
Change-Point Models: Some Considerations in Implementation

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Definition

Change Point Model

- A change-point is a *model* which has some parameter which is discontinuous in time.
 - ◆ A change-point = the time at which another parameter changes values.
- Method described allows use in multiple-dose environment

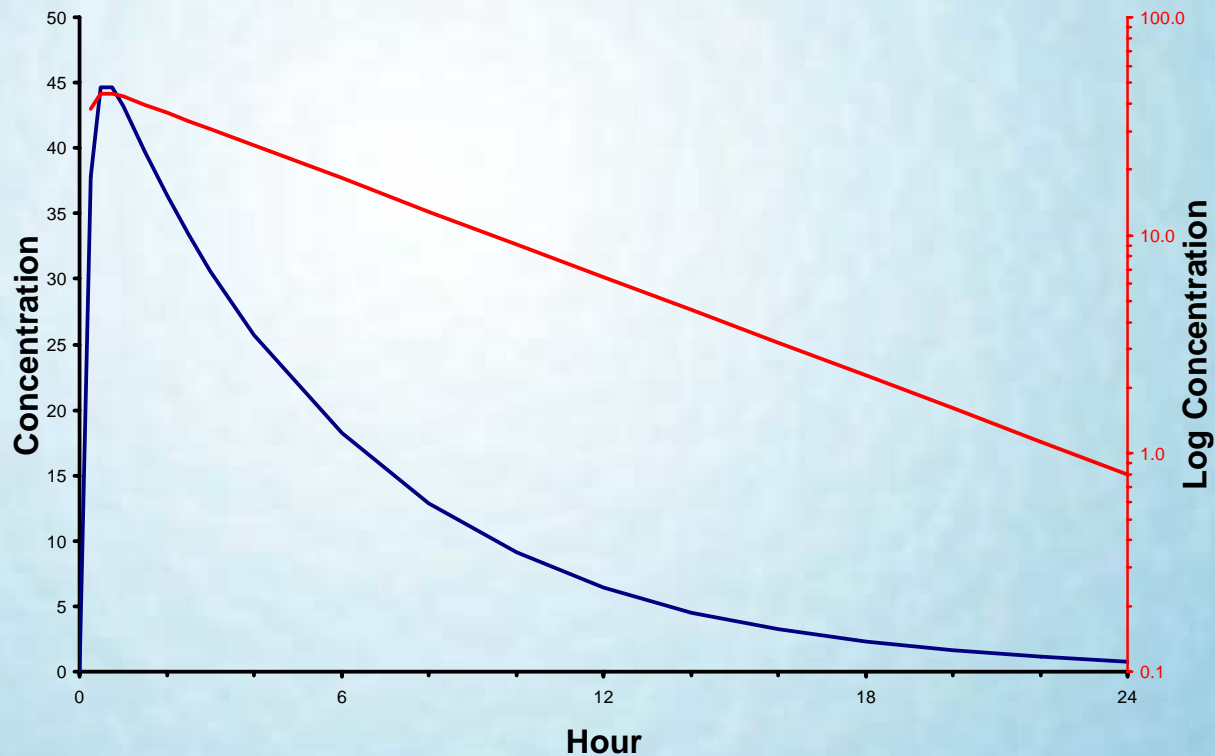
Examples of Potential Opportunities

- Internal
 - ◆ Extended-release formulation of a drug with different absorption characteristics in different regions of the GI tract
 - ◆ Gall bladder emptying
- External
 - ◆ Iontophoresis – current on versus off?
 - ◆ Heat/light activated release or clearance systems?

Example

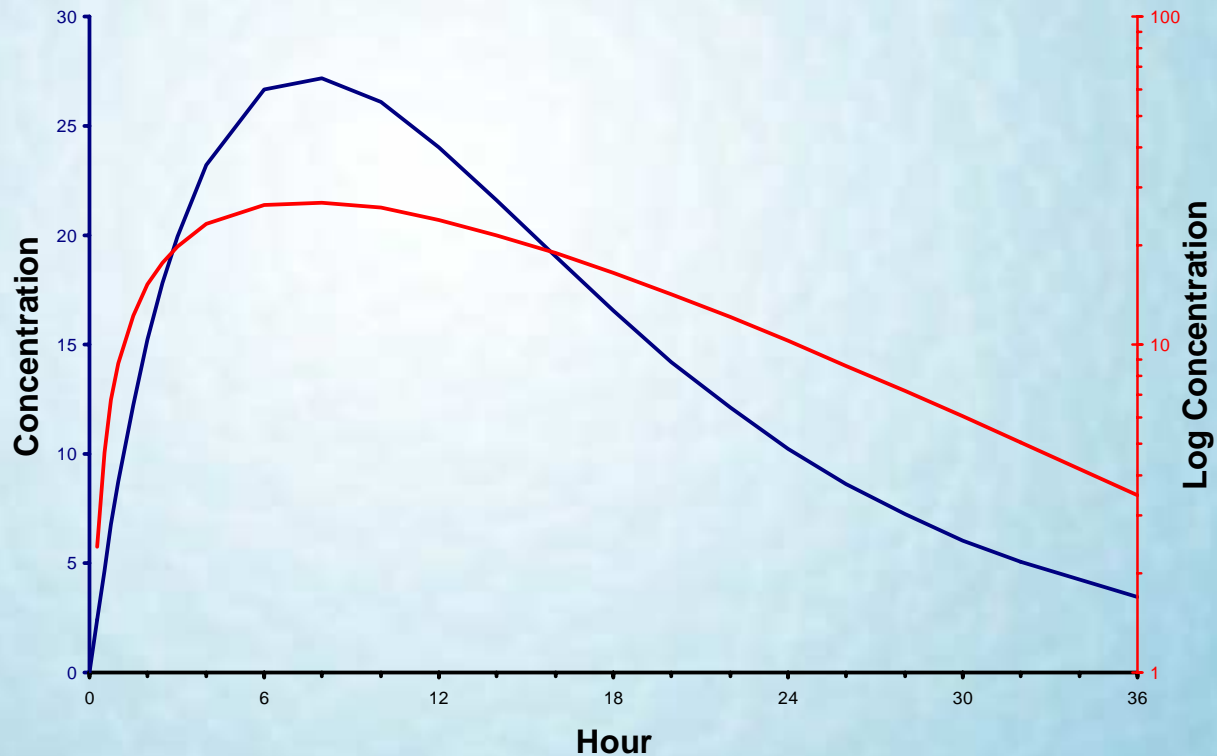
- Consider Drug X with:
 - ◆ High permeability in upper GI
 - ◆ Poor permeability in lower GI
 - ◆ Short half-life
 - ◆ Extended-Release Formulation solid oral dosage for with first-order release

PK Following a Single Dose of a Drug X Solution



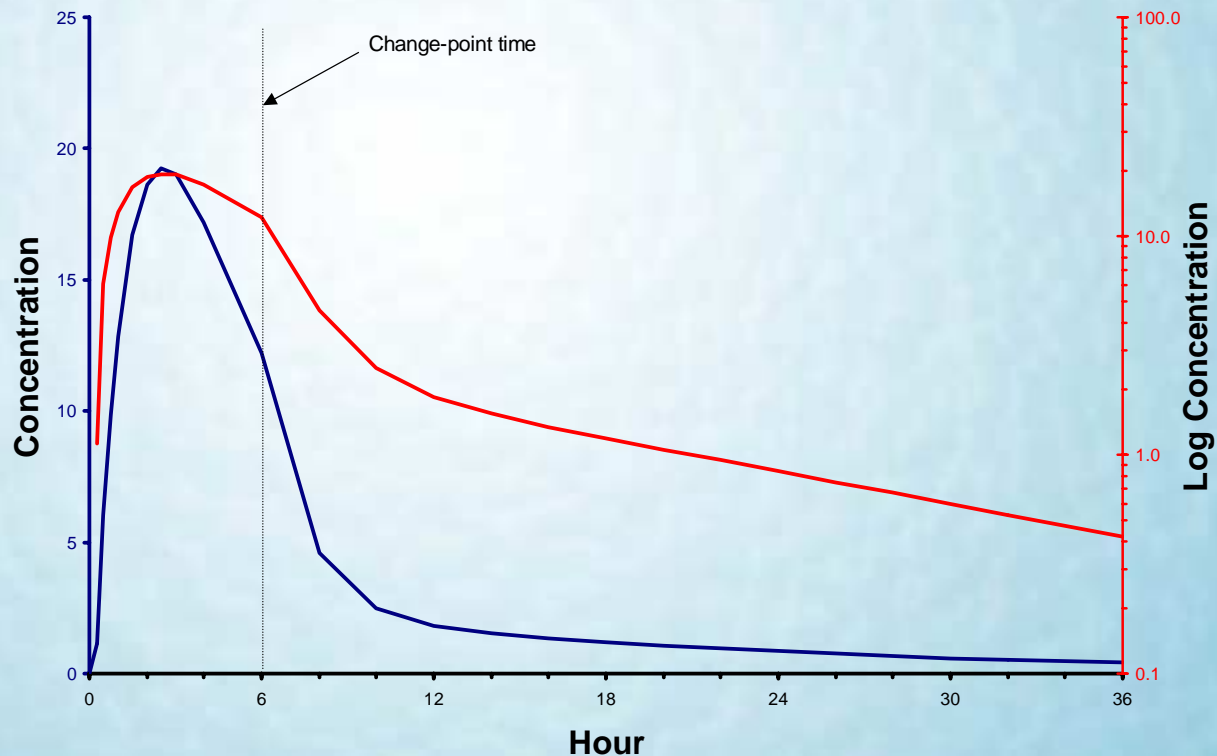
Rapid and complete absorption occurs in the upper GI following administration of a solution

PK Following a Single Dose of a Drug X ER Formulation



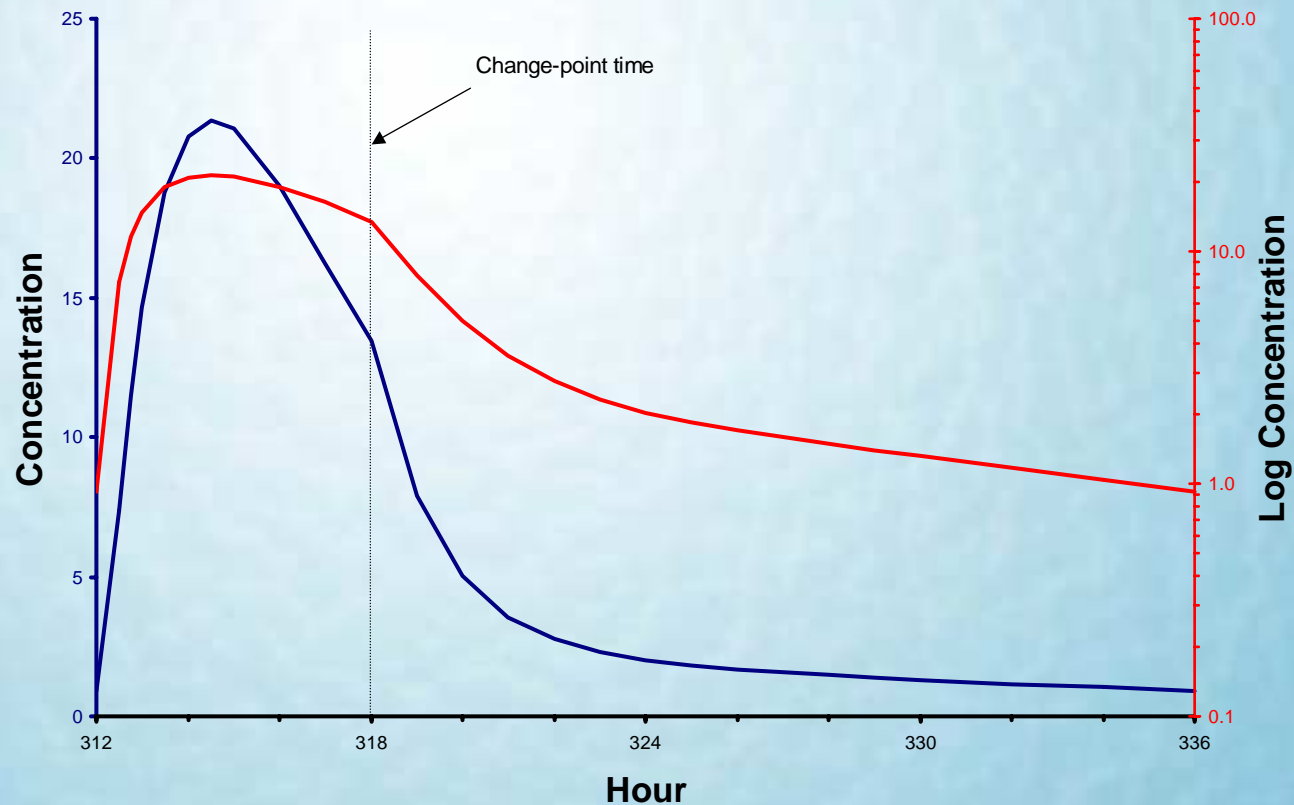
Expected Prolonged release of ER formulation

PK Following a Single Dose of a Drug X Extended Release Formulation



Rapid, but partial absorption occurs in the upper GI followed by slower, permeability limited absorption in the lower GI

PK Following Multiple-Dose Administration of a Drug X Extended-Release Formulation



Example

- Modeling the single or steady-state profile requires fitting both the rapid absorption and slower absorption processes
- Mechanistically the processes are sequential
- Expect KAF (fast K_a) first followed by KAS (slow K_a)

Implementation

- Define Compartmental Model
 - ◆ ADVAN 6
 - ◆ Include additional dosing compartment
 - ◆ Fix the value of the DE describing the change-point compartment to zero
 $DADT(x) = 0$
 - ◆ Change point is the lag time associated with this compartment

Implementation

- Define Dosing Records In Dataset

	ID	TIME	AMT	DV	CMT	MDV	EVID	II	ADDL
1	1	0	100	.	1	1	1	24	13
2	1	0	1	.	3	1	1	24	13
3	1	0.5	.	1.03	2	0	0	.	.
4	1	1.0	.	4.23	2	0	0	.	.
5			...						
6	2	0	100	.	1	1	1	24	13
7	2	0	1	.	3	1	1	24	13
8	2	0.5	.	1.21	2	0	0	.	.
9	2	1.0	.	5.57	2	0	0	.	.
10			...						

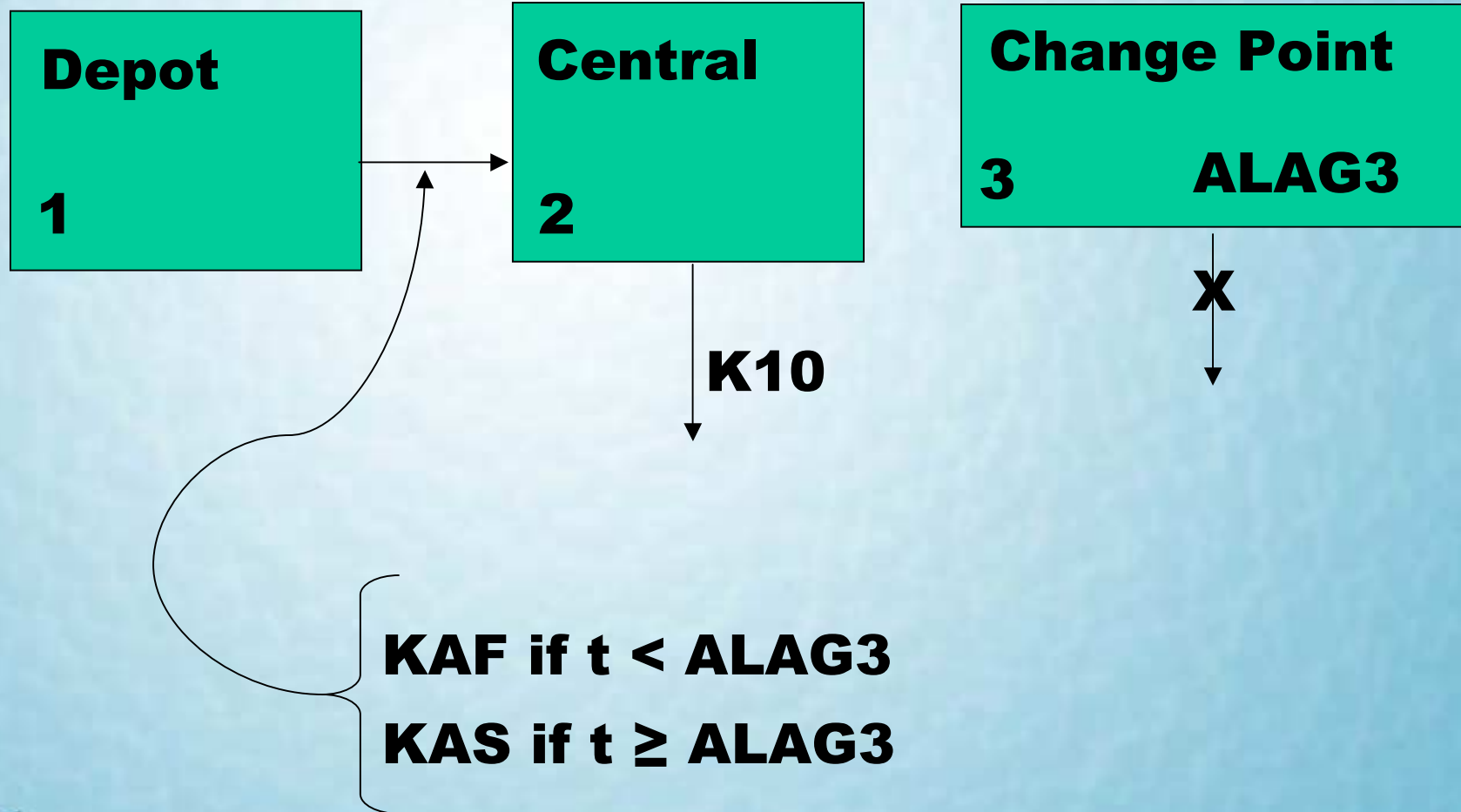
Implementation

- Define the Parameters (\$PK)
 - ◆ Include θ 's and η 's as appropriate
 - ◆ ALAG3 = Theta (1) – change-point
 - ◆ KAS = Theta (2)
 - ◆ KAF = Theta (3)
 - ◆ ALAG1 = lag time of absorption - depot
 - ◆ Plus other model parameters
 - ◆ Indicator variable (Z) used to switch between rate constants

Implementation

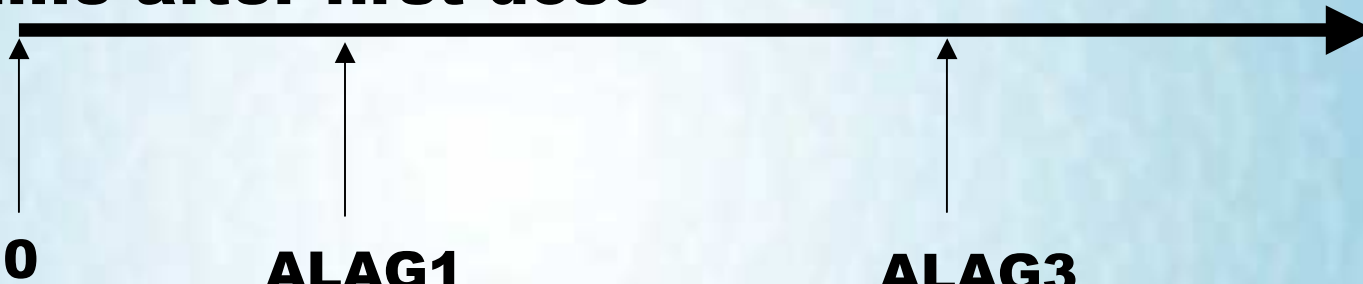
- dosrec(amt)
 - ◆ array with current values of the PK system (keeps up with additional and lagged doses)
 - ◆ = 0 prior to ALAG1
 - ◆ = 100 from ALAG1 to ALAG3
 - ◆ = 1 after ALAG3
- NEWIND (in our context)
 - ◆ =0; first record of dataset
 - ◆ =1; first record of subsequent individual
 - ◆ =2; subsequent record

Implementation



Implementation

Time after first dose



Lag time - Dose enters Depot compartment

Change point - Dose enters Compartment 3

	0	ALAG1	ALAG3
Dosrec (amt)	0	100	1
I1	1	1	0
I3	0	0	1
Z	0	0	1
Ka	KAF	KAF	KAS

Implementation

- Define Indicator Variables

\$PK

IF (NEWIND. LT.2) THEN

 I1 = 1

 I3 = 0

ENDIF

IF (I1.EQ.1) Z = 0

IF (I3.EQ.1) Z = 1

I1 = 0

I3 = 0

IF (DOSREC (AMT).NE.0.AND.DOSREC(AMT).NE.1) I1 = 1

IF (DOSREC (AMT).EQ.1) I3 =1

Implementation

- Define Differential Equations

\$DES

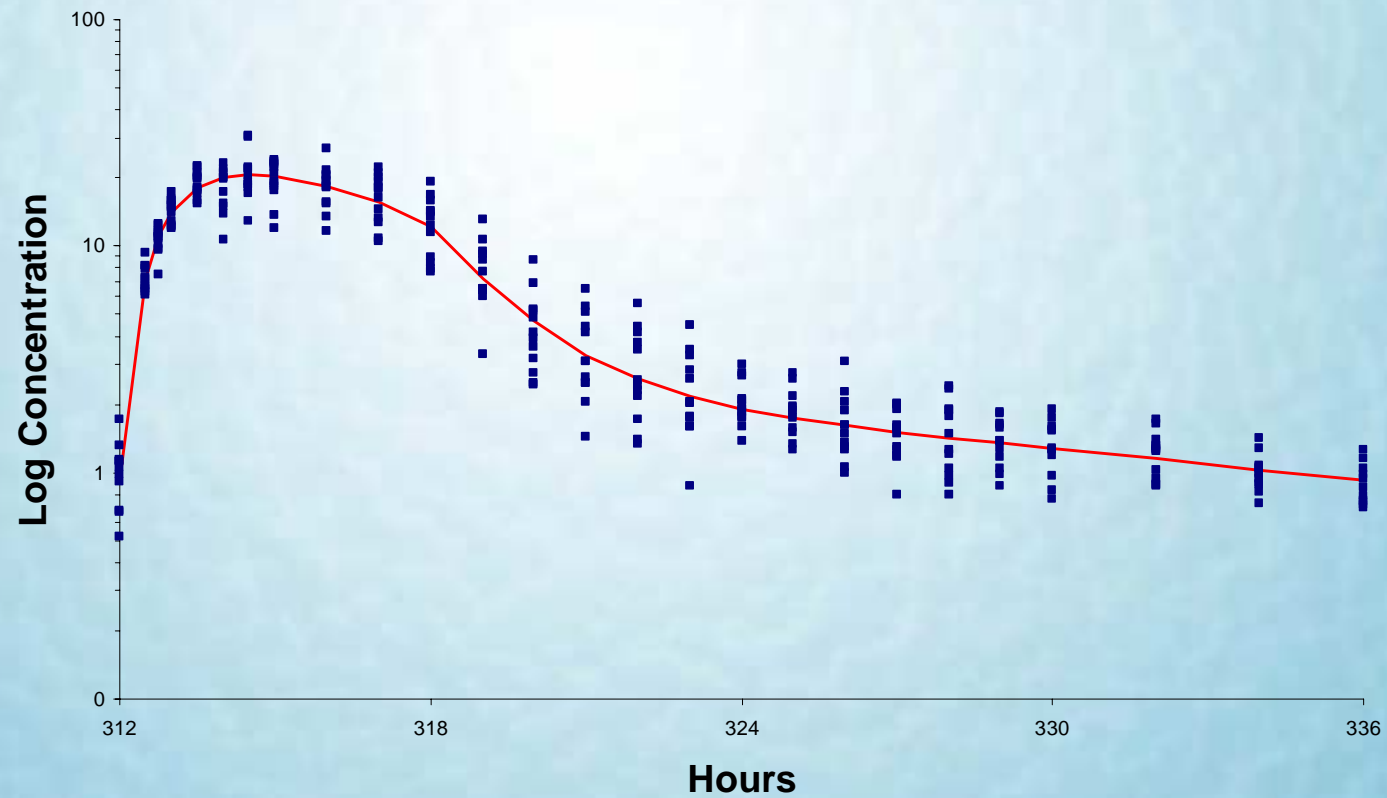
$$DADT(1) = (1-Z)*(-KAF)*A(1) + Z*(-KAS)*A(1)$$

$$DADT(2) = (1-Z)*(KAF)*A(1) + Z*(KAS)*A(1) - K10*A(2)$$

$$DADT(3) = 0$$

Implementation

Simulated Concentrations and Model Fit



Summary

- Change point models offer a method to model discontinuous processes with NONMEM[®] that lets the data estimate the time of change
- Change point models can model complex absorption processes in a population context



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Acknowledgements

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