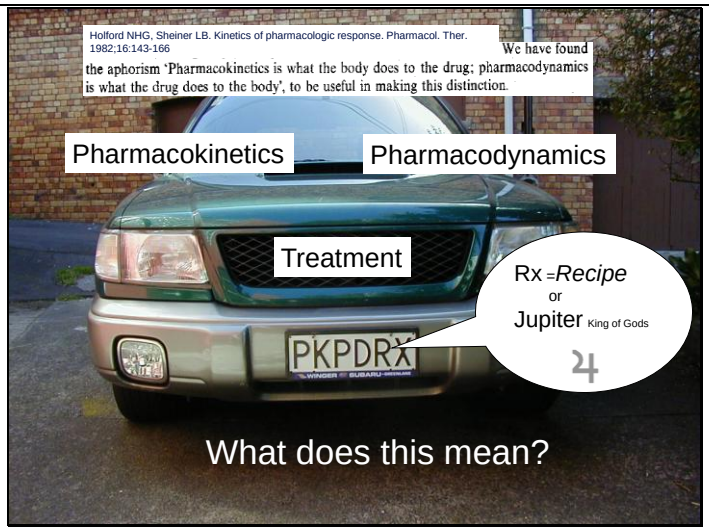
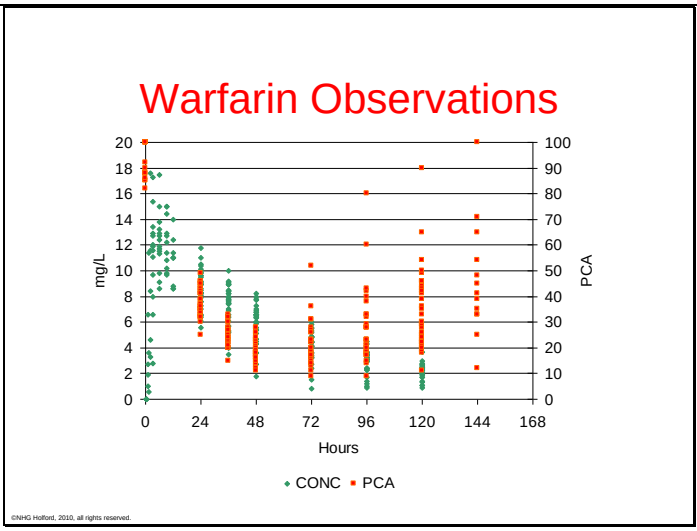
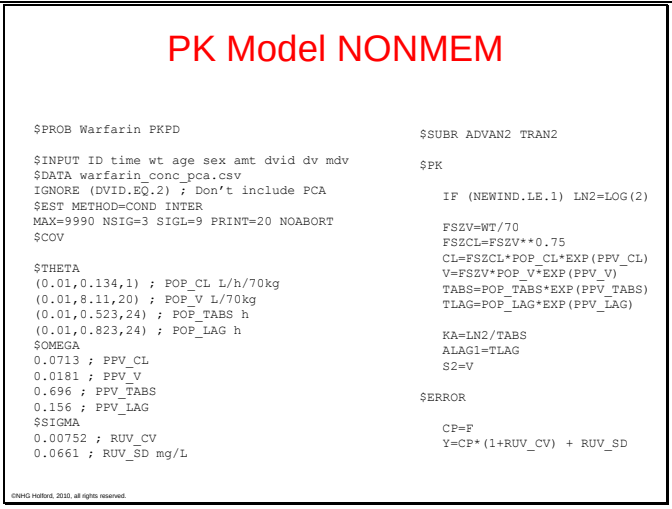
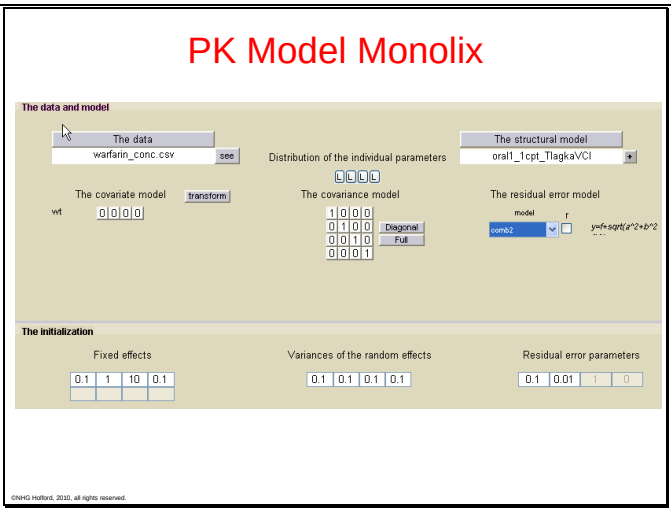
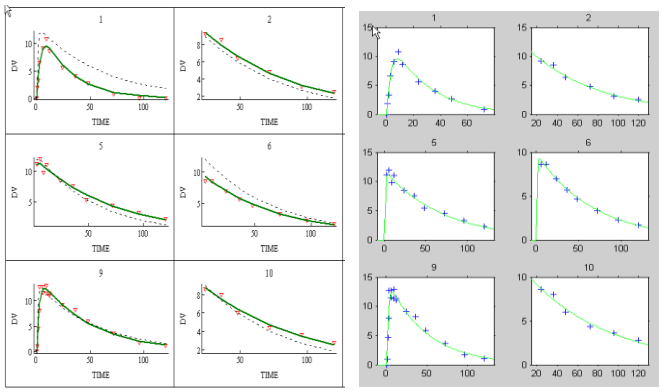
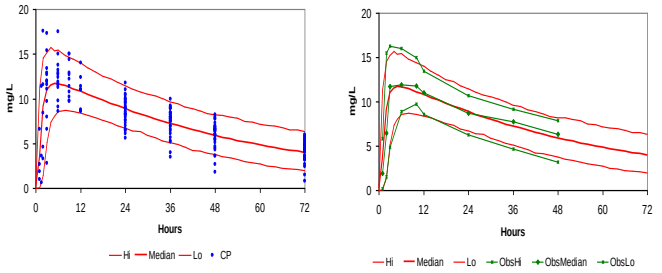
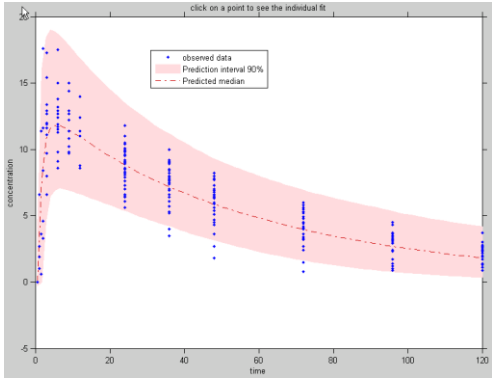
Slide 1	# PKPD ## NONMEM and Monolix ## Workshop Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand	
Slide 2		PK = Pharmacokinetics: What the body does to the drug PD=Pharmacodynamics: What the drug does to the body Rx=Treatment: What the prescribed and patient need to know.

Slide 3	# Warfarin Data
	
	- PKPD Studies in Healthy Subjects
	  – 1.5 mg/kg single oral dose
	  – Total racemic warfarin plasma concentration
	  – Prothrombin complex activity (PCA)
	- 32 subjects, 250 concentrations, 232 PCA
	
	- O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. Journal of Clinical Investigation 1963;42(10):1542-1551
	- O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs Initiation of warfarin therapy without a loading dose. Circulation 1968;38:169-177
	
		A classical clinical pharmacology study from 40 years ago.
		Prothrombin complex activity is inversely proportional to the International Normalized Ratio (INR)

Slide 4		Two features to notice about the time course of warfarin concentration and effect on PCA: • Peak concentration is about 6 h while greatest effect is at 72 h • Most marked between subject variability in PCA occurs when PK variability is least
Slide 5		One compartment model with first-order absorption and lag time. Note the use of IGNORE on the $DATA record so that only concentration observations are used in the fit (DVID=2 means PCA observation record).
Slide 6		ka1L_PKLIB_PROJECT.mat

Slide 7	Warfarin First-Order Input (KA1L) NONMEM (+CG) and Monolix  	Individual “post hoc” predictions of concentration fit the time course well and should be adequate for driving the pharmacodynamic model.
Slide 8	Warfarin KA1L Predictive Check NONMEM+Excel  	The visual predictive check reveals that the model overestimates the early variability in concentration.
Slide 9	Warfarin KA1L Predictive Check Monolix  	The Monolix visual predictive check does not suggest a problem with the model. But it does not allow a direct comparison of the distribution of observations with those of the predictions.

Slide 10

Immediate Effect Model NONMEM

- Two Basic Approaches
  - PREDPP
    - ADVAN2
    - ADVAN6 Differential Equations
  - $PRED
    - Write model for CP

An immediate effect model uses central compartment concentrations to predict the drug effect.
Concentrations can be predicted using $PRED or one of the PREDPP library ADVAN subroutines.
Using ADVAN subroutines is usually easier to code but the model is not so clear.

Slide 11

Immediate Effect Model Monolix

- Two Basic Approaches
  - PD Library
    - Immediate models
  - MLX-TRAN
    - Write model for CP and Effect

Slide 12

Central Compartment Using ADVAN2

```
$SUB ADVAN2 TRANS2
$PK
; Define LN2 for efficiency
 IF (NEWIND.EQ.0) THEN
      LN2=LOG(2)
 ENDIF
```

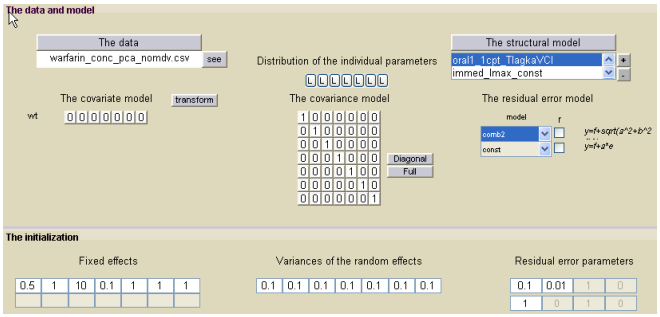
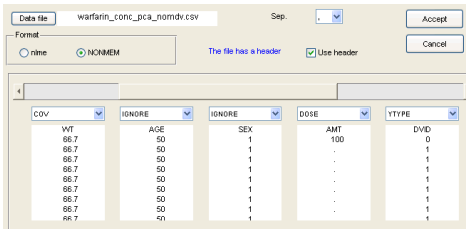
```
; Define parameters
   KA=LN2/TABS
   ALAG1=TLAG
   S2=V

$ERROR

   CP=A(2)/V ; or CP=F
   IF (DVID.LE.1) THEN
      Y=CP*(1+RUV_CV) + RUV_SD
   ENDIF

   CE=CP
   PCA=E0 + EMAX*CE/(C50+CE)
   IF (DVID.EQ.2) THEN
      Y=PCA + RUV_FX
   ENDIF
```


TABS is the half-life of absorption. The absorption rate is parameterised in terms of TABS but because ADVAN2 requires a value for KA it must be calculated from TABS in the code.
The NEWIND variable is a built in feature of NONMEM. When it is <= 1 it means this is the first record for this individual. The variable LN2 is calculated from LOG(2) just once for efficiency.
Note how the DVID data item is used to distinguish predictions of concentration (DVID=1) from predictions of PCA (DVID=2).

Slide 13	# Central Compartment Using PK and PD Library Models  	ka1_im_lmax_PKPDLIB_PROJECT.mat
Slide 14	# Data for Joint PKPD Model #ID time wt age sex amt dvid dv mdv 1 0 66.7 50 1 100 0 . 1 1 0 66.7 50 1 . 2 . 1 1 0.5 66.7 50 1 . 1 0 0 1 1 66.7 50 1 . 1 1.9 0 1 2 66.7 50 1 . 1 3.3 0 1 3 66.7 50 1 . 1 6.6 0 1 6 66.7 50 1 . 1 9.1 0 1 9 66.7 50 1 . 1 10.8 0 1 12 66.7 50 1 . 1 8.6 0  	NONMEM requires that all observations are in a single DV column. In order to distinguish concentrations from effects (PCA) the DVID data item is used to identify the kind of DV. A DVID of 0 is used to indicate a dose record, 1 for a concentration record and 2 for a PCA record. Note that MDV is used to indicate if there are missing observations e.g. this subject does not have a PCA observation at TIME=0. Note that Monolix sorts the data so that the DVID (YTYPE) values are arranged together (makes it harder to check data is correct).

Slide 15	# Central Compartment Using ADVAN6
	`$SUBR ADVAN6 TOL=9`
	`$MODEL`
	`COMP (GUT)`
	`COMP (CENTRAL)`
	`$PK`
	`; Define LN2`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`ENDIF`
	`; Define parameters`
	`KA=LN2/TABS`
	`ALAG1=TLAG`
	`S2=V`
	`$DES`
	`GUT=A(1)`
	`DCP=A(2)/V`
	`RATEIN=KA*GUT`
	`DADT(1)= -RATEIN`
	`DADT(2)= RATEIN - DCP*CL`
	`$ERROR`
	`CP=A(2)/V`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUV_CV) + RUV_SD`
	`ENDIF`
	`CE=CP`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUV_FX`
	`ENDIF`
	
		Note the variables defined in $DES cannot have the same name as variables in other blocks e.g. you cannot define CP=A(2)/V in $DES and also in $ERROR. In this example the variable name DCP is used in $DES and the variable name CP is used in $ERROR.

Slide 16	**Central Compartment Using $PRED**
	
	`$PRED`
	`; Get DOSE from AMT`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`DOSE=0`
	`ENDIF`
	`IF (AMT.GT.0) DOSE=AMT`
	
	`; Define parameters`
	`KA=LN2/TABS`
	`KE=CL/V`
	
	`; Adjust time for lagtime`
	`IF (TIME.LE.TLAG) THEN`
	`TAD=0`
	`ELSE`
	`TAD=TIME-TLAG`
	`ENDIF`
	
	`; Plasma concentration`
	`EXPKA=EXP(-KA*TAD)`
	`EXPKE=EXP(-KE*TAD)`
	`CP=DOSE*KA/(V*(KA-KE))*(EXPKE-EXPKA)`
	
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUV_CV) + RUV_SD`
	`ENDIF`
	
	`CE=CP`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUV_FX`
	`ENDIF`
	
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		Note that DOSE must be defined on every record so it is obtained 'on the fly' from the AMT value. The AMT value is only >0 at TIME=0.

Slide 17	**Central Compartment Using MLX-TRAN**
	
	`$PROBLEM Warfarin immediate`
	
	`$PSI`
	`tlag ka v cl ; PK parameters`
	`imax c50 s0 ; PD parameters`
	
	`$EQUATION`
	`dose=100`
	`if (T<tlag) then`
	`tad=0`
	`else`
	`tad=T-tlag`
	`end`
	`ke=cl/v`
	`expka=exp(-ka*tad)`
	`expke=exp(-ke*tad)`
	
	`CP=dose*ka/(v*(ka-ke))*(expke - expka)`
	
	`ce=CP`
	`PCA=s0 - imax*ce/(c50+ce)`
	
	`$OUTPUT`
	`OUTPUT1 = CP`
	`OUTPUT2 = PCA`
	
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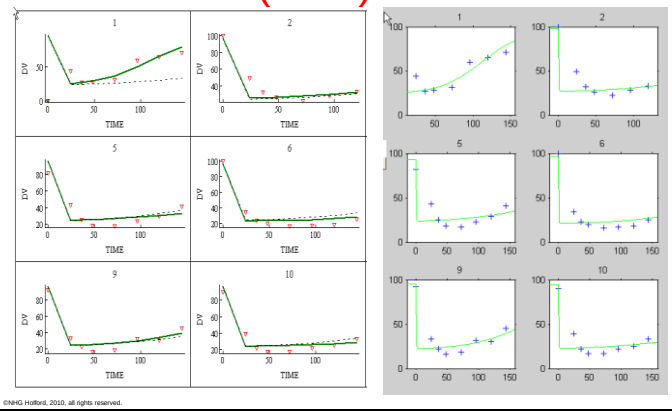
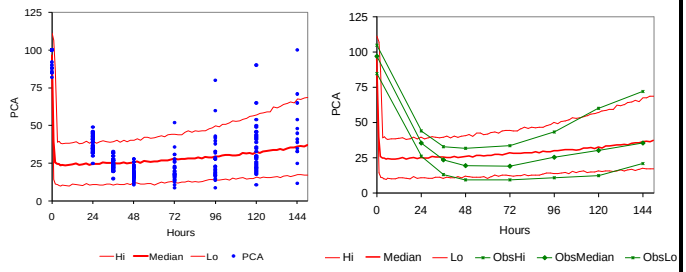
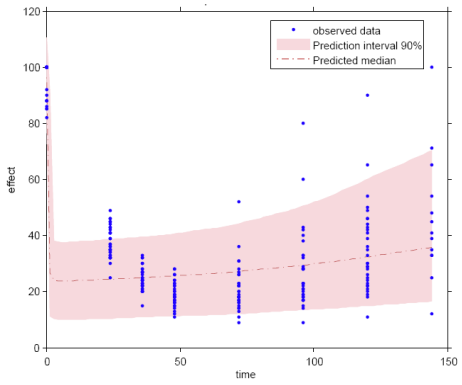
		ka1_im_Imax_CMT_mlx.txt
		ka1_im_Imax_CMT_PROJECT.mat

Slide 18	**Warfarin Immediate NONMEM (+CG) and Monolix**  ©NHG Holford, 2010, all rights reserved.	Individual 'post hoc' predictions from the immediate effect model describe most of the time course of PCA but in general the time of the predicted greatest effect is earlier than the observed effect.

Slide 19	**Warfarin Immediate VPC Excel**  	The VPC clearly shows there is something wrong with the model.
Slide 20	**Warfarin Immediate VPC Monolix**  	
Slide 21	**Delayed Effect Effect Compartment Model** • Two Basic Approaches – PREDPP • ADVAN4 Very small peripheral compartment • ADVAN6 Differential Equations – $PRED • Write model for CP and CE 	The visual predictive check points to using a model with a delayed effect. The simplest form of delayed effect model uses an effect compartment. This is usually considered an empirical model but if the delay in effect is only a few minutes then it might be a reasonable way to described the time course of drug distribution from plasma to the site of action in an organ. $PRED and ADVAN6 can be used to write exact solutions to the effect compartment model. Because ADVAN6 has to solve differential equations it is slower. ADVAN4 can be used by making the peripheral compartment have a negligible volume. This is helpful for complex dosing histories that would be hard to code in $PRED.

Slide 22	**Effect Compartment Using ADVAN4**
	
	`$SUB ADVAN4 TRANS4`
	`$PK`
	`; Define LN2`
	`IF (NEWIND.EQ.0) THEN`
	`  LN2=LOG(2)`
	`ENDIF`
	
	`; Define parameters`
	`  KA=LN2/TABS`
	`  ALAG1=TLAG`
	`  S2=V`
	`  V2=V`
	
	`  KEQ=LN2/TEQ`
	`  V3=V2*0.0001 ; negligible volume`
	`  Q=V3*KEQ`
	
	`$ERROR`
	`  CP=A(2)/V2`
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	
	`  CE=A(3)/V3`
	`  PCA=E0 + EMAX*CE/(C50+CE)`
	`  IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`  ENDIF`
	
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		Note how the peripheral compartment volume is scaled to be a very small fraction (0.0001) of the central compartment volume. This ensures it will have a negligible influence on the model predictions for the central compartment concentrations.

Slide 23	**Effect Compartment Using ADVAN6**
	
	`$SUBR ADVAN6 TOL=9`
	`$MODEL`
	`  COMP (GUT)`
	`  COMP (CENTRAL)`
	`  COMP (EFFECT)`
	
	`$PK`
	`; Define LN2`
	`  IF (NEWIND.LE.1) THEN`
	`  LN2=LOG(2)`
	`  ENDIF`
	`; Define parameters`
	`  KA=LN2/TABS`
	`  ALAG1=TLAG`
	`  S2=V`
	`  KEQ=LN2/TEQ`
	
	`$DES`
	`  GUT=A(1)`
	`  DCP=A(2)/V`
	`  DCE=A(3)`
	
	`  RATEIN=KA*GUT`
	`  DADT(1)= -RATEIN`
	`  DADT(2)= RATEIN - DCP*CL`
	`  DADT(3)= KEQ*(DCP - DCE)`
	
	`$ERROR`
	`  CP=A(2)/V`
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	
	`  CE=A(3)`
	`  PCA=E0 + EMAX*CE/(C50+CE)`
	`  IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`  ENDIF`
	
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		The solution to differential equation 3 is scaled in terms of concentration. There is no need to define a volume of this compartment. It has no meaning for this model.

Slide 24	**Effect Compartment Using MLX-TRAN**
	
	`$PROBLEM Warfarin effect`
	`  compartment`
	
	`$MODEL`
	`COMP=(AMTG) ; gut`
	`COMP=(AMTC) ; central`
	`COMP=(CE) ; effect`
	
	`$PSI`
	`tlag ka v cl ; PK parameters`
	`ke0 imax c50 s0 ; PD parameters`
	
	`$PK`
	`ALAG1=tlag`
	
	`$ODE`
	`AMTC_0 = 0`
	`CE_0 = 0`
	
	`C=AMTC/v`
	`ratein=AMTG*ka`
	
	`DDT_AMTG = -ratein`
	`DDT_AMTC = ratein - cl*C`
	`DDT_CE = ke0*(C - CE)`
	
	`PCA=s0 - imax*CE/(c50+CE)`
	
	`$OUTPUT`
	`OUTPUT1 = AMTC/v`
	`OUTPUT2 = PCA`
	
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		ka1_ce_Imax_CMT_mlx.txt
		ka1_ce_Imax_CMT_PROJECT.mat

Slide 25	**Effect Compartment Using $PRED**
	
	`$PRED`
	`; Get DOSE from AMT`
	`IF (NEWIND.LE.1) THEN`
	`LN2=LOG(2)`
	`DOSE=0`
	`ENDIF`
	`IF (AMT.GT.0) DOSE=AMT`
	
	`; Define parameters`
	`KA=LN2/TABS`
	`KE=CL/V`
	`KEQ=LN2/TEQ`
	
	`; Adjust time for lagtime`
	`IF (TIME.LE.TLAG) THEN`
	`TAD=0`
	`ELSE`
	`TAD=TIME-TLAG`
	`ENDIF`
	
	`; Plasma concentration`
	`EXPKA=EXP(-KA*TAD)`
	`EXPKE=EXP(-KE*TAD)`
	`CP=DOSE*KA/(V*(KA-KE))*(EXPKE-EXPKA)`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUV_CV) + RUV_SD`
	`ENDIF`
	
	`; Effect compartment model concentration`
	`EXPKQ=EXP(-KEQ*TAD)`
	`CEEXKE=EXPKE/(KA-KE)/(KEQ-KE)`
	`CEEXKA=EXPKA/(KE-KA)/(KEQ-KA)`
	`CEEXKQ=EXPKQ/(KA-KEQ)/(KE-KEQ)`
	`CE=DOSE*KA*KEQ/V*(CEEXKE+CEEXKA+CEEXKQ)`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUV_FX`
	`ENDIF`
	
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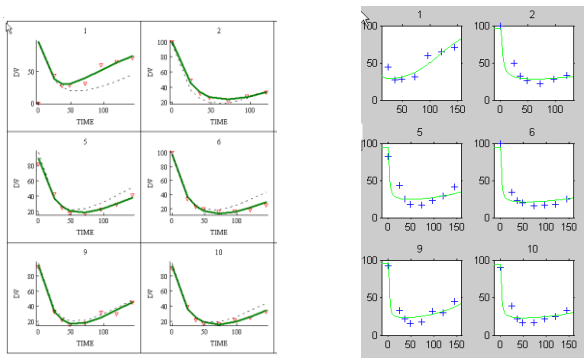
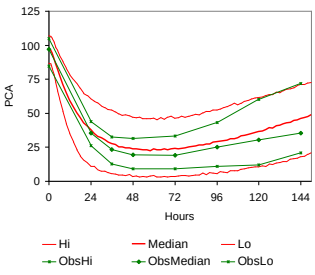
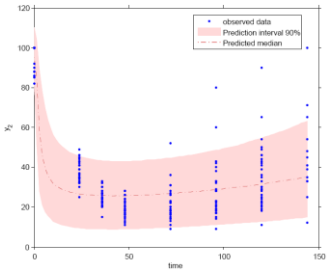
		The effect compartment model for a first-order input one compartment model requires an additional exponential term.

Slide 26	**Warfarin Ce Individual Predictions**  ©NHG Holford, 2010, all rights reserved.	The individual 'post hoc' predictions are much better than using the immediate model. This model looks fine. But are we missing something?
Slide 27	**Warfarin Ce Predictive Check**   ©NHG Holford, 2010, all rights reserved.	The NONMEM derived visual predictive check confirms that the average prediction matches the observed effect time course but the variability is clearly overestimated. Monolix predictive check does not look as good as that using NONMEM for the same model

Slide 28	**Turnover Using ADVAN6 NONMEM**
	
	`$SUBR ADVAN6 TOL=9`
	`$MODEL`
	`  COMP (GUT)`
	`  COMP (CENTRAL)`
	`  COMP (TRNOVR)`
	
	`$PK`
	`  A_0(3)=E0`
	`;TOVER is turnover half-life`
	`  KOUT=LN2/TOVER`
	`  RIN=E0*KOUT`
	
	`$DES`
	`  RATEIN=KA*A(1)`
	`  DCP=A(2)/V`
	`  DPCA=A(3)`
	`  PD=1+EMAX*DCP/(C50+DCP)`
	
	`  DADT(1)=-RATEIN`
	`  DADT(2)=RATEIN - CL*DCP`
	`  DADT(3)=RIN*PD - KOUT*DPCA`
	
	`$ERROR`
	`  CP=A(2)/V`
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	
	`  PCA=A(3)`
	`  IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`  ENDIF`
	
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		The turnover family of models describe delayed drug effects where the delay is due to the turnover of a physiological mediator. This is well understood as the mechanism of the delay for warfarin.
		NONMEM VI allows initialization of the turnover compartment directly using the special variable A_0().

Slide 29	**Turnover Using MLX-TRAN**
	
	`$PROBLEM Warfarin turnover`
	
	`$MODEL`
	`COMP=(AMTG) ; gut`
	`COMP=(AMTC) ; central`
	`COMP=(PCA) ; turnover`
	
	`$PSI`
	`tlag ka v cl ; PK parameters`
	`ke0 imax c50 s0 ; PD parameters`
	
	`$PK`
	`ALAG1=tlag`
	`rpca=s0*ke0`
	
	`$ODE`
	`AMTC_0 = 0`
	`PCA_0 = s0`
	
	`C=AMTC/v`
	`ratein=AMTG*ka`
	
	`DDT_AMTG = -ratein`
	`DDT_AMTC = ratein - cl*C`
	`DDT_PCA  = rpca*(1-imax*C/(C+c50))-ke0*PCA`
	
	`$OUTPUT`
	`OUTPUT1 = AMTC/v`
	`OUTPUT2 = PCA`
	
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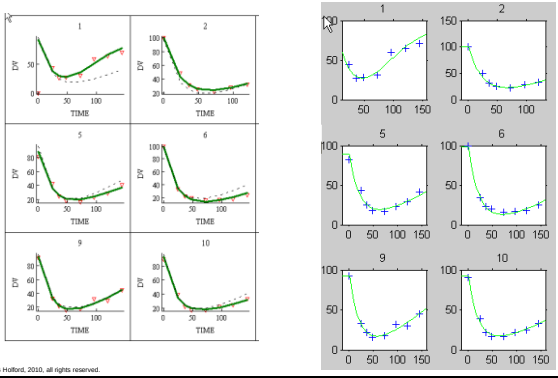
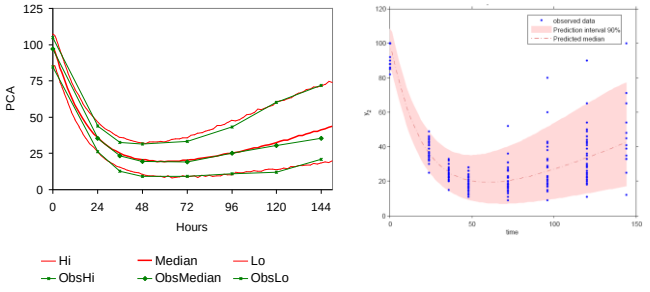
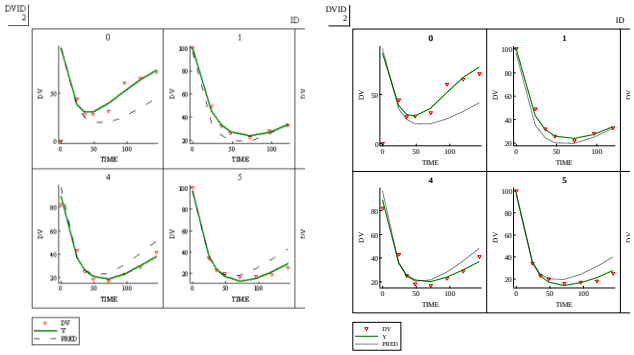
		ka1_to_Imax_CMT_PROJECT.mat
		ka1_to_Imax_CMT_mlx.txt

Slide 30	**Warfarin Turnover Individual Fits**  ©NHG Holford, 2010, all rights reserved.	Then individual fits look good for both NONMEM (right) and Monolix (left)

Slide 31	**Warfarin Turnover Predictive Check**  	The visual predictive check shows that the turnover model describes the variability of the observations much better than the effect compartment model.
Slide 32	**Effect Cpt vs Turnover**  	The individual “post hoc” predictions from the turnover model do not look any better than the predictions from the effect compartment model.
Slide 33	**Comparison of Models Monolix and NONMEM 7** Monolix = Full LogL – Obs*ln(2*pi) 	Monolix library models do worse than MLX-TRAN coded models. NONMEM OBJ is not the complete -2 * log likelihood. Monolix reports the full LogL. Monolix is slower than NONMEM.

Run	Full LogL	Monolix	NONMEM	MLX minutes	NM7 minutes
ka1_to_Imax_CMT_PROJECT	2113.05	1227.193	1202.815	3.24	3.04
ka1_to_Imax_PKPDLIB_PROJECT	2154.80	1268.943			
ka1_ce_Imax_CMT_PROJECT	2344.51	1458.653	1271.938	3.33	1.12
ka1_ce_Imax_PKPDLIB_PROJECT	2363.34	1477.483			
ka1_im_Imax_CMT_PROJECT	2334.25	1448.393	1442.873	0.35	0.064
ka1_im_Imax_PKPDLIB_PROJECT	2367.83	1481.973			

LLdelta	885.8567
Obs	482

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Comparison of Parameters Monolix and NONMEM

Method	Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
NONMEM 7	ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
Monolix 3.1SR2	ka1_to_Imax_MLX-TRAN	96.5	-1.03	1.33	13.46
NONMEM 7	ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
Monolix 3.1SR2	ka1_ce_Imax_MLX-TRAN	95.4	-77	0.523	20.57
NONMEM 7	ka1_im_emax_PRED	96.7	-72.7	0.088	.
Monolix 3.1SR2	ka1_im_Imax_MLX-TRAN	96.8	-74.9	0.203	.

The half-life of PCA is reported in the literature to be about 14 hours. This is very close to the TOVER estimate of 13 hours from this data set. Notice also the more physiological meaning of an Emax of -1 i.e. 100% inhibition of PCA formation.

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