Pmetrics Data and Models

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General Workflow

1. In R/Rstudio, use `setwd()` to ensure that your current working directory is the project /src folder
2. Use PM_data$new() to create a PM_data object in memory
3. Use PM_model$new() to create a PM_model object in memory
   - Source can be a file or a list in R
4. Combine the data and model with PM_fit$new()
5. Execute $run on the PM_fit object

Pmetrics Data Files

- One row, one event (dose or observation)
- All subjects continuous
- Column names are fixed
- Use “.” as placeholders in empty cells

Making Data files

- Manually, in Excel or another spreadsheet program
- Exporting from some other program and then manipulating in Excel or preferably, with R scripts
- Converting from NONMEM data files using `NM2PM()`
- Converting from old USC*PACK .wrk format using `PMwrk2csv()`
- Converting from old USC*PACK .mb format using `PMmb2csv()`

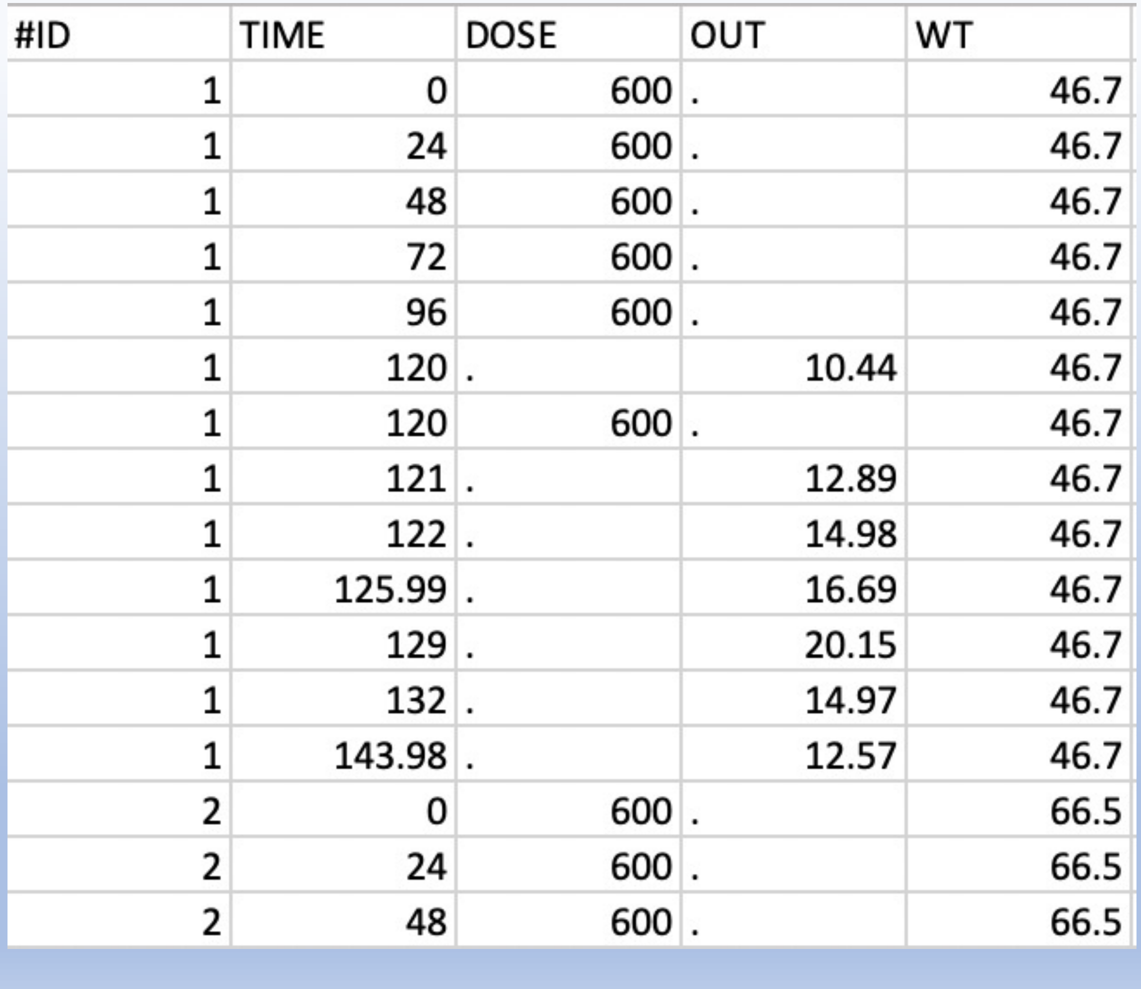
Why I like R scripts

- I never touch the original data file
- If the source data file is updated, I simply re-run the R script
- Can build in validation
- Useful R commands: `read.csv()`, `read.table()`, `read.xlsx()` [xlsx package], `read.spss()`, `read.ssd()`, `read.xport()`

More useful commands

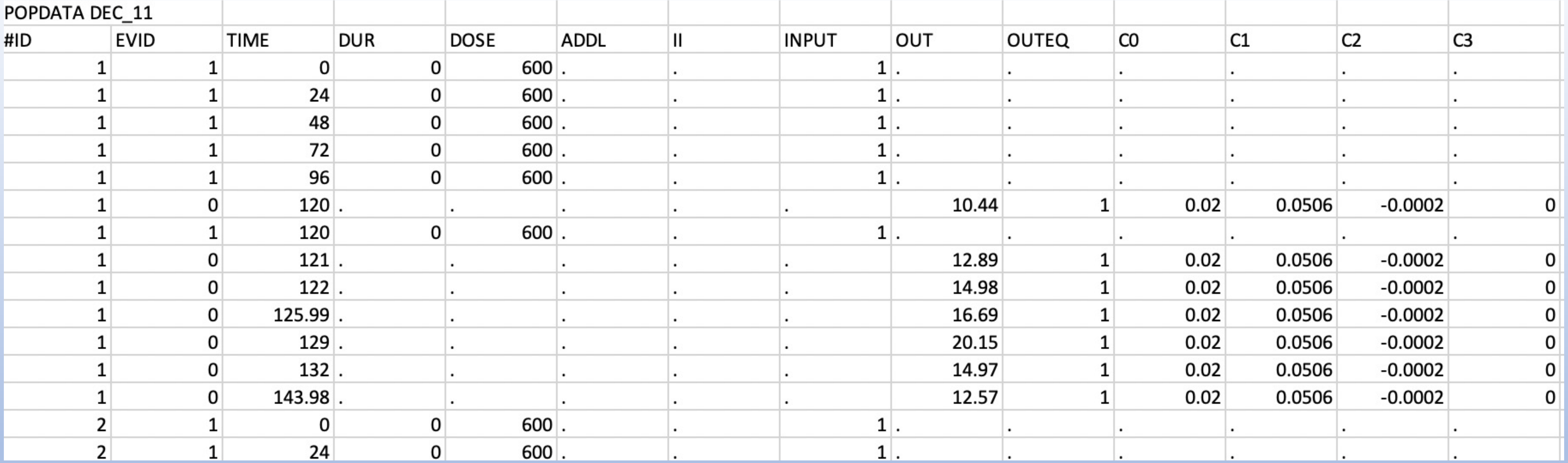
- `PM_data$new(file)` - read Pmetrics data file into R
- `PM_data$write(file)` - write a PM_data object to a file
- Both automatically call `PMcheck()` to check errors in the data and fix if possible, with report

Minimal format



#ID	TIME	DOSE	OUT	WT
1	0	600	.	46.7
1	24	600	.	46.7
1	48	600	.	46.7
1	72	600	.	46.7
1	96	600	.	46.7
1	120	.	10.44	46.7
1	120	600	.	46.7
1	121	.	12.89	46.7
1	122	.	14.98	46.7
1	125.99	.	16.69	46.7
1	129	.	20.15	46.7
1	132	.	14.97	46.7
1	143.98	.	12.57	46.7
2	0	600	.	66.5
2	24	600	.	66.5
2	48	600	.	66.5

Standardized format



POPDATA DEC_11

#ID	EVID	TIME	DUR	DOSE	ADDL	II	INPUT	OUT	OUTEQ	C0	C1	C2	C3
1	1	0	0	600	.	.	1	.	.	.	.	.	.
1	1	24	0	600	.	.	1	.	.	.	.	.	.
1	1	48	0	600	.	.	1	.	.	.	.	.	.
1	1	72	0	600	.	.	1	.	.	.	.	.	.
1	1	96	0	600	.	.	1	.	.	.	.	.	.
1	0	120	.	.	.	.	.	10.44	1	0.02	0.0506	-0.0002	0
1	1	120	0	600	.	.	1	.	.	.	.	.	.
1	0	121	.	.	.	.	.	12.89	1	0.02	0.0506	-0.0002	0
1	0	122	.	.	.	.	.	14.98	1	0.02	0.0506	-0.0002	0
1	0	125.99	.	.	.	.	.	16.69	1	0.02	0.0506	-0.0002	0
1	0	129	.	.	.	.	.	20.15	1	0.02	0.0506	-0.0002	0
1	0	132	.	.	.	.	.	14.97	1	0.02	0.0506	-0.0002	0
1	0	143.98	.	.	.	.	.	12.57	1	0.02	0.0506	-0.0002	0
2	1	0	0	600	.	.	1	.	.	.	.	.	.
2	1	24	0	600	.	.	1	.	.	.	.	.	.

#ID - mandatory

- Subject ID
- alphanumeric
- ≤11 characters
- ≤800 subjects / run

#EVID - optional

- EVent ID
- 0 = observation, i.e. concentration
- 1 = input, i.e. dose
- 2,3 are unused
- 4 = reset, all compartments are reset to 0, and time counter to 0, generating a new “block” in many Pmetrics objects

TIME - mandatory

- Elapsed decimal time, e.g. 1.5 or 2.34 or clock time e.g. 13:00.
  - If clock time, DATE must be present
- All subjects must start with TIME=0 if no DATE column
- All rows should have TIME entry
- Events for a subject should be sorted by TIME

DATE - optional

- If TIME is clock time, DATE must be present
- DATE and TIME formats are coerced if possible to YYYY-MM-DD and HH:MM by PM_data$new()

DUR - optional

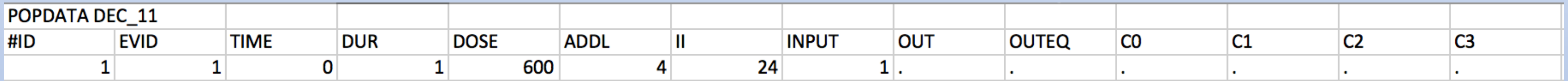
- DURation of an infusion for a dose (EVID=1) in decimal time, e.g. 2 or 1.5
- Only required for doses
- 0 = a bolus dose, given to compartment defined in model file
- >0 = infusion, given to compartment defined in model file
- Assumed to be 0 for all doses if missing

DOSE - mandatory

- What more can I say?

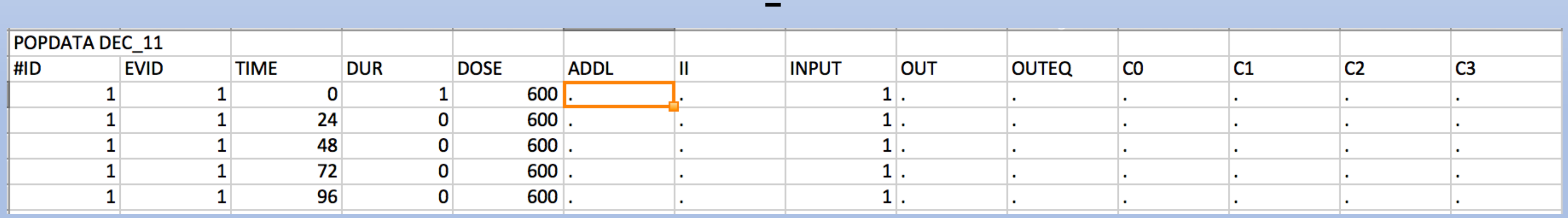
ADDL - optional

- For a given dose line, this is the number of ADDitionaL doses to be given at inter-dose interval (II)
- This shortcut is optional for EVID=1 and ignored for everything else



POPDATA DEC_11													
#ID	EVID	TIME	DUR	DOSE	ADDL	II	INPUT	OUT	OUTEQ	C0	C1	C2	C3
1	1	0	1	600	4	24	1	.	.	.	.	.	.

=



POPDATA DEC_11													
#ID	EVID	TIME	DUR	DOSE	ADDL	II	INPUT	OUT	OUTEQ	C0	C1	C2	C3
1	1	0	1	600	.	.	1	.	.	.	.	.	.
1	1	24	0	600	.	.	1	.	.	.	.	.	.
1	1	48	0	600	.	.	1	.	.	.	.	.	.
1	1	72	0	600	.	.	1	.	.	.	.	.	.
1	1	96	0	600	.	.	1	.	.	.	.	.	.

Additional ADDL

- Setting ADDL=-1 on the first dose at TIME=0, or a dose with EVID=4 simulates steady state conditions
- All compartments will be in a condition at the end of a steady state dosing interval of II

II - optional

- Interdose Interval is the interval in TIME units between ADDL doses
- Ignored if EVID ≠ 1 or ADDL is missing

INPUT - optional

- Defines the input, e.g. drug, number
- Only required for EVID=1
- Typically is 1 but could be >1 if multiple drugs are modeled simultaneously
- Assumed to be 1 if missing

OUT - mandatory

- OUTput, observation, concentration, etc.
- Only required for observations
- If an observation is missing, use -99, not “.”

OUTEQ - optional

- Output number for a corresponding OUT value
- Only required for observations
- Compartment that contains the output is defined in the model file
- The number is the number of the output equation in the model file
- Assumed to be 1 if missing

C0, C1, C2, C3 - optional

- Assay error coefficients
- Assay Error Polynomial (AEP): SD = $C_0[\text{out}]^0 + C_1[\text{out}]^1 + C_2[\text{out}]^2 + C_3[\text{out}]^3$
- If missing, model file values are used

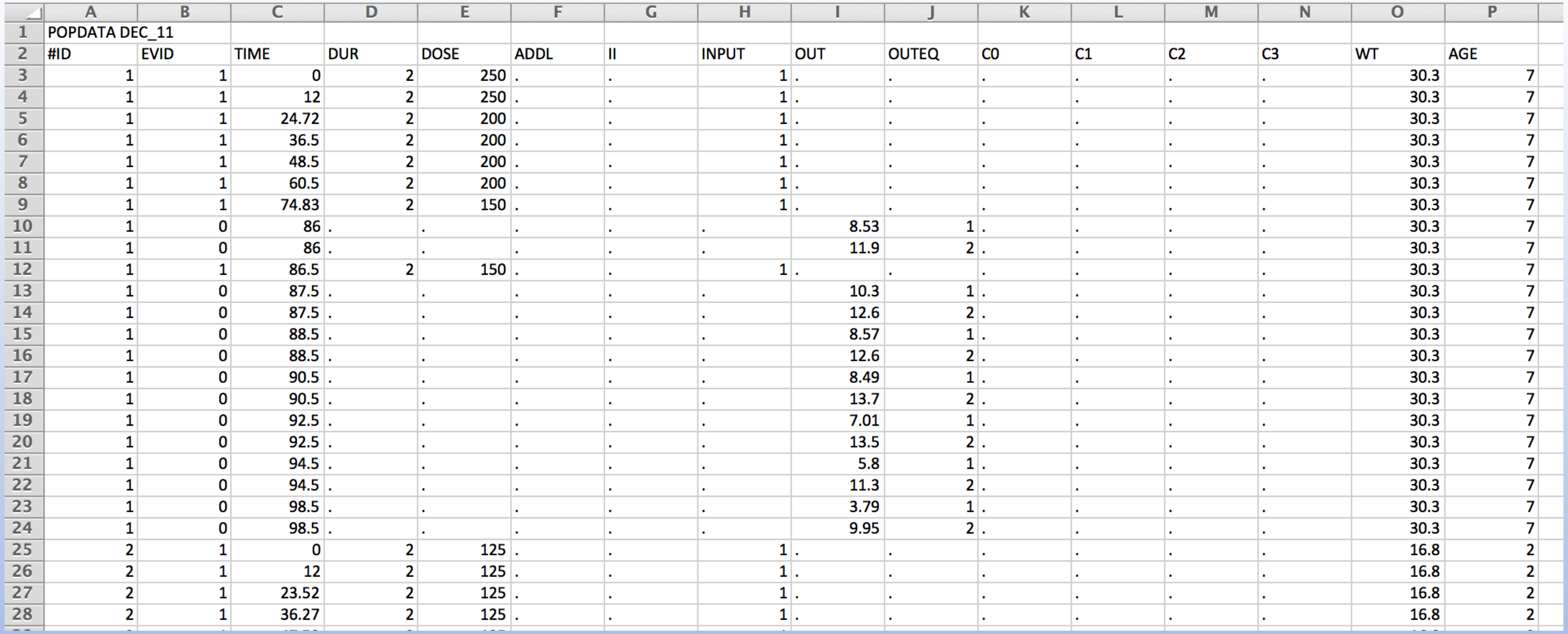
Covariates - optional

- Any column after C3 is a covariate
- Must be numeric
- Must have a value for every covariate at first time event for each subject, e.g. TIME=0 if DATE missing
- May have missing values after that; by default these missing values are linearly interpolated between bounding non-missing values

Covariates

- Covariates are applied at the time of doses
- Covariate values on observations are ignored
- To enter a changed covariate at a time other than a dose, use an dose record, with 0 DUR, 0 DOSE and the new covariate value

Example



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	POPDATA DEC_11															
2	#ID	EVID	TIME	DUR	DOSE	ADDL	II	INPUT	OUT	OUTEQ	C0	C1	C2	C3	WT	AGE
3	1	1	0	2	250	.	.	1	.	.	.	.	.	.	30.3	7
4	1	1	12	2	250	.	.	1	.	.	.	.	.	.	30.3	7
5	1	1	24.72	2	200	.	.	1	.	.	.	.	.	.	30.3	7
6	1	1	36.5	2	200	.	.	1	.	.	.	.	.	.	30.3	7
7	1	1	48.5	2	200	.	.	1	.	.	.	.	.	.	30.3	7
8	1	1	60.5	2	200	.	.	1	.	.	.	.	.	.	30.3	7
9	1	1	74.83	2	150	.	.	1	.	.	.	.	.	.	30.3	7
10	1	0	86	.	.	.	.	.	8.53	1	.	.	.	.	30.3	7
11	1	0	86	.	.	.	.	.	11.9	2	.	.	.	.	30.3	7
12	1	1	86.5	2	150	.	.	1	.	.	.	.	.	.	30.3	7
13	1	0	87.5	.	.	.	.	.	10.3	1	.	.	.	.	30.3	7
14	1	0	87.5	.	.	.	.	.	12.6	2	.	.	.	.	30.3	7
15	1	0	88.5	.	.	.	.	.	8.57	1	.	.	.	.	30.3	7
16	1	0	88.5	.	.	.	.	.	12.6	2	.	.	.	.	30.3	7
17	1	0	90.5	.	.	.	.	.	8.49	1	.	.	.	.	30.3	7
18	1	0	90.5	.	.	.	.	.	13.7	2	.	.	.	.	30.3	7
19	1	0	92.5	.	.	.	.	.	7.01	1	.	.	.	.	30.3	7
20	1	0	92.5	.	.	.	.	.	13.5	2	.	.	.	.	30.3	7
21	1	0	94.5	.	.	.	.	.	5.8	1	.	.	.	.	30.3	7
22	1	0	94.5	.	.	.	.	.	11.3	2	.	.	.	.	30.3	7
23	1	0	98.5	.	.	.	.	.	3.79	1	.	.	.	.	30.3	7
24	1	0	98.5	.	.	.	.	.	9.95	2	.	.	.	.	30.3	7
25	2	1	0	2	125	.	.	1	.	.	.	.	.	.	16.8	2
26	2	1	12	2	125	.	.	1	.	.	.	.	.	.	16.8	2
27	2	1	23.52	2	125	.	.	1	.	.	.	.	.	.	16.8	2
28	2	1	36.27	2	125	.	.	1	.	.	.	.	.	.	16.8	2

Pmetrics Model Files

Model Files

- Model files are at the heart of all Pmetrics functions
- You will spend most of your modeling time editing these model files
- Simple text documents
- Pmetrics expects them to have .txt extension

Model Files

- Contain up to 11 blocks marked by “#” and up to the first 3 letters of the block name
  - #PRImary variables Required
  - #COVariates
  - #SECondary variables
  - #BOLus inputs
  - #INItial conditions
  - #F (bioavailability)
  - #LAG time
  - #DIFferential equations
  - #OUTputs Required
  - #ERRor Required
  - #EXTra

#PRI

- The model parameters whose distributions are to be estimated
- Between 2-32 total may be specified, with 30 random and 20 fixed
- Random parameter format: *name, min, max*
- Fixed, unknown parameter format: *name, value*
- Fixed parameter format: *name, value!*💡
- Don’t use restricted words in names (see user manual)
- Once defined, primary variables can be used anywhere in the model file

💡 Hint: The “!” is used to fix the behavior of several model file blocks.

#PRI

- Behavior of the limits differs depending on the engine
  - NPAG - *min, max* are absolute
  - IT2B - *min, max* define the range, and the standard deviation of the prior is xsig*range, where xsig is an argument to `ITrun()`
  - Simulator - *min, max* are ignored unless limits argument to `SIMrun()` is `NA`, which uses min, max to truncate simulated parameter values

#PRI

- For IT2B only, adding a plus “+” to the parameter definition ensures that parameter values <0 will not be returned, even if the SD is sufficiently large to cross 0

#PRI Examples

#PRI
Ke, 0, 5
V, 0, 100+
Ka, 5
IC, 10!

#COV

- Declare the names of covariates
- Needs to match the names and order of covariates in the data file
- Covariates can be declared and not used (useful for covariate analysis later)
- Once defined, covariates can be used anywhere in the model file

#COV

- Default behavior is to linearly interpolate missing covariate values in the data file
- Use an “!” in the covariate declaration to change to piece-wise constant, i.e. carry forward previous value until new value is encountered

#COV Examples

#COV
wt
cyp
IC!

#SEC

- Define secondary variables
- Parameter value distributions are NOT generated for secondary variables; they are used only internally within the model file
- Once declared, secondary variables can be used anywhere in the model file

#SEC

- Need to be of the form X = Y
- For conditional variables or to include fortran code, preface lines with “&”

#SEC Examples

```
#Sec
CL = Ke * V * wt**0.75
& IF(cyp .GT. 1) CL = CL * cyp
```

#BOL

- By default, DUR=0 bolus inputs go into *compartment=input*, i.e. input 1 into compartment 1, and input 2 into compartment 2, etc.
- Use this block to override that default
- NBCOMP(n) = x, where n=input number, and x=compartment number

```
#BOL
NBCOMP(1)=2
```

#INI

- Set initial conditions of a compartment to be a non-zero amount
- Initial conditions are functions of fixed values, primary variables, secondary variables, and/or covariates, and conditional expressions may be used
- X(n), where n = compartment number

```
#INI
X(2) = IC*V
X(3) = IC3
X(4) = 50000
& IF(MALE==1) X(5) = 20
```

#F

- Define bioavailability (FA, fraction available) for a drug in a dataset with bolus and infusion dosing
- Bioavailability terms are functions of fixed values, primary variables, secondary variables, and/or covariates, and conditional expressions may be used
- FA(n), where n=input number

```
#F
FA(1) = F1
& IF(T>T0) FA(1) = F2
```

#LAG

- Define lag time for an input, i.e. the delay between bolus dose and beginning of absorption
- Not relevant for infusions
- Lag times are functions of fixed values, primary variables, secondary variables, and/or covariates, and conditional expressions may be used
- TLAG(n), where n=input number

```
#LAG
TLAG(1) = Lag1
& IF(DR==1) TLAG(1) = Lag2
```

#DIF

- Specify a model using differential equations in fortran format
  - XP(n) = dXn/dt, where n = compartment
  - X(n) = amount in compartment n
  - Use RATEIV(n) to place infusions for input n
  - Use any variable defined in #PRI, #SEC or any covariate
- Max of 20 equations

#DIF Example

```
#Dif
XP(1) = -KA*X(1)
XP(2) = RATEIV(1) + KA*X(1) - (KE+KCP)*X(2) + KPC*X(3)
XP(3) = KCP*X(2) - KPC*X(3)
```

#OUT

- Define the output equations as functions
- Y(n) = *function*, where n is 1, 2, 3,…
- n corresponds to OUTEQ in the data file
- *function* is comprised of fixed values, primary variables, secondary variables, and/or covariates, and conditional expressions may be used

#OUT Example

```
#Out
Y(1) = X(2)/V
```

#ERR

- Defines the error model to be used
- Two choices
  - error = (SD * gamma)^2
  - error = (SD + lambda)^2
- Recall SD = $C_0[\text{out}]^0 + C_1[\text{out}]^1 + C_2[\text{out}]^2 + C_3[\text{out}]^3$

#ERR

- First specify L/G = x, where x is the starting value for lambda or gamma
  - Lambda is not available in IT2B
  - Add an “!” to fix and not estimate; lambda can only be fixed to 0
- Then specify C0, C1, C2, C3 for each output equation in #OUT
  - Add an “!” to use these values regardless of those in data file; otherwise, datafile values will be used unless missing

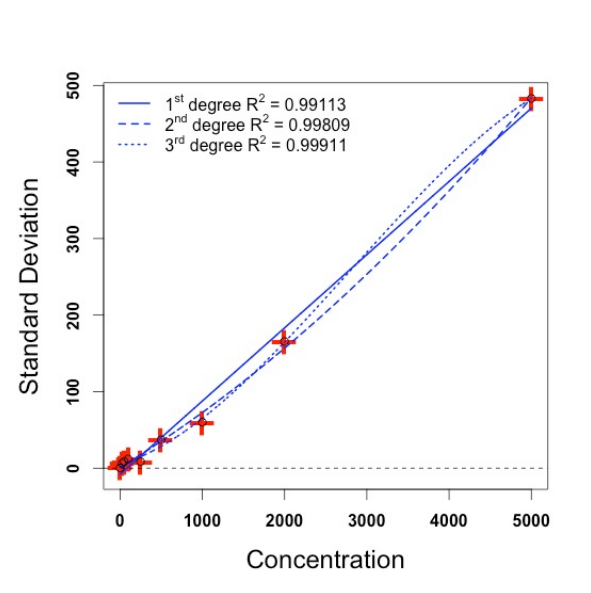
#ERR Examples

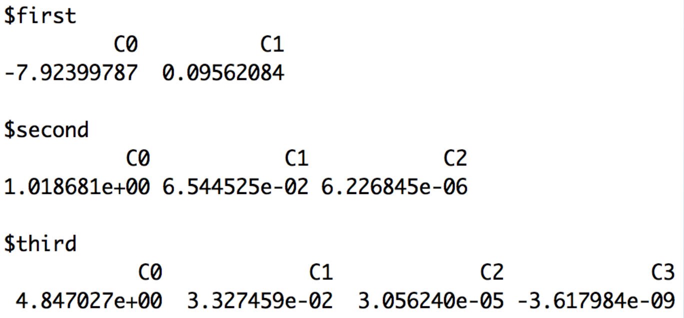
```
#ERR
L=0.4
0.1,0.1,0,0

#Err
G=2!
0.1,0.1,0,0
0.3,0.1,0,0!
```

Estimating Cs

1. Use assay validation data and `makeErrorPoly()`

Standard	SD
0	0.5
25	6.4
50	8.6
100	12
250	8.6
500	37.2
1000	60.1
2000	165.7
5000	483





```
$first
         C0          C1
-7.92399787  0.09562084

$second
          C0           C1           C2
1.018681e+00 6.544525e-02 6.226845e-06

$third
           C0            C1            C2            C3
 4.847027e+00  3.327459e-02  3.056240e-05 -3.617984e-09
```

```
obs <- c(0,25,50,100,250,500,1000,2000,5000)
sd <- c(0.5,6.4,8.6,12,8.6,37.2,60.1,165.7,483)
makeErrorPoly(obs=obs,sd=sd)
```

Estimating Cs

2. Estimate
   - C0 = 0.5 * LOQ or lowest concentration in data
   - C1 = 0.1 (assay with 10%CV)
   - C2 = 0
   - C3 = 0

Estimating Cs

- Use `ERRrun()`
- Similar to IT2B
- Model dependent, which makes this the least preferable way to estimate Cs
- Only with gamma, which will always be 1

Gamma/Lambda

- No particular rule on which to choose
- Interpreting Gamma
  - <<1…assay error polynomial likely too large; check to make sure C0 is in same units as concentration
  - 1-5…model OK, data OK
  - 5-10…model misspecification or data noisy, e.g. TDM data with errors in dose or concentration times
  - >10…severe model misspecification

Gamma/Lambda

- Interpreting Lambda
  - 0-3 x C0…model OK, data OK
  - 3-5 x C0…model misspecification or data noisy, e.g. TDM data with errors in dose or concentration times
  - >5 x C0…severe model misspecification

Gamma/Lambda

- Starting values
  - Gamma: 1 to 3
  - Lambda: C0 to 3xC0
- Increase if run ends with Hessian Error or “Probability of all points, given data for subject xx, is 0”
  - However, your model is likely misspecified (check model file very carefully) or structurally a bad choice (e.g. try adding another compartment)

#EXT

- Add Fortran subroutines for very advanced, customized model files

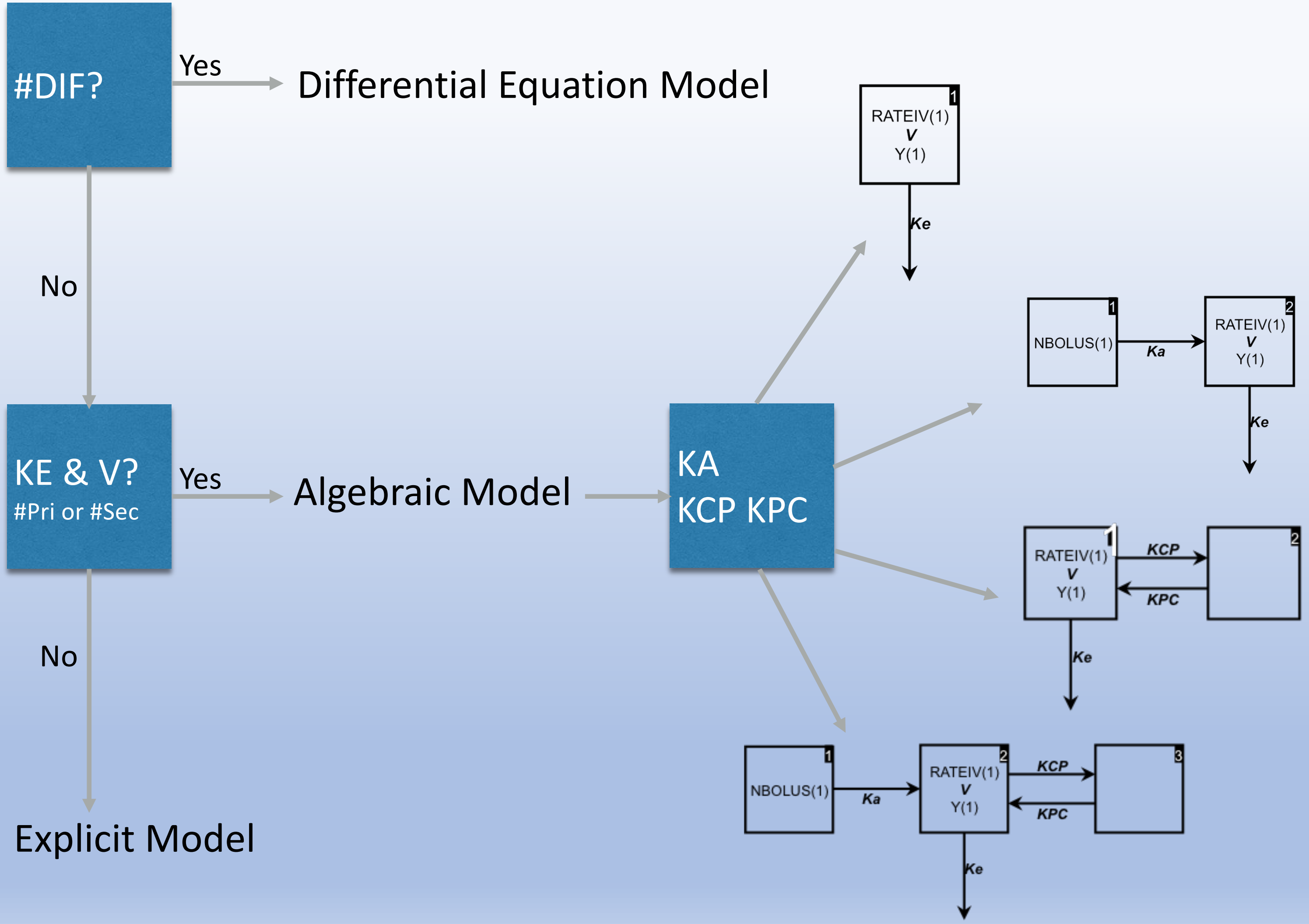
Comments

- Model files may contain comments
- Comment lines start with “C ”
- e.g. “C This weight is in kg”

Common model errors

- Forgetting ranges in #PRI block
- Forgetting covariates or not listing covariates in correct order in #COV block
- Forgetting “&” before lines in #SEC block that are not of the form A = B
- Not having minimum of #PRI, #OUT, #ERR in every model file
- Using a reserved name for a variable (see user manual)
- Mistakes in #DIF block
- Not matching number of output equations, Y(n) with maximum OUTEQ in data file
- Not matching number of C0,C1,C2,C3 in #ERR block to number of output equations

Model File Logic



#DIF?

Yes

Differential Equation Model

No

KE & V?

#Pri or #Sec

Yes

Algebraic Model

KA

KCP KPC

No

Explicit Model

Model library

- A basic model library is available on our website with downloadable files
- It is not exhaustive. The idea is to provide building blocks for more complicated models.
- http://www.lapk.org/ModelLib.php