



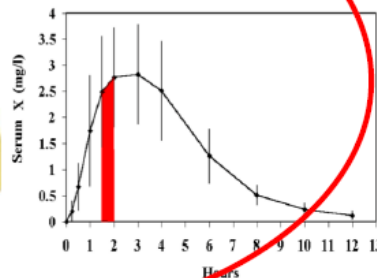
A Practical and Efficient Method of Calculating Actual Time Since Last Dose Data in PK Analysis

1. Introduction

Some PK Terminology

Pharmacokinetics

Referred to as "PK"
- in short: "What the body does to the drug". Often means "individual PK" in contrast to pop PK



ADME

Absorption,
Distribution,
Metabolism,
Excretion
– what happens to a drug in the body

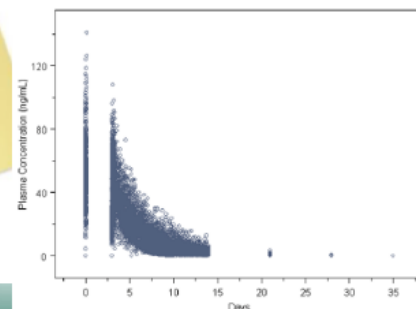
Pharmacodynamics

Referred to as "PD"
- in short: "What the drug does to the body"

PBPK

Physiologically-based PK, i.e. mechanistic models for ADME using mathematics to represent physiological components

Population PK
Analysis of data from a whole population using a unified model



1. Introduction

- **Pharmacokinetics (PK)**: is what the body does to the drug, it characterizes the time course of concentrations of the drug and/or the drug metabolite after drug administration in order to obtain information on drug disposition in the body.
- **4 phases of PK process** inside the body- **ADME**: Absorption, Distribution, Metabolism, Excretion.
- **Pharmacodynamics (PD)**: is what the drug does to the body, it studies the body's pharmacological response to a drug (measured in terms of AEs & Efficacy).
- **PKPD**: studies the dose-effect relationship.

2. EX & PC datasets

	EXSEQ	EXTRT	EXDOSE	EXDOSU	EXDOSFRM	EXROUTE	VISITNUM	VISIT	EPOCH	EXSTDTC	EXENDTDC	EXSTDY	EXENDY
1	1	PLACEBO	2000	mg		ORAL	20	DAY 1	SINGLE BLIND TREATMENT	2012-02-21T09:50	2012-02-21T09:50	1	1
2	2	PLACEBO	2000	mg		ORAL	20	DAY 1	SINGLE BLIND TREATMENT	2012-02-21T21:59	2012-02-21T21:59	1	1
3	3	PLACEBO	2000	mg		ORAL	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T10:10	2012-02-22T10:10	2	2
4	4	DRUGA	2000	mg		ORAL	40	DAY 3	SINGLE BLIND TREATMENT	2012-02-23T10:40	2012-02-23T10:40	3	3
5	5	DRUGA	2000	mg		ORAL	40	DAY 3	SINGLE BLIND TREATMENT	2012-02-23T22:39	2012-02-23T22:39	3	3
6	6	DRUGA	2000	mg		ORAL	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T10:50	2012-02-24T10:50	4	4

Figure 2. EX dataset

	PCSTRESN	PCSTRESU	PCSPEC	VISITNUM	VISIT	EPOCH	PCDTC	PCDY	PCTPT	PCTPTNUM	PCELTM	PCTPTREF
1		ug/L	PLASMA	20	DAY 1	SCREENING	2012-02-21T09:46	1	BASELINE	1		DOSE
2		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T09:57	2	PRE-DOSE	11		DOSE
3		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T11:15	2	1 HOUR POST DOSE	35	PT1H	DOSE
4		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T12:17	2	2 HOURS POST DOSE	55	PT2H	DOSE
5		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T13:15	2	3 HOURS POST DOSE	75	PT3H	DOSE
6		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T14:19	2	4 HOURS POST DOSE	95	PT4H	DOSE
7		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T16:15	2	6 HOURS POST DOSE	115	PT6H	DOSE
8		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T18:15	2	8 HOURS POST DOSE	135	PT8H	DOSE
9		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T20:15	2	10 HOURS POST DO...	155	PT10H	DOSE
10		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T22:15	2	12 HOURS POST DO...	175	PT12H	DOSE
11		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-23T10:25	3	24 HOURS POST DO...	195	PT24H	DOSE
12		ug/L	PLASMA	40	DAY 3	SINGLE BLIND TREATMENT	2012-02-23T10:25	3	BASELINE	1		DOSE
13	2633.5	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T10:45	4	PRE-DOSE	11		DOSE
14	2981.68	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T11:55	4	1 HOUR POST DOSE	35	PT1H	DOSE
15	3246.91	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T12:55	4	2 HOURS POST DOSE	55	PT2H	DOSE
16	3599.17	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T13:55	4	3 HOURS POST DOSE	75	PT3H	DOSE
17	3558.94	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T14:55	4	4 HOURS POST DOSE	95	PT4H	DOSE
18	3042.47	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T16:55	4	6 HOURS POST DOSE	115	PT6H	DOSE
19	2355.75	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T18:55	4	8 HOURS POST DOSE	135	PT8H	DOSE
20	2249.3	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T20:55	4	10 HOURS POST DO...	155	PT10H	DOSE
21	2123.6	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T22:55	4	12 HOURS POST DO...	175	PT12H	DOSE
22	1197.3	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-25T10:55	5	24 HOURS POST DO...	195	PT24H	DOSE

Figure 3. PC dataset.

2. ADPC dataset

	PCSEQ	AUNIT	AVISITN	AVISIT	ADY	ATPTREF	ATPTN	ATPT	AXLSDTM	ADTM	APRELTN	APRELTMU	ARELTN	ARELTMC	ARELTMU	AVAL	EXDOSE	APERADY	APERIOD	PARAMCD
1	13	ug/L	50	DAY 4	4	DOSE	11	PRE-DOSE	24FEB12:10:50:00	24FEB12:10:45:00			-0.0666...	-0h 4m	HRS	2633.5	2000	2	2	CONC
2	14	ug/L	50	DAY 4	4	DOSE	35	1 HOUR POST DOSE	24FEB12:10:50:00	24FEB12:11:55:00	1	HRS	1.1	1h 6m	HRS	2981.68	2000	2	2	CONC
3	15	ug/L	50	DAY 4	4	DOSE	55	2 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:12:55:00	2	HRS	2.1	2h 6m	HRS	3246.91	2000	2	2	CONC
4	16	ug/L	50	DAY 4	4	DOSE	75	3 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:13:55:00	3	HRS	3.1	3h 6m	HRS	3599.17	2000	2	2	CONC
5	17	ug/L	50	DAY 4	4	DOSE	95	4 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:14:55:00	4	HRS	4.1	4h 6m	HRS	3558.94	2000	2	2	CONC
6	18	ug/L	50	DAY 4	4	DOSE	115	6 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:16:55:00	6	HRS	6.1	6h 6m	HRS	3042.47	2000	2	2	CONC
7	19	ug/L	50	DAY 4	4	DOSE	135	8 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:18:55:00	8	HRS	8.1	8h 6m	HRS	2355.75	2000	2	2	CONC
8	20	ug/L	50	DAY 4	4	DOSE	155	10 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:20:55:00	10	HRS	10.1	10h 6m	HRS	2249.3	2000	2	2	CONC
9	21	ug/L	50	DAY 4	4	DOSE	175	12 HOURS POST DOSE	24FEB12:10:50:00	24FEB12:22:55:00	12	HRS	12.1	12h 6m	HRS	2123.6	2000	2	2	CONC
10	22	ug/L	50	DAY 4	5	DOSE	195	24 HOURS POST DOSE	24FEB12:10:50:00	25FEB12:10:55:00	24	HRS	24.1	24h 6m	HRS	1197.3	2000	3	2	CONC

Figure 4. ADPC dataset

	PCSTRESN	PCSTRESU	PCSPEC	VISITNUM	VISIT	EPOCH	PCDTC	PCDY	PCTPT	PCTPTNUM	PCELTM	PCTPTREF
1		ug/L	PLASMA	20	DAY 1	SCREENING	2012-02-21T09:46	1	BASELINE	1		DOSE
2		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T09:57	2	PRE-DOSE	11		DOSE
3		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T11:15	2	1 HOUR POST DOSE	35	PT1H	DOSE
4		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T12:17	2	2 HOURS POST DOSE	55	PT2H	DOSE
5		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T13:15	2	3 HOURS POST DOSE	75	PT3H	DOSE
6		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T14:19	2	4 HOURS POST DOSE	95	PT4H	DOSE
7		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T16:15	2	6 HOURS POST DOSE	115	PT6H	DOSE
8		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T18:15	2	8 HOURS POST DOSE	135	PT8H	DOSE
9		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T20:15	2	10 HOURS POST DO...	155	PT10H	DOSE
10		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-22T22:15	2	12 HOURS POST DO...	175	PT12H	DOSE
11		ug/L	PLASMA	30	DAY 2	SINGLE BLIND TREATMENT	2012-02-23T10:25	3	24 HOURS POST DO...	195	PT24H	DOSE
12		ug/L	PLASMA	40	DAY 3	SINGLE BLIND TREATMENT	2012-02-23T10:25	3	BASELINE	1		DOSE
13	2633.5	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T10:45	4	PRE-DOSE	11		DOSE
14	2981.68	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T11:55	4	1 HOUR POST DOSE	35	PT1H	DOSE
15	3246.91	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T12:55	4	2 HOURS POST DOSE	55	PT2H	DOSE
16	3599.17	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T13:55	4	3 HOURS POST DOSE	75	PT3H	DOSE
17	3558.94	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T14:55	4	4 HOURS POST DOSE	95	PT4H	DOSE
18	3042.47	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T16:55	4	6 HOURS POST DOSE	115	PT6H	DOSE
19	2355.75	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T18:55	4	8 HOURS POST DOSE	135	PT8H	DOSE
20	2249.3	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T20:55	4	10 HOURS POST DO...	155	PT10H	DOSE
21	2123.6	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-24T22:55	4	12 HOURS POST DO...	175	PT12H	DOSE
22	1197.3	ug/L	PLASMA	50	DAY 4	SINGLE BLIND TREATMENT	2012-02-25T10:55	5	24 HOURS POST DO...	195	PT24H	DOSE

Figure 3. PC dataset.

3. PKNCA: Non-Compartmental PK Analysis Dataset

3.1 Calculate ATSLD (Actual Time Since Last Dose)

Step 1: Create a common variable **DTM** in both ADPC and ADEX datasets.

```
data ex1(keep=usubjid exdtm dtm extrt exdose);  
set adex;  
exdtm=adtm;  
dtm = adtm;  
format exdtm dtm is8601dt.;  
run;
```

```
data pk1;  
set adpc;  
pkdtm=adtm;  
dtm = adtm;  
format pkdtm dtm is8601dt.;  
run;
```

3.1 Calculate **ATSLD** (Actual Time Since Last Dose)

Step 2: Set PK and EX together into **PKEX**. Using numeric flag **SRCFN** to differentiate data source whether data comes from EX of PK.

```
data pkex1;  
set ex(in=a) pk1(in=b) ;  
if a then srcfn = 1;  
if b then srcfn = 0;  
run;
```

Step 3: Sort PKEX by USUBJID, DTM, SRCFN.

```
proc sort data = pkex1;  
by usubjid dtm srcfn;  
run;
```

3.1 Calculate **ATSLD** (Actual Time Since Last Dose)

EXTRT	EXDOSE	EXDOSU	ADTM
DRUGA	2000	mg	2012-02-01T10:00:00
DRUGA	2000	mg	2012-02-02T10:00:00

EX1 (step1)

PCTPT	PCTPTNUM	ADTM
PRE-DOSE	10	2012-02-01T09:54:00
1 HR POST DOSE	20	2012-02-01T11:00:00
2 HR POST DOSE	30	2012-02-01T12:00:00
3HR POST DOSE	40	2012-02-01T13:00:00
PRE-DOSE	10	2012-02-02T09:54:00
1 HR POST DOSE	20	2012-02-02T11:00:00
2 HR POST DOSE	30	2012-02-02T12:00:00
3HR POST DOSE	40	2012-02-02T13:00:00

PK1 (step 1)

SRCFN	DTM	EXDTM	PKDTM
0	2012-02-01T09:54:00		2012-02-01T09:54:00
1	2012-02-01T10:00:00	2012-02-01T10:00:00	
0	2012-02-01T11:00:00		2012-02-01T11:00:00
0	2012-02-01T12:00:00		2012-02-01T12:00:00
0	2012-02-01T13:00:00		2012-02-01T13:00:00
0	2012-02-02T09:54:00		2012-02-02T09:54:00
1	2012-02-02T10:00:00	2012-02-02T10:00:00	
0	2012-02-02T11:00:00		2012-02-02T11:00:00
0	2012-02-02T12:00:00		2012-02-02T12:00:00
0	2012-02-02T13:00:00		2012-02-02T13:00:00

PKEX1
(step 3)

3.1 Calculate ATSLD (Actual Time Since Last Dose)

Step 4: Using **LAG()** function and **RETAIN** statement to populate LDosedtm for each post-dose PK record.

```
data pkex2;  
set pkex1;  
by usubjid dtm;  
  
format lagexdtm ldosedtm is8601dt. ;  
retain ldosedtm;  
lagexdtm = lag(exdtm);  
  
if first.usubjid then do;  
lagexdtm = .;  
ldosedtm = .;  
end;  
  
if lagexdtm ne . then ldosedtm = lagexdtm;  
run;
```

3.1 Calculate **ATSLD** (Actual Time Since Last Dose)

A	B	C	D	E	F
SRCFN	DTM	EXDTM	PKDTM	LAGEXDTM	LDOSEDTM
0	2012-02-01T09:54:00		2012-02-01T09:54:00		
1	2012-02-01T10:00:00	2012-02-01T10:00:00			
0	2012-02-01T11:00:00		2012-02-01T11:00:00	2012-02-01T10:00:00	2012-02-01T10:00:00
0	2012-02-01T12:00:00		2012-02-01T12:00:00		2012-02-01T10:00:00
0	2012-02-01T13:00:00		2012-02-01T13:00:00		2012-02-01T10:00:00
0	2012-02-02T09:54:00		2012-02-02T09:54:00		2012-02-01T10:00:00
1	2012-02-02T10:00:00	2012-02-02T10:00:00			2012-02-01T10:00:00
0	2012-02-02T11:00:00		2012-02-02T11:00:00	2012-02-02T10:00:00	2012-02-02T10:00:00
0	2012-02-02T12:00:00		2012-02-02T12:00:00		2012-02-02T10:00:00
0	2012-02-02T13:00:00		2012-02-02T13:00:00		2012-02-02T10:00:00

PKEX2 (step 4)

3.1 Calculate **ATSLD** (Actual Time Since Last Dose)

Step 5: Only keep PK records.

```
data pkex3;  
set pkex2;  
by usubjid dtm;  
where srcfn = 0;  
run;
```

Step 6: Calculate **ATSLD** for each post-dose PK record, set ATSLD = 0 for pre-dose record.

```
data pkex4;  
set pkex3;  
if n(pkdtm,ldosedtm) = 2 then atslld= (pkdtm - ldosedtm)/3600;  
if index(upcase(TPT), "PRE-DOSE") > 0 then ATSLD = 0;  
run;
```

3.1 Calculate **ATSLD** (Actual Time Since Last Dose)

SRCFN	PKDTM	LDOSDTM	ATSLD	PCTPT
0	2012-02-01T09:54:00		0	PRE-DOSE
0	2012-02-01T11:00:00	2012-02-01T10:00:00	1	1 HR POST DOSE
0	2012-02-01T12:00:00	2012-02-01T10:00:00	2	2 HR POST DOSE
0	2012-02-01T13:00:00	2012-02-01T10:00:00	3	3HR POST DOSE
0	2012-02-02T09:54:00	2012-02-01T10:00:00	0	PRE-DOSE
0	2012-02-02T11:00:00	2012-02-02T10:00:00	1	1 HR POST DOSE
0	2012-02-02T12:00:00	2012-02-02T10:00:00	2	2 HR POST DOSE
0	2012-02-02T13:00:00	2012-02-02T10:00:00	3	3HR POST DOSE

PKEX4 (step 6)

3.2 Calculate **ATSFD** (Actual Time Since First Dose)

Step 1: keep only **first dose record** for each subject in EX dataset.

```
data ex2(keep=usubjid fdosedtm);  
set ex1;  
by usubjid dtm;  
if first.usubjid;  
fdosedtm = exdtm;  
format fdosedtm is8601dt.;  
run;
```

Step 2: merge EX2 with PKEX4 by USUBJID, now each PK record has FDOSED TM.

```
data pkex5;  
merge pkex4(in=a) ex2(in=b);  
by usubjid;  
if a;  
run;
```

3.2 Calculate **ATSFD** (Actual Time Since First Dose)

Step 3: calculating **ATSFD**, set $ATSFD = 0$ for pre-dose record.

```
data pkex6;  
set pkex5;  
if n(pkdtm,fdosedtm) = 2 then atsfd = (pkdtm - fldosedtm) / 3600;  
If first.usubjid & index(upcase(TPT), "PRE-DOSE") > 0 then  $ATSFD = 0$ ;  
run;
```

3.2 Calculate **ATSFD** (Actual Time Since First Dose)

SRCFN	PKDTM	FDOSEDTM	ATSFD	PCTPT
0	2012-02-01T09:54:00	2012-02-01T10:00:00	0	PRE-DOSE
0	2012-02-01T11:00:00	2012-02-01T10:00:00	1	1 HR POST DOSE
0	2012-02-01T12:00:00	2012-02-01T10:00:00	2	2 HR POST DOSE
0	2012-02-01T13:00:00	2012-02-01T10:00:00	3	3HR POST DOSE
0	2012-02-02T09:54:00	2012-02-01T10:00:00	23.9	PRE-DOSE
0	2012-02-02T11:00:00	2012-02-01T10:00:00	25	1 HR POST DOSE
0	2012-02-02T12:00:00	2012-02-01T10:00:00	26	2 HR POST DOSE
0	2012-02-02T13:00:00	2012-02-01T10:00:00	27	3HR POST DOSE

PKEX6 (step 3)

3.3 ATSF_D vs. ATSL_D

In general, ATSF_D should only be set to 0 for the pre-dose associated with the very first dose of the drug associated with the analyte (i.e. parent drug or its metabolite) of interest, across all periods. ATSF_D should also include the time spent during the washout between periods.

NTSF_D, however, should be calculated for each period, with the reference day corresponding to the day that the first dose of the drug of interest was given.

So basically, NTSF_D is used to keep track of the time since the first dose of the drug given within a period (note, this isn't always Day 1). While ATSF_D is keeping track of the real time since the subject took the very first dose of the drug of interest (which includes the washout periods).



Thanks!

Questions?

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