Slide 1

# NONMEM PREDPP

## Pharmacokinetic Model Library

Nick Holford
Dept Pharmacology & Clinical Pharmacology
University of Auckland, New Zealand

Slide 2

# NM-TRAN Models

Using PRED

```
$PRED
   CL=THETA(1)+ETA(1)
   V=THETA(2)+ETA(2)
   C=DOSE/V*EXP(-CL/V*TIME)
   Y=C+ERR(1)
```

Using PREDPP

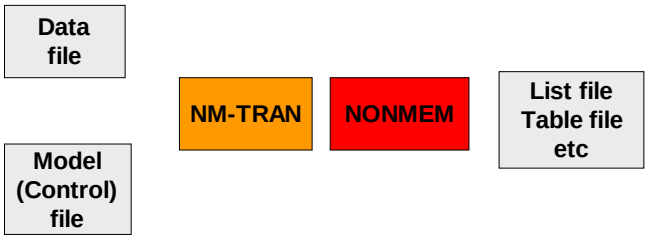
```
$SUBR
   ADVAN1 TRAN2
$PK
   CL=THETA(1)+ETA(1)
   V=THETA(2)+ETA(2)
   S1=V
$ERROR
   Y=F+ERR(1)
```



NONMEM provides a flexible library of pre-written models to solve pharmacokinetic problems. This library is called PREDD (PREDictions for Population Pharmacokinetics).
Using PREDPP requires 3 separate records:
$SUBR specifies the PREDPP subroutine to use and how it should be parameterised
$PK specifies the individual PK parameters. Typically this involves a fixed effect model for the covariate effects and a random effects model for population parameter variability. The names of the individual parameters are pre-defined in PREDPP and must match those indicated in $SUBR
$ERROR returns the model prediction (F) with a model for the residual error random effect

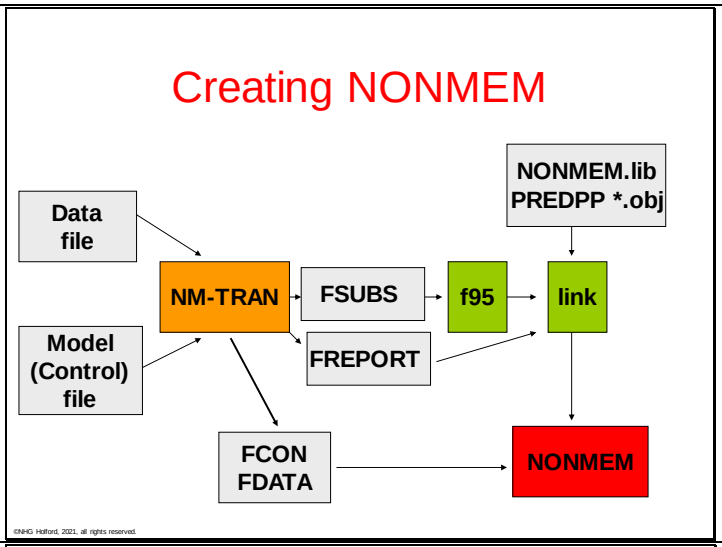
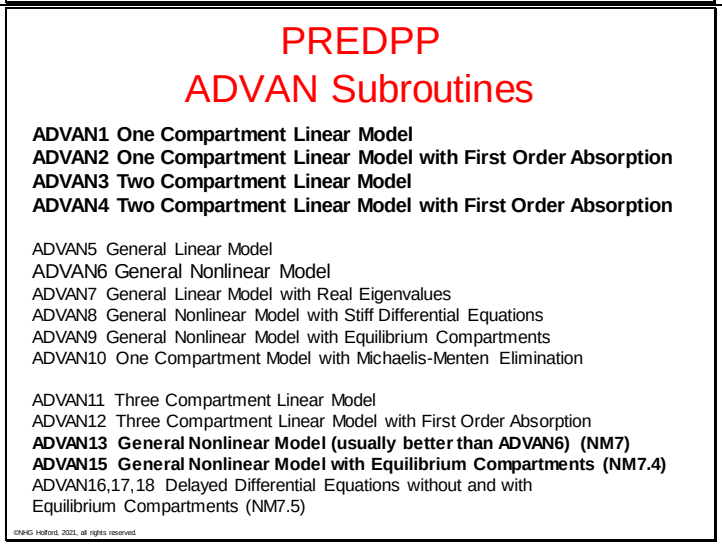
Slide 3

# NM-TRAN and NONMEM

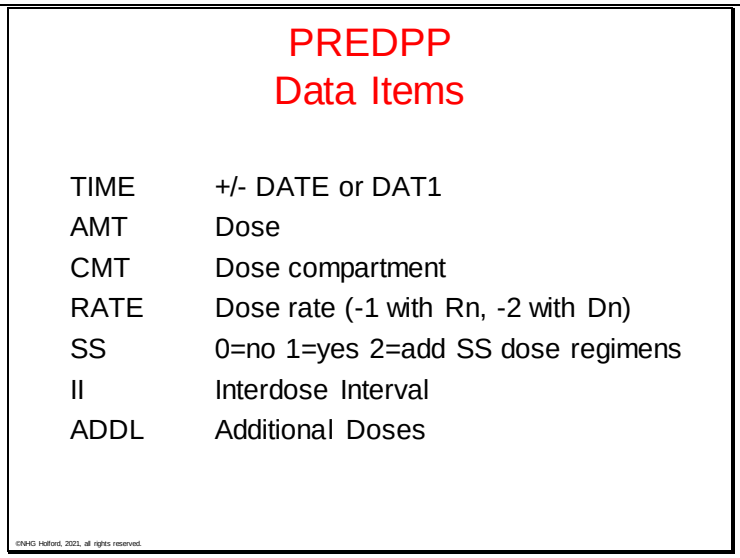





Nearly all users are familiar with NONMEM through files used by NM-TRAN. Learning how to provide the input to NONMEM is really learning how to provide input to NM-TRAN. NM-TRAN then translates the input into a format used by NONMEM to do the modelling.

| | | |
|---|---|---|
| Slide 4 |  | The connection between NM-TRAN and NONMEM is quite complex. It involves the use of a Fortran compiler to turn a Fortran source file (FSUBS) into an object file which can be linked with the main NONMEM and PREDPP object files. Because NONMEM and PREDPP are pre-compiled this makes the creation of a NONMEM executable model very quick.<br>NM-TRAN also rewrites its input data file into a format suitable for NONMEM (FDATA) and creates a control stream that tells NONMEM what to do (FCON). |
| Slide 5 |  | The most commonly used PREDPP subroutines are shown in bold. They are named ADVAN subroutines because the advance the solution of the model from one record in the data file to the next in time sequence. This is a clever way of allowing arbitrary dosing patterns. There are some shortcuts for specifying regular dosing patterns which can aid in making the input data file simpler in structure.<br>ADVAN7 may be faster than ADVAN5. Most PK models have real eigenvalues.<br>The ADVAN6 subroutine allows the user to write their own model in differential equations. This is quite general (just like other programs such as Berkeley Madonna or WinNonLin). The models are not restricted to PK problems but can be used to solve any kind of model defined by ordinary differential equations.<br>ADVAN13 and ADVAN15 may be faster with the newer NM7 estimation methods.<br>ADVAN9 and ADVAN15 have similar properties but use different algorithms for finding solutions. |

| | | |
|---|---|---|
| Slide 6 | PREDPP<br>TRAN Subroutines<br>Basic PK Parameters<br><br>TRANS1 Dummy, or null, translator; (K,V)<br>TRANS2 Used with ADVAN1 and ADVAN2 (CL,V).<br>TRANS3 Used with ADVAN3 and ADVAN4 (CL,V,Q,VSS).<br>TRANS4 Used with ADVAN3, ADVAN4(CL,V1,Q,V2)<br>TRANS4 Used with ADVAN11, ADVAN12 (CL,V1,Q2,V2,Q3,V3)<br>TRANS5 Used with ADVAN3 and ADVAN4 (AOB, ALPHA, BETA)<br>TRANS6 Used with ADVAN3, ADVAN4, ADVAN11, ADVAN12 (ALPHA, BETA, K21)<br> | The TRAN subroutines are options specified for each ADVAN subroutine. They determine the parameters that need to be defined in $PK. In most cases the CL and V parameterisation is preferred for population analysis. |
| Slide 7 | PREDPP<br>Additional PK Parameters<br><br>Scale parameters Sn, e.g.: S1 S2 S3 S4 SC S0<br>Bio-availability fractions Fn, e.g.: F1 F2 F3<br>Output fractions Fn, e.g.: F2 F3 F4 F0 FO<br>Infusion rates Rn, e.g.: R1 R2 R3<br>Infusion durations Dn, e.g.: D1 D2 D3<br>Absorption lags ALAGn, e.g.: ALAG1 ALAG2 ALAG3<br>Time scale: TSCALE (may be written XSCALE)<br>Model event times MTIME(i), e.g.: MTIME(1) MTIME(2)<br> | Each of the ADVAN subroutines has additional PK parameters. These are typically associated with particular compartments of the PK model by a numeric suffix e.g. the bioavailability of doses put into compartment one is F1 and into compartment two is F2. The scale parameters control how the amounts in each compartment are used to create the F prediction variable used by $ERROR. Most commonly the scale parameter is the volume of distribution so that F which is always calculated from the amount divided by the compartment scale (A(n)/Sn ) becomes the concentration predicted in that compartment. Note that F is the compartment prediction in $ERROR. It has nothing to do with the F1, …, Fn bioavailability fractions which are defined in $PK.<br>Zero-order input models need a RATE data item in the data set. This defines the rate of input. The duration will then be determined by the AMT available for input. If the RATE data item is -1 this is special value which means the rate will be specified in $PK by the R1,…,Rn compartment specific rate item. If the RATE item is -2 then $PK provided the D1,…,Dn compartment specific duration of the input. This means either the rate or the duration can be estimated as a parameter. Most commonly it is the duration which is estimated.<br>Lag times for absorption are defined by the ALAG1,…,ALAGn compartment specific lag time.<br>Output fractions and time scale parameters are very rarely used. Output fractions in the format F2, F3, F4, etc can only refer to the compartment number after the largest disposition compartment e.g. F2 for 1 cpt model, F3 for a 2 cpt model and F4 for a 3 cpt model. F0 and FO are synonyms for the output compartment. |

| | | |
|---|---|---|
| Slide 8 |  | Dosing for PREDPP models is controlled by special data items. It is possible to use DATE e.g. 12/31/2008 with a TIME e.g. 10:30 to specify the TIME of a record. NM-TRAN converts the date and time values into hours from the first record for each subject. This works for $PRED as well as PREDPP models.<br>The dose to be put into a compartment is indicated by the AMT data item. It is usually helpful to make the units of the dose match those of the predicted concentrations e.g. specify AMT in micrograms if the concentration measurements are micrograms/L. This is not necessary but typically helps reduce confusion about the meaning of parameters.<br>The CMT data item indicates which compartment the AMT should be put into. This item is not required but is often useful. The default value is typically compartment 1.<br>The RATE data item is frequently set to -2 so that the duration of a zero order input can be estimated. It is only needed for zero-order input models.<br>The SS and ADDL data items must be combined with II. They can be used to make the data set simpler if you can assume that doses are given at regular intervals (defined by II). You can assume that steady state has been reached using SS or you can specify the number of additional doses to be added to the system after the dosing record with a positive ADDL value.<br>SS=2 may be used with a second dose record to combine 2 SS dosing regimens e.g. 500 mg q24 morning and 1000 mg q24 evening. |