

Supplemental Digital Content 2: NONMEM control stream and demo data

\$PROBLEM Hydromorphon NRS logistic regression with 3 levels

\$INPUT ID,TIME,SAMPLE,CPHM,CEHM,CPS,CES,DV,EVID,AGE,SEX,BW,HT,LBM,BMI,GROUP

;CPHM= plasma concentration of hydromorphone (individual predictions from PK model)

;CEHM= effect site concentration of hydromorphone (individual predictions with $ke_0=0.015$ 1/min)

;CPS= plasma concentration of sufentanil (individual predictions from PK model)

;CES= effect site concentration of sufentanil (individual predictions with $ke_0=0.11$ 1/min)

;DV= NRS value under inspiration

\$DATA PD_HM.csv IGNORE=@ WIDE

\$PRED

;typical parameter values

A1TV=THETA(1)

A2TV=THETA(1)+THETA(2)

B1TV=THETA(3)

B2TV=THETA(4)

;typical probabilities for $NRS \leq 1$ and $NRS \leq 4$

LOGIT1TV=A1TV+B1TV*CEHM+B2TV*CES

LOGIT2TV=A2TV+B1TV*CEHM+B2TV*CES

PS1TV=EXP(LOGIT1TV)/(1+EXP(LOGIT1TV))

PS2TV=EXP(LOGIT2TV)/(1+EXP(LOGIT2TV))

;typical probabilities for $NRS=[0,1]$, $NRS=[2,4]$ and $NRS=[5,10]$

PE1TV=PS1TV

PE2TV=PS2TV-PS1TV

PE3TV=1-PS2TV

;individual parameter values

A1LOG=A1TV*EXP(ETA(1))

A2LOG=A1TV*EXP(ETA(1))+THETA(2)*EXP(ETA(2))

B1LOG=B1TV*EXP(ETA(3))

B2LOG=B2TV*EXP(ETA(4))

;individual probabilities for $NRS \leq 1$ and $NRS \leq 4$

LOGIT1=A1LOG+B1LOG*CEHM+B2LOG*CES

LOGIT2=A2LOG+B1LOG*CEHM+B2LOG*CES

PS1=EXP(LOGIT1)/(1+EXP(LOGIT1))

PS2=EXP(LOGIT2)/(1+EXP(LOGIT2))

;individual probabilities for $NRS=[0,1]$, $NRS=[2,4]$ and $NRS=[5,10]$

PE1=PS1

PE2=PS2-PS1

PE3=1-PS2

IF (DV.LE.1) Y=PE1

IF (DV.EQ.2 .OR. DV.EQ.3 .OR. DV.EQ.4) Y=PE2

IF (DV.GT.4) Y=PE3

\$THETA (-50,-10,0) (0,5,100) (.01,2,10) (1,40,100)

\$OMEGA 1 1 1 1

\$ESTIMATION METHOD=COND NUMERICAL SLOW NOABORT LAPLACIAN LIKELIHOOD

NSIG=3 PRINT=5 MAX=9999

| id | time(min since 00:00) | sampleid | CP HM | CE HM | CP Sufenta | CE Sufenta | DV (NRS | | | | | | | | |
|-------------------|-----------------------|----------|------------|------------|------------|-------------------------|---------------|---|----|---|-----|-----|-------|------|---|
| inspiration) evid | age(yrs) | sex | weight(kg) | height(cm) | lbm(kg) | bmi(kg/m ²) | sufenta_group | | | | | | | | |
| 8 | 919.5 | 1 | 2.6952 | 2.7133 | 0.07373 | 0.07373 | 0 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 934.5 | 2 | 2.6846 | 2.708 | 0.07091 | 0.072283 | 0 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 949.5 | 3 | 2.6685 | 2.7023 | 0.068242 | 0.069806 | 0 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 964.5 | 4 | 2.1794 | 2.576 | 0.065702 | 0.06724 | 0 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 979.5 | 5 | 2.1952 | 2.4966 | 0.063274 | 0.064752 | 0 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1009.5 | 6 | 1.768 | 2.2078 | 0.058706 | 0.06007 | 0 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1039.5 | 7 | 4.2428 | 1.8931 | 0.054489 | 0.055749 | 4 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1069.5 | 8 | 1.8194 | 2.1228 | 0.050581 | 0.051748 | 4 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1099.5 | 9 | 2.8121 | 2.4109 | 0.046956 | 0.048039 | 5 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1129.5 | 10 | 3.2233 | 2.7184 | 0.043592 | 0.044596 | 3 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1159.5 | 11 | 2.6317 | 2.7006 | 0.040469 | 0.041401 | 3 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1189.5 | 12 | 2.1429 | 2.5 | 0.03757 | 0.038436 | 2 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1219.5 | 13 | 2.7466 | 2.382 | 0.034879 | 0.035682 | 2 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1249.5 | 14 | 2.2386 | 2.431 | 0.03238 | 0.033126 | 3 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1279.5 | 15 | 1.7277 | 2.2826 | 0.030061 | 0.030753 | 3 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 8 | 1309.5 | 16 | 1.175 | 2.0399 | 0.027907 | 0.02855 | 3 | 0 | 79 | 0 | 104 | 182 | 72.6 | 31.4 | 1 |
| 9 | 978 | 1 | 3.4329 | 1.9503 | 0.13113 | 0.13113 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 993 | 2 | 3.2271 | 2.2291 | 0.1261 | 0.12855 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1008 | 3 | 2.9739 | 2.4028 | 0.12128 | 0.1241 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1023 | 4 | 2.1713 | 2.3811 | 0.11663 | 0.11943 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1038 | 5 | 2.0179 | 2.3204 | 0.11215 | 0.11487 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1068 | 6 | 1.3748 | 1.9914 | 0.10372 | 0.10624 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1098 | 7 | 0.91174 | 1.5969 | 0.095918 | 0.098245 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1128 | 8 | 0.55909 | 1.2205 | 0.088703 | 0.090856 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1158 | 9 | 0.36654 | 0.91376 | 0.082032 | 0.084023 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1188 | 10 | 0.61564 | 0.76415 | 0.075862 | 0.077703 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1218 | 11 | 0.79785 | 0.74839 | 0.070156 | 0.071859 | 1 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1248 | 12 | 0.89103 | 0.78592 | 0.064879 | 0.066454 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1278 | 13 | 0.93951 | 0.83427 | 0.06 | 0.061456 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1308 | 14 | 0.96116 | 0.87593 | 0.055487 | 0.056833 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1338 | 15 | 0.97304 | 0.90964 | 0.051313 | 0.052559 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 9 | 1368 | 16 | 0.9763 | 0.93334 | 0.047454 | 0.048606 | 0 | 0 | 61 | 0 | 79 | 179 | 61.97 | 24.7 | 2 |
| 10 | 1032 | 2 | 4.3203 | 4.0631 | 0.1154 | 0.11739 | 8 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1045 | 3 | 5.2926 | 4.2377 | 0.11144 | 0.11375 | 7 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1057 | 4 | 6.326 | 4.5618 | 0.10762 | 0.10993 | 7 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1072 | 5 | 7.1829 | 5.0275 | 0.10393 | 0.10617 | 5 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1103 | 6 | 8.0536 | 6.0094 | 0.096928 | 0.099021 | 4 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1133 | 7 | 7.6558 | 6.6297 | 0.090396 | 0.092348 | 4 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |

| | | | | | | | | | | | | | | | |
|----|------|----|--------|--------|----------|----------|---|---|----|---|----|-----|-------|------|---|
| 10 | 1163 | 8 | 7.0804 | 6.8563 | 0.084305 | 0.086125 | 4 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | |
| | 2 | | | | | | | | | | | | | | |
| 10 | 1193 | 9 | 6.7883 | 6.8665 | 0.078624 | 0.080322 | 4 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | |
| | 2 | | | | | | | | | | | | | | |
| 10 | 1223 | 10 | 6.4518 | 6.7629 | 0.073325 | 0.074909 | 4 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1253 | 11 | 6.1796 | 6.5976 | 0.068384 | 0.069861 | 3 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1283 | 12 | 5.8882 | 6.3887 | 0.063776 | 0.065153 | 3 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1313 | 13 | 5.5606 | 6.1491 | 0.059478 | 0.060763 | 3 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1343 | 14 | 5.2633 | 5.884 | 0.05547 | 0.056668 | 6 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1373 | 15 | 7.2125 | 6.2318 | 0.051732 | 0.05285 | 6 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |
| 10 | 1403 | 16 | 6.6857 | 6.4776 | 0.048246 | 0.049288 | 4 | 0 | 73 | 0 | 95 | 180 | 68.85 | 29.3 | 2 |

