**Supplemental Material: Model codes**

**Part 1**: to simulate a pseudo dataset. Without loss of generality, we assume all Ns to have a same expected value, and omit subgroup 6 in Table 1. For all patterns of exposure and all drug pairs, the data included the following variables (equation 3): true odds ratio (OR) , probability = , and X and N. In this example, we assumed = = 1.

###### general settings

install.packages("extraDistr") ### install and load R package

library(extraDistr)

N\_pairs = 10000 ### total number of drug pairs

E\_N = 200 ### expected value for N

sim\_alpha = 1 ### alpha in equation 3

sim\_beta = 1 ### beta in equation 3

###### to generate data

N\_all = rpois(N\_pairs \* 5, E\_N) ### all N

G\_all = (exp(0.1 \* N\_all) - 1) / (exp(0.1 \* N\_all) + 1) ### to define relationship between N and theta

G\_all = ifelse(is.na(G\_all) == TRUE, 1, G\_all) ### to prevent overflow

sim\_alpha\_all = sim\_alpha \* G\_all

sim\_beta\_all = sim\_beta \* G\_all

theta\_all = rbetapr(N\_pairs \* 5, sim\_alpha\_all, sim\_beta\_all) ### true odds ratios

P\_all = theta\_all / (1 + theta\_all) ### probabilities

X\_all = rbinom(N\_pairs \* 5, N\_all, P\_all) ### all X

###### to define timing of exposure aware data

### We used 1 – 5 to define the timing of drug exposure according to Table 1

### 1 for "no drug -> drug A" and "drug A -> no drug"

### 2 for "no drug -> drug B" and "drug B -> no drug"

### 3 for "drug B -> drug A+B" and "drug A+B -> drug B"

### 4 for "drug A -> drug A+B" and "drug A+B -> drug A"

### 5 for "no drug -> drug A+B" and "drug A+B -> no drug"

data\_N = as.data.frame(matrix(N\_all, N\_pairs, 5))

names(data\_N) = c("N1", "N2", "N3", "N4", "N5")

data\_X = as.data.frame(matrix(X\_all, N\_pairs, 5))

names(data\_X) = c("X1", "X2", "X3", "X4", "X5")

data\_theta = as.data.frame(matrix(theta\_all, N\_pairs, 5))

names(data\_theta) = c("theta1", "theta2", "theta3", "theta4", "theta5")

data\_final = data.frame(data\_N, data\_X, data\_theta) ### final data, each row is a drug pair

###### define true interaction

### "drug B -> drug A+B" > "no drug -> drug A"

### "drug A -> drug A+B" > “no drug -> drug B"

### "no drug -> drug A+B" > “no drug -> drug B" \* "no drug -> drug B"

temp\_AonB = (data\_final$theta3 > data\_final$theta1)

temp\_BonA = (data\_final$theta4 > data\_final$theta2)

temp\_joint = (data\_final$theta5 > (data\_final$theta1 \* data\_final$theta2))

data\_final$DDI = (temp\_AonB == TRUE | temp\_BonA == TRUE | temp\_joint == TRUE)

**Part 2:** to determine the parameter of the sensitive and timing-aware (STEM) model. The parameters under Bayesian framework were set to be = = 1. The parameters under empirical Bayes framework were estimated from the observed distribution based on N and X, which was a beta-binomial distribution. In this example, the true parameters were = = 1. We estimated the parameters under the empirical Bayes framework.

###### a function to compute observed likelihood for X and N

func\_STEM = function(fun\_para){

fun\_alpha = exp(fun\_para[1]) ### alpha in equation 3

fun\_beta = exp(fun\_para[2]) ### beta in equation 3

fun\_g = (exp(0.1 \* N\_all) - 1) / (exp(0.1 \* N\_all) + 1) ### relationship between sample size and OR

fun\_g = ifelse(is.na(fun\_g) == TRUE, 1, fun\_g) ### prevent overflow

alpha.star = fun\_alpha \* fun\_g

beta.star = fun\_beta \* fun\_g

### parts 1-3 are subcomponents of observed likelihood function

part1 = lgamma(alpha.star + X\_all) - lgamma(alpha.star)

part2 = lgamma(beta.star + N\_all - X\_all) - lgamma(beta.star)

part3 = lgamma(alpha.star + beta.star + N\_all) - lgamma(alpha.star + beta.star)

ll = part1 + part2 - part3 ### value of observed likelihood function

-sum(ll)

}

###### to compute maximum likelihood estimator under empirical Bayes framework

para = exp(nlminb(c(0,0), func\_STEM)$par) ### compute estimator

para ### estimated alpha and beta

g = (exp(0.1 \* N\_all) - 1) / (exp(0.1 \* N\_all) + 1) ### relationship between sample size and parameter

g = ifelse(is.na(g) == TRUE, 1, g) ### prevent overflow

###### parameters for empirical Bayes framework (all alpha = 1 and all beta = 1 under Bayesian framework)

data\_EB\_alpha = as.data.frame(matrix(para[1] \* g, N\_pairs, 5))

names(data\_EB\_alpha) = c("alpha1", "alpha2", "alpha3", "alpha4", "alpha5")

data\_EB\_beta = as.data.frame(matrix(para[2] \* g, N\_pairs, 5))

names(data\_EB\_beta) = c("beta1", "beta2", "beta3", "beta4", "beta5")

**Part 3:** to compute posterior probability of no DDI (equation 6) and posterior probability of no TOE-dependent risk (equation 7) under empirical Bayes framework (all = 1 and all = 1 under Bayesian framework).

###### general settings

N.MC = 40000 ### size for Monte Carlo method

w1 = w2 = w3 = c(0:100) / 100 ### all grids for grid searching in following 3 lines

weight\_matrix = expand.grid(w1, w2, w3)

weight\_matrix = as.matrix(weight\_matrix[which(rowSums(weight\_matrix)==1), ])

###### compute three estimated TOE-aware odds ratios

data\_final$AonB = NA

data\_final$BonA = NA

data\_final$joint = NA

###### compute the posterior probability of no DDI under empirical Bayes framework

data\_final$FDR\_DDI = NA

###### compute the posterior probability of no TOE-dependent risk under empirical Bayes framework

data\_final$FDR\_TOE = NA

###### loop over all drug pairs

for (i in 1:N\_pairs){

### generate theta from the posterior distributions (equation4)

theta1 = rbetapr(N.MC, data\_EB\_alpha$alpha1[i] + data\_final$X1[i],

data\_EB\_beta$beta1 + data\_final$N1[i] - data\_final$X1[i])

theta2 = rbetapr(N.MC, data\_EB\_alpha$alpha2[i] + data\_final$X2[i],

data\_EB\_beta$beta2 + data\_final$N2[i] - data\_final$X2[i])

theta3 = rbetapr(N.MC, data\_EB\_alpha$alpha3[i]+data\_final$X3[i],

data\_EB\_beta$beta3 + data\_final$N3[i] - data\_final$X3[i])

theta4 = rbetapr(N.MC, data\_EB\_alpha$alpha4[i] + data\_final$X4[i],

data\_EB\_beta$beta4 + data\_final$N4[i] - data\_final$X4[i])

theta5 = rbetapr(N.MC, data\_EB\_alpha$alpha5[i] + data\_final$X5[i],

data\_EB\_beta$beta5 + data\_final$N5[i] - data\_final$X5[i])

### define the three timing of exposure aware drug interaction effect

### "no drug -> drug A+B" > "no drug -> drug B" \* "no drug -> drug B"

loop\_joint = theta5 / (theta1 \* theta2)

loop\_AonB = theta3 / theta1 ### "drug B -> drug A+B" > "no drug -> drug A"

loop\_BonA = theta4 / theta2 ### "drug A -> drug A+B" > "no drug -> drug B"

data\_final$AonB[i] = mean(loop\_AonB)

data\_final$BonA[i] = mean(loop\_BonA)

data\_final$joint[i] = mean(loop\_joint)

### use grid searching to identify FDR\_DDI (equation 6)

ror.matrix = cbind(loop\_joint, loop\_AonB, loop\_BonA)

### use matrix calculation to estimate the effect of interaction

ror.weighted = ror.matrix %\*% t(weight\_matrix)

FDR.weight.all = colSums(ror.weighted <= 1) ### all FDR\_DDIs under all grids

optimal.location = which.min(FDR.weight.all) ### minimum FDR\_DDI

data\_final$FDR\_DDI[i] = FDR.weight.all[optimal.location] / N.MC ### final FDR\_DDI output

### use all pairwise ratios to identify FDR\_TOE (equation 7)

### define TOE-aware odds ratios under different patterns of timing of drug exposure

### E1: "no drug -> drug A -> drugs A+B"/ "no drug -> drugs A+B"

### E2: "no drug -> drug B -> drugs A+B"/ "no drug -> drugs A+B"

### E3: "no drug -> drug A -> drugs A+B"/ "no drug -> drug B -> drugs A+B"

### E4: "no drug -> drugs A+B"/ "no drug -> drug A -> drugs A+B"

### E5: "no drug -> drugs A+B"/ "no drug -> drug B -> drugs A+B"

### E6: "no drug -> drug B -> drugs A+B"/ "no drug -> drug A -> drugs A+B"

delta = 0.25

loop\_E1 = sum((theta1 \* theta4) / theta5 <= (1 + delta)) / N.MC

loop\_E2 = sum((theta2 \* theta3) / theta5 <= (1 + delta)) / N.MC

loop\_E3 = sum((theta1 \* theta4) / (theta2 \* theta3) <= (1 + delta)) / N.MC

loop\_E4 = sum(theta5 / (theta1 \* theta4) <= 1 / (1 + delta)) / N.MC

loop\_E5 = sum(theta5 / (theta2 \* theta3) <= 1 / (1 + delta)) / N.MC

loop\_E6 = sum((theta2 \* theta3) / (theta1 \* theta4) <= 1 / (1 + delta)) / N.MC

### final FDR\_TOE output

data\_final$FDR\_TOE[i] = min(loop\_E1, loop\_E2, loop\_E3, loop\_E4, loop\_E5, loop\_E6)

}

**Part 4:** to view examples.

### Find an example

location\_signal = which(data\_final$FDR\_DDI<0.05 & data\_final$FDR\_TOE<0.05)

data\_final[location\_signal[1], c("AonB", "BonA", "joint")]