Multiple Mediators

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Simulations with multiple treatments (x) and multiple mediators (m) are demonstrated. In this work the mediators are assumed independent conditioned on treatments. There are no confounders, i.e. $c = \emptyset$

```
library(graph)
```

```
## Loading required package: BiocGenerics

## Loading required package: parallel

##
## Attaching package: 'BiocGenerics'

## The following objects are masked from 'package:parallel':
##
##     clusterApply, clusterApplyLB, clusterCall, clusterEvalQ,
##     clusterExport, clusterMap, parApply, parCapply, parLapply,
##     parLapplyLB, parRapply, parSapply, parSapplyLB

## The following objects are masked from 'package:stats':
##
##     IQR, mad, sd, var, xtabs

## The following objects are masked from 'package:base':
##
##     anyDuplicated, append, as.data.frame, basename, cbind,
##     colMeans, colnames, colSums, dirname, do.call, duplicated,
##     eval, evalq, Filter, Find, get, grep, grepl, intersect,
##     is.unsorted, lapply, lengths, Map, mapply, match, mget, order,
##     paste, pmax, pmax.int, pmin, pmin.int, Position, rank, rbind,
##     Reduce, rowMeans, rownames, rowSums, sapply, setdiff, sort,
##     table, tapply, union, unique, unsplit, which, which.max,
##     which.min
```

```
library(kableExtra)
library(Rgraphviz)
```

```
## Loading required package: grid
```

```
library(mediateR)
set.seed(280920181)
```

Simulation 1: Linear

Simulate `n` observations from the "True Graph" using independent, binary SNPs drawn from Bernoulli(1/2) and path coefficients given below.

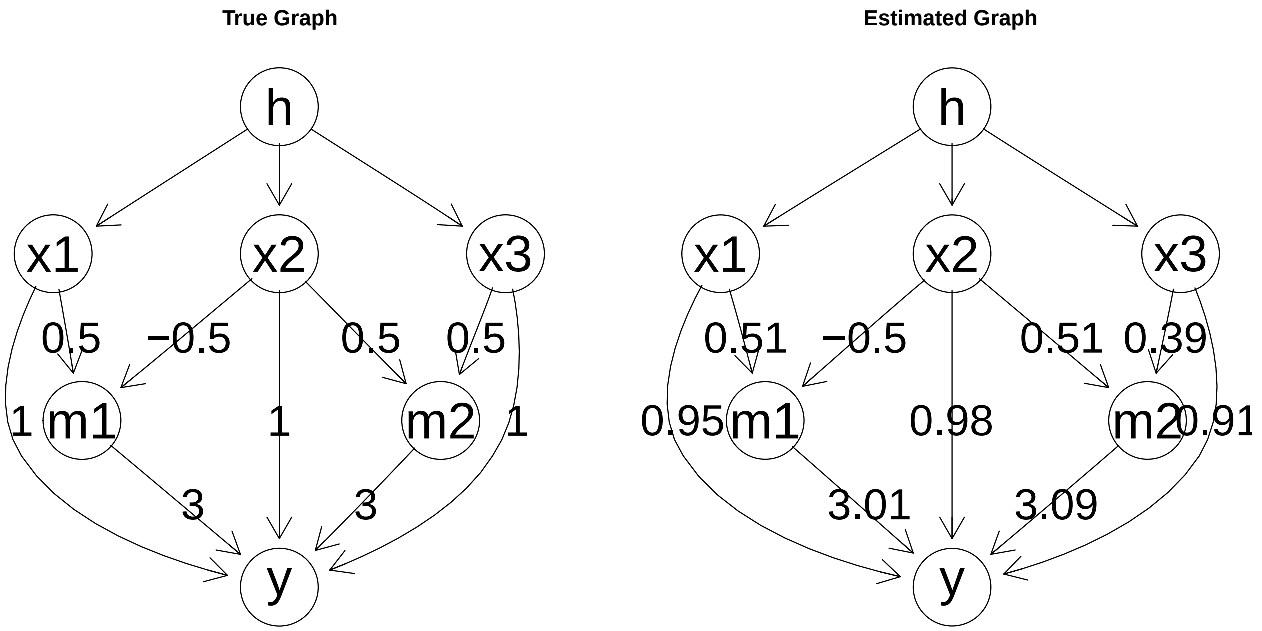
```
n <- 500
sim_params <- mediateR:::QuickSim(n,3,2,"gaussian")
dat <- SimulateData(sim_params)
```

```
gR <- mediateR:::MakeGraphNELObject(sim_params$path,sim_params$xx_direct,sim_params$mm_direct)
attrs <- list()
attrs$edge <- list()
```

```
attrs$edge$fontsize <- 12
edgeAttrs <- mediateR:::MakeedgeAttrs(sim_params$path_model,sim_params$xx_direct,sim_params$mm_direct)
```

```
fit <- ComputePath(dat)
eff_est <- ComputeEffectsLinear(fit)
```

```
gR2 <- mediateR:::MakeGraphNELObject(fit$path_model,fit$xx_direct,fit$mm_direct)
attrs2 <- list()
attrs2$edge <- list()
attrs2$edge$fontsize <- 12
edgeAttrs2 <- mediateR:::MakeedgeAttrs(fit$path_model,fit$xx_direct,fit$mm_direct)
par(mfcol=c(1,2))
plot(gR,edgeAttrs=edgeAttrs,attrs=attrs,main="True Graph")
plot(gR2,edgeAttrs=edgeAttrs2,attrs=attrs2,main="Estimated Graph")
```



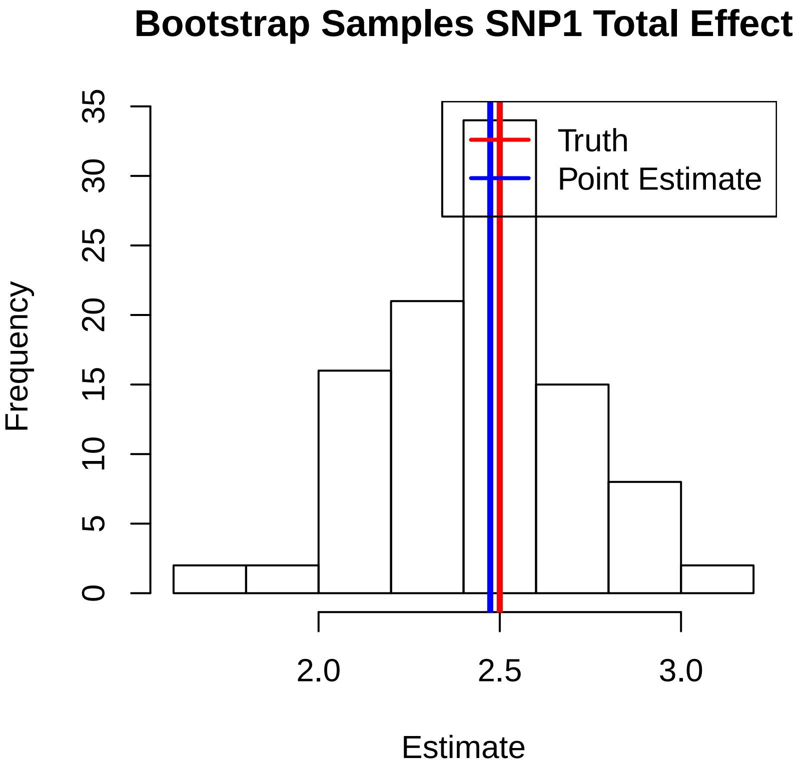
```
eff <- ComputeEffectsLinear(sim_params)
eff_comb <- matrix(0,nrow(eff),ncol=2*ncol(eff))
for(ii in 1:ncol(eff)){
  eff_comb[,2*ii-1] <- eff_est[,ii]
  eff_comb[,2*ii] <- eff[,ii]
}
for(ii in (ncol(dat$xx)+1):(ncol(dat$xx)+ncol(dat$mm))){
  eff_comb[ii,3:ncol(eff_comb)] <- NA
}
colnames(eff_comb) <- rep(c("est","true"),ncol(eff))
rownames(eff_comb) <- rownames(eff)
```

```
B <- 100
eff_est_boot <- vector("list",length=B)
for(ii in 1:B){
  ix <- sample(1:sim_params$n,replace=TRUE)
  dat_sub <- mediateR:::SubsetDat(dat,ix)
  fit <- ComputePath(dat_sub)
  eff_est_boot[[ii]] <- ComputeEffectsLinear(fit)
}
```

```
kable(eff_comb,digits=2) %>%
  kable_styling(bootstrap_options = "striped", full_width = F) %>%
  add_header_above(c(" ", "direct" = 2, "indirect" = 2, "total" = 2))
```

	direct		indirect		total	
	est	true	est	true	est	true
x1	0.95	1	1.52	1.5	2.47	2.5
x2	0.98	1	0.09	0.0	1.07	1.0
x3	0.91	1	1.19	1.5	2.10	2.5
m1	3.01	3				
m2	3.09	3				

```
total_xx1 <- vapply(eff_est_boot,function(x){x[1,3]},c(0))
hist(total_xx1,main="Bootstrap Samples SNP1 Total Effect",xlab="Estimate")
abline(v=eff[1,3],lwd=3,col='red')
abline(v=eff_est[1,3],lwd=3,col='blue')
legend("topright",c("Truth","Point Estimate"),col=c("red","blue"),lwd=2)
```



Simulation 2: Logistic

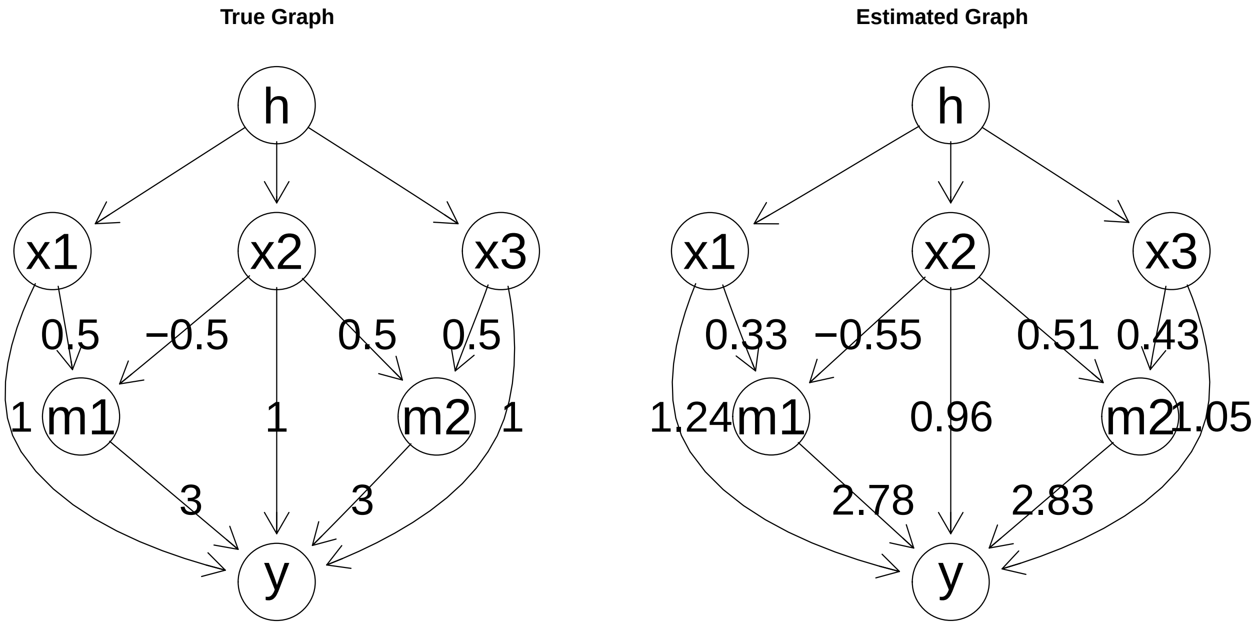
Same as simulation 1 but with binomial link function connecting y with snps and gene sets.

```
sim_params$family <- "binomial"
dat <- SimulateData(sim_params)
```

```r
gR <- mediateR:::MakeGraphNELObject(sim_params$path,sim_params$xx_direct,sim_params$mm_direct)
attrs <- list()
attrs$edge <- list()
attrs$edge$fontsize <- 12
edgeAttrs <- mediateR:::MakeedgeAttrs(sim_params$path_model,sim_params$xx_direct,sim_params$mm_direct)
```

```r
fit <- ComputePath(dat)
```

```r
gR2 <- mediateR:::MakeGraphNELObject(fit$path_model,fit$xx_direct,fit$mm_direct)
attrs2 <- list()
attrs2$edge <- list()
attrs2$edge$fontsize <- 12
edgeAttrs2 <- mediateR:::MakeedgeAttrs(fit$path_model,fit$xx_direct,fit$mm_direct)
par(mfcol=c(1,2))
plot(gR,edgeAttrs=edgeAttrs,attrs=attrs,main="True Graph")
plot(gR2,edgeAttrs=edgeAttrs2,attrs=attrs2,main="Estimated Graph")
```



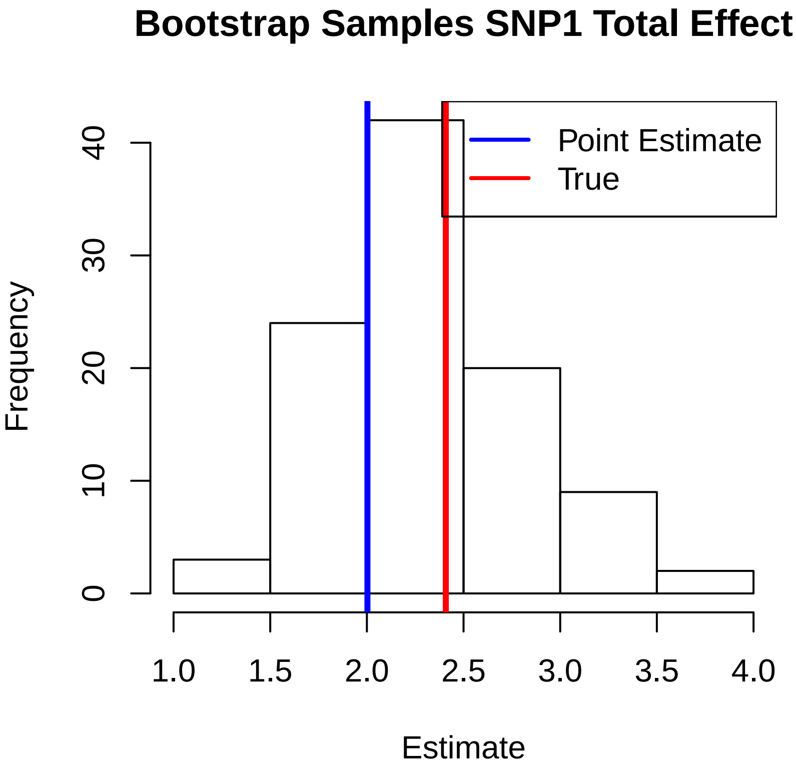
```r
## compute true effects by approximating integral with large sample size
sim_params2 <- sim_params
sim_params2$n <- 1e6 ## use million observations to approximate effects
dat2 <- SimulateData(sim_params2)
direct_t <- ComputeEffectxx(dat2,sim_params,"direct")
indirect_t <- ComputeEffectxx(dat2,sim_params,"indirect")
total_t <- ComputeEffectxx(dat2,sim_params,"total")

direct <- ComputeEffectxx(dat,fit,"direct")
indirect <- ComputeEffectxx(dat,fit,"indirect")
total <- ComputeEffectxx(dat,fit,"total")
eff_comb <- cbind(direct,direct_t,indirect,indirect_t,total,total_t)
rownames(eff_comb) <- names(fit$xx_direct)
colnames(eff_comb) <- c("est","true","est","true","est","true")
xx1total_sample <- eff_comb[1,5]
xx1total_true <- eff_comb[1,6]
```

```
B <- 100
total_xx1 <- rep(0,length=B)
for(ii in 1:B){
  ix <- sample(1:sim_params$n,replace=TRUE)
  dat_boot <- mediateR:::SubsetDat(dat,ix)
  fit_boot <- ComputePath(dat_boot)
  total_xx1[ii] <- ComputeEffectxx(dat_boot,fit_boot,"total")[1]
}
```

```
kable(eff_comb,digits=2) %>%
  kable_styling(bootstrap_options = "striped", full_width = F) %>%
  add_header_above(c(" ", "direct" = 2, "indirect" = 2, "total" = 2))
```

	direct		indirect		total	
	est	true	est	true	est	true
x1	1.61	1.40	1.33	1.7	2.00	2.41
x2	1.34	1.40	0.90	1.0	1.47	1.40
x3	1.73	1.41	1.86	1.7	2.40	2.41

```
hist(total_xx1,main="Bootstrap Samples SNP1 Total Effect",xlab="Estimate")
abline(v=xx1total_sample,lwd=3,col='blue')
abline(v=xx1total_true,lwd=3,col='red')
legend("topright",c("Point Estimate","True"),col=c("blue","red"),lwd=2)
```



Simulation 3: Survival

Same as simulation 1 and 3 but with exponentially distributed survival times. The rate is $e^{\beta^T x}$ where x are the covariates. This model can be fit with Cox Proportional Hazards.

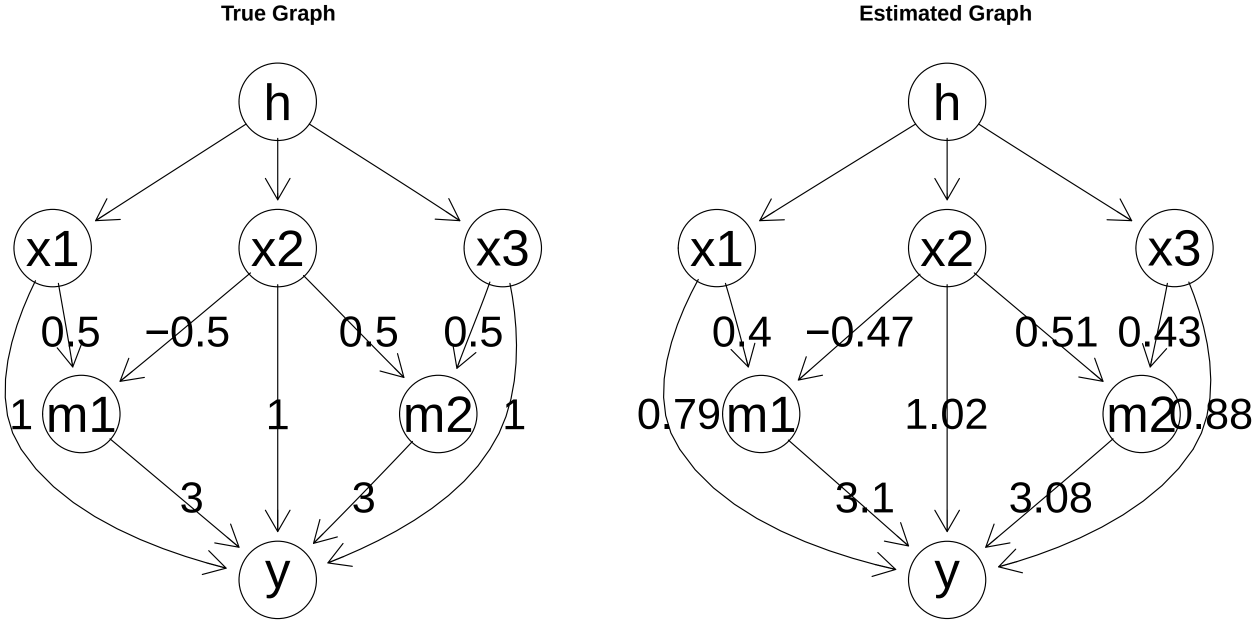
```
sim_params$family <- "cox"
dat <- SimulateData(sim_params)
rmean <- max(as.matrix(dat$y)[,1])
```

Same as simulation 1 and 3 but with exponentially distributed survival times. The rate is $e^{\beta^T x}$ where x are the covariates. This model can be fit with Cox Proportional Hazards. We compute the effects on mean survival restricted to 357.

```
gR <- mediateR:::MakeGraphNELObject(sim_params$path,sim_params$xx_direct,sim_params$mm_direct)
attrs <- list()
attrs$edge <- list()
attrs$edge$fontsize <- 12
edgeAttrs <- mediateR:::MakeedgeAttrs(sim_params$path_model,sim_params$xx_direct,sim_params$mm_direct)
```

```
fit <- ComputePath(dat)
```

```
gR2 <- mediateR:::MakeGraphNELObject(fit$path_model,fit$xx_direct,fit$mm_direct)
attrs2 <- list()
attrs2$edge <- list()
attrs2$edge$fontsize <- 12
edgeAttrs2 <- mediateR:::MakeedgeAttrs(fit$path_model,fit$xx_direct,fit$mm_direct)
par(mfcol=c(1,2))
plot(gR,edgeAttrs=edgeAttrs,attrs=attrs,main="True Graph")
plot(gR2,edgeAttrs=edgeAttrs2,attrs=attrs2,main="Estimated Graph")
```



```
## compute true effects by approximating integral with large sample size
## use the maximum observed time as the restricted mean time
sim_params2 <- sim_params
sim_params2$n <- 1e4 ## use many observations to approximate effects
dat2 <- SimulateData(sim_params2)
fit2 <- ComputePath(dat2) ## perhaps better to modify fit by entering new coefficients

direct_t <- ComputeEffectxx(dat2,fit2,"direct",rmean=rmean)
indirect_t <- ComputeEffectxx(dat2,fit2,"indirect",rmean=rmean)
total_t <- ComputeEffectxx(dat2,fit2,"total",rmean=rmean)
```

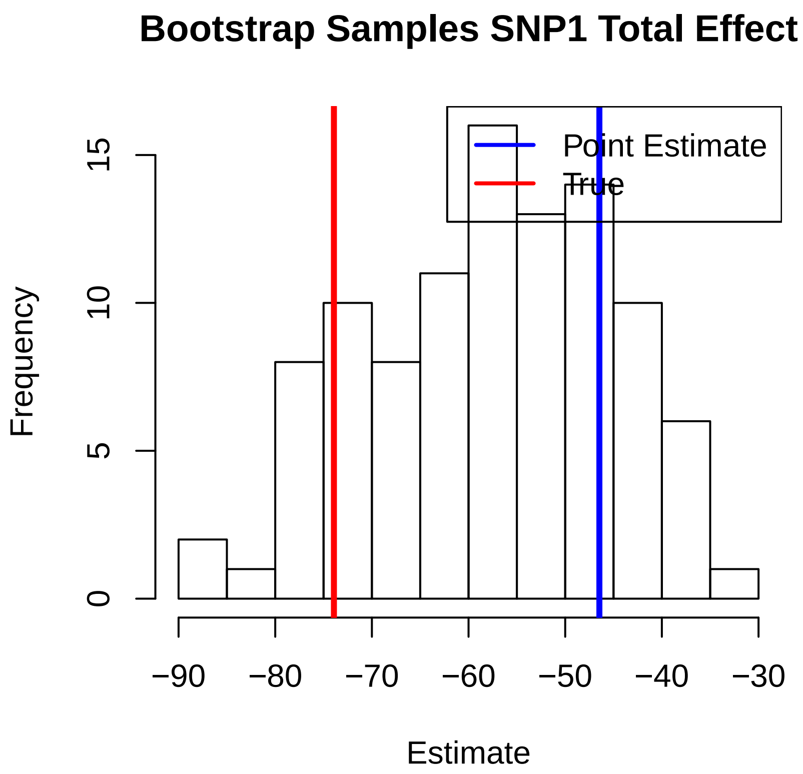
```r
direct <- ComputeEffectxx(dat,fit,"direct",rmean=rmean)
indirect <- ComputeEffectxx(dat,fit,"indirect",rmean=rmean)
total <- ComputeEffectxx(dat,fit,"total",rmean=rmean)
eff_comb <- cbind(direct,direct_t,indirect,indirect_t,total,total_t)
rownames(eff_comb) <- names(fit$xx_direct)
colnames(eff_comb) <- c("est","true","est","true","est","true")
xx1total_sample <- eff_comb[1,5]
xx1total_true <- eff_comb[1,6]
```

```r
B <- 100
total_xx1 <- rep(0,length=B)
for(ii in 1:B){
  ix <- sample(1:sim_params$n,replace=TRUE)
  dat_boot <- mediateR:::SubsetDat(dat,ix)
  fit_boot <- ComputePath(dat_boot)
  total_xx1[ii] <- ComputeEffectxx(dat_boot,fit_boot,"total",rmean=rmean)[1]
}
```

```r
kable(eff_comb,digits=2) %>%
  kable_styling(bootstrap_options = "striped", full_width = F) %>%
  add_header_above(c(" ", "direct" = 2, "indirect" = 2, "total" = 2))
```

	direct		indirect		total	
	est	true	est	true	est	true
x1	-13.75	-24.86	-48.72	-48.11	-46.46	-73.93
x2	-21.66	-27.77	9.71	2.04	-37.47	-27.46
x3	-21.31	-28.01	-15.60	-49.78	-59.35	-79.49

```r
hist(total_xx1,main="Bootstrap Samples SNP1 Total Effect",xlab="Estimate")
abline(v=xx1total_sample,lwd=3,col='blue')
abline(v=xx1total_true,lwd=3,col='red')
legend("topright",c("Point Estimate","True"),col=c("blue","red"),lwd=2)
```


Bootstrap Samples SNP1 Total Effect
Point Estimate
True
Frequency
0
5
10
15
−90
−80
−70
−60
−50
−40
−30
Estimate