The Monte-Carlo Parametric Expectation Maximization Algorithm

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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**

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

- ❖**Compute the individual variance covariance matrix**

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

MC-PEM METHODOLOGY (Direct Sampling)

- **Update the prior**

Update the Population means

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

Update the Population Variances and Covariances

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

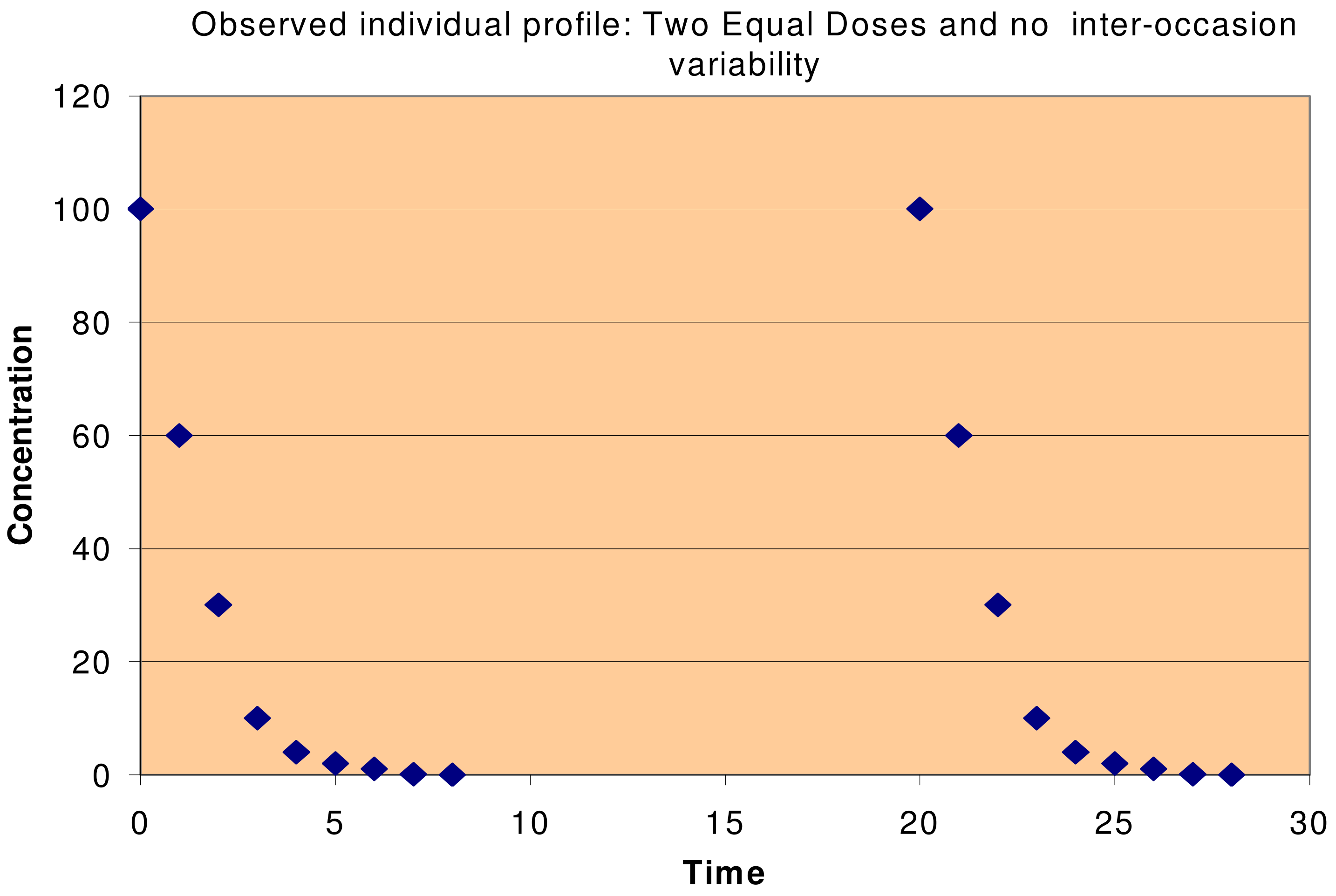
MC-PEM METHODOLOGY (Prior Sampling)

- **Repeat all the previous steps with the new population means, variances, covariances and σ (new prior) until no change is reported in the prior**

- **The objective function will be optimal once no change is detected in each of the estimated parameters**

Inter-Occasion Variability in MC-PEM

Typical Individual Profile without inter-occasion variability



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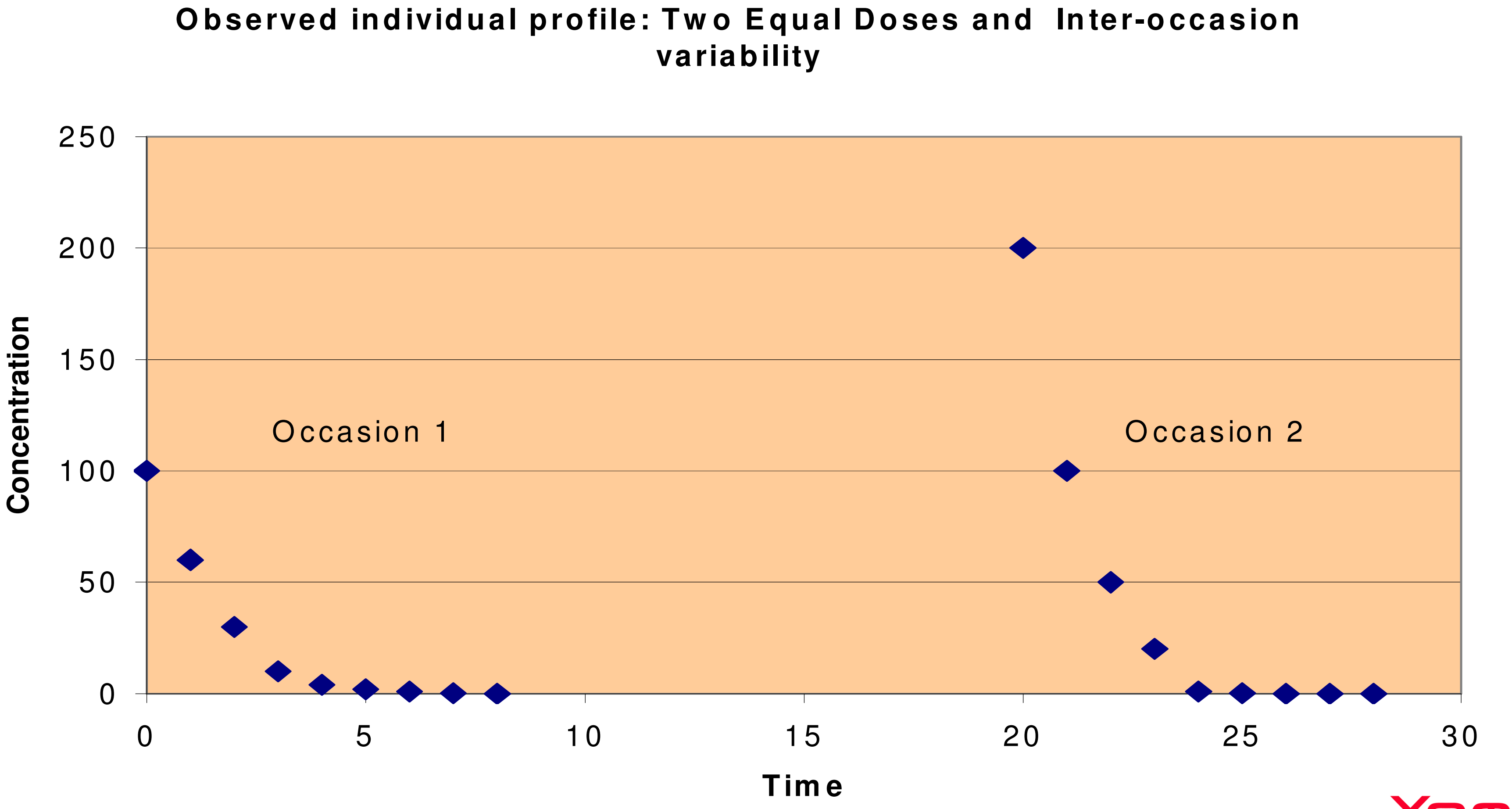
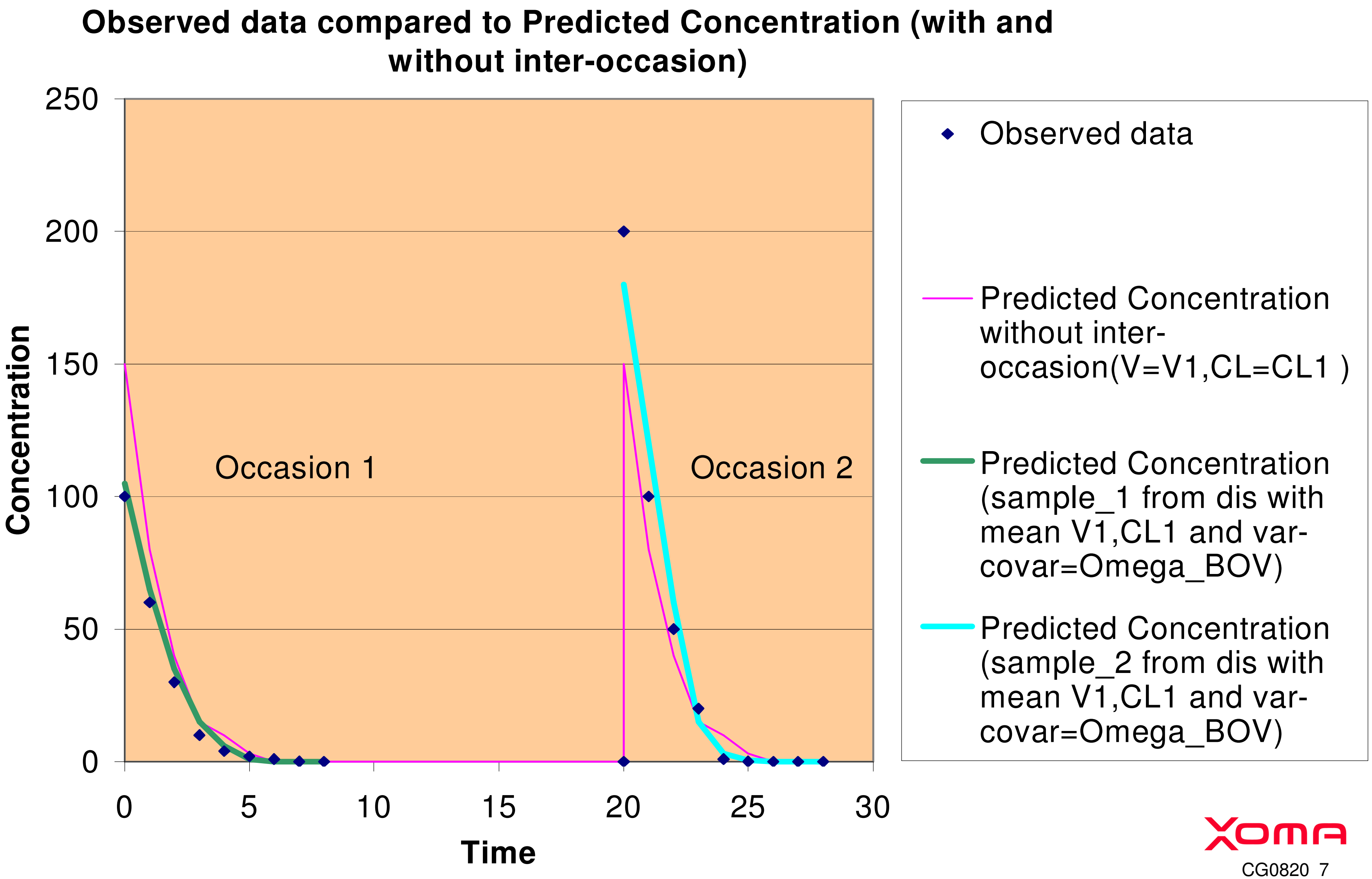
Typical Individual Profile with inter-occasion variability



Inter-Occasion Variability in MC-PEM



Inter-Occasion Variability in MC-PEM

The Algorithm

1. Start with first individual, i
2. Sample one set of parameters (k=1) from the prior distribution (One value of V and CL)
3. Sample one set of parameters for each occasion with mean V,CL and initial variance-covariance matrix you selected for Inter-occasion variability, Ω_{IOV}
4. Compute the normalized likelihood ($z_{k(i)}$)
5. k=k+1 and repeat steps 2-4 until the last sample ($k=r_i$)
6. i=i+1 and repeat Steps 1-5 until the last individual (i=n)
7. Update Population Mean, Between Subject and Inter-Occasion variability as follows

Inter-Occasion Variability in MC-PEM

Update of the Between subject Population

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

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

Inter-Occasion Variability in MC-PEM

Update of the Inter-occasion variability

$$\Omega_{IOV} = \frac{1}{n}\sum_{i=1}^{n}\sum_{k=1}^{r_i} z_{(k)_i} \sum_{j=1}^{noccasion} (\theta_{(k)_i} - \theta_{(k)_{i,j}})(\theta_{(k)_i} - \theta_{(k)_{i,j}})'$$

where:

$\theta_{(k)_i}$: kth simulated vector from the prior distribution

$\theta_{(k)_{i,j}}$: simulated vector at the jth occasion with mean $\theta_{(k)_i}$ and variance-covariance matrix Ω_{IOV}

n : number of individuals

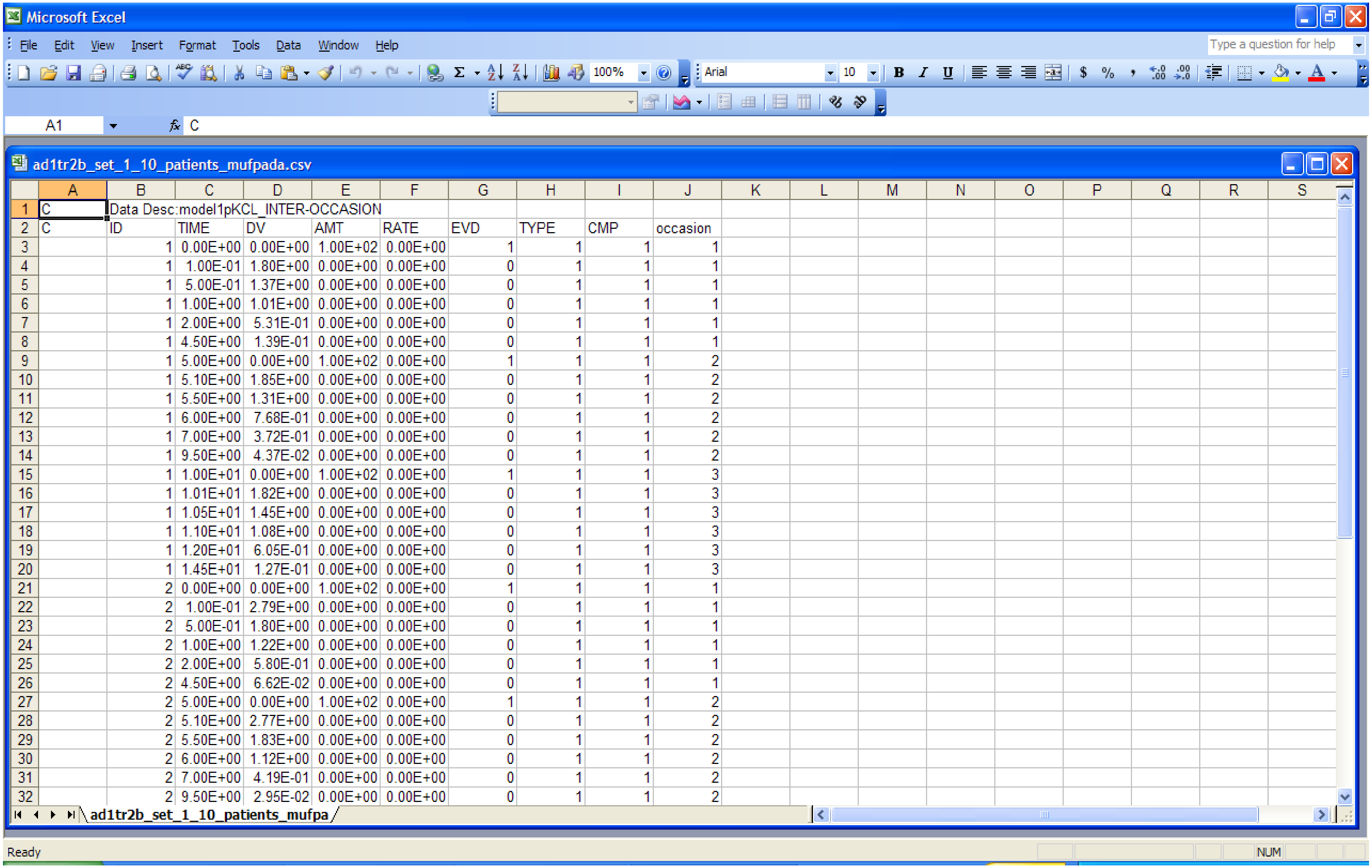
r_i : number of random vectors for individual i

Example 1

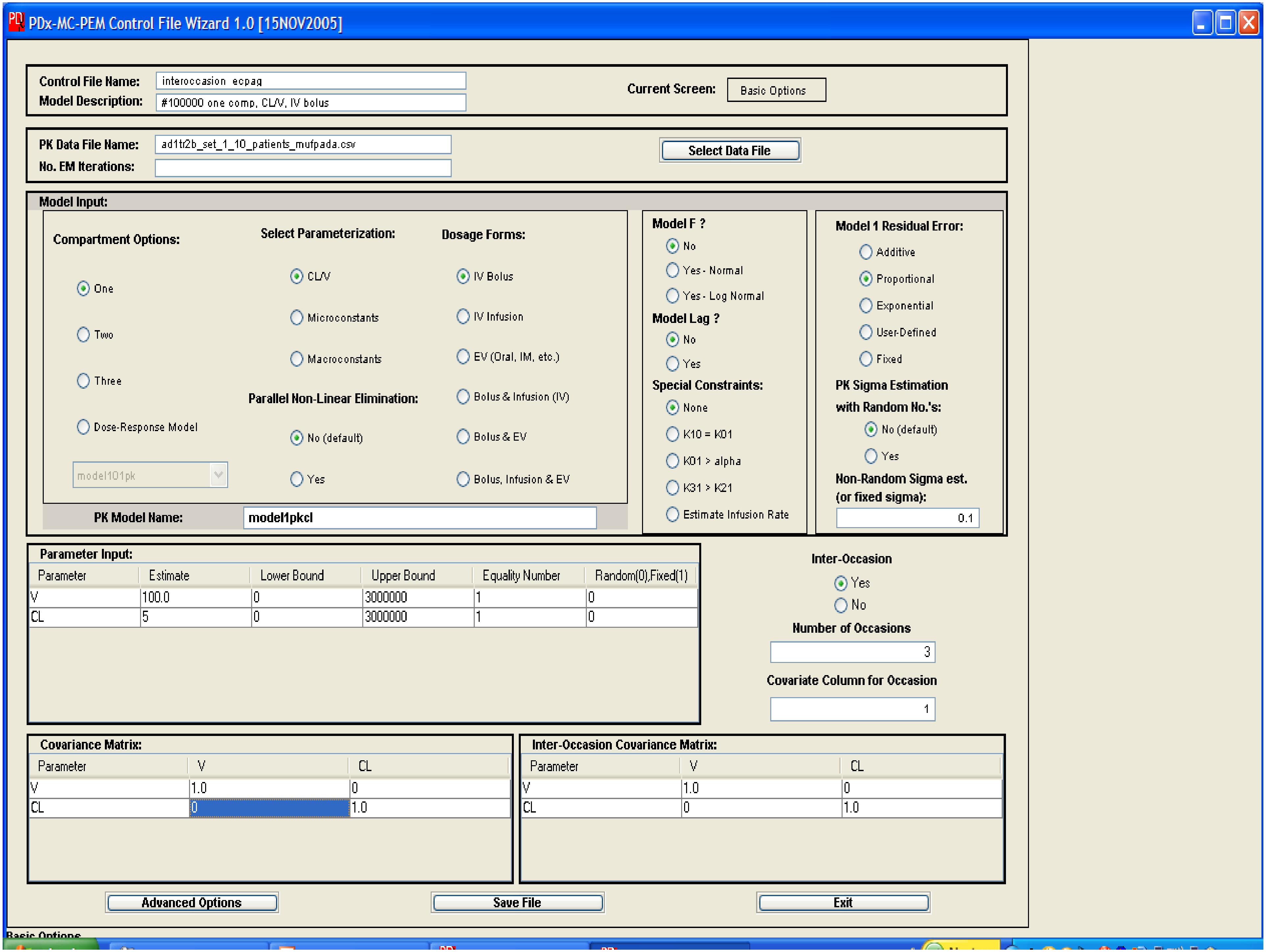
◆ 1 compartment model

- IV Bolus
- V and CL are the population parameters
- Inter-occasion on CL

Example 1: data set



	A	B	C	D	E	F	G	H	I	J
1	C	Data Desc:model1pKCL_INTER-OCCASION								
2	C	ID	TIME	DV	AMT	RATE	EVD	TYPE	CMP	occasion
3		1	0.00E+00	0.00E+00	1.00E+02	0.00E+00	1	1	1	1
4		1	1.00E-01	1.80E+00	0.00E+00	0.00E+00	0	1	1	1
5		1	5.00E-01	1.37E+00	0.00E+00	0.00E+00	0	1	1	1
6		1	1.00E+00	1.01E+00	0.00E+00	0.00E+00	0	1	1	1
7		1	2.00E+00	5.31E-01	0.00E+00	0.00E+00	0	1	1	1
8		1	4.50E+00	1.39E-01	0.00E+00	0.00E+00	0	1	1	1
9		1	5.00E+00	0.00E+00	1.00E+02	0.00E+00	1	1	1	2
10		1	5.10E+00	1.85E+00	0.00E+00	0.00E+00	0	1	1	2
11		1	5.50E+00	1.31E+00	0.00E+00	0.00E+00	0	1	1	2
12		1	6.00E+00	7.68E-01	0.00E+00	0.00E+00	0	1	1	2
13		1	7.00E+00	3.72E-01	0.00E+00	0.00E+00	0	1	1	2
14		1	9.50E+00	4.37E-02	0.00E+00	0.00E+00	0	1	1	2
15		1	1.00E+01	0.00E+00	1.00E+02	0.00E+00	1	1	1	3
16		1	1.01E+01	1.82E+00	0.00E+00	0.00E+00	0	1	1	3
17		1	1.05E+01	1.45E+00	0.00E+00	0.00E+00	0	1	1	3
18		1	1.10E+01	1.08E+00	0.00E+00	0.00E+00	0	1	1	3
19		1	1.20E+01	6.05E-01	0.00E+00	0.00E+00	0	1	1	3
20		1	1.45E+01	1.27E-01	0.00E+00	0.00E+00	0	1	1	3
21		2	0.00E+00	0.00E+00	1.00E+02	0.00E+00	1	1	1	1
22		2	1.00E-01	2.79E+00	0.00E+00	0.00E+00	0	1	1	1
23		2	5.00E-01	1.80E+00	0.00E+00	0.00E+00	0	1	1	1
24		2	1.00E+00	1.22E+00	0.00E+00	0.00E+00	0	1	1	1
25		2	2.00E+00	5.80E-01	0.00E+00	0.00E+00	0	1	1	1
26		2	4.50E+00	6.62E-02	0.00E+00	0.00E+00	0	1	1	1
27		2	5.00E+00	0.00E+00	1.00E+02	0.00E+00	1	1	1	2
28		2	5.10E+00	2.77E+00	0.00E+00	0.00E+00	0	1	1	2
29		2	5.50E+00	1.83E+00	0.00E+00	0.00E+00	0	1	1	2
30		2	6.00E+00	1.12E+00	0.00E+00	0.00E+00	0	1	1	2
31		2	7.00E+00	4.19E-01	0.00E+00	0.00E+00	0	1	1	2
32		2	9.50E+00	2.95E-02	0.00E+00	0.00E+00	0	1	1	2



Control File Name: interoccasion_ecpag
Model Description: #100000 one comp, CL/V, IV bolus
Current Screen: Basic Options

PK Data File Name: ad1tr2b_set_1_10_patients_mufpada.csv
No. EM Iterations:

Model Input:

Compartment Options:
- ● One
- ○ Two
- ○ Three
- ○ Dose-Response Model

model101pk

Select Parameterization:
- ● CL/V
- ○ Microconstants
- ○ Macroconstants

Parallel Non-Linear Elimination:
- ● No (default)
- ○ Yes

Dosage Forms:
- ● IV Bolus
- ○ IV Infusion
- ○ EV (Oral, IM, etc.)
- ○ Bolus & Infusion (IV)
- ○ Bolus & EV
- ○ Bolus, Infusion & EV

PK Model Name: model1pkcl

Model F ?
- ● No
- ○ Yes - Normal
- ○ Yes - Log Normal

Model Lag ?
- ● No
- ○ Yes

Special Constraints:
- ● None
- ○ K10 = K01
- ○ K01 > alpha
- ○ K31 > K21
- ○ Estimate Infusion Rate

Model 1 Residual Error:
- ○ Additive
- ● Proportional
- ○ Exponential
- ○ User-Defined
- ○ Fixed

PK Sigma Estimation with Random No.'s:
- ● No (default)
- ○ Yes

Non-Random Sigma est. (or fixed sigma): 0.1

Parameter Input:

Parameter	Estimate	Lower Bound	Upper Bound	Equality Number	Random(0),Fixed(1)
V	100.0	0	3000000	1	0
CL	5	0	3000000	1	0

Inter-Occasion
- ● Yes
- ○ No

Number of Occasions 3

Covariate Column for Occasion 1

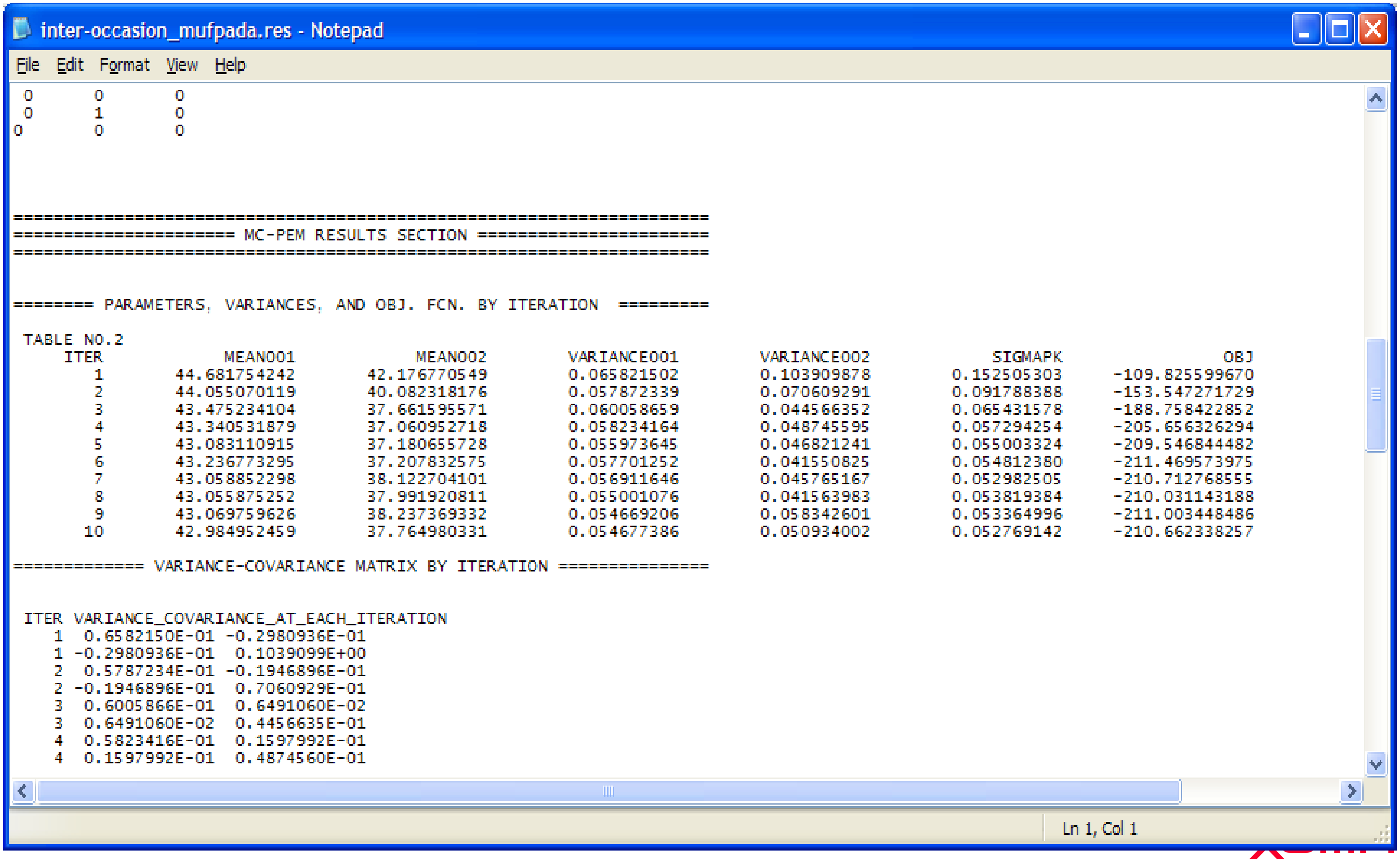
Covariance Matrix:

Parameter	V	CL
V	1.0	0
CL	0	1.0

Inter-Occasion Covariance Matrix:

Parameter	V	CL
V	1.0	0
CL	0	1.0

Output: Population means and Between Subject Variability



```
 0      0       0
 0      0       0
0       0       0



=====================================================================
====================== MC-PEM RESULTS SECTION =======================
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======== PARAMETERS, VARIANCES, AND OBJ. FCN. BY ITERATION  =========

 TABLE NO.2
     ITER            MEAN001            MEAN002        VARIANCE001        VARIANCE002            SIGMAPK                OBJ
        1       44.681754242       42.176770549        0.065821502        0.103909878        0.152505303     -109.825599670
        2       44.055070119       40.082318176        0.057872339        0.070609291        0.091788388     -153.547271729
        3       43.475234104       37.661595571        0.060058659        0.044566352        0.065431578     -188.758422852
        4       43.340531879       37.060952718        0.058234164        0.048745595        0.057294254     -205.656326294
        5       43.083110915       37.180655728        0.055973645        0.046821241        0.055003324     -209.546844482
        6       43.236773295       37.207832575        0.057701252        0.041550825        0.054812380     -211.469573975
        7       43.058852298       38.122704101        0.056911646        0.045765167        0.052982505     -210.712768555
        8       43.055875252       37.991920811        0.055001076        0.041563983        0.053819384     -210.031143188
        9       43.069759626       38.237369332        0.054669206        0.058342601        0.053364996     -211.003448486
       10       42.984952459       37.764980331        0.054677386        0.050934002        0.052769142     -210.662338257

============= VARIANCE-COVARIANCE MATRIX BY ITERATION ===============


 ITER VARIANCE_COVARIANCE_AT_EACH_ITERATION
    1  0.6582150E-01 -0.2980936E-01
    1 -0.2980936E-01  0.1039099E+00
    2  0.5787234E-01 -0.1946896E-01
    2 -0.1946896E-01  0.7060929E-01
    3  0.6005866E-01  0.6491060E-02
    3  0.6491060E-02  0.4456635E-01
    4  0.5823416E-01  0.1597992E-01
    4  0.1597992E-01  0.4874560E-01
```
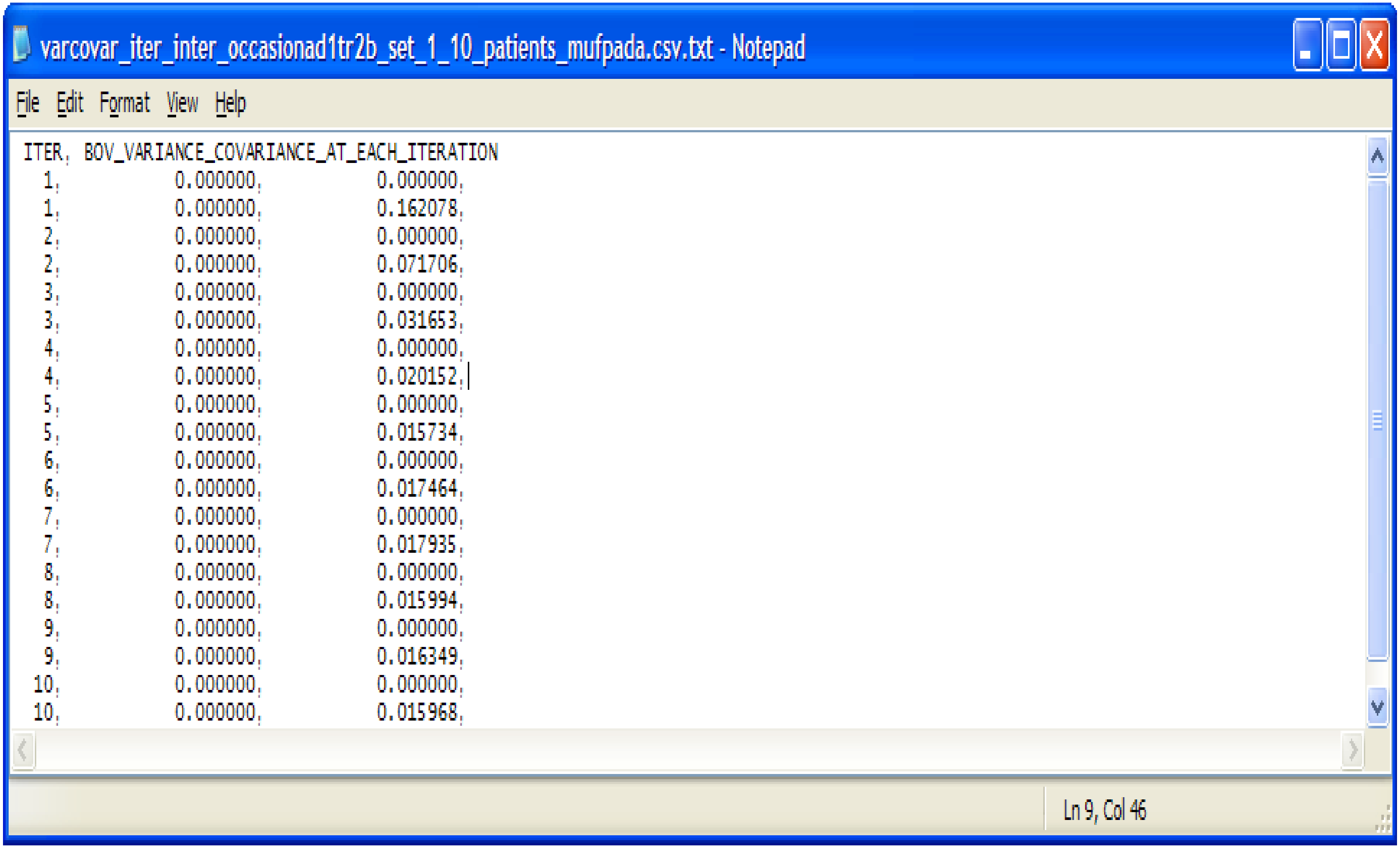
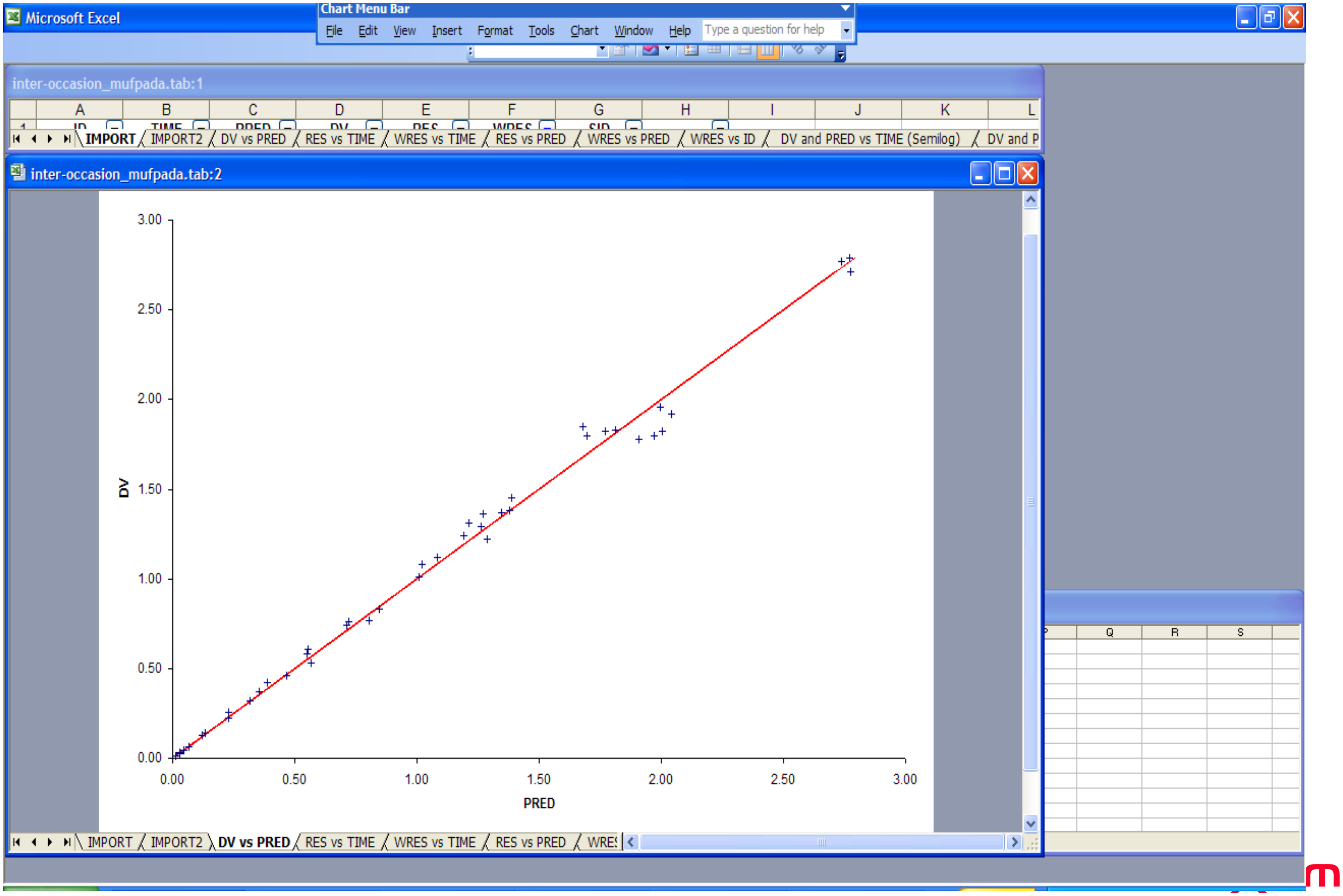

Output: Inter-occasion variability



```
ITER, BOV_VARIANCE_COVARIANCE_AT_EACH_ITERATION
  1,           0.000000,           0.000000,
  1,           0.000000,           0.162078,
  2,           0.000000,           0.000000,
  2,           0.000000,           0.071706,
  3,           0.000000,           0.000000,
  3,           0.000000,           0.031653,
  4,           0.000000,           0.000000,
  4,           0.000000,           0.020152,
  5,           0.000000,           0.000000,
  5,           0.000000,           0.015734,
  6,           0.000000,           0.000000,
  6,           0.000000,           0.017464,
  7,           0.000000,           0.000000,
  7,           0.000000,           0.017935,
  8,           0.000000,           0.000000,
  8,           0.000000,           0.015994,
  9,           0.000000,           0.000000,
  9,           0.000000,           0.016349,
 10,           0.000000,           0.000000,
 10,           0.000000,           0.015968,
```

Example 1: Diagnostic Plot



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

$$\sim \underset{\text{}}{p_1 \times \text{pi,1}} + \quad (1-p_1) \times \text{pi,2}$$

MC-PEM Mixture algorithm

Contribution from distribution 1 in percent

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

Contribution from distribution 2 in percent

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

The algorithm

Update of p for each distribution

At the first iteration must enter initial estimate for p_k

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

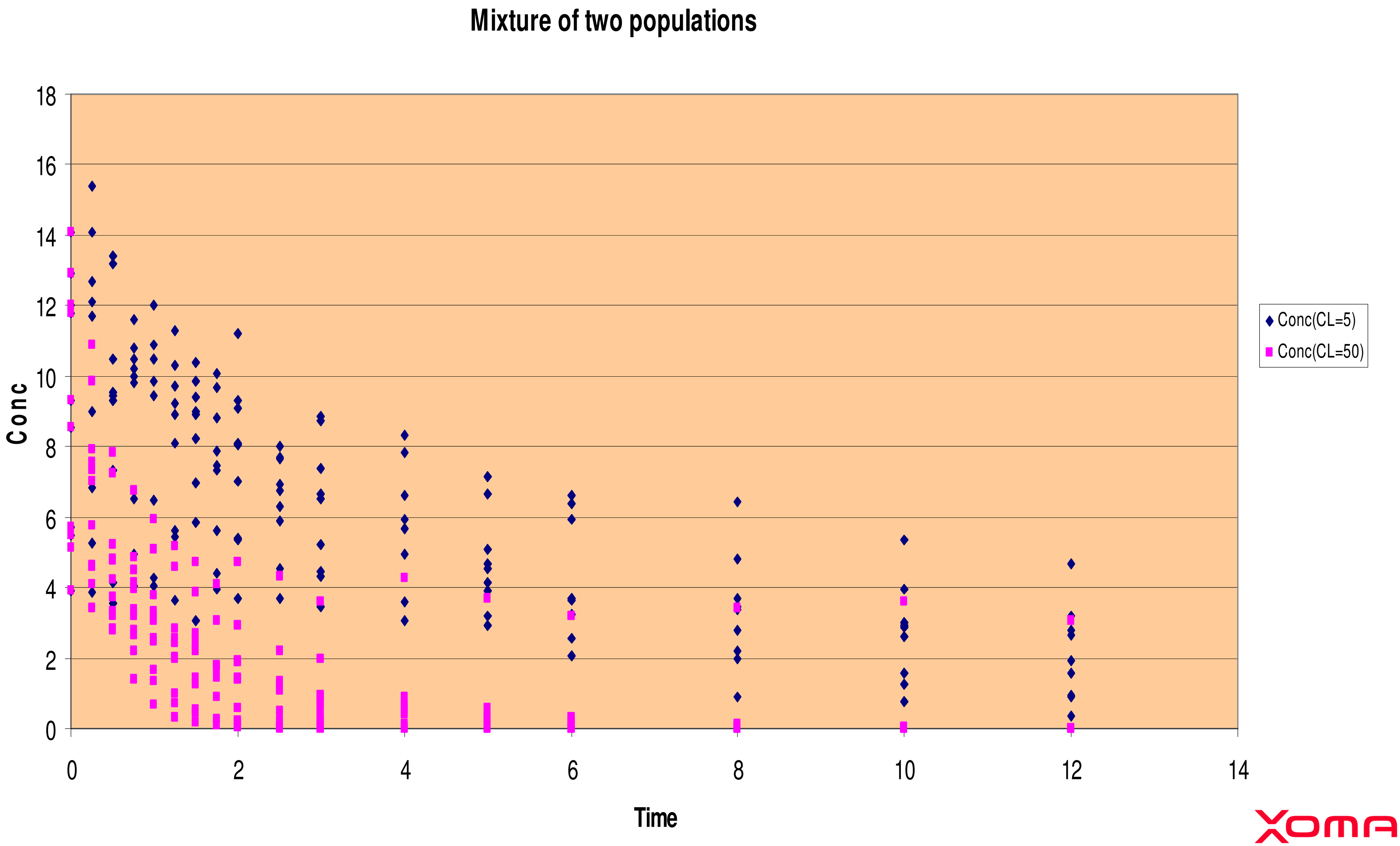
Update of population mean and variances

For each distribution

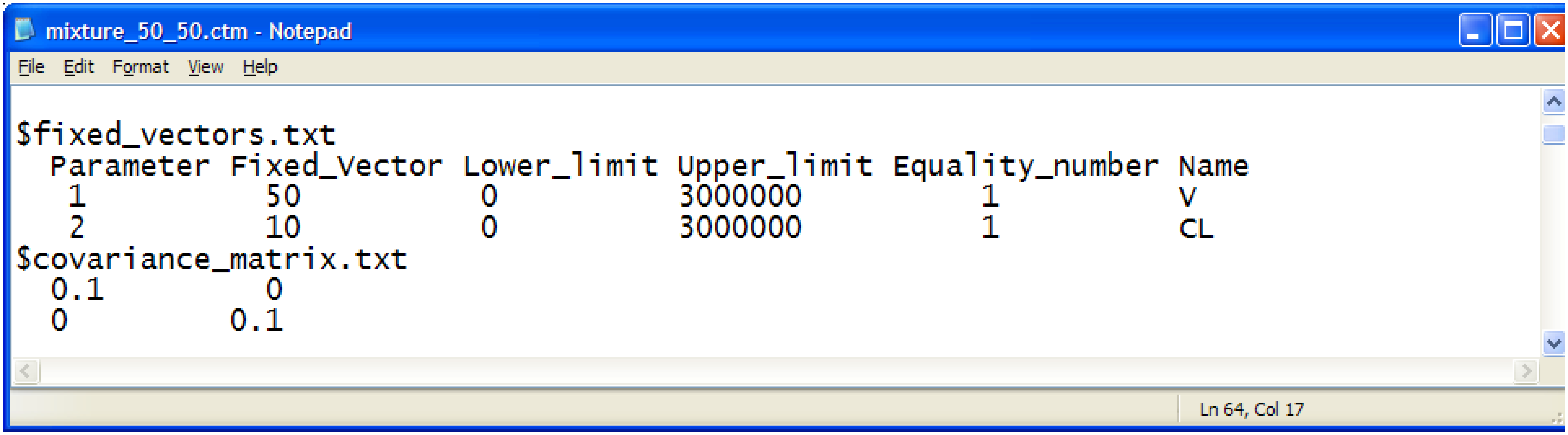
$$\mu_{new,k} = \frac{\sum_{i=1}^{m} weight_{i,k}\bar{\theta}_{Gi,k}}{\sum_{i=1}^{m} weight_{i,k}}$$

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

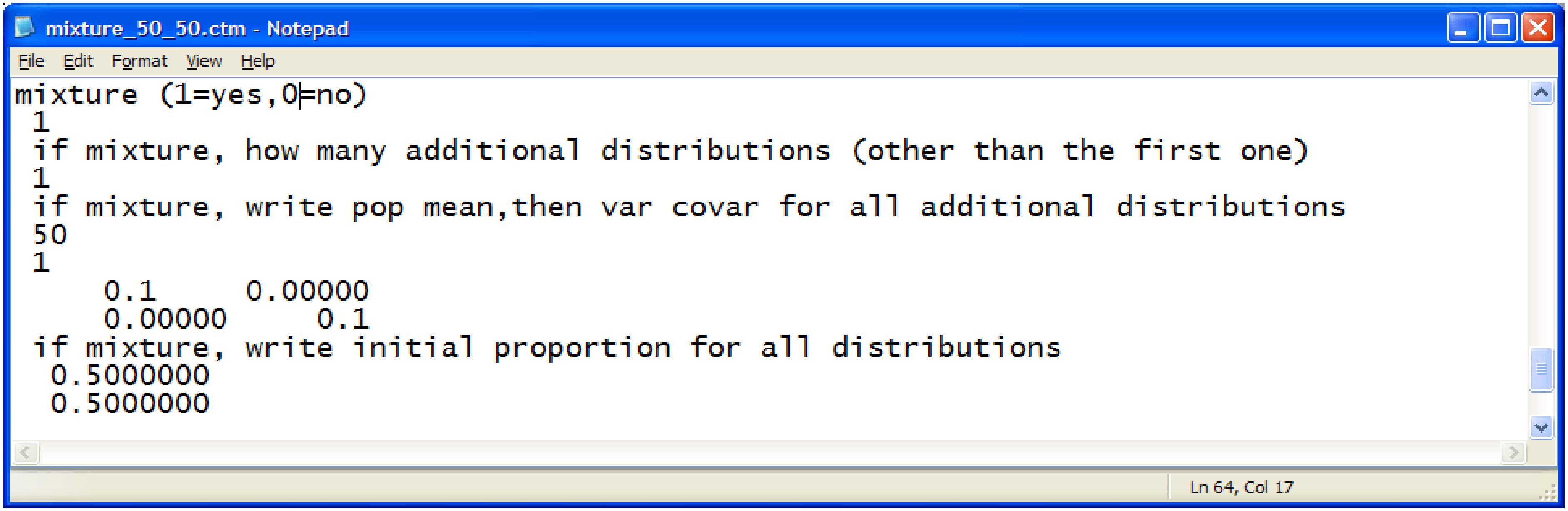
Example 2: One compartment model with mixture of two Populations in Cl



Example 2: PDx-MC-PEM mixture control stream part

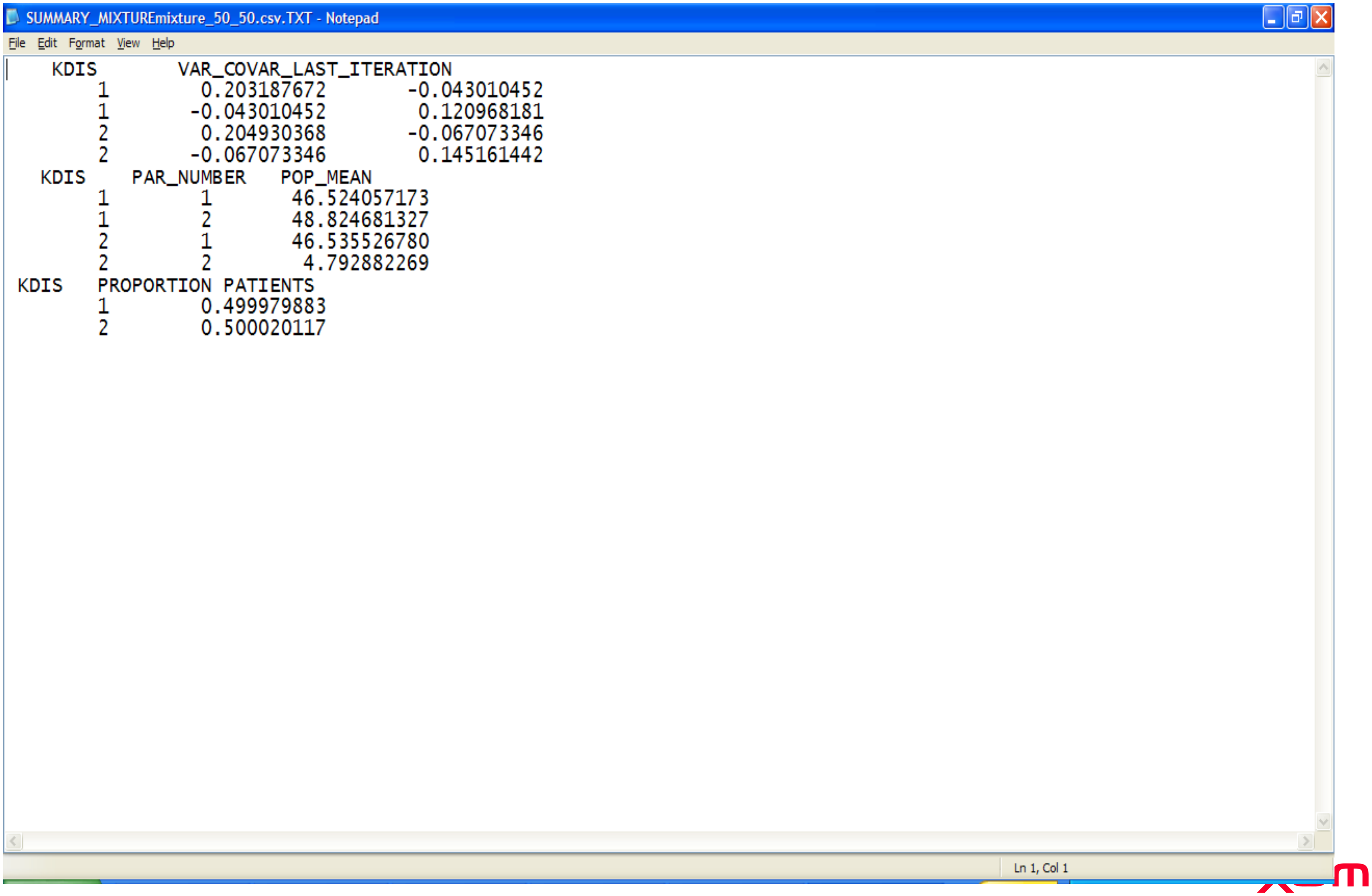


```
$fixed_vectors.txt
  Parameter Fixed_Vector Lower_limit Upper_limit Equality_number Name
   1           50          0           3000000         1           V
   2           10          0           3000000         1           CL
$covariance_matrix.txt
  0.1          0
  0          0.1
```



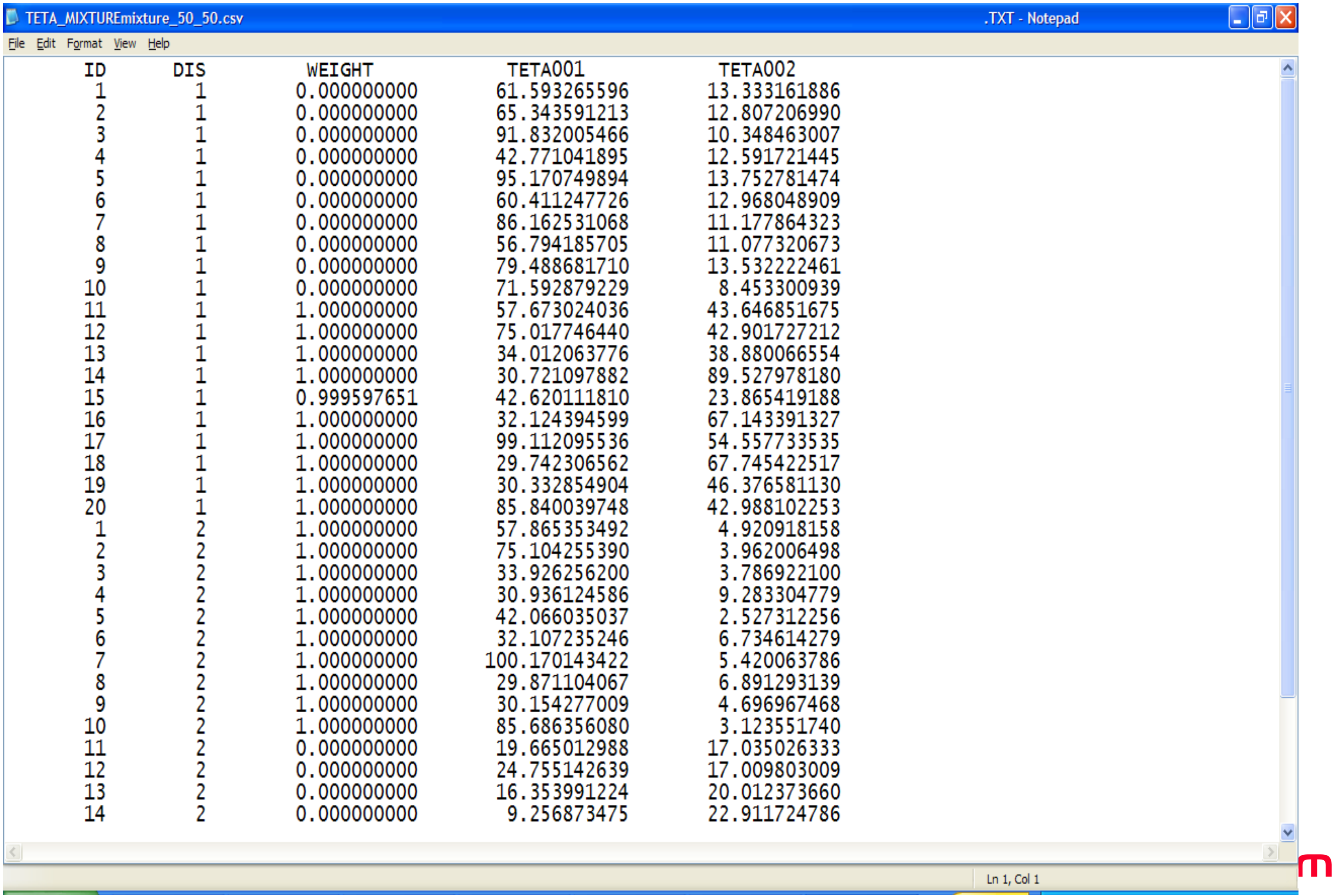
```
mixture (1=yes,0=no)
 1
 if mixture, how many additional distributions (other than the first one)
 1
 if mixture, write pop mean,then var covar for all additional distributions
 50
 1
     0.1     0.00000
     0.00000     0.1
 if mixture, write initial proportion for all distributions
  0.5000000
  0.5000000
```

Example 2: Output Summary



```
   KDIS       VAR_COVAR_LAST_ITERATION
       1        0.203187672       -0.043010452
       1       -0.043010452        0.120968181
       2        0.204930368       -0.067073346
       2       -0.067073346        0.145161442
  KDIS    PAR_NUMBER   POP_MEAN
       1        1       46.524057173
       1        2       48.824681327
       2        1       46.535526780
       2        2        4.792882269
KDIS   PROPORTION PATIENTS
       1        0.499979883
       2        0.500020117
```

Example 2: Probability for each individual to belong to anyone distribution



```
   ID      DIS        WEIGHT         TETA001         TETA002
    1        1   0.000000000    61.593265596    13.333161886
    2        1   0.000000000    65.343591213    12.807206990
    3        1   0.000000000    91.832005466    10.348463007
    4        1   0.000000000    42.771041895    12.591721445
    5        1   0.000000000    95.170749894    13.752781474
    6        1   0.000000000    60.411247726    12.968048909
    7        1   0.000000000    86.162531068    11.177864323
    8        1   0.000000000    56.794185705    11.077320673
    9        1   0.000000000    79.488681710    13.532222461
   10        1   0.000000000    71.592879229     8.453300939
   11        1   1.000000000    57.673024036    43.646851675
   12        1   1.000000000    75.017746440    42.901727212
   13        1   1.000000000    34.012063776    38.880066554
   14        1   1.000000000    30.721097882    89.527978180
   15        1   0.999597651    42.620111810    23.865419188
   16        1   1.000000000    32.124394599    67.143391327
   17        1   1.000000000    99.112095536    54.557733535
   18        1   1.000000000    29.742306562    67.745422517
   19        1   1.000000000    30.332854904    46.376581130
   20        1   1.000000000    85.840039748    42.988102253
    1        2   1.000000000    57.865353492     4.920918158
    2        2   1.000000000    75.104255390     3.962006498
    3        2   1.000000000    33.926256200     3.786922100
    4        2   1.000000000    30.936124586     9.283304779
    5        2   1.000000000    42.066035037     2.527312256
    6        2   1.000000000    32.107235246     6.734614279
    7        2   1.000000000   100.170143422     5.420063786
    8        2   1.000000000    29.871104067     6.891293139
    9        2   1.000000000    30.154277009     4.696967468
   10        2   1.000000000    85.686356080     3.123551740
   11        2   0.000000000    19.665012988    17.035026333
   12        2   0.000000000    24.755142639    17.009803009
   13        2   0.000000000    16.353991224    20.012373660
   14        2   0.000000000     9.256873475    22.911724786
```

Example 2: Diagnostic Plot