

# Package ‘ceRNAetsim’

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**Type** Package

**Title** Regulation Simulator of Interaction between miRNA and Competing RNAs (ceRNA)

**Version** 1.18.0

**Description** This package simulates regulations of ceRNA (Competing Endogenous) expression levels after a expression level change in one or more miRNA/mRNAs. The methodology adopted by the package has potential to incorporate any ceRNA (circRNA, lincRNA, etc.) into miRNA:target interaction network. The package basically distributes miRNA expression over available ceRNAs where each ceRNA attracts miRNAs proportional to its amount. But, the package can utilize multiple parameters that modify miRNA effect on its target (seed type, binding energy, binding location, etc.). The functions handle the given dataset as graph object and the processes progress via edge and node variables.

**License** GPL ( $\geq 3.0$ )

**URL** <https://github.com/selcenari/ceRNAetsim>

**BugReports** <https://github.com/selcenari/ceRNAetsim/issues>

**Depends** R ( $\geq 4.0.0$ ), dplyr, tidygraph

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## Contents

calc_perturbation	2
find_affected_nodes	3
find_iteration	4
find_node_perturbation	5
find_targeting_nodes	6
gene_knockdown	7
huge_example	8
midsamp	8
midsamp_new_counts	9
minsamp	9
mirtarbasegene	10
new_counts	10
normalize	11
prepare_rhs	11
prepare_rhs_once	12
priming_graph	12
simulate	13
simulate_vis	14
TCGA_E9_A1N5_mirnanormal	15
TCGA_E9_A1N5_mirnatumor	16
TCGA_E9_A1N5_normal	17
TCGA_E9_A1N5_tumor	17
update_how	18
update_nodes	19
update_variables	19
vis_graph	20
<b>Index</b>	<b>22</b>

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calc_perturbation	<i>Calculates average expression changes of all nodes except trigger and finds the perturbed node count for a given node.</i>
-------------------	---

---

### Description

Calculates average expression changes of all nodes except trigger and finds the perturbed node count for a given node.

### Usage

```
calc_perturbation(input_graph, node_name, how = 1, cycle = 1, limit = 0)
```

**Arguments**

input_graph	the graph object that was processed with priming graph in previous step.
node_name	The node that is trigger for simulation.
how	The change of count of the given node in terms of fold change.
cycle	The iteration of simulation.
limit	The minimum fold change which can be taken into account for perturbation calculation on all nodes in terms of percentage.

**Details**

calc\_perturbation calculates mean expression changes of elements except trigger after the change in the network in terms of percentage. It also calculates the number of nodes that have expression changes after the change occur in the network. The function determines the perturbation efficiency and number of perturbed nodes after given change with how, cycle and limit parameter.

**Value**

a tibble with two columns, the perturbation efficiency and number of perturbed nodes.

**Examples**

```
data('minsamp')

minsamp%>%
  priming_graph(competing_count = Competing_expression,
                miRNA_count = miRNA_expression)%>%
  calc_perturbation('Gene6', how= 3, cycle = 4)

minsamp%>%
  priming_graph(competing_count = Competing_expression, miRNA_count = miRNA_expression,
                aff_factor = c(energy,seed_type), deg_factor = region)%>%
  calc_perturbation('Gene6',3, cycle = 4)
```

---

find\_affected\_nodes     *Finds top affected nodes for perturbation from a particular node*

---

**Description**

Finds top affected nodes for perturbation from a particular node

**Usage**

```
find_affected_nodes(
  input_graph,
  node_name,
  how = 1,
  cycle = 1,
  limit = 0,
  top = 5
)
```

**Arguments**

input_graph	The graph object that was processed with priming_graph function.
node_name	The node to trigger perturbations.
how	The change of count (expression) of the given node in terms of fold change.
cycle	The iteration of simulation.
limit	The minimum fold change which can be taken into account for perturbation calculation on all nodes in terms of percentage.
top	Determines how many nodes most affected will be listed.

**Details**

Lists the most affected nodes after perturbation initiated from a particular node. In the background, it compares the calculated values after the simulation with their initial values.

**Value**

It gives a tibble form dataset that includes perturbation node, affected nodes and changes of them.

**Examples**

```
data('midsamp')

midsamp%>%
  priming_graph(competing_count = Gene_expression,
               miRNA_count = miRNA_expression)%>%
  find_affected_nodes(node_name = "Gene1",
                    how = 2,
                    cycle = 2,
                    top = 2)
```

---

find_iteration	<i>Finds the iteration which provides maximum affected node number</i>
----------------	--

---

**Description**

searches the iteration that provides maximum affected node number. The user defines a symbolic iteration with .iter. The function calculates the number of affected nodes for each iteration and then selects the iteration that has maximum affected nodes' number.

**Usage**

```
find_iteration(df, limit = 0.1, plot = FALSE)
```

**Arguments**

df	A tbl graph that includes the miRNA and competing targets triggered and simulated for number of cycles.
limit	The minimum amount of change of any node.
plot	If TRUE, returns a plot.

**Value**

It gives an iteration number to use in simulate() function.

**Examples**

```
data('midsamp')

midsamp %>%
  priming_graph(Gene_expression, miRNA_expression) %>%
  update_how('Gene2',2) %>%
  simulate(10) %>%
  find_iteration(limit=0)
```

---

find\_node\_perturbation

*Calculates average expression changes of all (or specified) nodes except trigger and finds the perturbed node count for all (or specified) nodes in system.*

---

**Description**

Calculates average expression changes of all (or specified) nodes except trigger and finds the perturbed node count for all (or specified) nodes in system.

**Usage**

```
find_node_perturbation(input_graph, how = 2, cycle = 1, limit = 0, fast = 0)
```

**Arguments**

input_graph	The graph object that was processed with priming_graph function.
how	The change of count (expression) of the given node in terms of fold change.
cycle	The iteration of simulation.
limit	The minimum fold change which can be taken into account for perturbation calculation on all nodes in terms of percentage.
fast	specifies percentage of affected target in target expression. For example, if fast = 1, the nodes that are affected from miRNA repression activity more than one percent of their expression is determined as subgraph.

**Details**

find\_node\_perturbation calculates mean expression changes of elements after the change in the network in terms of percentage. It also calculates the number of nodes that have expression changes after the change occur in the network. The outputs of the function are the perturbation efficiency and perturbed count of nodes for each nodes.

**Value**

It gives a tibble form dataset that includes node names, perturbation efficiency and perturbed count of nodes.

**Examples**

```

data('minsamp')
data('midsamp')

minsamp%>%
  priming_graph(competing_count = Competing_expression, miRNA_count = miRNA_expression)%>%
  find_node_perturbation()%>%
  select(name, perturbation_efficiency, perturbed_count)

minsamp%>%
  priming_graph(competing_count = Competing_expression, miRNA_count = miRNA_expression,
    aff_factor = c(energy,seed_type), deg_factor = region)%>%
  find_node_perturbation(how = 3, cycle = 4)%>%
  select(name, perturbation_efficiency, perturbed_count)

midsamp%>%
  priming_graph(competing_count = Gene_expression, miRNA_count = miRNA_expression)%>%
  find_node_perturbation(how = 2, cycle= 3, limit=1, fast = 5)%>%
  select(name, perturbation_efficiency, perturbed_count)

```

---

find\_targeting\_nodes *Finds potential affecting node for given particular target.*

---

**Description**

Finds potential affecting node for given particular target.

**Usage**

```

find_targeting_nodes(
  input_graph,
  how = 2,
  cycle = 1,
  limit = 0,
  fast = 0,
  top = 5,
  target = NULL
)

```

**Arguments**

input_graph	The graph object that was processed with priming_graph function.
how	The change of count (expression) of the given node in terms of fold change.
cycle	The iteration of simulation.
limit	The minimum fold change which can be taken into account for perturbation calculation on all nodes in terms of percentage.
fast	specifies percentage of affected target in target expression. For example, if fast = 1, the nodes that are affected from miRNA repression activity more than one percent of their expression is determined as subgraph.

top                    Determines how many nodes most affected will be evaluated.  
 target                The target node in which is being investigated.

### Details

Lists potential targeting nodes by running `find_affected_nodes` function for all nodes in network.

### Value

It gives a tibble form dataset that includes perturbation node (source) and change in count of targeting node

### Examples

```
data('midsamp')

midsamp%>%
  priming_graph(competing_count = Gene_expression,
                miRNA_count = miRNA_expression)%>%
  find_targeting_nodes(how = 2,
                      cycle = 2,
                      target = "Gene1",
                      top = 2)
```

---

gene_knockdown	<i>Knocks down given node.</i>
----------------	--------------------------------

---

### Description

Knocks down given node.

### Usage

```
gene_knockdown(input_graph, node_name)
```

### Arguments

input\_graph        The graph object that processed in previous step/s.  
 node\_name         The name of the node whose count is to be knocked down.

### Details

knocks down a given gene target.

### Value

the graph object.

---

huge_example	<i>huge example</i>
--------------	---------------------

---

### Description

A sample dataset which is utilised through integration of TCGA\_E9\_A1N5\_normal, TCGA\_E9\_A1N5\_mirnormal and high-throughput experimental miRNA:gene dataset.

### Format

A data frame with 7 variables and 26176 observation:

**competing** name of gene

**miRNA** name of miRNA

**competing\_counts** Expression values of competing element (gene)

**mirnaexpression\_normal** Expression value of miRNA elements in normal tissue

**Energy** Energy of miRNA:target binding

**region\_effect** Coefficient for efficiency of location on target

**seed\_type\_effect** Coefficient for efficiency of seed sequence of miRNA:target interaction

### Source

Dataset was integrated by us.

---

midsamp	<i>midsamp</i>
---------	----------------

---

### Description

middle sized sample dataset

### Format

A data frame with 7 variables and 26 observation of them:

**Genes** symbol of gene

**miRNAs** symol of miRNA

**Gene\_expression** Expression values of competing gene

**miRNA\_expression** Expression value of miRNA

**seeds** Coefficient for efficiency of seed type of miRNA:target interaction

**targeting\_region** Coefficient for efficiency of location on target

**Energy** Energy of miRNA:target binding

### Source

Dataset was created by us.



---

midsamp_new_counts	<i>midsamp_new_counts</i>
--------------------	---------------------------

---

**Description**

includes new expression values for middle sized sample dataset

**Format**

A data frame with 4 variables and 26 observation of them:

**Competing** symbol of gene

**miRNA** symol of miRNA

**Competing\_count** Expression values of competing gene

**miRNA\_count** Expression value of miRNA

**Source**

Dataset was created by us.

---

minsamp	<i>minsamp</i>
---------	----------------

---

**Description**

minimal sample dataset

**Format**

A data frame with 7 variables and 7 observation of them:

**competing** symbol of gene

**miRNA** symol of miRNA

**Competing\_expression** Expression values of competing gene

**miRNA\_expression** Expression value of miRNA

**seed\_type** Coefficient for efficiency of seed sequence of miRNA:target interaction

**region** Coefficient for efficiency of location on target

**energy** Energy of miRNA:target binding

**Source**

Dataset was created by us.

---

mirtarbasegene	<i>mirtarbasegene</i>
----------------	-----------------------

---

**Description**

the dataset that includes miRNA:target gene interactions downloaded from mirtarbase

**Format**

Classes tbl\_df, tbl and data.frame with 380627 observation of 2 variables:

**miRNA** miRNA symbol

**Target** target gene symbol

**Source**

<http://mirtarbase.mbc.nctu.edu.tw/php/index.php>

---

new_counts	<i>new_counts</i>
------------	-------------------

---

**Description**

includes new expression values for minimal sample dataset

**Format**

A data frame with 7 variables and 7 observation of them:

**Competing** symbol of gene

**miRNA** symol of miRNA

**Competing\_count** Expression values of competing gene

**miRNA\_count** Expression value of miRNA

**Source**

Dataset was created by us.

---

normalize	<i>normalize</i>
-----------	------------------

---

**Description**

normalizes the values according to maximum values inside a group. The helper function of `priming_graph`.

**Usage**

```
normalize(x)
```

**Arguments**

`x` The variable name that is normalized.

**Value**

normalized values

---

prepare_rhs	<i>Carries the variables from edge to node</i>
-------------	--

---

**Description**

Carries the variables from edge to node.

**Usage**

```
prepare_rhs(input_graph)
```

**Arguments**

`input_graph` Processed graph object in previous step.

**Details**

The function is a helper function for processing of graph object with `update_nodes` function.

**Value**

tibble object

---

prepare_rhs_once	<i>Carries the variables from edge to node.</i>
------------------	---

---

**Description**

Carries the variables from edge to node.

**Usage**

```
prepare_rhs_once(input_graph)
```

**Arguments**

input\_graph      Processed graph object in previous step.

**Details**

The function is a helper function for processing of graph object with update\_nodes function.

**Value**

tibble object

---

priming_graph	<i>Converts the given dataframe using first variable as competing and the second as miRNA. The function converts the given dataframe using first variable as competing and the second as miRNA. If user defines interaction factors as affinity or degradation, the factors are taken into account.</i>
---------------	---

---

**Description**

Converts the given dataframe using first variable as competing and the second as miRNA. The function converts the given dataframe using first variable as competing and the second as miRNA. If user defines interaction factors as affinity or degradation, the factors are taken into account.

**Usage**

```
priming_graph(
  df,
  competing_count,
  miRNA_count,
  aff_factor = dummy,
  deg_factor = dummy
)
```

**Arguments**

df	A data frame that includes the miRNA and competing targets.
competing_count	The counts (or expression) of competing elements of the dataset.
miRNA_count	The counts (or expression) of repressive element (miRNA) of the dataset.
aff_factor	The parameter/s of binding between miRNA and targets.
deg_factor	The parameter/s for degradation of bound miRNA:target complex.

**Details**

priming\_graph provides grouping of competing targets and evaluation of targets within the groups taking into account miRNA:target, target:total target, interaction and degradation parameters. The target groups are determined according to miRNAs. If the factors that are important in target interactions are specified as arguments, the factors also are evaluated separately within each group. priming\_graph also calculates the miRNA efficiency in steady-state conditions. It is assumed that quantity of competing targets and miRNAs are shown in the steady-state system after the miRNAs exhibit repressive efficiency. Note that the data must not include missing values such as NA or '-'.

**Value**

the graph object.

**Examples**

```
data('minsamp')

priming_graph(minsamp, Competing_expression, miRNA_expression)

priming_graph(minsamp, Competing_expression, miRNA_expression,
  aff_factor = c(seed_type,energy), deg_factor = region)
```

---

simulate

*Utilizes the change in expression value/s as triggering.*

---

**Description**

simulate function uses the change in expression value/s as triggering.

**Usage**

```
simulate(input_graph, cycle = 1, threshold = 0, knockdown = TRUE)
```

**Arguments**

input_graph	The graph object that processed in previous steps.
cycle	Optimal iteration number for gaining steady-state.
threshold	absolute minimum amount of change required to be considered as up/down regulated element
knockdown	specifies gene knockdown with default TRUE

## Details

The steady-state conditions of the system are disturbed after the change in the graph (with `update_how` or `update_variables`). In this case, the system tend to be steady state again. The arrangement of competitive profiles of the targets continue until all nodes are updated and steady-state nearly. Note that, If 'how' argument is specified as '0', `*simulate()*` and `*update_how()*` functions process the variables to knockdown of specified gene with default 'knockdown = TRUE' and knocked down competing RNA is kept at zero. However, if 'knockdown= FALSE' argument is applied, competing RNA which has initial expression level of zero is allowed to increase or fluctuate during calculations.

## Value

The graph.

## Examples

```
data('minsamp')
data('new_counts')

## new_counts, the dataset that includes the current counts of nodes.

priming_graph(minsamp, Competing_expression, miRNA_expression)%>%
  update_variables(new_counts)%>%
  simulate()

priming_graph(minsamp, Competing_expression, miRNA_expression,
  aff_factor = c(seed_type,energy), deg_factor = region)%>%
  update_variables(new_counts)%>%
  simulate(cycle = 3)
```

---

simulate\_vis

*Provides visualisation of the graph in addition to simulate function.*

---

## Description

simulate\_vis provides visualisation of the graph in addition to simulate function.

## Usage

```
simulate_vis(
  input_graph,
  cycle = 1,
  threshold = 0,
  save = FALSE,
  Competing_color = "green",
  mirna_color = "orange",
  Upregulation = "red",
  Downregulation = "blue",
  title = "GRAPH",
  layout = "kk"
)
```

**Arguments**

input_graph	The graph object that processed in previous steps.
cycle	Optimal iteration number for gaining steady-state.
threshold	absolute minimum amount of change required to be considered as up/down regulated element
save	provides to save graph output
Competing_color	The color of competing elements on the graph with "green" default.
mirna_color	The color of miRNAs on the graph with "orange" default.
Upregulation	The color of Upregulated elements on the graph with "red" default.
Downregulation	The color of Downregulated elements on the graph with "blue" default.
title	Title of the given graph.
layout	The layout that will be used for visualisation of the graph.

**Details**

simulate\_vis gives the last graph object and each iterations' image.

**Value**

It gives a graph and the images of states in each iteration until the end of the simulation.

**Examples**

```
# When does the system gain steady-state conditions again?

## new_counts, the dataset that includes the current counts of nodes.

data("minsamp")
data("new_counts")

priming_graph(minsamp, Competing_expression, miRNA_expression)%>%
  update_variables(new_counts)%>%
  simulate_vis()

priming_graph(minsamp, Competing_expression, miRNA_expression,
  aff_factor = c(seed_type,energy), deg_factor = c(region))%>%
  update_variables(new_counts)%>%
  simulate_vis(cycle = 12)
```

---

TCGA\_E9\_A1N5\_mirnanormal

*TCGA\_E9\_A1N5\_mirnanormal*

---

**Description**

The dataset contains mirna expression values for normal tissue sample of TCGA-E9-A1N5 bar-coded patient

**Format**

Classes tbl\_df, tbl and data.frame with 750 observation of 6 variables:

**barcode** Sample, normal tissue, barcode of patient based on TCGA

**mirbase\_ID** mirbase id of miRNA

**miRNA** miRNA name

**Precursor** Precursor id of miRNA which is given in miRNA variable

**total\_read** total reading count of miRNA which is produced from different gene locations

**total\_RPM** total RPM (reading per million) of miRNA

**Source**

<https://portal.gdc.cancer.gov/>

---

TCGA\_E9\_A1N5\_mirnatumor

*TCGA\_E9\_A1N5\_mirnatumor*

---

**Description**

The dataset contains mirna expression values for tumor tissue sample of TCGA-E9-A1N5 barcoded patient

**Format**

Classes tbl\_df, tbl and data.frame with 648 observation of 6 variables:

**barcode** Sample, tumor tissue, barcode of patient based on TCGA

**mirbase\_ID** mirbase id of miRNA

**miRNA** miRNA name

**Precursor** Precursor id of miRNA which is given in miRNA variable

**total\_read** total reading count of miRNA which is produced from different gene locations

**total\_RPM** total RPM (reading per million) of miRNA

**Source**

<https://portal.gdc.cancer.gov/>



---

TCGA\_E9\_A1N5\_normal     *TCGA\_E9\_A1N5\_normal*

---

**Description**

The dataset contains gene expression values for normal tissue sample of TCGA-E9-A1N5 barcoded patient

**Format**

Classes tbl\_df, tbl and data.frame with 56830 observation of 7 variables:

**patient** Barcode of patient based on TCGA  
**sample** Tissue sample barcode of the patient  
**barcode** Sample barcode of the patient  
**definition** Tissue type of sample (Solid Tissue Normal)  
**ensembl\_gene\_id** Gene id  
**external\_gene\_name** Gene symbol  
**gene\_expression** Gene expression value

**Source**

<https://portal.gdc.cancer.gov/>

---

TCGA\_E9\_A1N5\_tumor     *TCGA\_E9\_A1N5\_tumor*

---

**Description**

The dataset contains gene expression values for cancer tissue sample of TCGA-E9-A1N5 barcoded patient

**Format**

Classes tbl\_df, tbl and data.frame with 56830 observtion of 7 variables:

**patient** Barcode of patient based on TCGA  
**sample** Tissue sample barcode of the patient  
**barcode** Sample barcode of the patient  
**definition** Tissue type of sample (Primary solid Tumor)  
**ensembl\_gene\_id** Gene id  
**external\_gene\_name** Gene symbol  
**gene\_expression** Gene expression value

**Source**

<https://portal.gdc.cancer.gov/>

---

update_how	<i>Converts the count value of the given node.</i>
------------	--

---

### Description

this function converts the count value of the given node.

### Usage

```
update_how(input_graph, node_name, how, knockdown = TRUE)
```

### Arguments

input_graph	The graph object that processed in previous step/s.
node_name	The name of the node whose count is to be changed.
how	The change in terms of fold change.
knockdown	specifies gene knockdown with default TRUE

### Details

update\_how function calculates the current value of given mirna or gene node on the graph object. User must specify current value as fold change.

### Value

the graph object.

### Examples

```
data('minsamp')

priming_graph(minsamp, Competing_expression, miRNA_expression)%>%
  update_how('Gene1', 3)

priming_graph(minsamp, Competing_expression, miRNA_expression,
  aff_factor = c(seed_type,energy), deg_factor = region)%>%
  update_how('Gene1', 3)

priming_graph(minsamp, Competing_expression, miRNA_expression,
  aff_factor = c(seed_type,energy), deg_factor = region)%>%
  update_how('Gene1', how=0, knockdown= TRUE)
```

---

update_nodes	<i>Carries variables from edge to node.</i>
--------------	---

---

### Description

This function carries variables from edge to node and should be used after ‘update\_how’ or ‘update\_variables’ functions

### Usage

```
update_nodes(input_graph, once = FALSE, limit = 0)
```

### Arguments

input_graph	Processed graph object in previous step.
once	The argument is about when the carrying process runs (internal use only)
limit	absolute minimum amount of change required to be considered as up/down regulated element

### Details

If the carrying process performs after priming\_graph function, the argument must be TRUE. The function helps to visualisation of processed graph object, especially that includes too many nodes. This step makes it easily to follow the processes.

### Value

the graph object.

### Examples

```
data('minsamp')

minsamp %>%
  priming_graph(Competing_expression, miRNA_expression) %>%
  update_how('Gene2', 2)
```

---

update_variables	<i>Replaces new values with previous values of competing or miRNA counts.</i>
------------------	---

---

### Description

This function replaces new values with previous values of competing or miRNA counts.

### Usage

```
update_variables(input_graph, current_counts)
```

**Arguments**

`input_graph` The processed graph object.  
`current_counts` The additional df that provided by user.

**Details**

`update_variables` function provides updating edge variables to current values. If the microRNA or competing expression (or both) change (decreasing or increasing), this function switches the values that are found in a new dataset provided by user. But the current value dataset must be equal with initial dataset in terms of node name.

**Value**

the graph object.

**Examples**

```
data('minsamp')
data('new_counts')

minsamp%>%
  priming_graph(Competing_expression, miRNA_expression,
    aff_factor = c(seed_type,energy), deg_factor = region)%>%
  update_variables(new_counts)
#new_counts includes the current counts of nodes.
```

---

vis\_graph

*Provides visualisation of the graph.*

---

**Description**

‘vis\_graph’ Provides visualisation of the graph.

**Usage**

```
vis_graph(
  input_graph,
  Competing_color = "green",
  mirna_color = "orange",
  Upregulation = "red",
  Downregulation = "blue",
  title = "GRAPH",
  layout = "kk"
)
```

**Arguments**

input_graph	The graph object.
Competing_color	The color of competing elements on the graph with 'green' default.
mirna_color	The color of miRNAs on the graph with 'orange' default.
Upregulation	The color of Upregulated elements on the graph with 'red' default.
Downregulation	The color of Downregulated elements on the graph with 'blue' default.
title	Title of the given graph.
layout	The layout that will be used for visualisation of the graph.

**Details**

vis\_graph ensures the process to be followed.

**Value**

The graph object.

**Examples**

```
data('minsamp')
data('new_counts')

# Visualisation of graph in steady-state.

priming_graph(minsamp, Competing_expression, miRNA_expression,
  aff_factor = c(seed_type,energy), deg_factor = region)%>%
  vis_graph()

# Visualisation of graph after the change.

priming_graph(minsamp, Competing_expression, miRNA_expression,
  aff_factor = c(seed_type,energy), deg_factor = region)%>%
  update_variables(new_counts)%>%
  vis_graph()
```

# Index

## \* internal

- gene\_knockdown, 7
- normalize, 11
- prepare\_rhs, 11
- prepare\_rhs\_once, 12

calc\_perturbation, 2

find\_affected\_nodes, 3  
find\_iteration, 4  
find\_node\_perturbation, 5  
find\_targeting\_nodes, 6

gene\_knockdown, 7

huge\_example, 8

midsamp, 8  
midsamp\_new\_counts, 9  
minsamp, 9  
mirtarbasegene, 10

new\_counts, 10  
normalize, 11

prepare\_rhs, 11  
prepare\_rhs\_once, 12  
priming\_graph, 12

simulate, 13  
simulate\_vis, 14

TCGA\_E9\_A1N5\_mirnanormal, 15  
TCGA\_E9\_A1N5\_mirnatumor, 16  
TCGA\_E9\_A1N5\_normal, 17  
TCGA\_E9\_A1N5\_tumor, 17

update\_how, 18  
update\_nodes, 19  
update\_variables, 19

vis\_graph, 20