Supplementary Figures

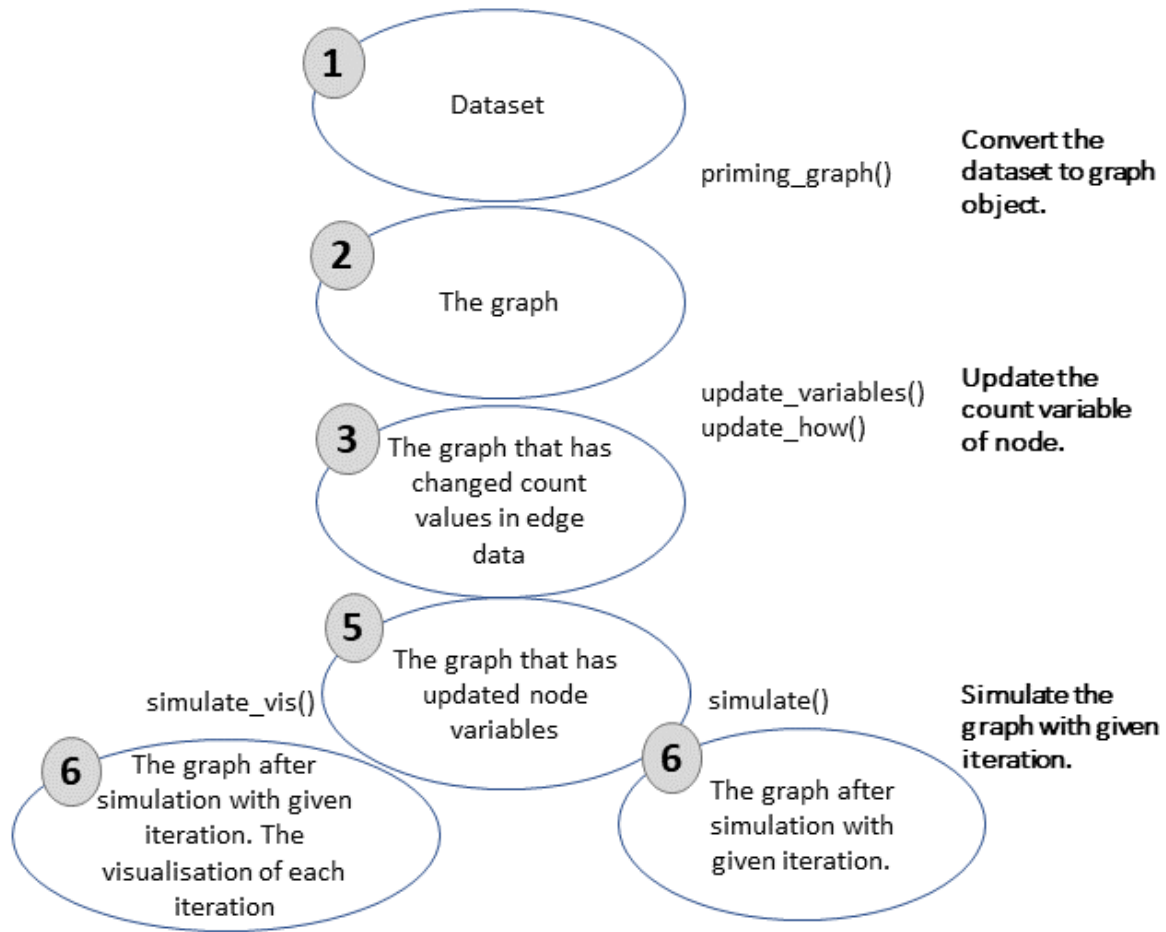Selcen Ari Yuka   Alper Yilmaz

2019-12-27

Figure S1: Workflow for simulation of competing endogenous RNA regulations. Graph object in steps 2-6 is saved and updated continuously.

```
#install.packages("devtools")
#devtools::install_github("selcenari/ceRNAnetsim")
library(ceRNAnetsim)
```

minsamp dataset analysis in absence of interaction factors.

```
minsamp<-readRDS("data/minsamp.RDS")
```

```
priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            title = "Minimal dataset in\nsteady-state conditions")
```


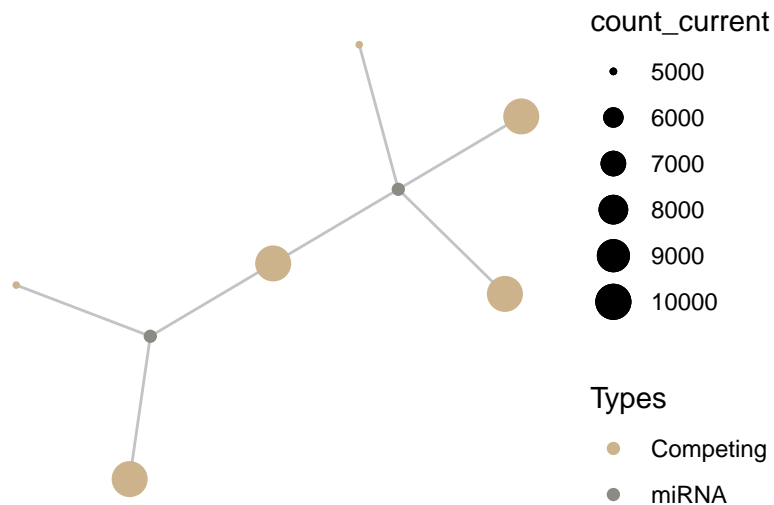
Figure S2: Minimal Dataset in Steady-state

```
priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression)%>%
  update_how("Gene2", 2)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            title = "Gene2 Upregulation\nwithout interaction factors")
```
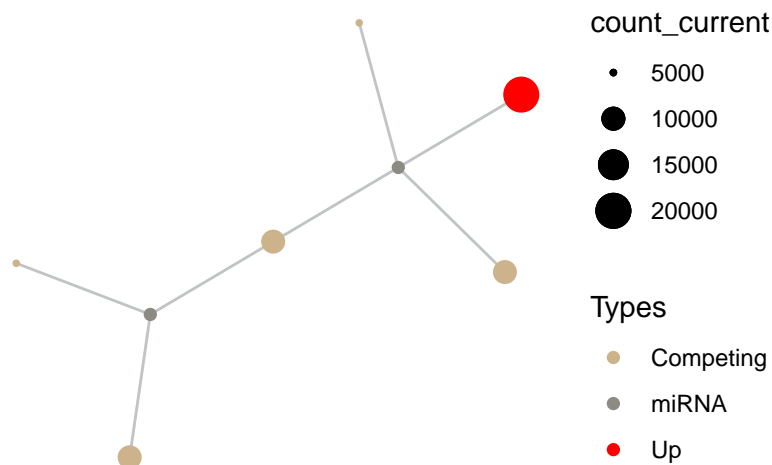
Figure S3: Gene2 Upregulation on Minimal Dataset

```
priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression) %>%
  update_how("Gene2", 2) %>%
  simulate(cycle=1) %>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            Downregulation = "blue",
            title = "A")

priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression)%>%
  update_how("Gene2", 2)%>%
  simulate(2)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            Downregulation = "blue",
            title = "B")
```
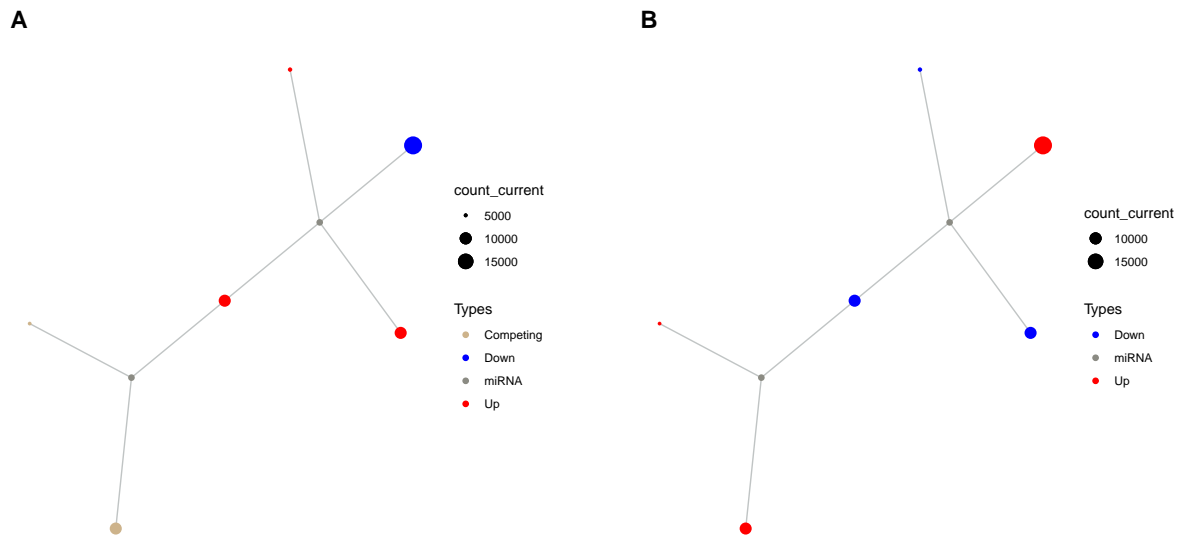
Figure S4: Sequential iteration of minsamp data. A) First response of system to Gene2 upregulation (2nd iteration). B) Spreading of perturbation on system (3th iteration)

minsamp dataset analysis with interaction factors.

```
priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression,
              aff_factor = c(energy, seed_type),
              deg_factor = region)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            title = "Minimal dataset with interaction\nfactors in steady-state conditions")
```

Minimal dataset with interaction factors in steady–state conditions

count_current

- 5000
- 6000
- 7000
- 8000
- 9000
- 10000

Types

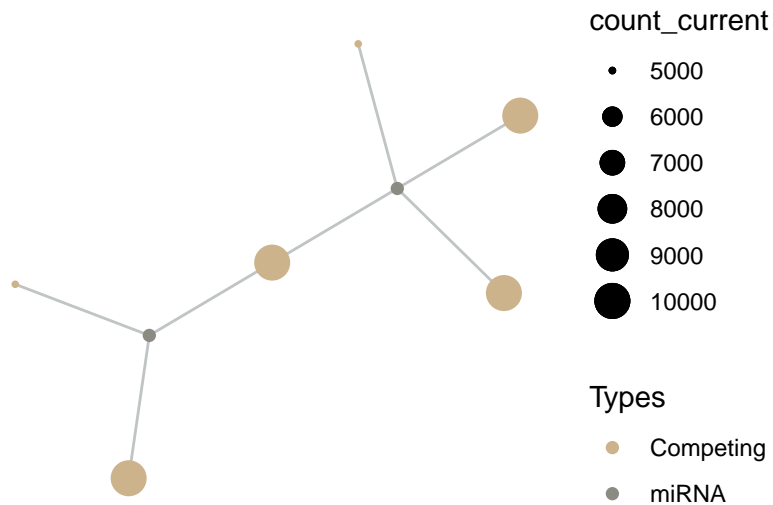- Competing
- miRNA

Figure S5: Minimal Dataset with interaction factors in Steady-state

```
priming_graph(minsamp,
             competing_count = Competing_expression,
             miRNA_count = miRNA_expression,
             aff_factor = c(energy, seed_type),
             deg_factor = region)%>%
  update_how("Gene2", 2)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            title = "Gene2 Upregulation\nwith interaction factors")
```

Gene2 Upregulation
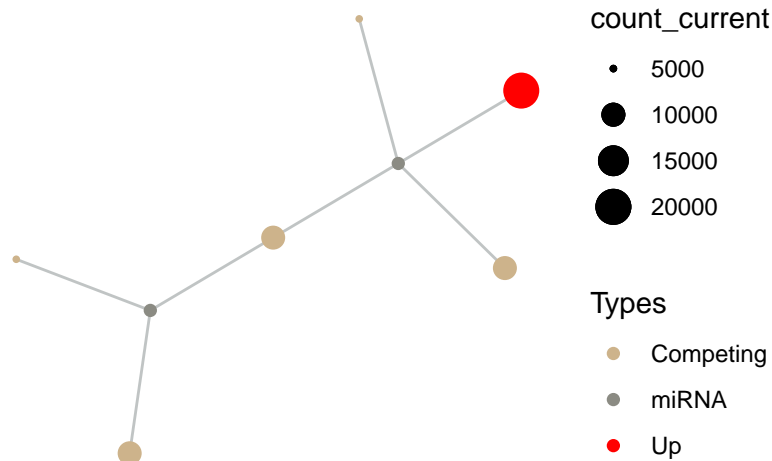# with interaction factors

Figure S6: When Gene2 is upregulated on Minimal Dataset with interaction factors

```r
priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression,
              aff_factor = c(energy, seed_type),
              deg_factor = region)%>%
  update_how("Gene2", 2)%>%
  simulate(cycle = 1)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            Downregulation = "blue",
            title = "A")

priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression,
              aff_factor = c(energy, seed_type),
              deg_factor = region)%>%
  update_how("Gene2", 2)%>%
  simulate(cycle = 2)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            Downregulation = "blue",
            title = "B")
```
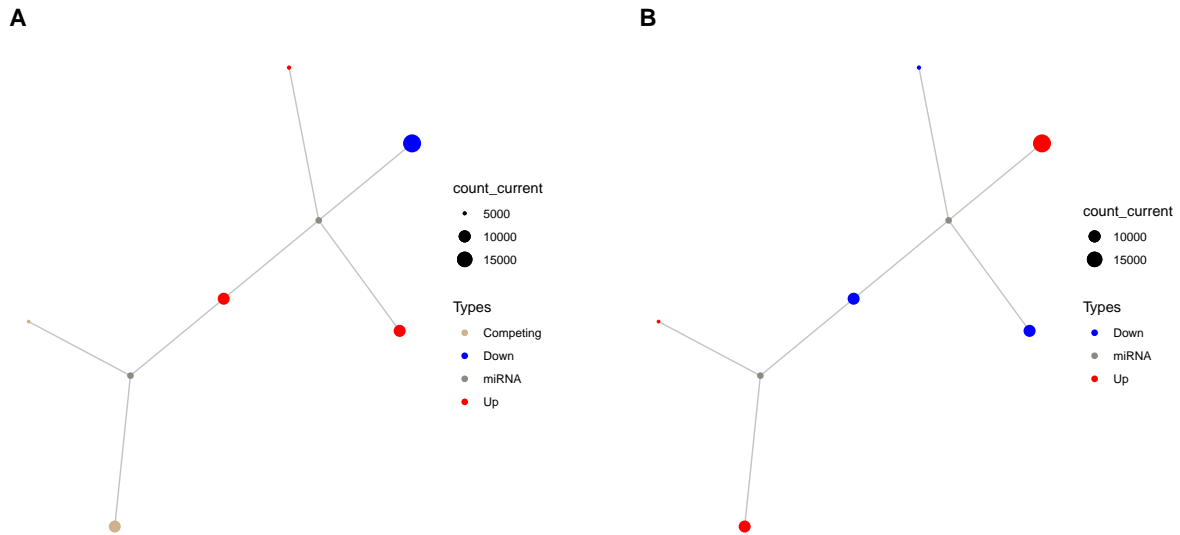
Figure S7: Sequential iteration of minsamp data with interaction factors A)First response of system to Gene2 upregulation (2nd iteration). B)Spreading of perturbation on system (3th iteration)

Common target perturbation in *minsamp* dataset.

```r
priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression,
              aff_factor = c(energy, seed_type),
              deg_factor = region)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            title = "A")

priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression,
              aff_factor = c(energy, seed_type),
              deg_factor = region)%>%
  update_how("Gene4", 2)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            title = "B")

priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression,
              aff_factor = c(energy, seed_type),
              deg_factor = region)%>%
  update_how("Gene4", 2)%>%
```

```
    simulate(cycle=1)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            title = "C")

priming_graph(minsamp,
              competing_count = Competing_expression,
              miRNA_count = miRNA_expression,
              aff_factor = c(energy, seed_type),
              deg_factor = region)%>%
  update_how("Gene4", 2)%>%
  simulate(cycle=2)%>%
  vis_graph(Competing_color = "navajowhite3",
            mirna_color = "ivory4",
            Upregulation = "red",
            title = "D")
```
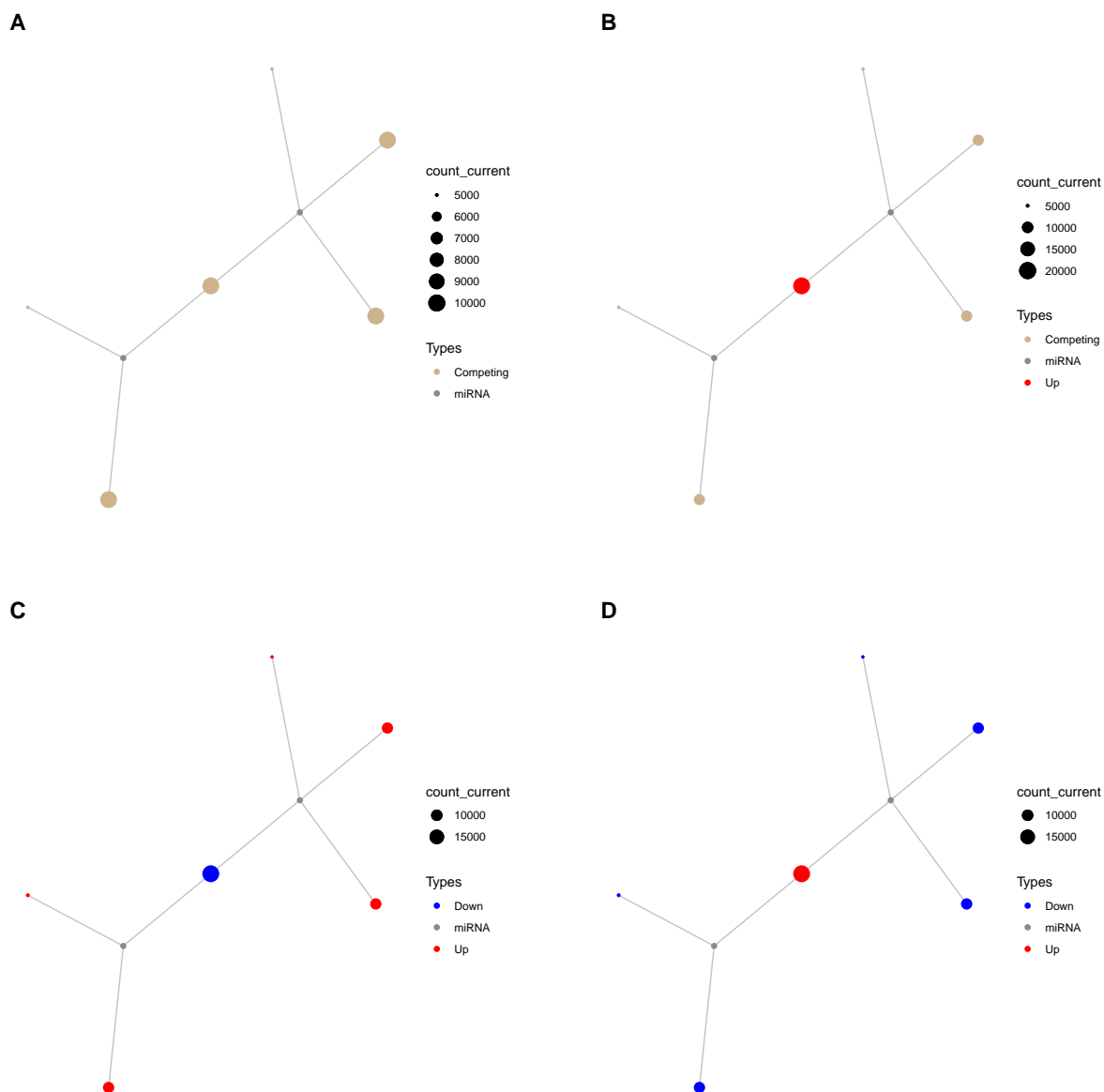
Figure S8: Perturbation of Gene4 on minsamp data with interaction factors. A) Network at steady-state. B) Upregulation of Gene4. C) Primary response of network to upregulation of Gene4. D) Re-regulation of whole nodes on system (3th iteration)

Determination of optimum iteration for Upregulation of SERPINE2 gene from Breast cancer patient dataset

```
E9GE_mirnagenenormal<-readRDS("data/E9GE_mirnagenenormal.RDS")
head(E9GE_mirnagenenormal)
```

```
## # A tibble: 6 x 7
```

```
##    hgnc_symbol miRNA_name mirna_RPM GE_normal Energy seed_type_effect
##    <chr>       <chr>          <dbl>     <dbl> <dbl>            <dbl>
## 1 CCNG1        hsa-let-7...  111204.      5245  -25.1             0.05
## 2 DICER1       hsa-let-7...  111204.      3285  -24.4             0.43
## 3 SESN1        hsa-let-7...  111204.      1179  -22.2             0.05
## 4 NIPBL        hsa-let-7...  111204.      4503  -22.1             0.05
## 5 INTS12       hsa-let-7...  111204.       600  -21.9             0.05
## 6 FNIP1        hsa-let-7...  111204.      1248  -21.8             0.43
## # ... with 1 more variable: region_effect <dbl>
```

```r
as.data.frame(E9GE_mirnagenenormal)%>%
 priming_graph(competing_count = GE_normal,
               miRNA_count = mirna_RPM,
               aff_factor = c(Energy, seed_type_effect),
               deg_factor = region_effect)%>%
 update_how("SERPINE2",2.75) %>%
 simulate(150) %>%
 find_iteration(limit=1, plot= TRUE)
```

```
## Warning in priming_graph(., competing_count = GE_normal, miRNA_count = mirna_RPM, : First column is
```
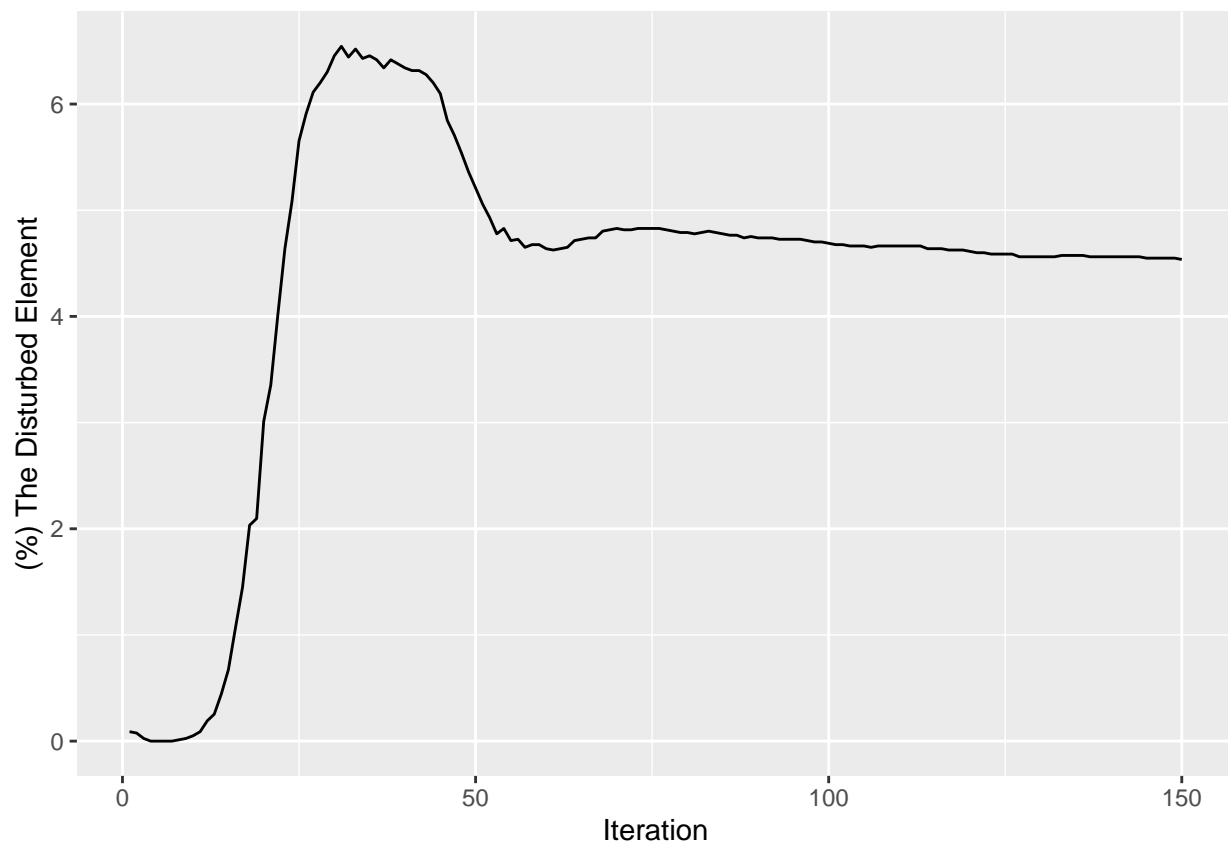

Figure S9: Percentage of affected nodes of each iteration for SERPINE2 Gene

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Highly effective perturbing elements in network

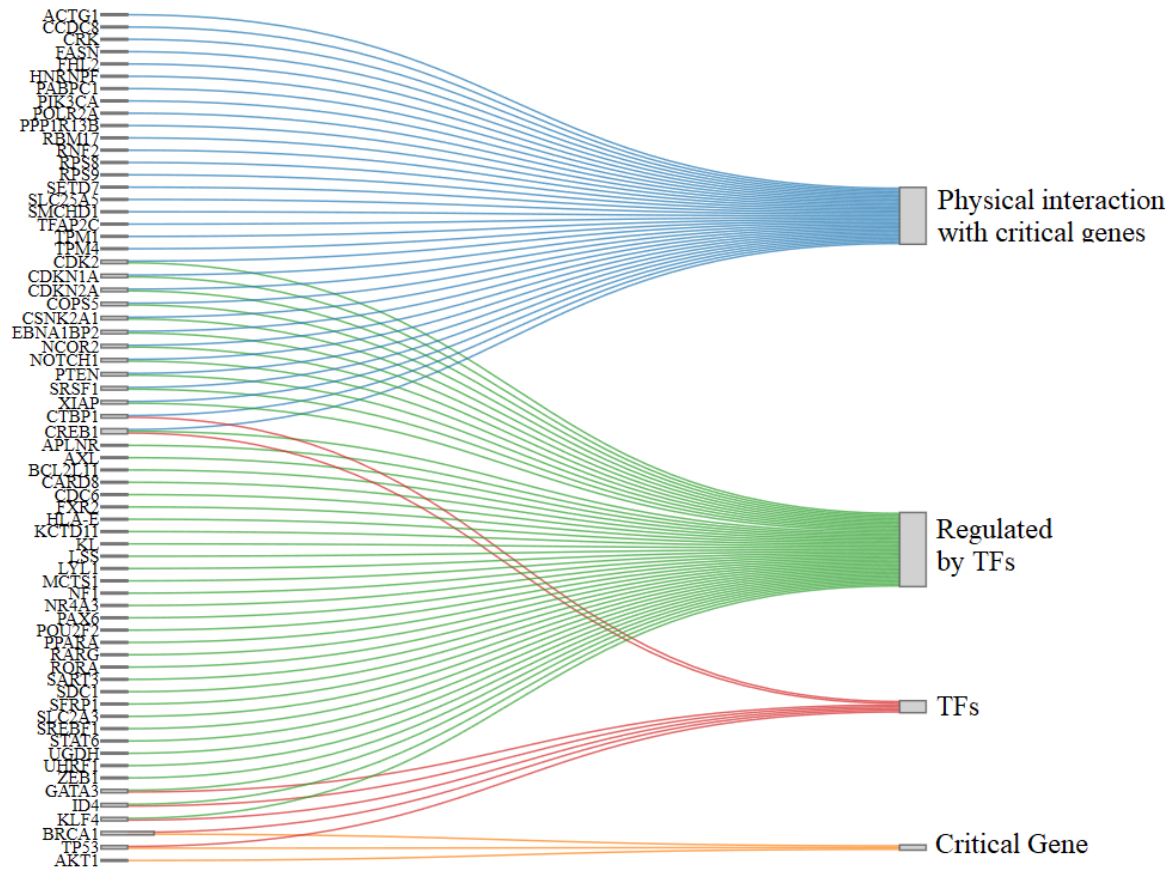

Figure S10: Interactions of genes that have high perturbation efficiency. Critical gene, represents crucial genes for breast cancer,provided by eDGAR; TFs, transcription factors; Regulated by TFs, regulated genes with these transcription factors; Physical interaction with critical genes; shared genes in physical interactions between critical genes