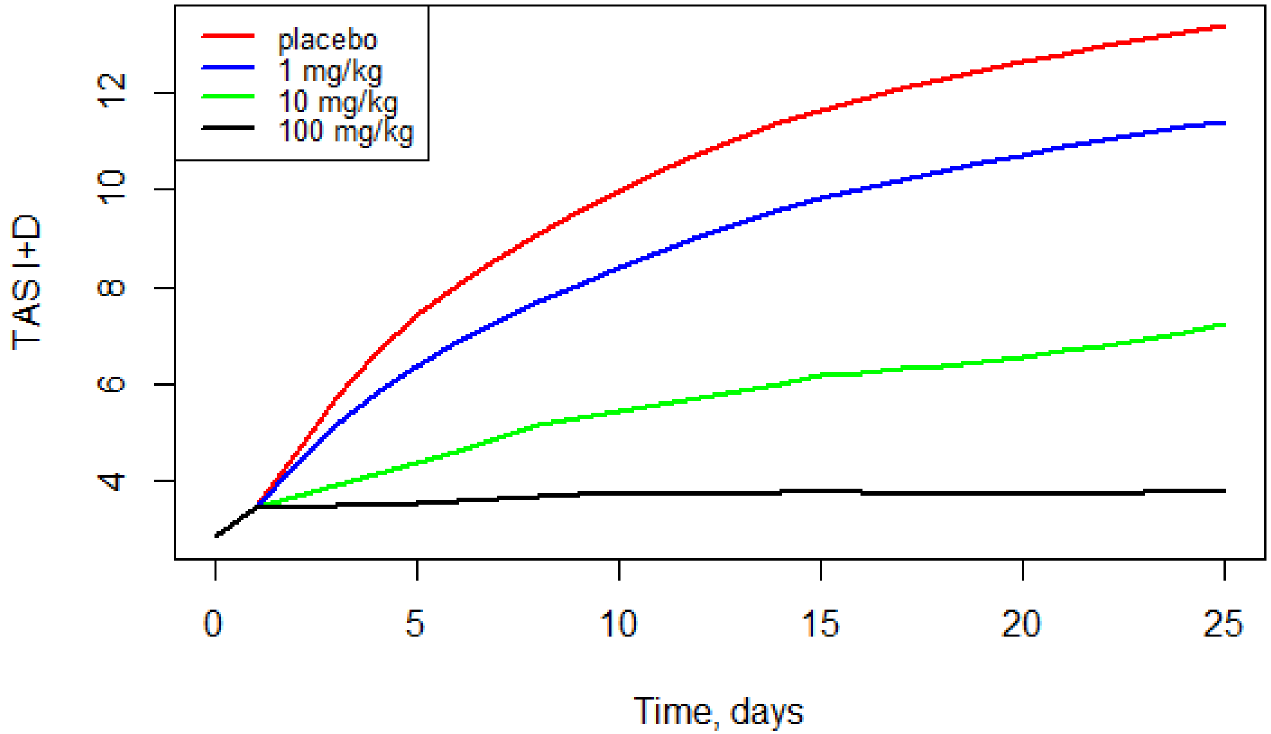
```
c:\DDEXPAND\RA>ddexpand RA.dde RA.ctl
 finedata file is fine.ftl
 executing: finedata fine.ftl
 PROBLEM              1 : FILE C:\DDEXPAND\RA\RA_dde.csv
```

NM data set

Run NM-TRAN Control Stream

```
c:\nm730\run>nmfe73 c:\ddexpand\ra\ra.ctl c:\ddexpand\ra\ra.out
Starting NMTRAN

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM    1

 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

 (WARNING  3) THERE MAY BE AN ERROR IN THE ABBREVIATED CODE. THE FOLLOWING
 ONE OR MORE RANDOM VARIABLES ARE DEFINED WITH "IF" STATEMENTS THAT DO NOT
 PROVIDE DEFINITIONS FOR BOTH THE "THEN" AND "ELSE" CASES. IF ALL
 CONDITIONS FAIL, THE VALUES OF THESE VARIABLES WILL BE ZERO.

   IPRED Y

        1 file(s) copied.
Building NONMEM Executable
Starting nonmem execution ...
 PROBLEM NO.:         1     SUBPROBLEM NO.:      1
```

Results: Total Arthritic Score



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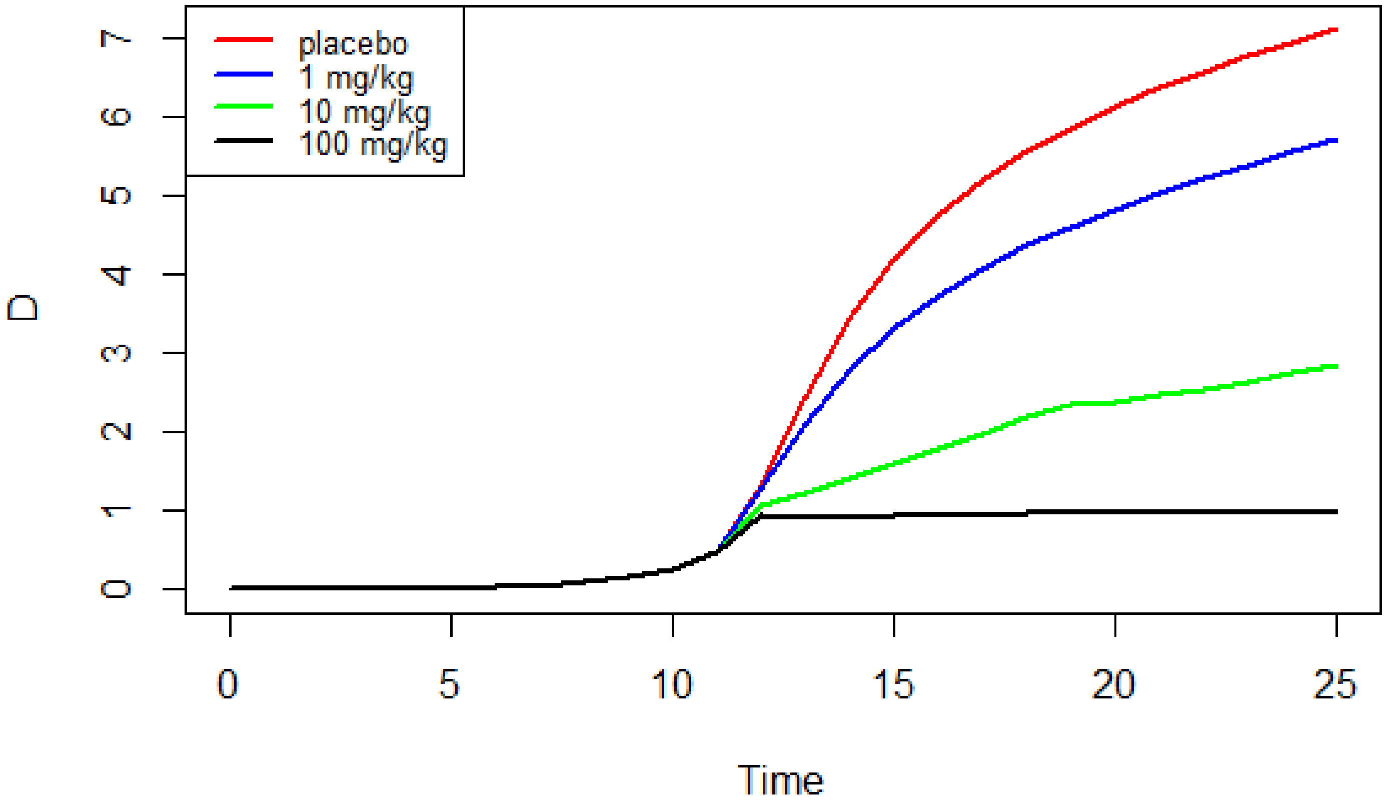
Results: Ankylosis Score



Model of Influenza A Virus Infection DDEXPAND

Wojciech Krzyzanski, PhD

Bob Bauer, PhD

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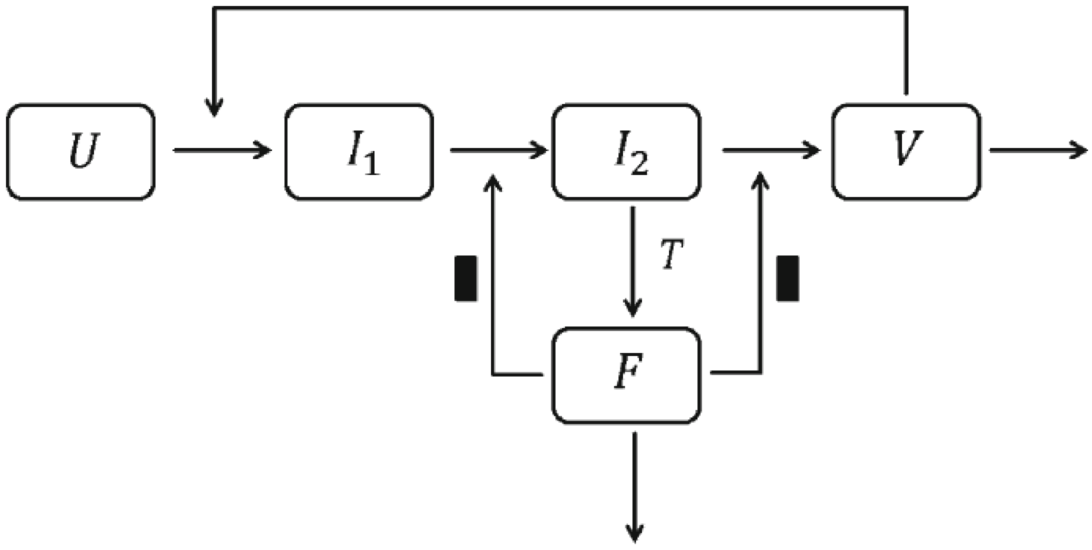
Objective

- Implement in NM a PKPD model of infection with influenza A virus using the method of steps.
- Simulate time courses the viral titer.

Model of Influenza A Virus Infection



$U(t)$ - number of uninfected target cells
$V(t)$ - infectious viral titer of nasal wash
$I_1(t)$ - infected cells which are not able to produce virus
$I_2(t)$ - infected cells which are actively producing virus
$F(t)$ - cytokines (interferons) secreted by virus-producing cells
T - delay after cells begin producing virus and influence the rate at which infected cells move into the virus producing state

Koch G et al. (2014) J Pharmacokinet Pharmacodyn 41(4): 291-318
Baccam P et al. (2006) J Virol 80(15):7590-99

Model Equations

$$\frac{d}{dt}U(t) = -\beta U(t)V(t) \qquad U(0) = U^0$$

$$\frac{d}{dt}I_1(t) = \beta U(t)V(t) - \frac{k}{1+\varepsilon_1 F(t)}I_1(t) \qquad I_1(0) = 0$$

$$\frac{d}{dt}I_2(t) = \frac{k}{1+\varepsilon_1 F(t)}I_1(t) - \delta I_2(t) \qquad I_2(t) = 0 \qquad t \le 0$$

$$\frac{d}{dt}V(t) = \frac{p}{1+\varepsilon_2 F(t)}I_2(t) - cV(t) \qquad V(0) = V^0$$

$$\frac{d}{dt}F(t) = sI_2(t-T) - \alpha F(t) \qquad F(0) = 0$$

$$U^0 = \frac{c\delta R_0}{p\beta}$$

Reproductive number

Koch G et al. J Pharmacokinet Pharmacodyn 41: 291-318 (2014)

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Model Parameters

Model parameter	Definition	Value
β	Infection rate constant	2.1 E−5
k	Transit rate	48.6 E0
δ	Rate infected cells die	10.9 E0
p	Rate virus increase	1.3 E−1
c	Viral clearance rate	11 E0[c]
R^0	Reproductive number	6.4 E0
V^0	Initial virus titer	1 E−5
ε_1	Transit rate	2.7 E−3
ε_2	Transit rate	0[c]
α	Interferon degradation rate	4.7 E0
T	Delay	1.0 E0

Koch G et al. J Pharmacokinet Pharmacodyn 41: 291-318 (2014)

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Install ddexpand and finedata

```
c:\DDEXPAND\IAV>ifort ddexpand.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

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Microsoft (R) Incremental Linker Version 9.00.21022.08
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-out:ddexpand.exe
-subsystem:console
ddexpand.obj

c:\DDEXPAND\IAV>ifort finedata.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

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-out:finedata.exe
-subsystem:console
finedata.obj

c:\DDEXPAND\IAV>
```

ddexpand and finedata should be installed in a working directory where pre-control stream and data files are.

Pre-control Stream IAV.dde

```
$SIZES PC=50 DIMNEW=1600 DIMTMP=200 PG=60 PAL=60 LNP4=1600
$PROBLEM IAV
;TAU1=1.0
;TSTOP=8.0
$INPUT ID AMT TIME DV EVID MDV CMT
$DATA C:\DDEXPAND\IAV\IAV.csv IGNORE=C
$SUBROUTINES ADVAN13 TOL=12
$MODEL NCOMPARTMENTS=5

$PK
BETA=THETA(1)*EXP(ETA(1))
K=THETA(2)
DELTA=THETA(3)
PP=THETA(4)
CC=THETA(5)
RR0=THETA(6)
V0=THETA(7)
EP=THETA(8)
ALPHA=THETA(9)
;  TAUy
TAU1=THETA(10)

U0=CC*DELTA*RR0/(PP*BETA)
```

Lower bound for model delay (;TAU1=1.0)

End time for simulation or last time point (;TSTOP=8.0)

Definition of model delay (TAU1=THETA(10))

$SIZES need to be manually adjusted to account for large MOS model dimension

Pre-control Stream IAV.dde

```
; Initial conditions
A_0(1)=U0
A_0(2)=0
A_0(3)=0
A_0(4)=V0
A_0(5)=0

$DES
; AD_x_y is the State value of A(x) delayed for time TAUy.
; AP_x_y is the State value of A(x) in the past, for time delay
TAUy.
AP_3_1=0
;BASE EQUATIONS
DADT(1)=-BETA*A(1)*A(4)
DADT(2)=BETA*A(1)*A(4)-K*A(2)/(1+EP*A(5))
DADT(3)=K*A(2)/(1+EP*A(5))-DELTA*A(3)
DADT(4)=PP*A(3)-CC*A(4)
DADT(5)=AD_3_1-ALPHA*A(5)

$ERROR
```

Definitions of pasts for delayed states

Model equations

Run ddexpand

Pre-control stream

NM-TRAN control stream

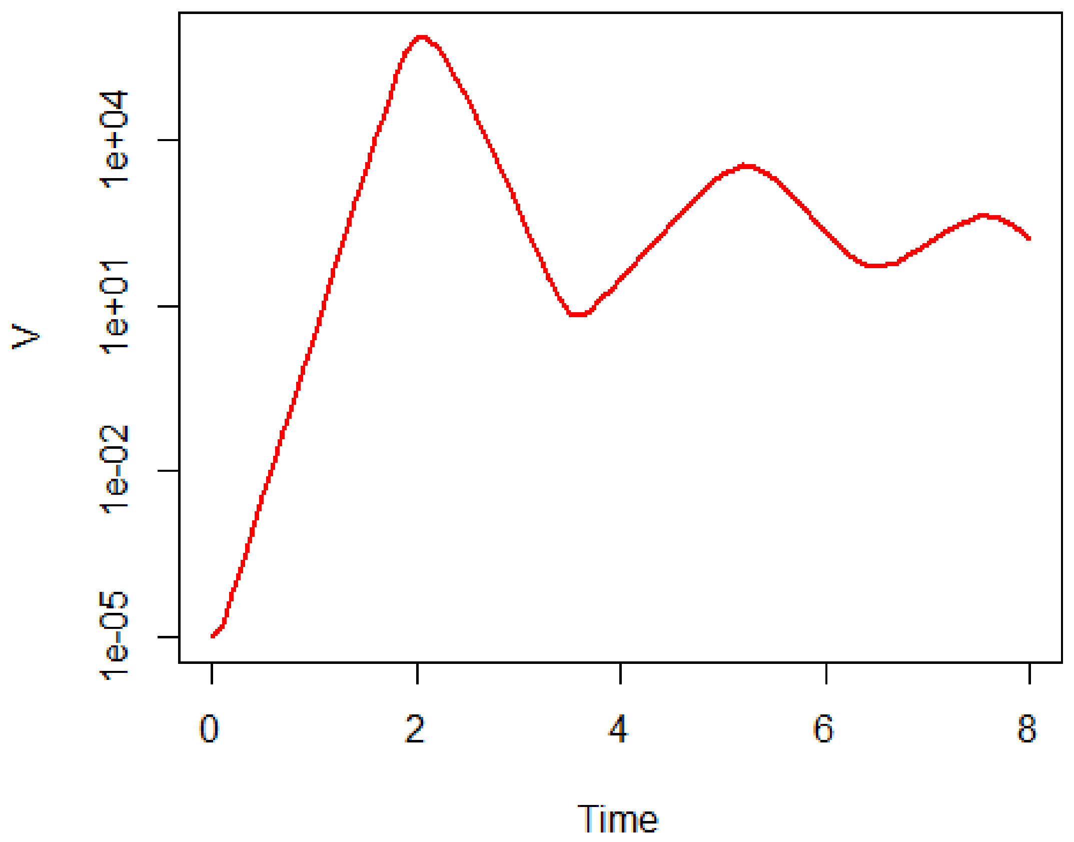
```
c:\DDEXPAND\IAV>ddexpand IAV.dde IAV.ctl
 finedata file is fine.ftl
 executing: finedata fine.ftl
 PROBLEM                1  : FILE C:\DDEXPAND\IAV\IAV_dde.csv
```

NM data set

Run NM-TRAN Control Stream

```
c:\nm730\run>nmfe73 c:\ddexpand\iav\iav.ctl c:\ddexpand\iav\iav.out
Starting NMTRAN

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM    1

 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

 (WARNING  3) THERE MAY BE AN ERROR IN THE ABBREVIATED CODE. THE FOLLOWING
 ONE OR MORE RANDOM VARIABLES ARE DEFINED WITH "IF" STATEMENTS THAT DO NOT
 PROVIDE DEFINITIONS FOR BOTH THE "THEN" AND "ELSE" CASES. IF ALL
 CONDITIONS FAIL, THE VALUES OF THESE VARIABLES WILL BE ZERO.

   IPRED Y

 PROBLEM NO.:         1     SUBPROBLEM NO.:      1
```

Results: V vs. t



Erythropoietin Stimulation of RBCs DDEXPAND

Wojciech Krzyzanski, PhD

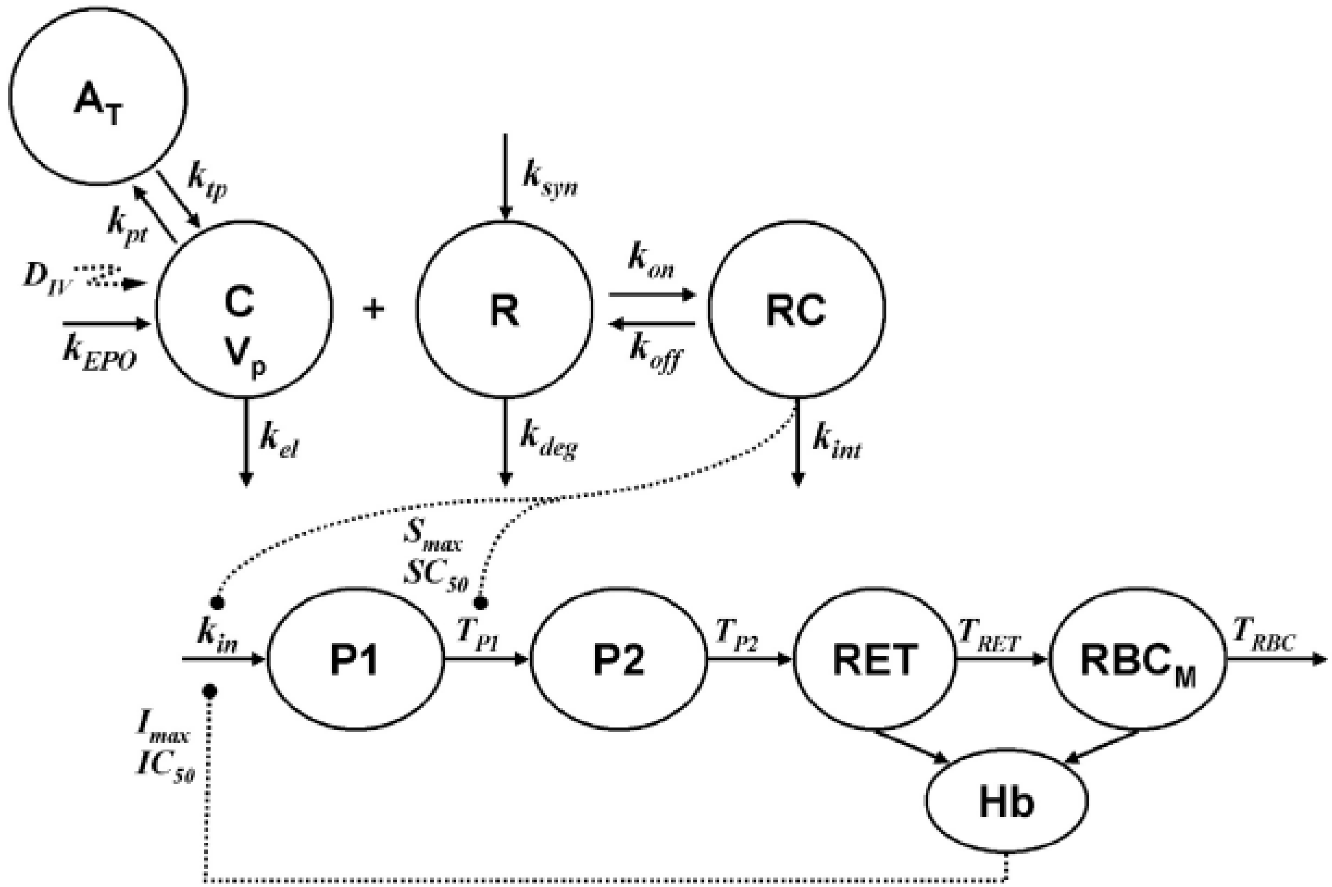
Bob Bauer, PhD

PAGE 2017 Budapest

Objective

- Implement in NM a PKPD model effect on RBC production in rats using the method of steps.
- Simulate time courses of rHuEPO , reticulocytes, and RBCs in individual animal following a bolus dose of 92.51 pmol/kg.

PKPD Model of EPO Effect on RET and RBC in Rats



Bauer and Krzyzanski, Computer Methods and Programs in Biomedicine. 111:715–734 (2013)

Model Equations

$$\frac{dC}{dt} = \frac{D_{IV}}{V_p}\delta(t) + k_{EPO} - k_{on}R\cdot C + k_{off}\cdot RC - \left(k_{el} + k_{pt}\right)\cdot C + k_{tp}A_T/V_p \qquad C(t) = C_0 \quad t \le 0$$

$$\frac{dA_T}{dt} = k_{pt}CV_p - k_{tp}A_T \qquad A_T(t) = \frac{k_{pt}C_0V_p}{k_{tp}} \quad t \le 0$$

$$\frac{dR}{dt} = k_{syn} - k_{on}RC + k_{off}RC - k_{deg}R \qquad R(t) = R_0 \quad t \le 0$$

$$\frac{dRC}{dt} = k_{on}RC - (k_{off} + k_{int})RC \qquad RC(t) = RC_0 \quad t \le 0$$

$$\frac{dRET}{dt} = k_{in}S(t - T_{P1} - T_{P2})S(t - T_{P2})I(t - T_{P1} - T_{P2}) - k_{in}S(t - T_{P1} - T_{P2} - T_{RET})S(t - T_{P2} - T_{RET})I(t - T_{P1} - T_{P2} - T_{RET}) \qquad RET(t) = RET_0 \quad t \le 0$$

$$\frac{dRBC_M}{dt} = k_{in}S(t - T_{P1} - T_{P2} - T_{RET})S(t - T_{P2} - T_{RET})I(t - T_{P1} - T_{P2} - T_{RET}) - k_{in}S(t - T_{P1} - T_{P2} - T_{RET} - T_{RBC})S(t - T_{P2} - T_{RET} - T_{RBC})I(t - T_{P1} - T_{P2} - T_{RET} - T_{RBC})$$

$$RBC_M(t) = RBC_0 - RET_0 \quad t \le 0$$

$$RBC(t) = RET(t) + RBC_M(t) \qquad Hb(t) = MCH\cdot RBC(t) \qquad \Delta Hb(t) = Hb(t) - Hb(0)$$

$$S(t) = \left(1 + \frac{S_{max}\cdot RC(t)}{SC_{50} + RC(t)}\right) \qquad I(t) = \left(1 - \frac{I_{max}\Delta Hb(t)}{IC_{50} + \Delta Hb(t)}\right)$$

Bauer and Krzyzanski, Computer Methods and Programs in Biomedicine. 111:715–734 (2013)

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Model Parameters

Parameter	Value	Reference
D_{IV} (pmol/kg)	92.51	[10]
V_p (ml/kg)	56.94	[10]
k_{el} (h^{-1})	0.2256	[10]
k_{pt} (h^{-1})	0.2092	[10]
k_{tp} (h^{-1})	0.1721	[10]
k_{int} (h^{-1})	0.8228	[10]
k_{deg} (h^{-1})	0.1133	[10]
k_{on} ($nM^{-1}h^{-1}$)	0.01132	[10]
k_{off} (h^{-1})	1.297	[10]
R_0 (pM)	63.2	[10]
C_0 (pM)	3.248	[13]
RBC_0 (10^6 cells/μl)	6.128	[14]
MCH (10^{-1} pg/cell)	2.0	[14]
T_{P1} (h)	42.97	[14]
T_{P2} (h)	3.02	[14]
T_{RET} (h)	72.33	[14]
T_{RBC} (h)	1440	[14]
S_{max}	3.48	[10]
SC_{50} (pM)	1.7	[10]
I_{max}	1.0	[10]
IC_{50} (g/dl)	1.79	[13]

33.6

Bauer and Krzyzanski, Computer Methods and Programs in Biomedicine. 111:715–734 (2013)

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Install ddexpand and finedata

```
c:\DDEXPAND\EPO>ifort ddexpand.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

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-out:ddexpand.exe
-subsystem:console
ddexpand.obj

c:\DDEXPAND\EPO>ifort finedata.f90
Intel(R) Visual Fortran Intel(R) 64 Compiler Professional for applications runni
ng on Intel(R) 64, Version 11.1    Build 20101201 Package ID: w_cprof_p_11.1.072

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-out:finedata.exe
-subsystem:console
finedata.obj

c:\DDEXPAND\EPO>_
```

ddexpand and finedata should be installed in a working directory where pre-control stream and data files are.

Pre-control Stream EPO.dde

```
; Pre-Control stream template
;TAU1=77.0
;TAU2=43.0
;TAU3=150.0
;TAU4=116.0
;TAU5=1590.0
;TAU6=1556.0
;TSTOP=200.0
$SIZES PC=245 DIMNEW=8000 DIMTMP=1000 PG=300 PAL=300 LNP4=8000
$PROB EPO
$ABBR DERIV2=NO DERIV2=NOCOMMON ; DERIV1=NO
$INPUT ID AMT TIME DV EVID MDV  CMT
$DATA C:\DDEXPAND\EPO\EPO.csv IGNORE=C
$SUBROUTINES ADVAN13  TOL=9
$MODEL NCOMPARTMENTS=6
```

Upper bounds for model delays

End time for simulation or last time point

$SIZES need to be manually adjusted to account for large MOS model dimension

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Pre-control Stream EPO.dde

```
; Pre-Control stream template
;TAU1=75.0
;TAU2=42.0
;TAU3=147.0
;TAU4=114.0
;TAU5=1587.0
;TAU6=1554.0
;TSTOP=200.0
$SIZES PC=245 DIMNEW=8000 DIMTMP=1000 PG=300 PAL=300 LNP4=8000
$PROB EPO
$ABBR DERIV2=NO DERIV2=NOCOMMON ; DERIV1=NO
$INPUT ID AMT TIME DV EVID MDV  CMT
$DATA C:\DDEXPAND\EPO\EPO.csv IGNORE=C
$SUBROUTINES ADVAN13  TOL=9
$MODEL NCOMPARTMENTS=6
```

Lower bounds for model delays

End time for simulation or last time point

$SIZES need to be manually adjusted to account for large MOS model dimension

Pre-control Stream EPO.dde

```
;TAUy
TAU1=TP1+TP2
TAU2=TP2
TAU3=TP1+TP2+TRET
TAU4=TP2+TRET
TAU5=TP1+TP2+TRET+TRBC
TAU6=TP2+TRET+TRBC
```

Definitions of model delays

```
; PASTS
 AP_4_1=RC0
 AP_4_2=RC0
 AP_4_3=RC0
 AP_4_4=RC0
 AP_4_5=RC0
 AP_4_6=RC0
 AP_5_1=RET0
 AP_5_3=RET0
 AP_5_5=RET0
 AP_6_1=RBCM0
 AP_6_3=RBCM0
 AP_6_5=RBCM0
```

Definitions of pasts for delayed states

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Pre-control Stream EPO.dde

```
X1 = 1+SMAX*AD_4_1/(SC50+AD_4_1)
X2 = 1+SMAX*AD_4_2/(SC50+AD_4_2)
X3 = 1+SMAX*AD_4_3/(SC50+AD_4_3)
X4 = 1+SMAX*AD_4_4/(SC50+AD_4_4)
X5 = 1+SMAX*AD_4_5/(SC50+AD_4_5)
X6 = 1+SMAX*AD_4_6/(SC50+AD_4_6)
X0 = 1+SMAX*RC0/(SC50+RC0)

I1 = 1-IMAX*(MCH*(AD_5_1+AD_6_1)-HB0)/(IC50+(MCH*(AD_5_1+AD_6_
1)-HB0))
I3 = 1-IMAX*(MCH*(AD_5_3+AD_6_3)-HB0)/(IC50+(MCH*(AD_5_3+AD_6_
3)-HB0))
I5 = 1-IMAX*(MCH*(AD_5_5+AD_6_5)-HB0)/(IC50+(MCH*(AD_5_5+AD_6_
5)-HB0))

 ; BASE EQUATIONS.

 DADT(1)=KEPO-KON*CC*VP*RR+KOFF*RC*VP-(KEL+KPT)*CC*VP+KTP*AT
 DADT(2)=KPT*CC*VP-KTP*AT
 DADT(3)=KSYN-KON*CC*RR+KOFF*RC-KDEG*RR
 DADT(4)=KON*CC*RR-(KOFF+KINT)*RC
 DADT(5)=KIN*X1*X2*I1-KIN*X3*X4*I3
 DADT(6)=KIN*X3*X4*I3-KIN*X5*X6*I5
```

Model equations

Run ddexpand

Pre-control stream

NM-TRAN control stream

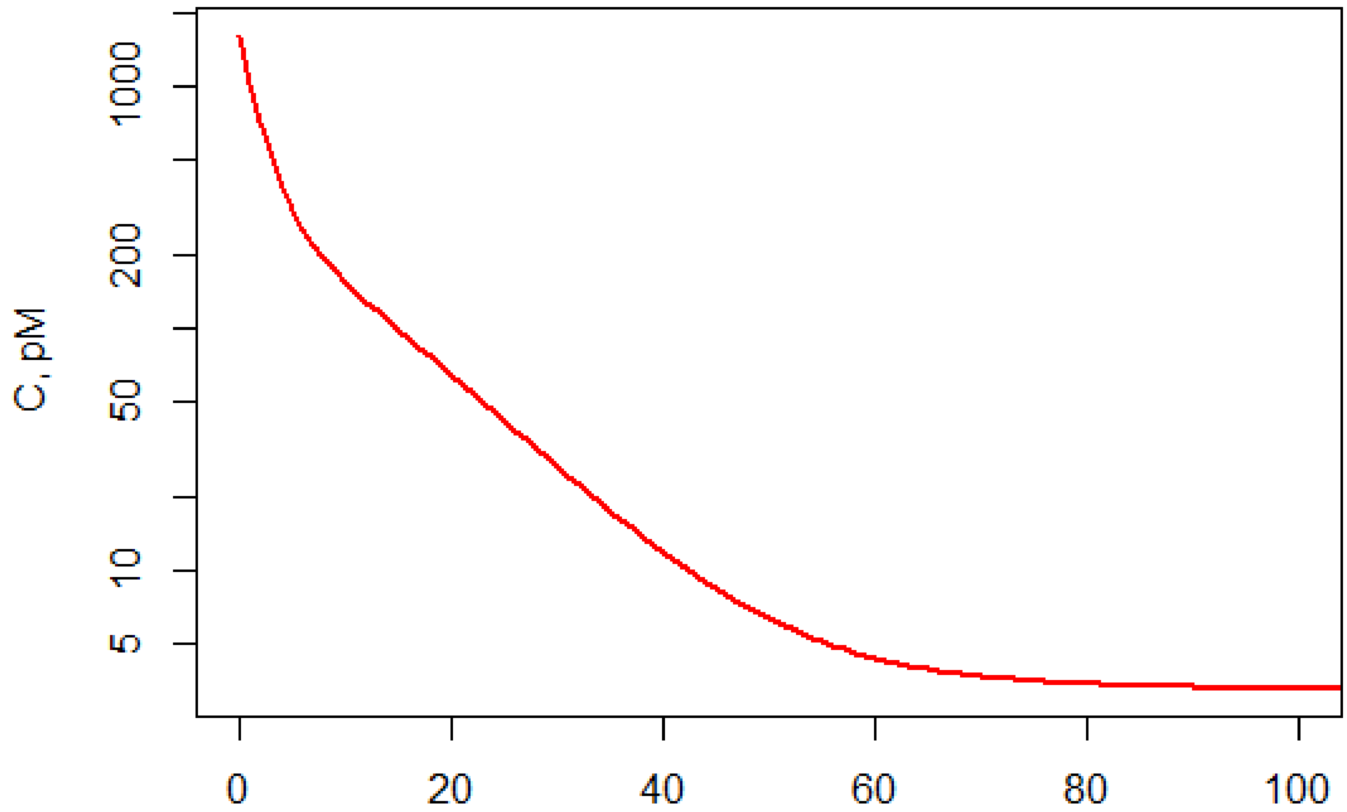
```
c:\DDEXPAND\EPO>ddexpand epo.dde epo.ctl
 finedata file is fine.ftl
 executing: finedata fine.ftl
 PROBLEM                1 : FILE C:\DDEXPAND\EPO\EPO_dde.csv
```

NM data set

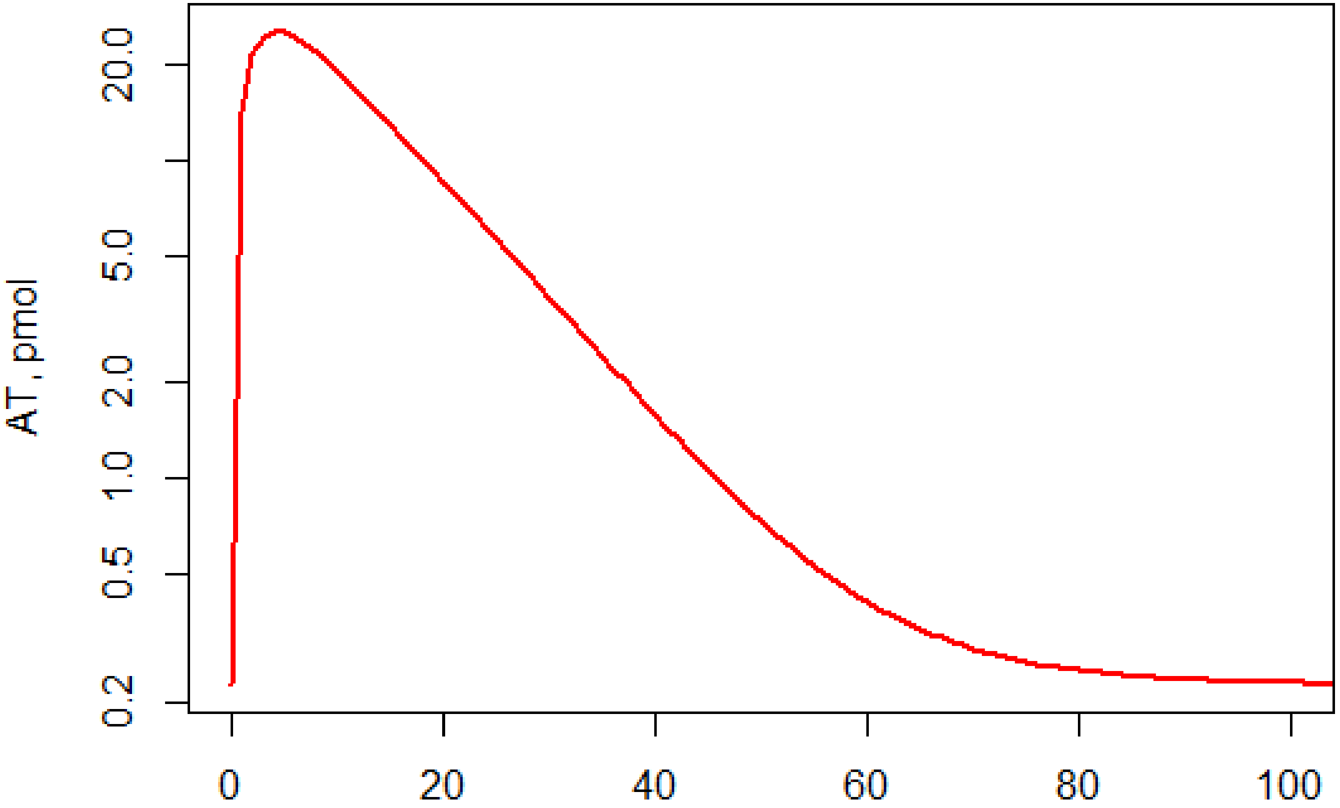
Run NM-TRAN Control Stream

```
c:\nm730\run>nmfe73 C:\DDEXPAND\EPO\EPO.ctl C:\DDEXPAND\EPO\EPO.out
Starting NMTRAN

 WARNINGS AND ERRORS (IF ANY) FOR PROBLEM    1

 (WARNING  2) NM-TRAN INFERS THAT THE DATA ARE POPULATION.

 (WARNING  3) THERE MAY BE AN ERROR IN THE ABBREVIATED CODE. THE FOLLOWING
 ONE OR MORE RANDOM VARIABLES ARE DEFINED WITH "IF" STATEMENTS THAT DO NOT
 PROVIDE DEFINITIONS FOR BOTH THE "THEN" AND "ELSE" CASES. IF ALL
 CONDITIONS FAIL, THE VALUES OF THESE VARIABLES WILL BE ZERO.

   IPRED


 (WARNING  45) $DES: VALUES HAVE NOT BEEN ASSIGNED TO ALL DADT VARIABLES.
 UNUSED COMPARTMENTS SHOULD BE OFF.
        1 file(s) copied.
Building NONMEM Executable

 PROBLEM NO.:         1     SUBPROBLEM NO.:      1
```

Results: C vs. t



Results: A_T vs. t



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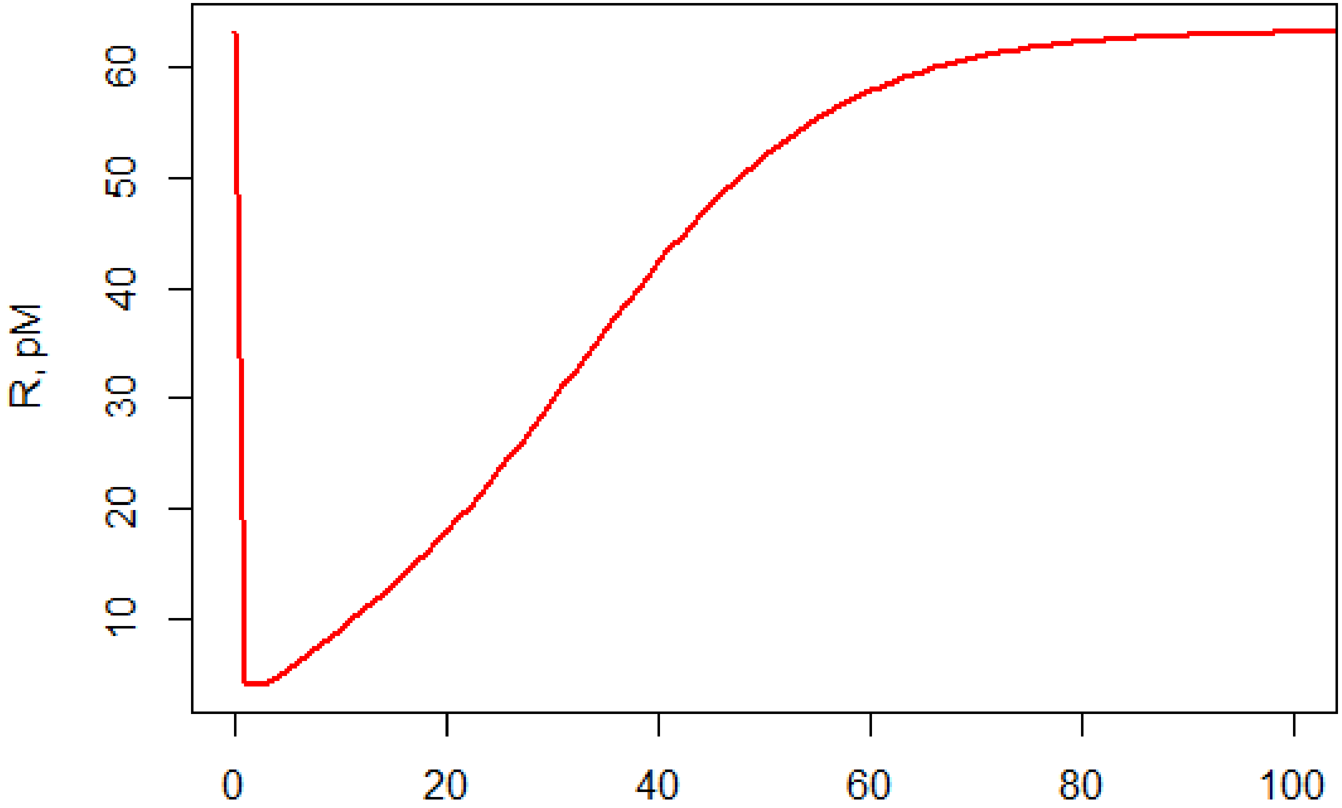
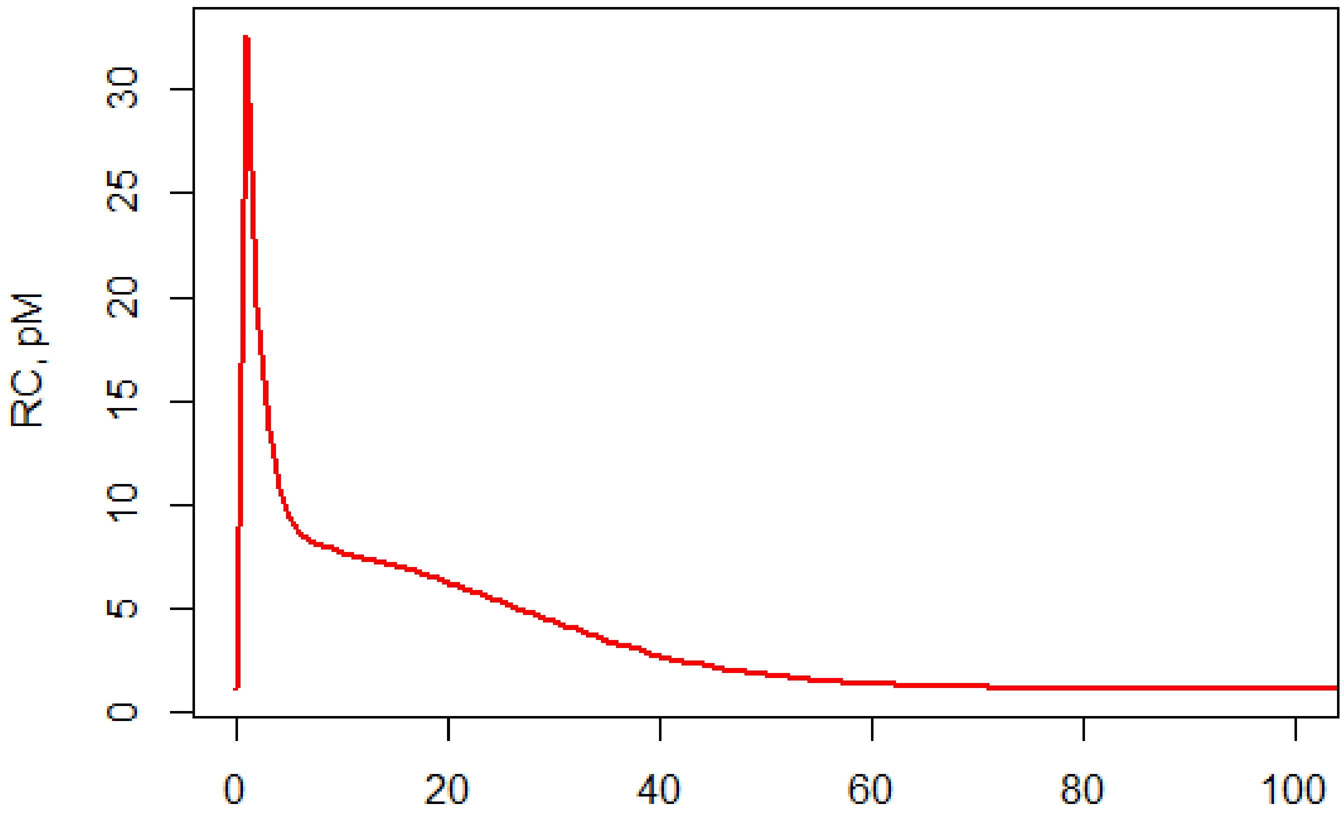
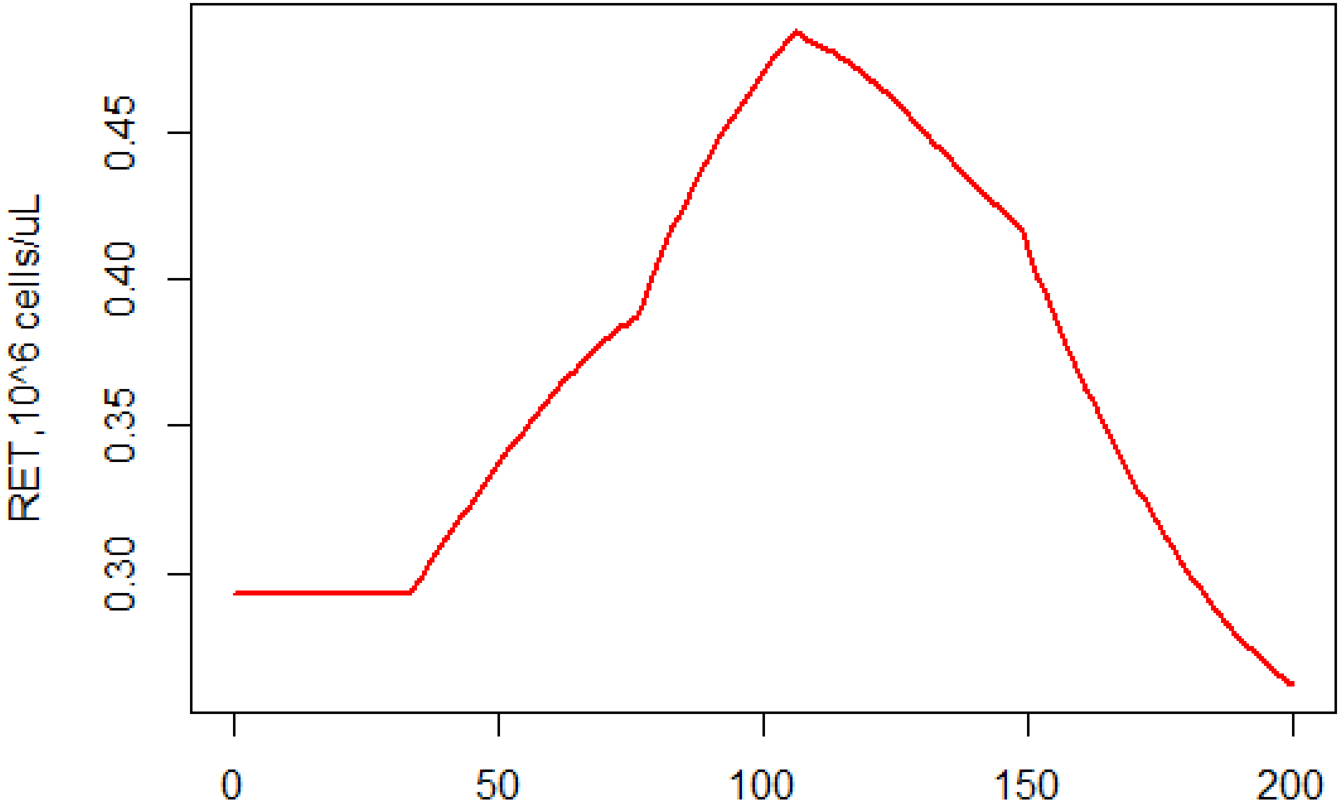
Results: R vs. t



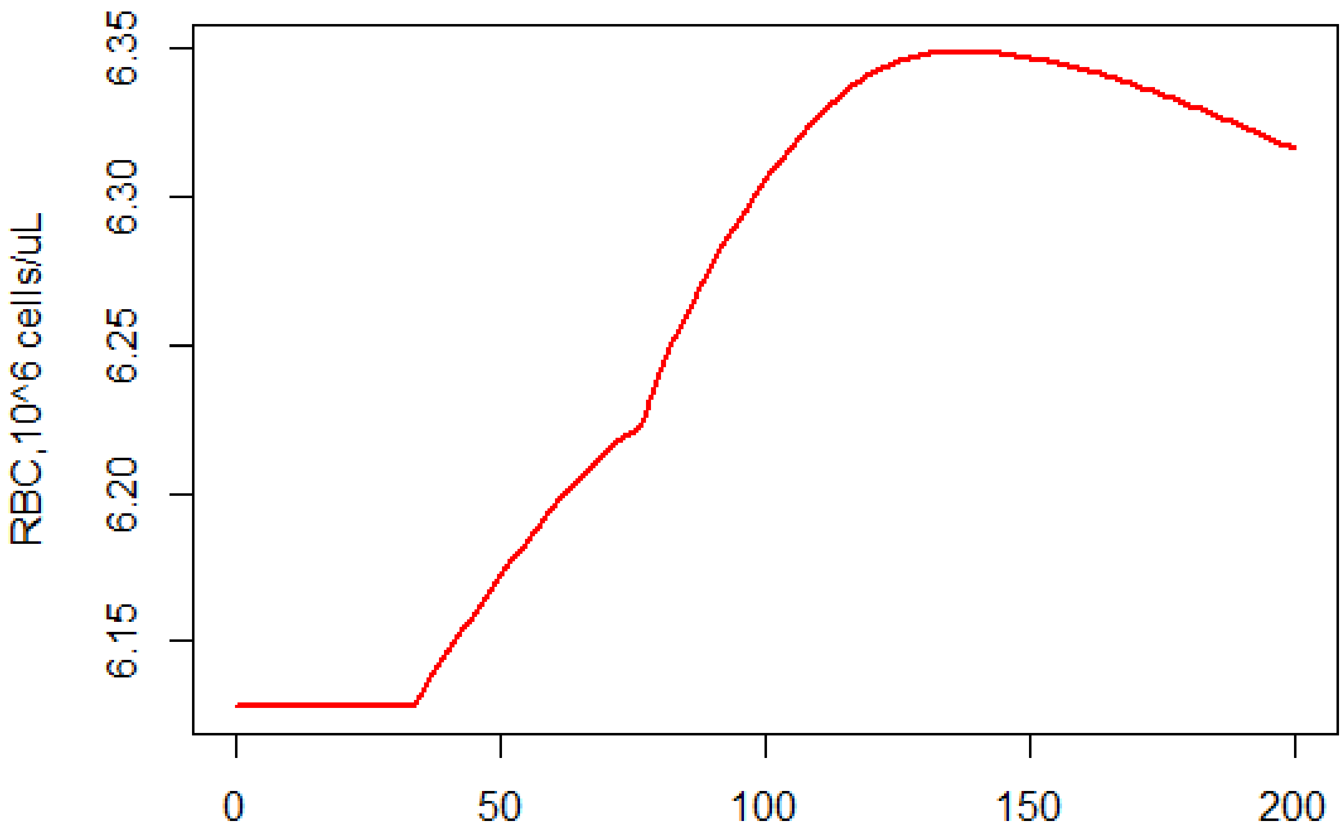
Results: RC vs. t



Results: RET vs. t



Results: RBC



Results: Hb vs. t