Mixture models in PDx-MC-PEM

Serge Guzy, PhD

President POP-PHARM; Inc
Department of Pharmacokinetics, XOMA

MC-PEM METHODOLOGY (Prior Sampling)

- Sample from the prior distribution and evaluate the weighted individual likelihood at each sample k

$$z_{(k)i} = \frac{l(y_i, \theta_{(k)i})}{\sum_{k=1}^{r_i} l(y_i, \theta_{(k)i})}$$

- Compute the individual weighted mean

$$\overline{\theta}_{Gi} = \sum_{k=1}^{r_i} z_{(k)i} \theta_{(k)i}$$

- Compute the individual variance covariance matrix

$$\overline{B}_{Gi} = \sum_{k=1}^{r_i} z_{(k)i} (\theta_{(k)i} - \overline{\theta}_{Gi})(\theta_{(k)i} - \overline{\theta}_{Gi})'$$

MC-PEM METHODOLOGY (Direct Sampling)

◆Update the prior

Update the Population means

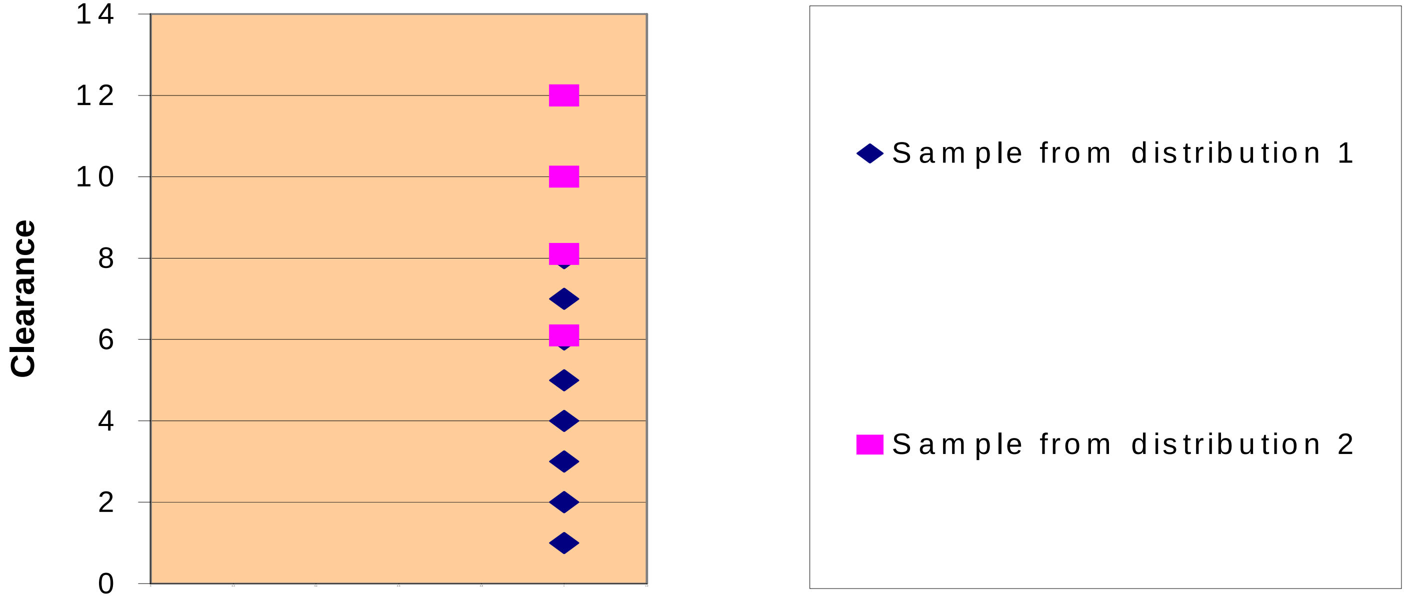
$$\mu_{new} = \frac{1}{m}\sum_{i=1}^{m}\overline{\theta}_{Gi}$$

Update the Population Variances and Covariances

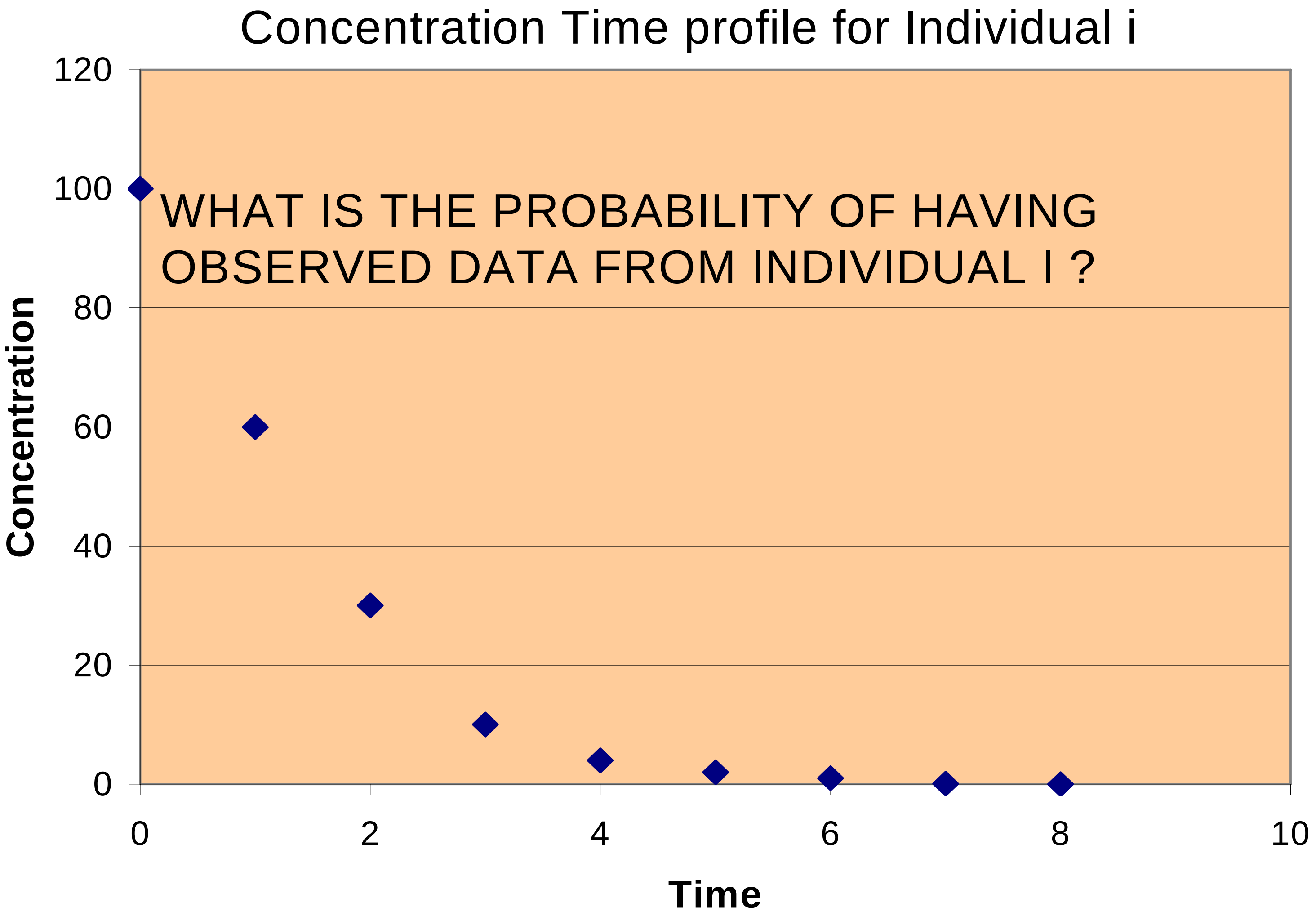
$$\Omega_{new} = \frac{1}{m}\sum_{i=1}^{m}\left(\overline{\theta}_{Gi} - \mu_{new}\right)\left(\overline{\theta}_{Gi} - \mu_{new}\right)' + \frac{1}{m}\sum_{i=1}^{m}\overline{B}_{Gi}$$

MC-PEM Mixture algorithm

Suppose 1/3 individuals sampled from distribution 1 (p) and 2/3 individuals sampled from distribution 2 (1-p): Example shows the different Clearance we could have



MC-PEM Mixture algorithm



MC-PEM Mixture algorithm

Probability to observe individual I data =
Probability that any individual is coming from distribution 1 (p_1) x Probability to observe data from individual I, given the individual is coming from distribution 1 (EXP(LOG-LIKELIHOOD)=pi,1)

+ Probability that any individual is coming from distribution 2 ($1-p_1$) x Probability to observe data from individual I, given the individual is coming from distribution 2 (EXP(LOG-LIKELIHOOD)=pi,2)

Contribution from distribution 1 Contribution from distribution 2

~ p_1 x pi,1 + ($1-p_1$) x pi,2

XOMA

MC-PEM Mixture algorithm

Contribution from distribution 1 in percent

$$\frac{p \times pi,1}{p \times pi,1 + (1-p) \times pi,2} = \text{weight}_{i,1}$$

Contribution from distribution 2 in percent

$$\frac{(1-p) \times pi,2}{p \times pi,1 + (1-p) \times pi,2} = \text{weight}_{i,2}$$

XOMA

The algorithm

Update of p for each distribution
At the first iteration must enter initial estimate for *p_k*

From iteration 2: $p_k = \frac{1}{n}\sum_{i=1}^{n} weight_{i,k}$

Update of population mean and variances
For each distribution

$$\mu_{new,k} = \frac{\sum_{i=1}^{m} weight_{i,k}\bar{\theta}_{Gi,k}}{\sum_{i=1}^{m} weight_{i,k}}$$

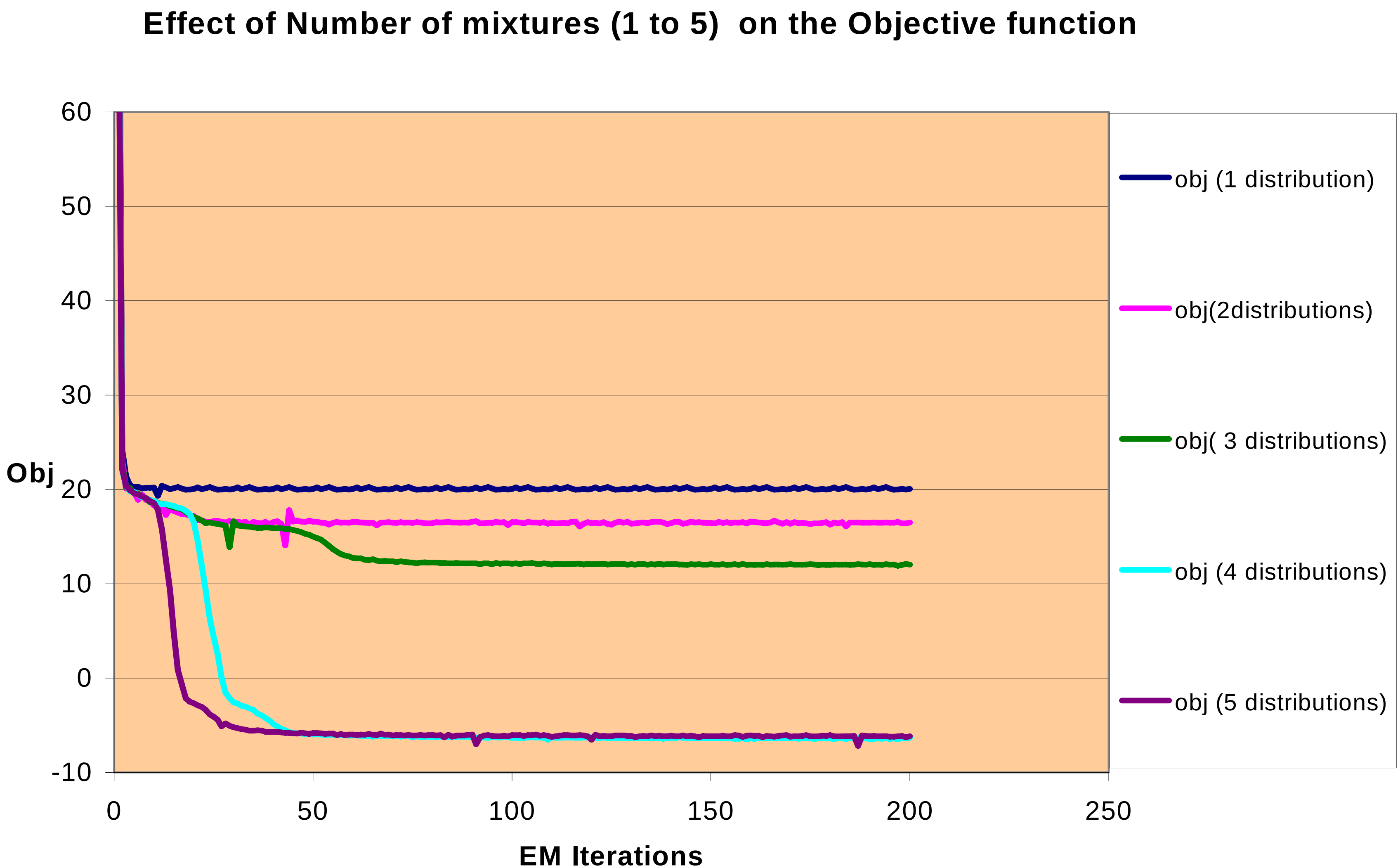
$$\Omega_{new,k} = \frac{\sum_{i=1}^{m} weight_{i,k}\left(\bar{\theta}_{Gi,k} - \mu_{new,k}\right)\left(\bar{\theta}_{Gi,k} - \mu_{new,k}\right)' + \sum_{i=1}^{m} weight_{i,k}\bar{B}_{Gi,k}}{\sum_{i=1}^{m} weight_{i,k}}$$

PDx-MC-PEM Example

True Population Characteristics

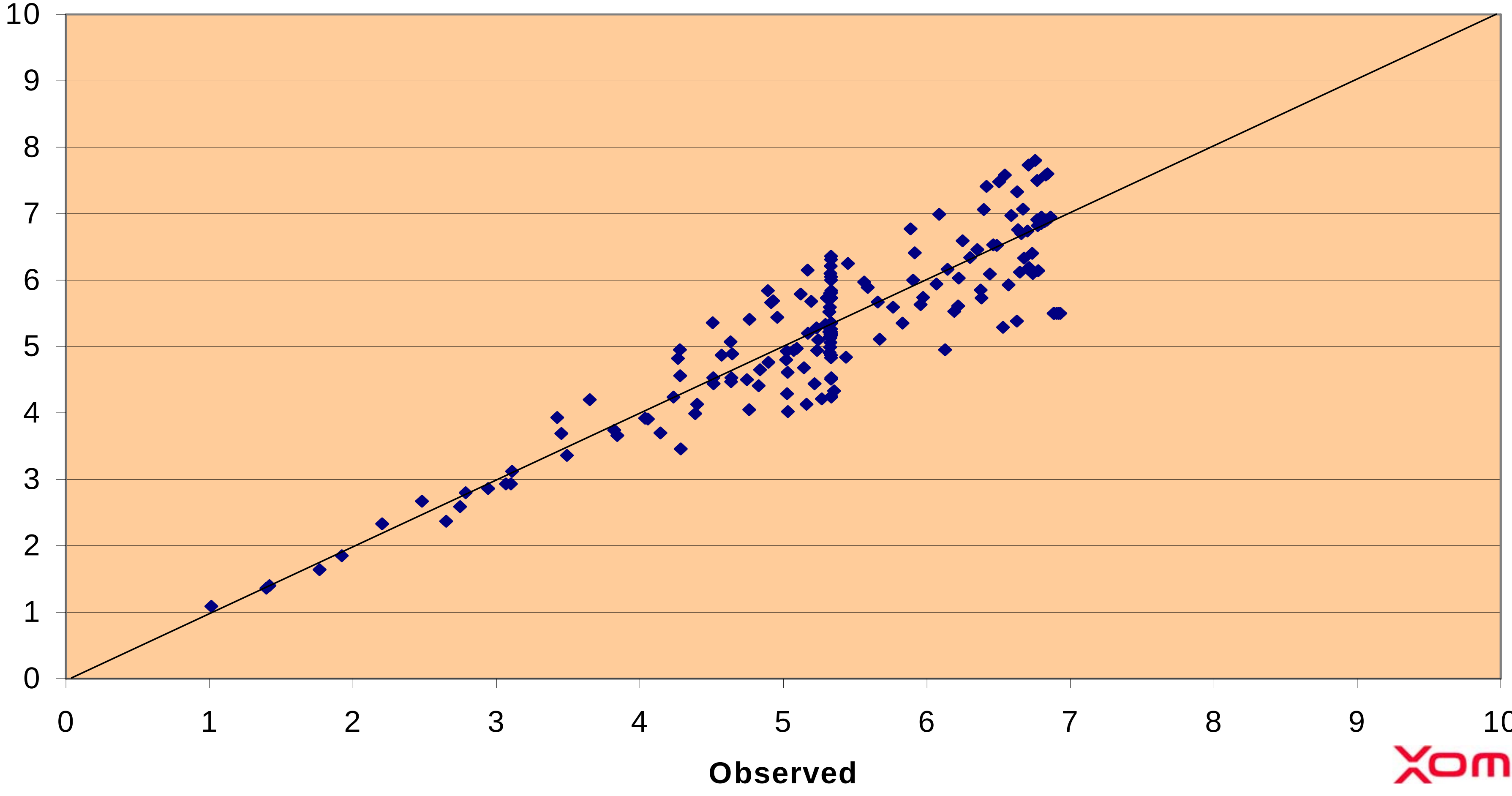
	Proportion	Cl mean	% Variability
Distribution			
1	20%	0.1	30%
2	20%	0.5	30%
3	20%	2	30%
4	20%	5	30%
5	20%	10	30%

Results


Effect of Number of mixtures (1 to 5) on the Objective function
60
50
40
30
20
10
0
-10
Obj
0
50
100
150
200
250
EM Iterations
obj (1 distribution)
obj(2distributions)
obj(3 distributions)
obj (4 distributions)
obj (5 distributions)

Results

Observed vs predicted Individual Concentration (predicted from the most likely distribution)



Results

Comparison between True and fitting Population

Fitting Population	Proportion	Cl mean	% Variability
Distribution			
1	20%	0.01	46.30%
2	8%	1.42	1.92%
3	2%	1.45	2.23%
4	20%	2.4	96.40%
5	50%	5.78	36.61%

	Proportion	Cl mean	% Variability
Distribution			
1	20%	0.1	30%
2	20%	0.5	30%
3	20%	2	30%
4	20%	5	30%
5	20%	10	30%

Fitting Results