



MIXTURE MODELS AND MODEL MIXTURES WITH MONOLIX

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(2) J & J Pharmaceutical R & D

Some mixtures...

Yesterday night...



Some mixtures...

or this morning...



Outline

- **Mixture distributions**
 - Supervised learning
 - Unsupervised learning
- **Model mixtures**
 - Between subject model mixture
 - Within subject model mixture
- **The methodology**
- **Conclusions**

Mixture models

N subjects, $i = 1, 2, \dots, N$
 K groups, $k = 1, 2, \dots, K$

y_i vector of observations from subject i

ψ_i vector of individual parameter of subject i

z_i label (categorical covariate): $z_i \in \{1, 2, \dots, K\}$

If $z_i = k$, then $(y_i, \psi_i) \sim p_k(y_i, \psi_i)$

Mixture models

$$p_k(y_i, \psi_i) = p_k(\psi_i) p_k(y_i | \psi_i)$$

1) Mixture of distributions

$$\text{If } z_i = k, \text{ then } \psi_i \sim p_k(\psi_i)$$

2) Mixture of models

$$\text{If } z_i = k, \text{ then } y_i | \psi_i \sim p_k(y_i | \psi_i)$$



I

Mixture of distributions

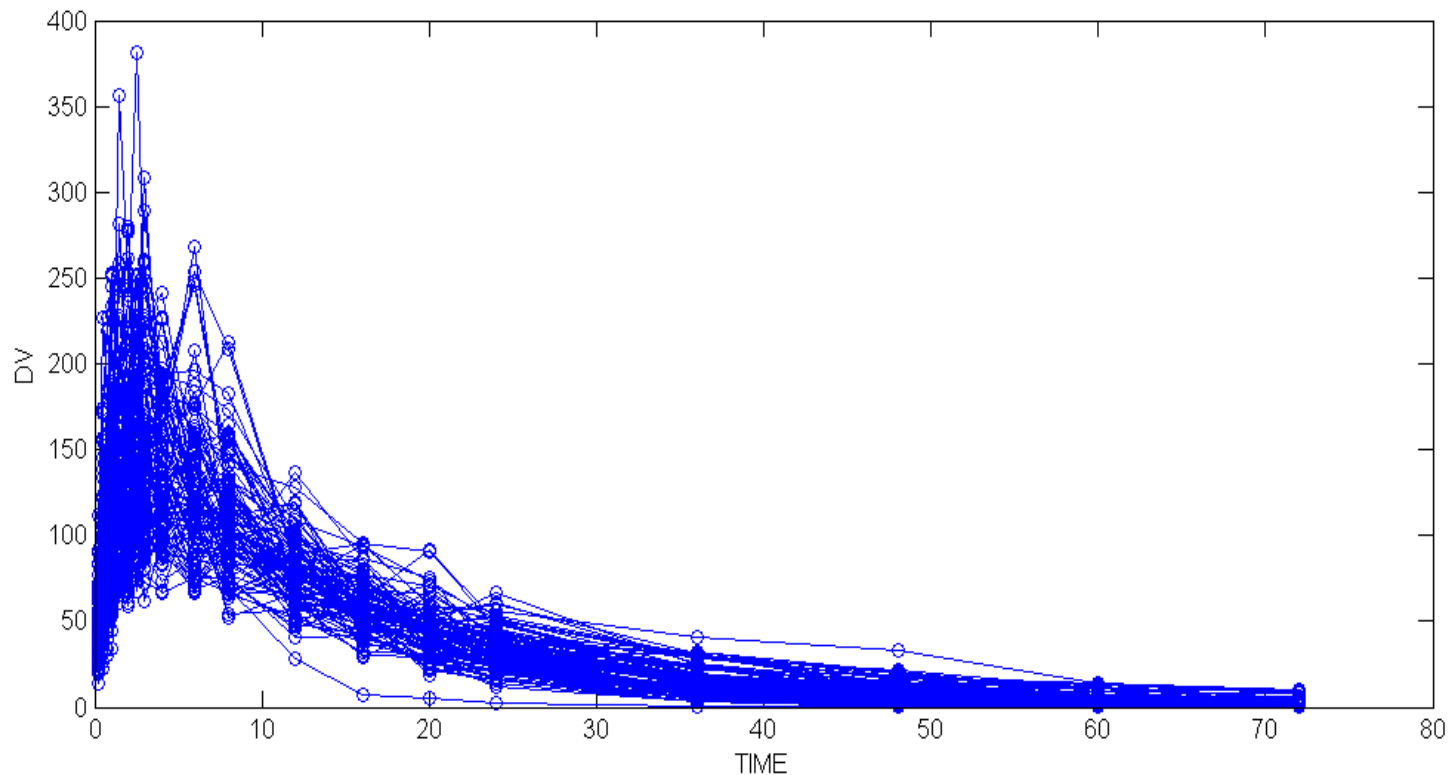
Mixture of distributions

Exemple: $\psi_i = (ka_i, Vol_i, Cl_i)$

Total number of subjects: 100

Average number of doses per subject: 1

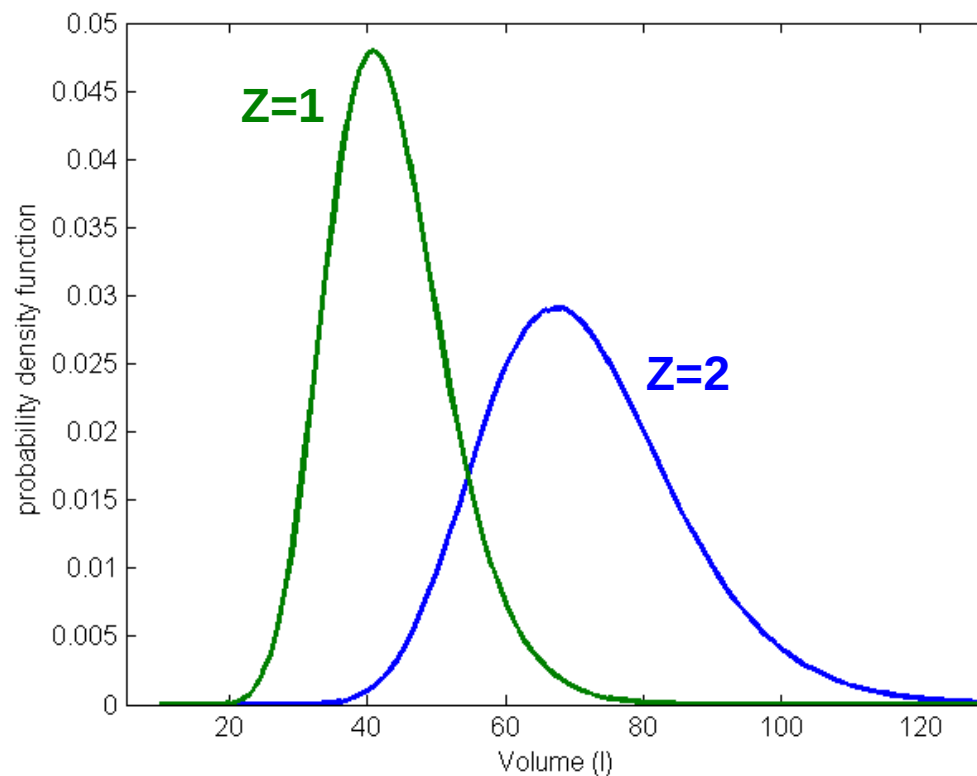
Total/Average/Min/Max numbers of observations: 1895 18.95 17 19



Mixture of distributions

Group 1 $\text{Vol}_i \sim \text{lognormal}(\mu_1, \omega_1)$

Group 2 $\text{Vol}_i \sim \text{lognormal}(\mu_2, \omega_2)$



1) Supervised learning (the labels are known)

Categorical covariate model building with MONOLIX

The data
oral_data.txt

see

Distribution of the individual parameters

The structural model
oral1_1cpt_kaVCI

The covariate model

0 1 0

Fixed effects

2	100	2
	0	

Data Information

Data file

oral_data.txt

Sep.

lt

Accept

Format

☐ nlme ☒ NONMEM

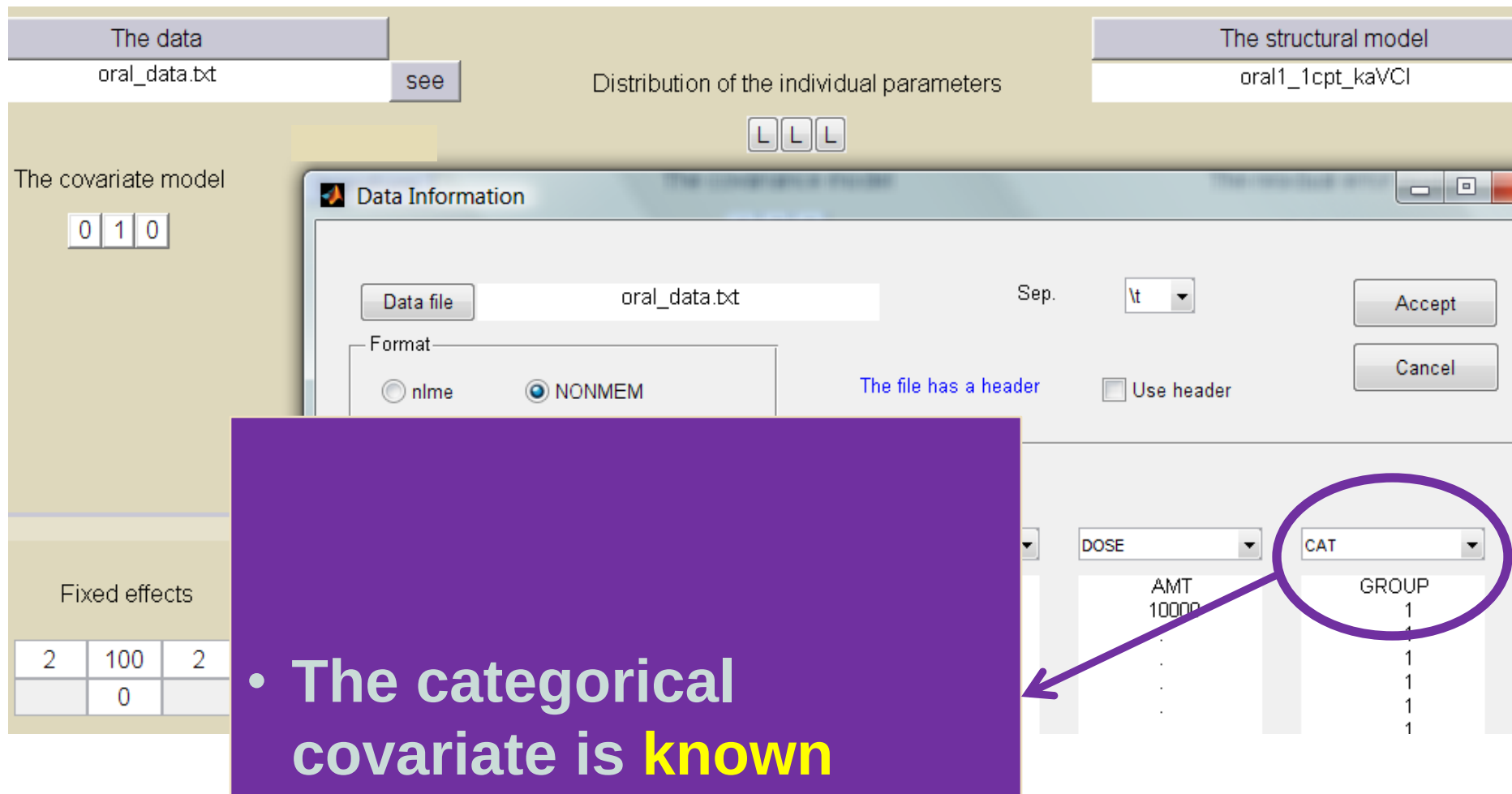
The file has a header ☐ Use header

Cancel

ID	TIME	Y	DOSE	CAT
ID	TIME	DV	AMT	GROUP
1	0	.	10000	1
1	0.25	65.6722	.	1
1	0.5	91.8429	.	1
1	0.75	141.897	.	1
1	1	113.549	.	1
1	1.5	170.305	.	1

1) Supervised learning (the labels are known)

Categorical covariate model building with MONOLIX



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Distribution of the individual parameters

The structural model
oral1_1cpt_kaVCI

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Data Information

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☐ Use header

Accept

Cancel

DOSE

AMT
10000

CAT

GROUP

1
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1
1

- The categorical covariate is **known**

1) Supervised learning (the labels are known)

Categorical covariate model building with MONOLIX

The data
oral_data.txt

see

Distribution of the individual parameters

The structural model
oral1_1cpt_kaVCl

The covariate model
0 1 0

Data Information

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Sep.: \t

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Accept

Cancel

Fixed effects

2	100	2
	0	

- Different volumes in the 2 groups
- The categorical covariate is **known**

DOSE

AMT
10000

CAT

GROUP

1
1
1
1
1

2) Unsupervised learning (the labels are unknown)

Mixture model building with MONOLIX

The data
oral_data.txt

see

Distribution of the individual parameters

The structural model
oral1_1cpt_kaVCI

mixture

There is no covariate

Fixed effects
2 100 2

Data file

oral_data.txt

Sep.

lt

Format

☐ nlme

☒ NONMEM

The file has a header

☐ Use header

Accept

Cancel

IDTIMEYDOSE

IDTIMEYDOSE

100.2565.672210000

10.591.8429.

10.5141.897.

10.5113.549.

10.5170.305.

2) Unsupervised learning (the labels are unknown)

Mixture model building with MONOLIX

The data
oral_data.txt

see

Distribution of the individual parameters

The structural model
oral1_1cpt_kaVCI

mixture

There is no covariate

Data Information

Data file: oral_data.txt

Sep.: \t

Format: ☐ nlme ☒ NONMEM

The file has a header

☐ Use header

Accept

Cancel

Fixed effects

2	100	2
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DOSE

AMT
10000
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- The categorical covariate is **unknown**

2) Unsupervised learning (the labels are unknown)

Mixture model building with MONOLIX

The data
oral_data.txt

The structural model
oral1_1cpt_kaVCI

Distribution of the individual parameters
L L L

There is no covariate

Fixed effects
2 100 2

mixture

Data Information

Data file: oral_data.txt

Sep.: t

Format: ☐ nlme ☒ NONMEM

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Accept

Cancel

ID	TIME	Y	DOSE
ID	TIME	DV	AMT
1	0	.	10000
1	0.25	65.6722	.
1	0.5	91.8429	.
1	0.75	141.897	.
1	1	113.549	.
1	1.5	170.305	.

2) Unsupervised learning (the labels are unknown)

Mixture model building with MONOLIX

The screenshot displays the MONOLIX software interface for building a mixture model. The main window is titled 'Distribution of the individual parameters' and contains several sections:

- The data:** 'oral_data.txt' with a 'see' button.
- The structural model:** 'oral1_1cpt_kaVCI'.
- The residual error model:** 'model' set to 'prop' and 'r' set to '1'.
- Fixed effects:** A table with values 2, 100, and 2.
- Residual error parameters:** A table with values 0, 1, and 1.

A 'mixture' dialog box is open, showing 'Latent Categorical Covariates' with 'lcat1' set to 2. The dialog also includes buttons for '+', '-', and 'Full'.

Overlaid on the bottom of the screenshot is a purple box containing the following list:

- 1 « latent » categorical covariate
- 2 categories (2 groups)

2) Unsupervised learning (the labels are unknown)

Mixture model building with MONOLIX

The screenshot displays the MONOLIX software interface for building a mixture model. The interface is divided into several sections:

- The data:** Shows the file `oral_data.txt` and a `see` button.
- The structural model:** Shows the model name `oral1_1cpt_kaVCI`.
- The residual error model:** Shows the `model` set to `prop` and the `r` parameter set to `y=f+t`.
- Fixed effects:** A table with values 2, 100, 2 in the first row and 0 in the second row.
- The covariate model:** A section circled in purple, showing a table with values 0, 1, 0. An arrow points from this section to a dialog box.
- mlxLatCov dialog box:** A window titled `mlxLatCov` showing `Latent Categorical Covariates` with a `+` button. Below it, `lcat1` is set to 2 with a `-` button.
- Buttons:** `mixture`, `L L L`, `diagonal`, `Full`, and `cat. var.` buttons are visible.

A purple box at the bottom contains the following text:

- Different volumes in the 2 groups
- The categorical covariate is **estimated**

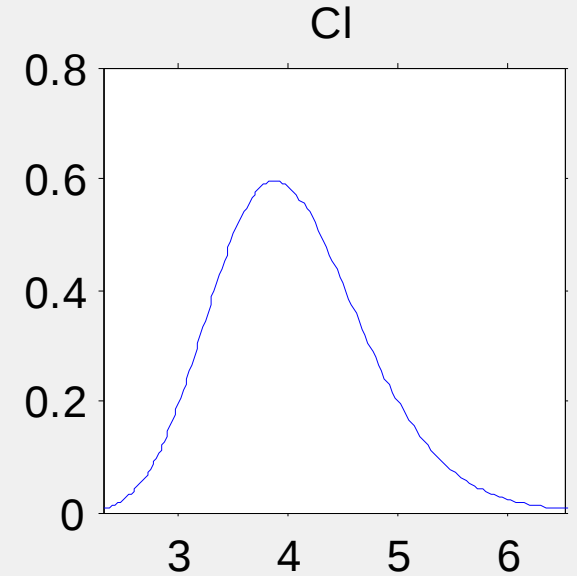
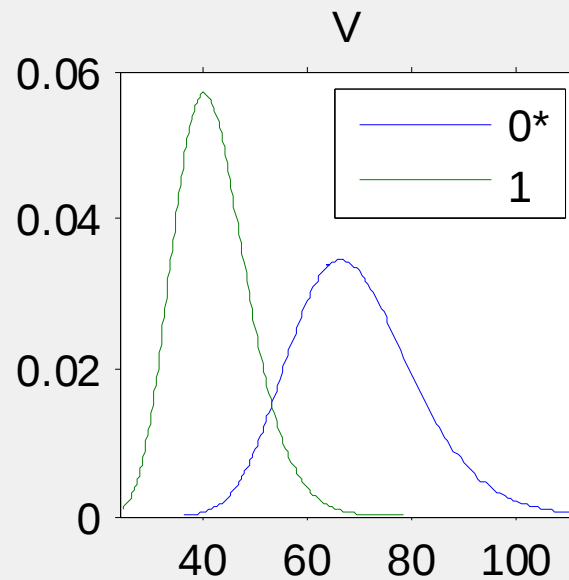
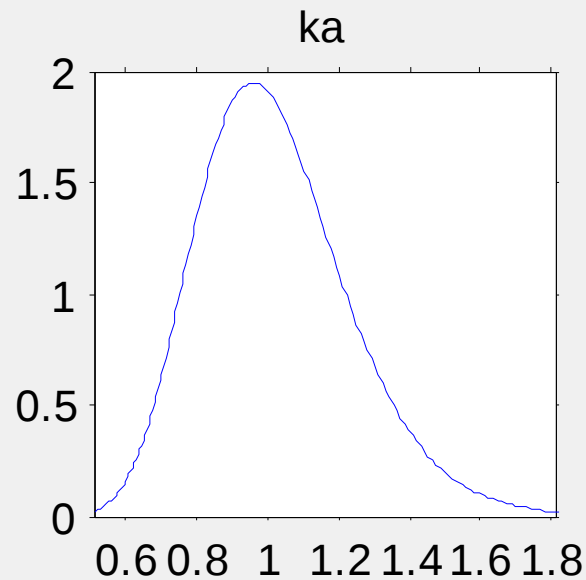
The estimated population parameters (SAEM for mixtures)

Known
categorical covariate

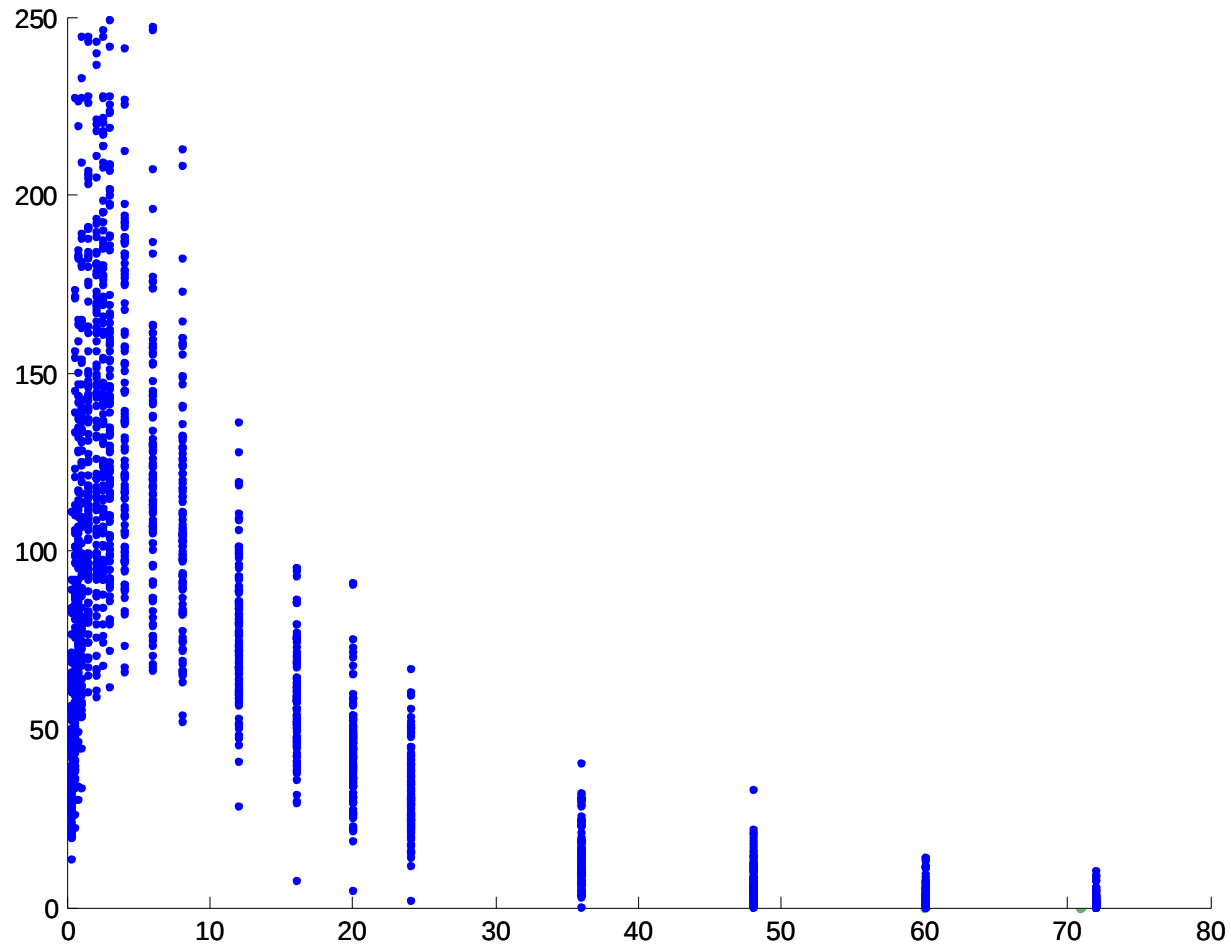
Estimated
categorical covariate

	« true values »	estimations	r.s.e.(%)	estimations	r.s.e.(%)
ka	1	1	3	1	3
V	70	68.3	2	65.6	3
β_V	-0.5	-0.507	8	-0.517	10
Cl	4	4	2	4	2
ω_{ka}	0.2	0.197	11	0.208	11
ω_V	0.2	0.179	8	0.186	11
ω_{Cl}	0.2	0.169	8	0.168	7
b	0.2	0.199	2	0.199	2
π_1	0.6	0.6	-	0.686	10
π_2	0.4	0.4	-	0.314	21

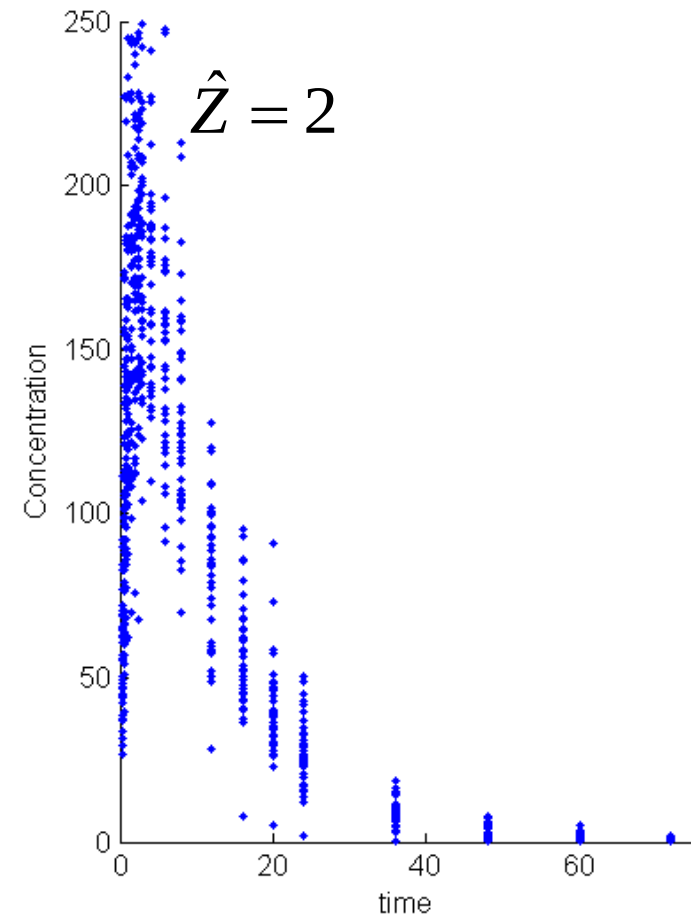
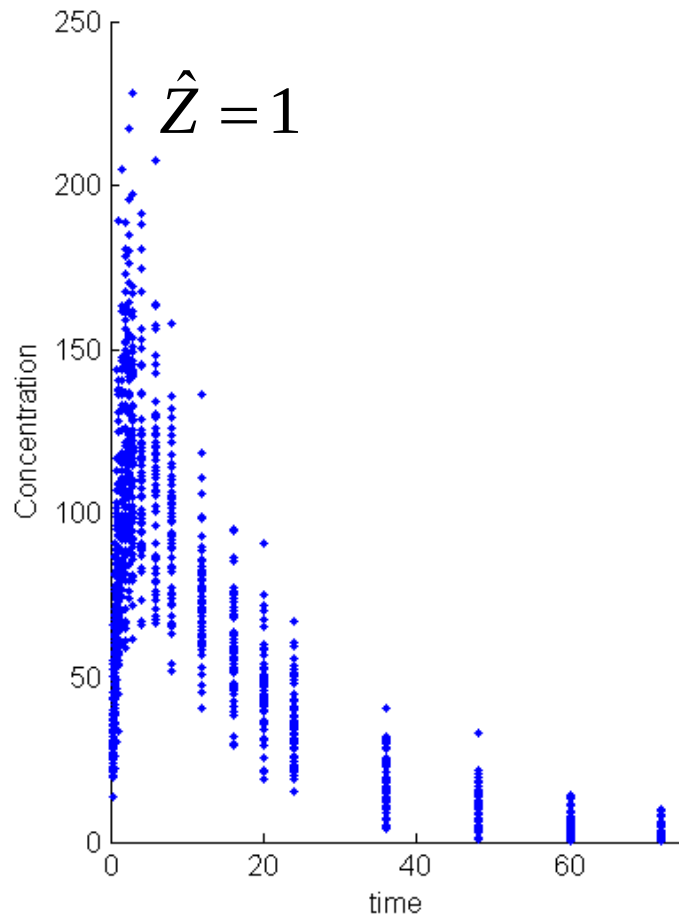
The estimated population distributions



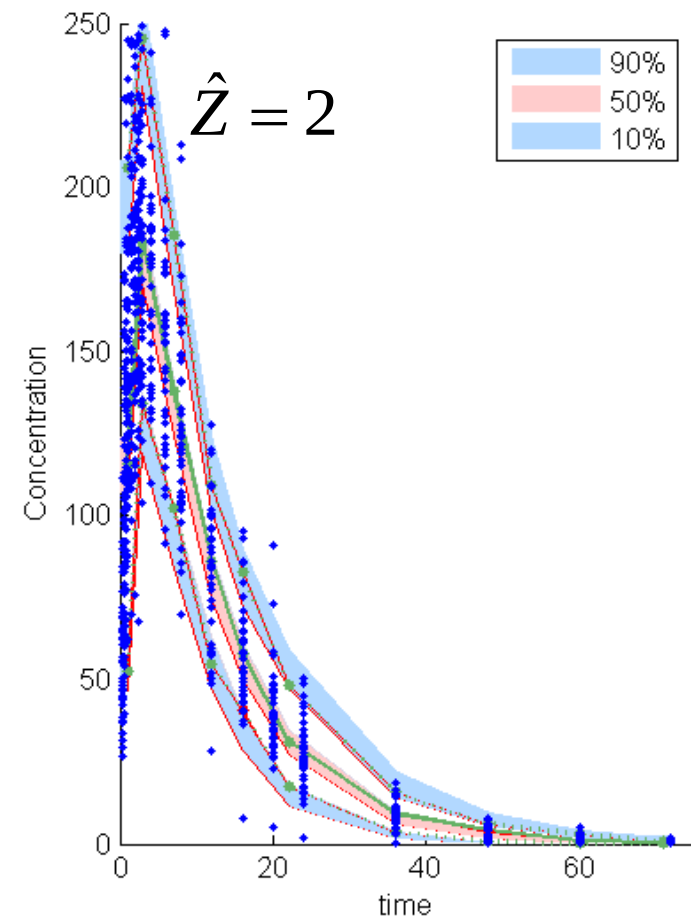
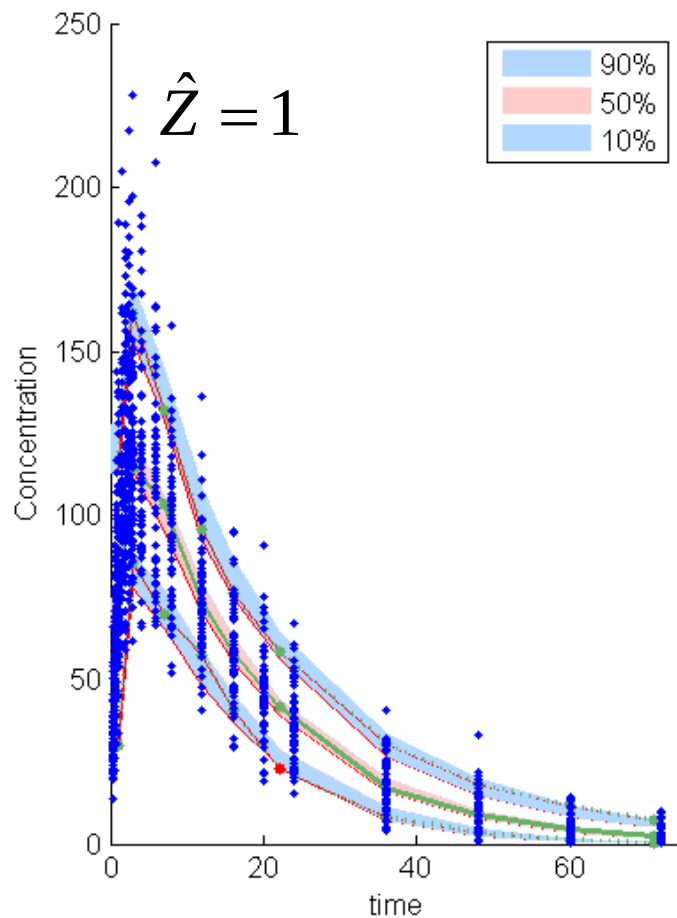
VPCs: global VPC includes both groups



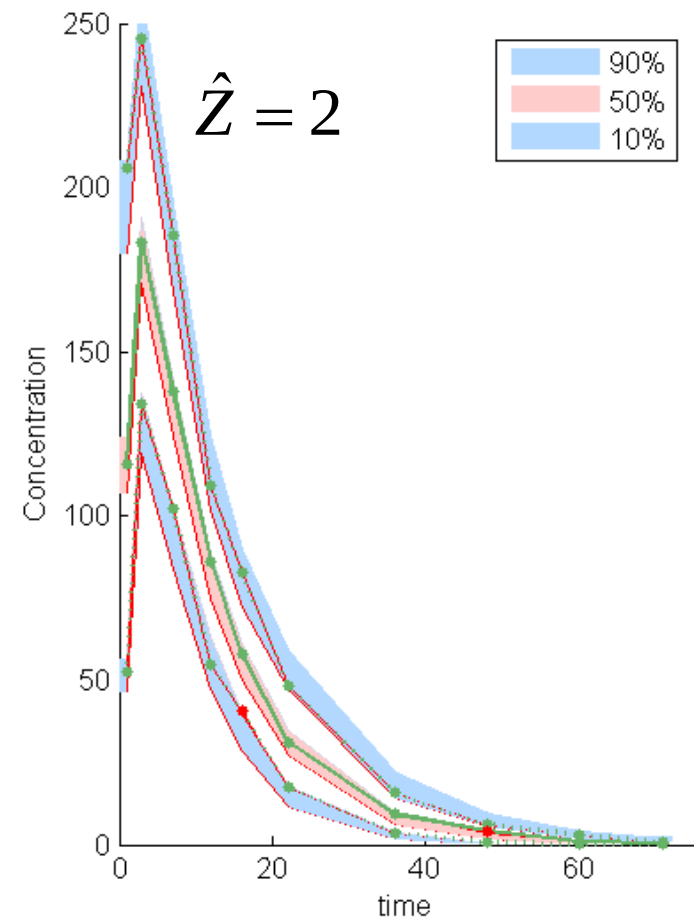
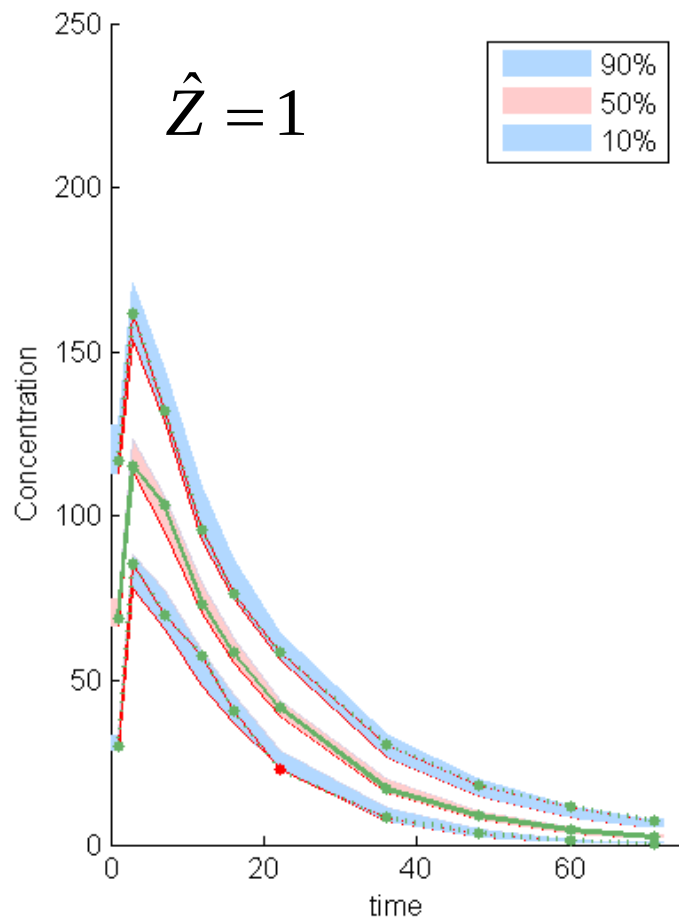
VPCs: use the estimated latent categorical covariate to stratify the data



VPCs: use the estimated latent categorical covariate to stratify the data



VPCs: use the estimated latent categorical covariate to stratify the data



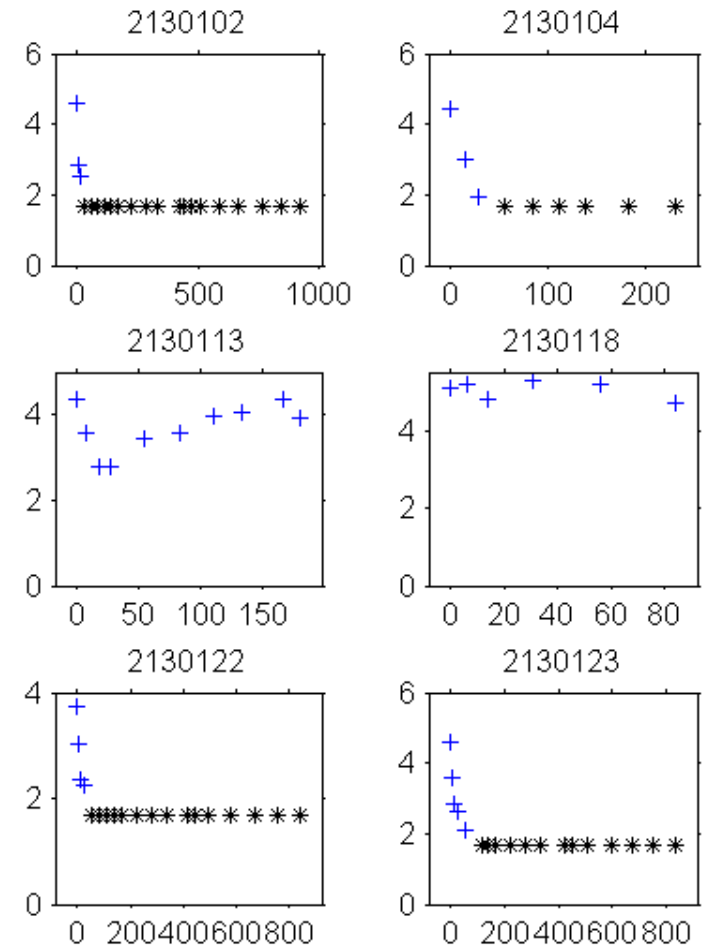


II

Mixture of models

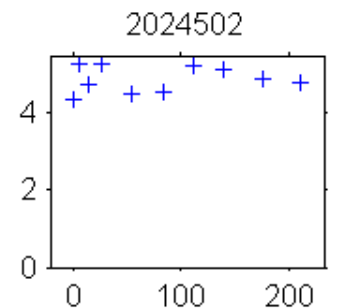
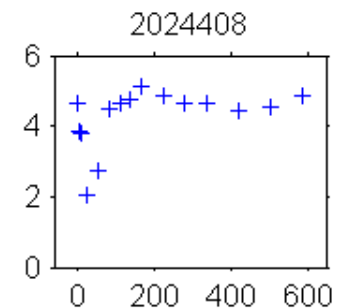
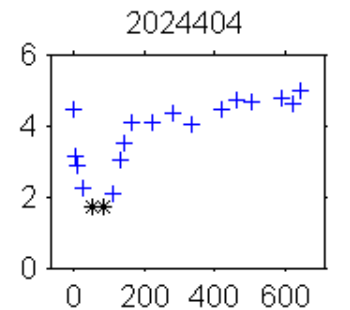
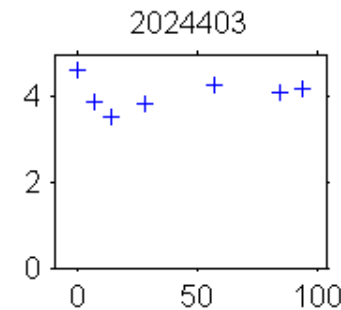
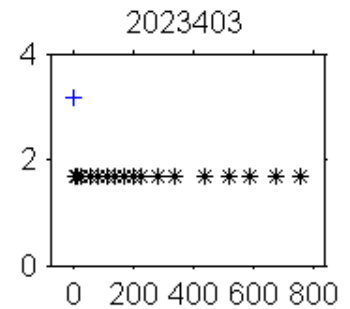
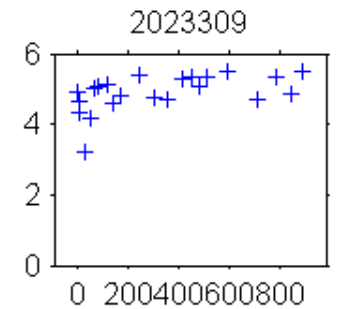
Some data

- POWER studies were conducted by TIBOTEC
- Viral load data from 578 HIV infected patients
- Randomized, controlled, partially blinded studies
- 3 studies of up to 144 weeks, performed in highly treatment experienced patients, using darunavir/ritonavir (DRV/RTV) or an investigator-selected control PI, combined with an optimised background regimen (OBR), consisting of nucleoside reverse transcriptase inhibitors with or without the fusion inhibitor enfuvirtide.



Some data

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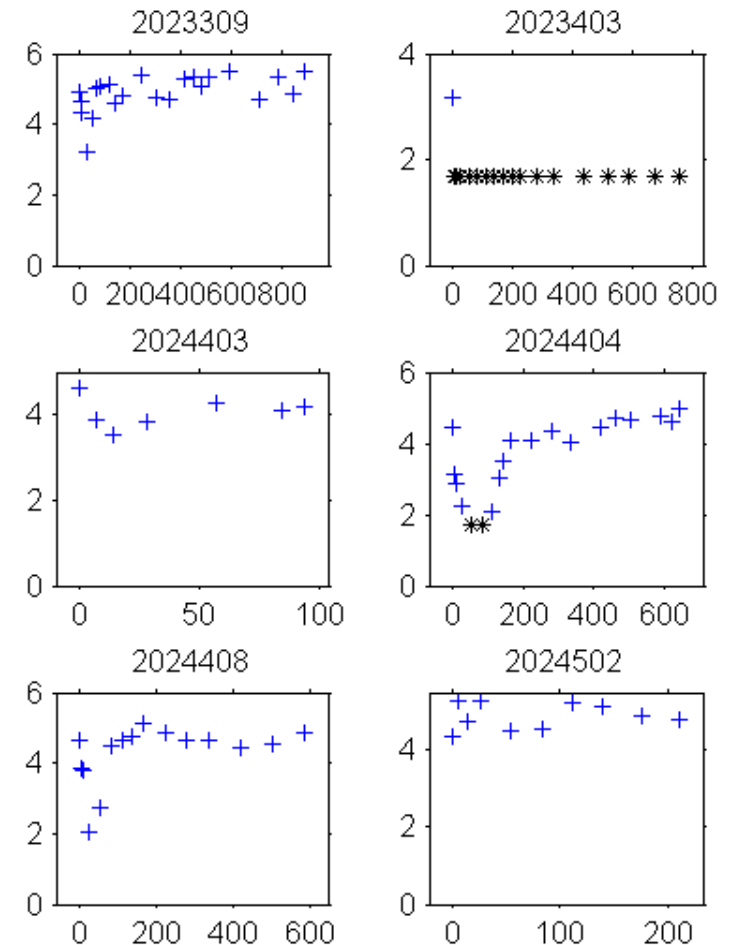


Some data

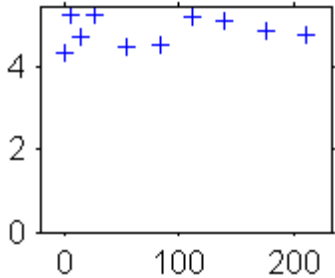
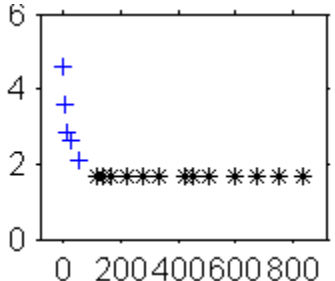
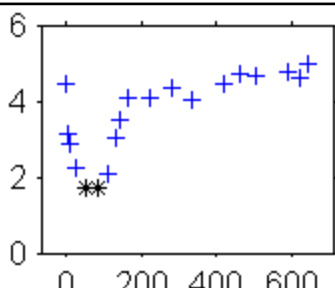
The data exhibit three different typical profiles:

- non-responders,
- responders,
- rebounders.

=> We propose to describe these viral load data with a mixture of three models



Between subject model mixture (unsupervised learning)

3 different profiles	3 different groups	3 different VK models
	nonresponder $z_i = 1$	$f_1(t) = A_1 + A_2$
	responder $z_i = 2$	$f_2(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$
	rebounder $z_i = 3$	$f_3(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + \frac{A_3}{1 + e^{-\lambda_3(t-t^*)}}$

Between subject model mixture (unsupervised learning)

$$f_1(t) = A_1 + A_2$$

$$f_2(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t}$$

$$f_3(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + \frac{A_3}{1 + e^{-\lambda_3(t-t^*)}}$$

$$p_1 = P(z_i = 1)$$

$$p_2 = P(z_i = 2)$$

$$p_3 = P(z_i = 3)$$

Population approach:

- IIV on $A_1, \lambda_1, A_2, \lambda_2, A_3, \lambda_3, t^*$
- No variability on p_1, p_2, p_3

Between subject model mixture MLXTRAN implementation

\$PROBLEM Between Subject Model Mixture

\$PSI A1 L1 A2 L2 A3 L3 TL S1 S2

\$EQUATION

$f1 = A1 + A2$

$f2 = A1 * \exp(-L1 * T) + A2 * \exp(-L2 * T)$

$f3 = A1 * \exp(-L1 * T) + A2 * \exp(-L2 * T) + A3 / (1 + \exp(-L3 * (T - TL)))$

$p1 = 1 / (1 + S1 + S2)$

$p2 = S1 / (1 + S1 + S2)$

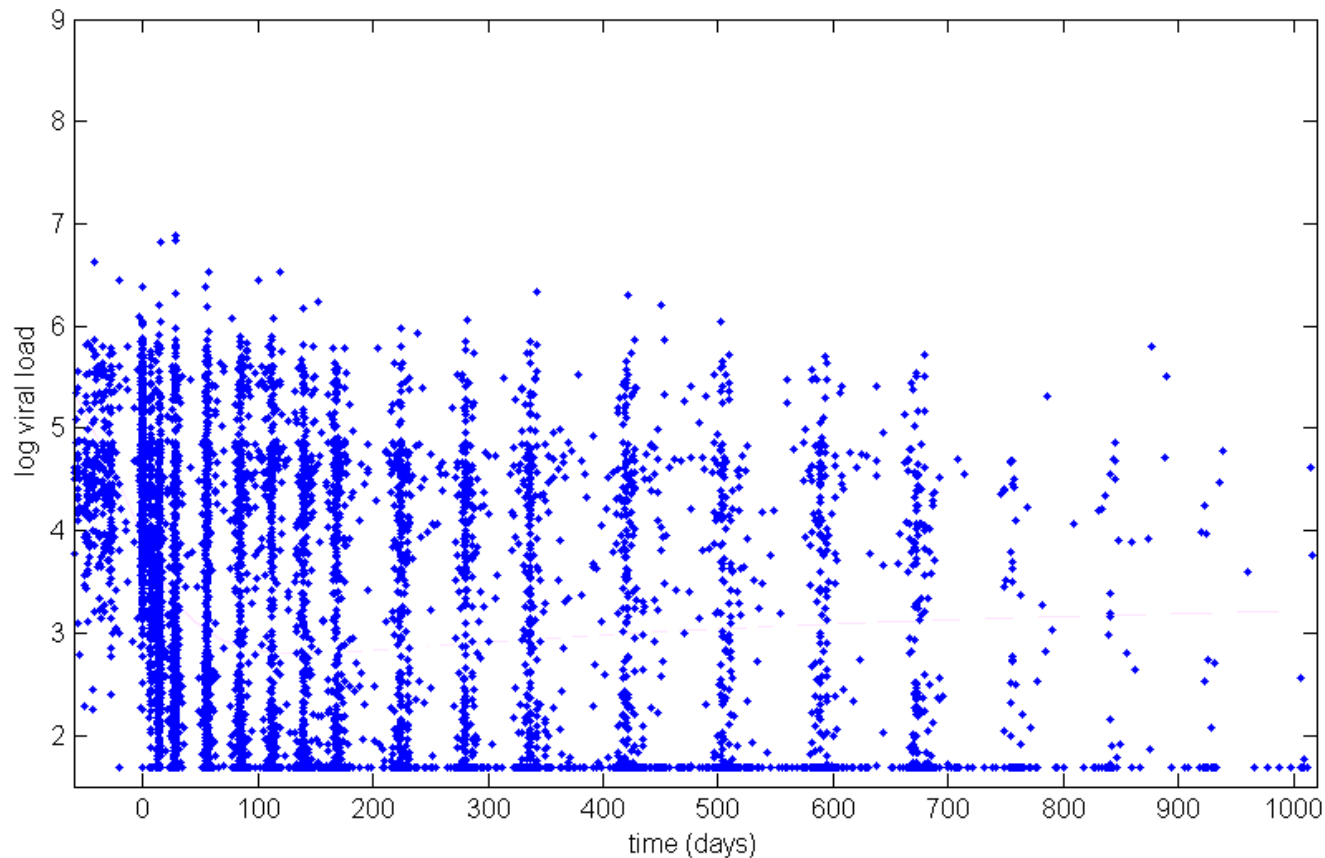
$p3 = S2 / (1 + S1 + S2)$

\$OUTPUT

OUTPUT1 = BSMM(f1,p1,f2,p2,f3,p3)

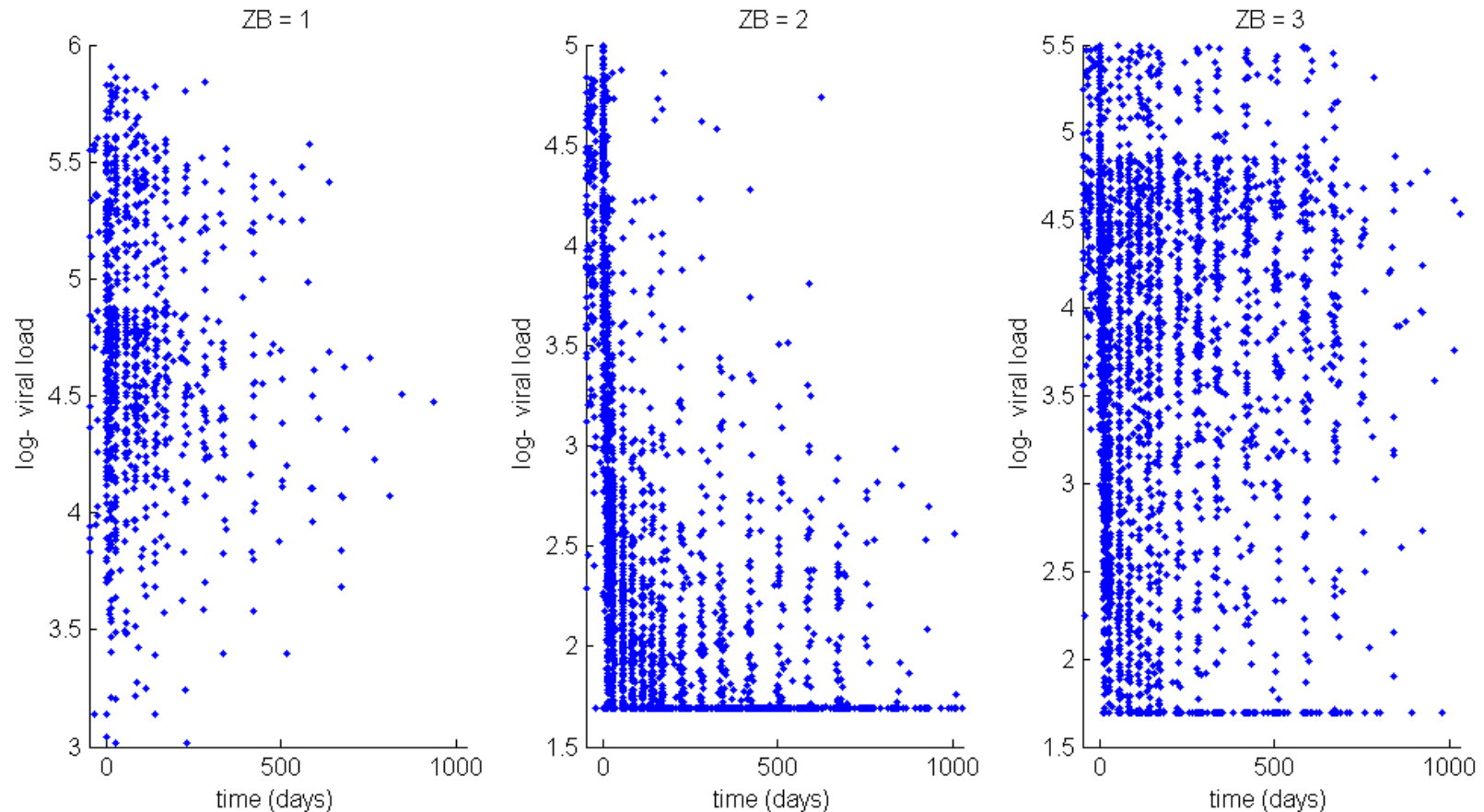
Between subject model mixture

Some results



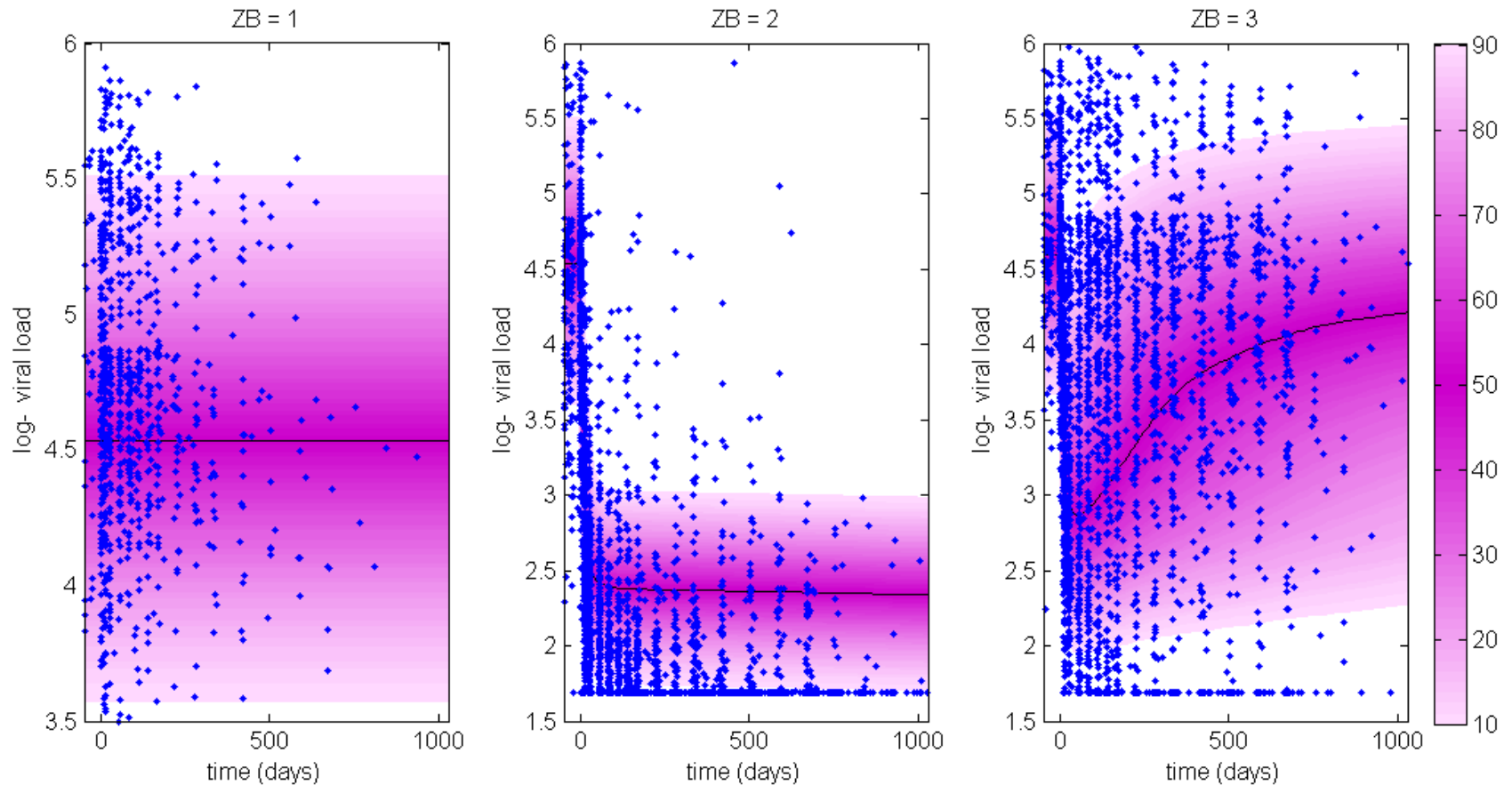
Between subject model mixture

Some results



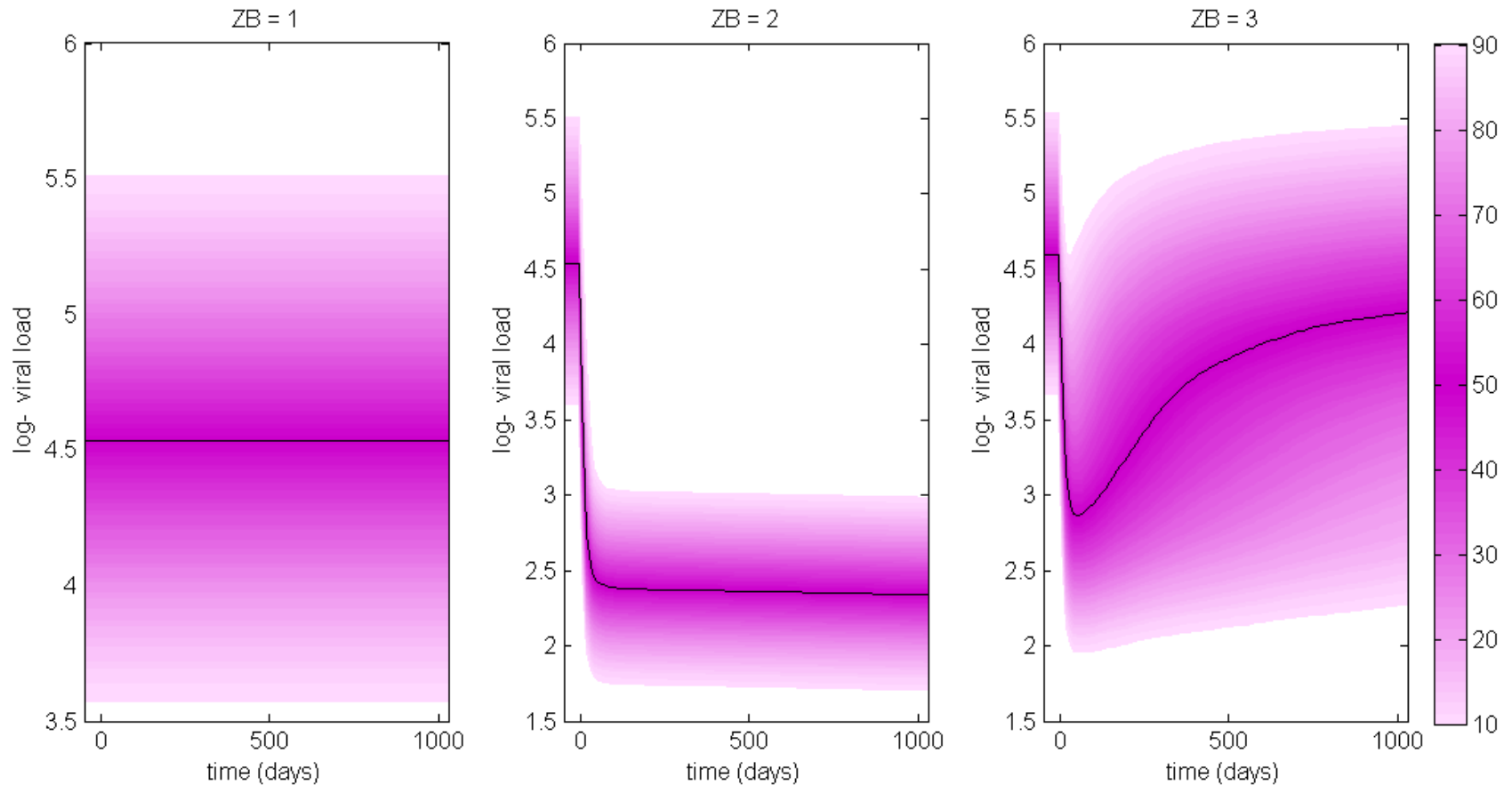
Between subject model mixture

Some results



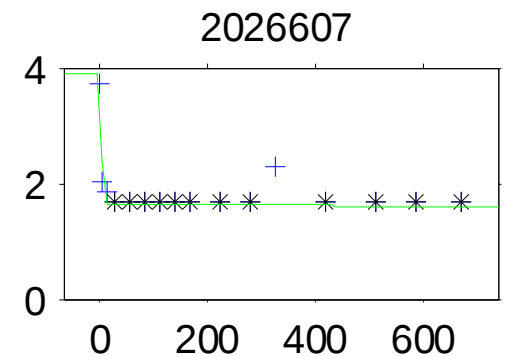
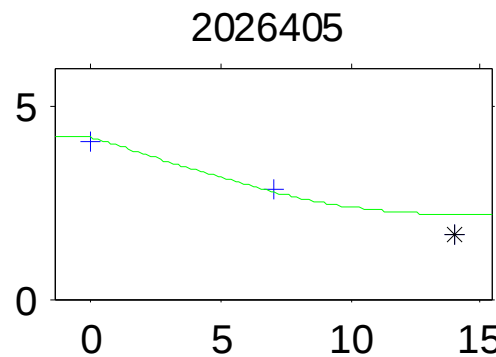
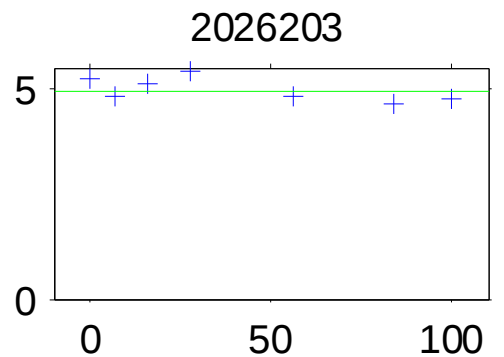
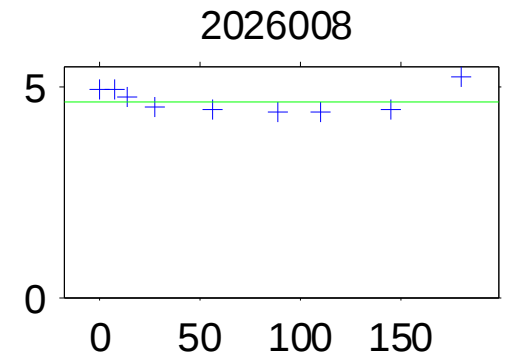
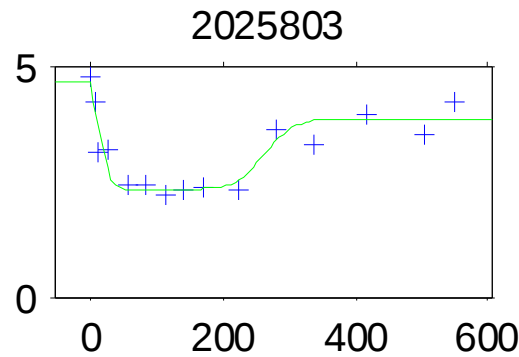
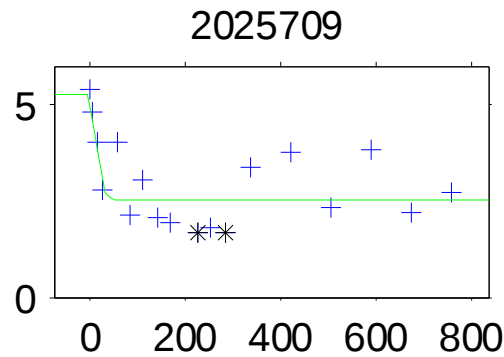
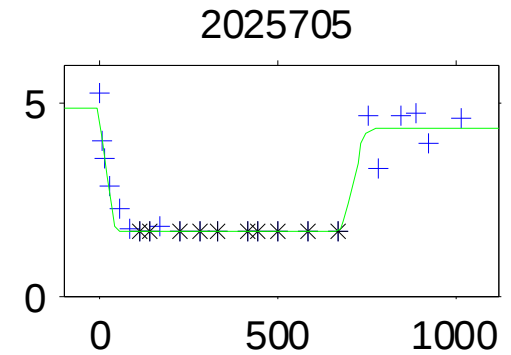
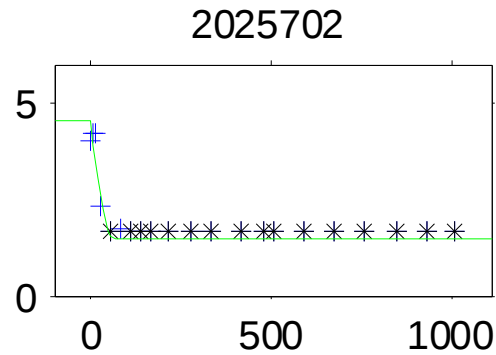
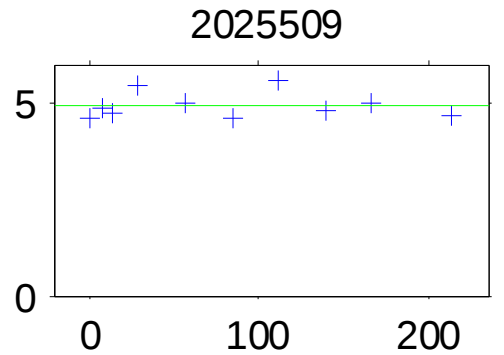
Between subject model mixture

Some results



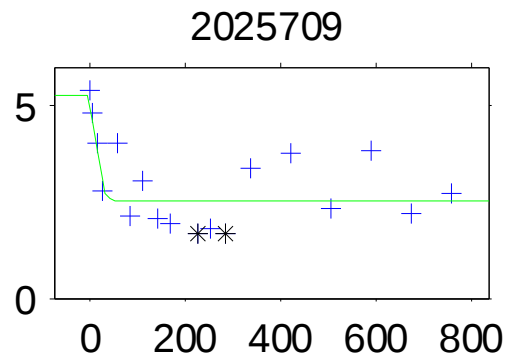
Between subject model mixture

Some results



Between subject model mixture

Some results



Should we consider this subject

- as a non responder?
- as a responder?
- as a rebounder?

Or someone « in between »?

Within subject model mixture

$$\left. \begin{aligned} f_1(t) &= A_1 + A_2 \\ f_2(t) &= A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} \\ f_3(t) &= A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + \frac{A_3}{1 + e^{-\lambda_3(t-t^*)}} \end{aligned} \right\} \quad f = p_1 f_1 + p_2 f_2 + p_3 f_3$$

Population approach:

- IIV on $A_1, \lambda_1, A_2, \lambda_2, A_3, \lambda_3, t^*$
- **IIV on p_1, p_2, p_3**

MONOLIX IMPLEMENTATION

Within Subject Model Mixture

\$PROBLEM Within Subject Model Mixture

\$PSI A1 L1 A2 L2 A3 L3 TL S1 S2

\$EQUATION

$f1 = A1 + A2$

$f2 = A1 * \exp(-L1 * T) + A2 * \exp(-L2 * T)$

$f3 = A1 * \exp(-L1 * T) + A2 * \exp(-L2 * T) + A3 / (1 + \exp(-L3 * (T - TL)))$

$p1 = 1 / (1 + S1 + S2)$

$p2 = S1 / (1 + S1 + S2)$

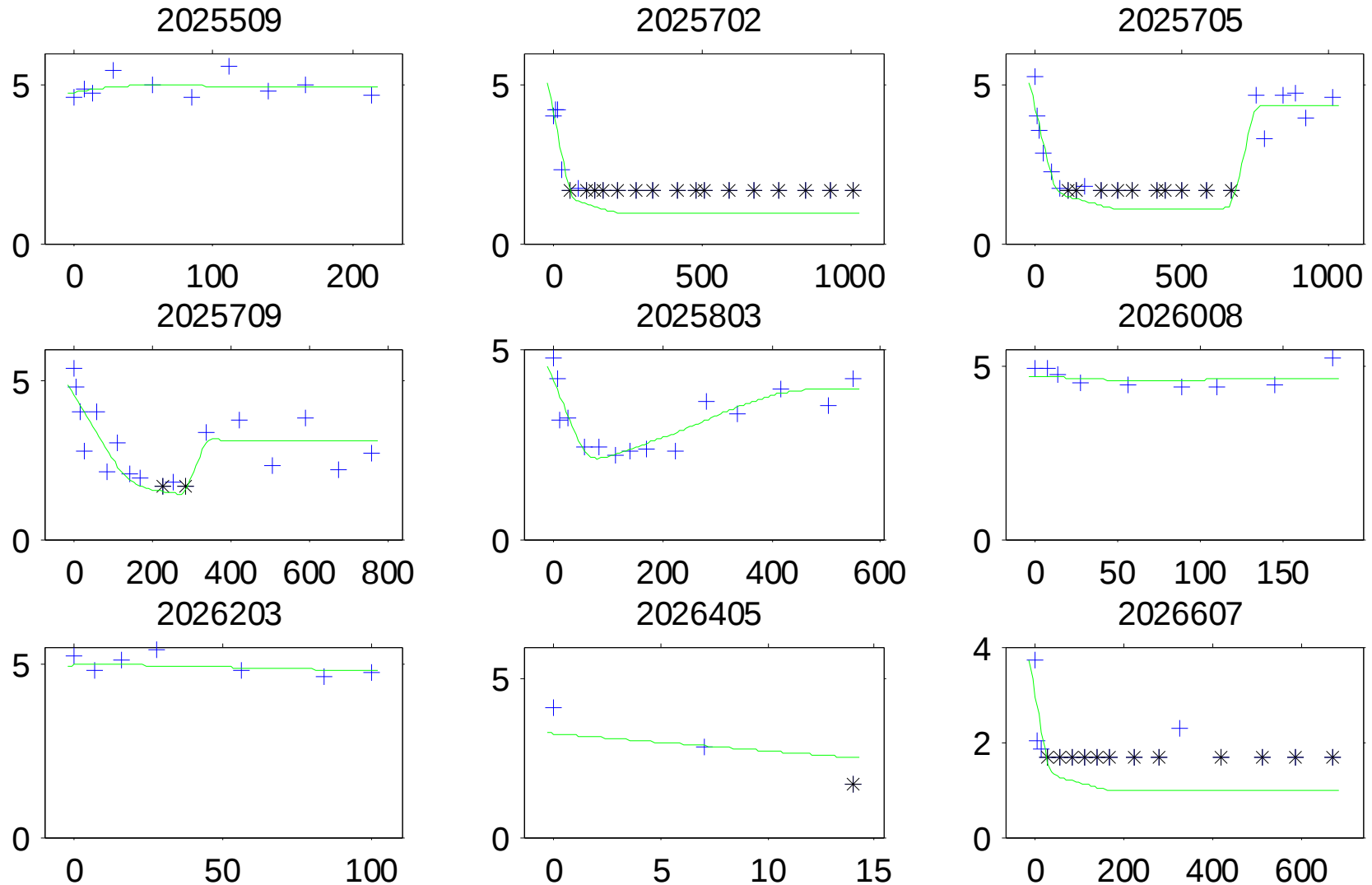
$p3 = S2 / (1 + S1 + S2)$

\$OUTPUT

OUTPUT1 = WSMM(f1,p1,f2,p2,f3,p3)

Within subject model mixture

Some results



SAEM for mixture models

at iteration k,

- i) **simulate** the latent categorical covariates (z_i) and the individual parameters (ψ_i)

$$\left(z_i^{(k)}, \psi_i^{(k)}\right) \sim p\left(z_i, \psi_i \mid y_i; \theta^{(k)}\right)$$

- ii) **estimate** the expectation of the complete log-likelihood using stochastic approximation

$$Q_{k+1}(\theta) = Q_k(\theta) + \gamma_k \left(LL(y_i, z_i^{(k)}, \psi_i^{(k)}; \theta) - Q_k(\theta) \right)$$

- iii) **update** the estimation of the population parameters

$$\theta_{k+1} = \text{Argmax} Q_{k+1}(\theta)$$

Conclusions

- The SAEM algorithm was extended for the analysis of mixture models
- The algorithm handles different types of mixtures (mixture distributions, between and within model mixtures)
- The estimated labels can be used to stratify the data
- The algorithms are implemented in new MONOLIX 3.2 and supported by MLXTRAN
- Other possible extensions are straightforward (mixture of error models...)