# PHONEMeS-ILP

ILP implementation of PHONEMeS - Enio GJERGA

**PHONEMeS** (**PHO**sphorylation **NE**tworks for **M**ass **S**pectrometry) is a method to model signalling networks based on untargeted phosphoproteomics mass spectrometry data and kinase/phosphatase-substrate interactions. Please see [Terfve et al.](http://www.nature.com/articles/ncomms9033) for an explanation of the methodolgy.

This repository contains the scripts of the ILP (Integer Linear Programming) implementation of the [PHONEMeS R package](https://github.com/saezlab/PHONEMeS/tree/master/Package) and accompanying scripts that implement the method. ILP is a mathematical optimisation problem in which the objective function and constraints are linear, while the variables are integers.

### License

Distributed under the GNU GPLv2 License. See accompanying file [LICENSE.txt](https://github.com/saezlab/PHONEMeS/blob/master/LICENSE.txt) or copy at <https://www.gnu.org/licenses/gpl-2.0.html>.

### Installation

Before using the method, please install the current R package for PHONEMeS. For installation, download the tar file of the package and type in R:

install.packages("PHONEMeS\_0.2.7.tar.gz", repos=NULL)

Other supportive R packages needed are:

igraph which you can easily install by typing in R the below line:

install.packages("igraph")

BioNet which you can easily install by typing in R the below line:

source("https://bioconductor.org/biocLite.R") biocLite("BioNet")

XML which can be downloaded [here](https://cran.r-project.org/src/contrib/XML_3.98-1.9.tar.gz) and then you can install by typing in R:

install.packages("XML\_3.98-1.9.tar.gz", repos=NULL)

### CPLEX

PHONEMeS-ILP is CPLEX depndent meaning that the user needs to obtain an IBM ILOG CPLEX licence and then save the executable file to the working directory. The IBM ILOG CPLEX Optimization Studio license can be obtained for free by:

* Students: <https://ibm.onthehub.com/WebStore/OfferingDetails.aspx?o=9b4eadea-9776-e611-9421-b8ca3a5db7a1>
* Teachers, researchers and university staff: <https://ibm.onthehub.com/WebStore/OfferingDetails.aspx?o=6fcc1096-7169-e611-9420-b8ca3a5db7a1>

### References

[Terfve et al.](http://www.nature.com/articles/ncomms9033):

Terfve, C. D. A., Wilkes, E. H., Casado, P., Cutillas, P. R., and Saez-Rodriguez, J. (2015). Large-scale models of signal propagation in human cells derived from discovery phosphoproteomic data. Nature Communications, 6:8033.

[Wilkes et al.](http://www.pnas.org/content/112/25/7719.abstract) (description of parts of the data)

Wilkes, E. H., Terfve, C., Gribben, J. G., Saez-Rodriguez, J., and Cutillas, P. R. (2015). Empirical inference of circuitry and plasticity in a kinase signaling network. Proceedings of the National Academy of Sciences of the United States of America, 112(25):7719–24.

### Usage

For a guide how to run a PHONEMeS analysis, please refer to the instructions below:

# Running PHONEMeS

Running PHONEMeS-ILP is easy and straightforward once you have downloaded and installed [R](https://www.r-project.org/) on your computer and get a license for the [IBM CPLEX Optimizer](https://www-01.ibm.com/software/commerce/optimization/cplex-optimizer/) which can be obtained for free for academic use. Also required is to have installed the supportive [R packages](https://github.com/saezlab/PHONEMeS-ILP) mentioned.

## Data input

The inputs should be as shown in the **Data & Background Network** directory.

1. The **allD\*** files contains the K-S interaction database for both HUMAN (Omnipath or NetworKIN) and MOUSE. You can of course insert any background network you like as long as long as it fits the format as the databases shared.
2. **Mapping Table.csv** contains the mapped peptide measurements to uniprot and gene names identifiers.
3. The **log\_measurements.csv** file contains the normalized measurements.
4. The **targets.csv** file contains the conditions for each of the samples in the data.

## Running the scripts

* By running the *buildTT.R* script, you are able to create a list of Table-Top’s. The length of such list will correspond to the number of conditions you are considering. The output for this weill serve as an input for the *buildInputs.R* function called in the next step.
* Then by running the executionScript.R you execute all the functions called from which you obtain the final resultsSIF.txt  and a nodes attributes file which is basically the result that PHONEMeS gives you and which represents the optimal reconstructed pathway activity model and which can be visualized in Cytoscape (for both: the analysis put in a perturbation context and the upside-down analysis).

## Network Visualization

* resultsSIF.txt  (and resultSIFUD.txt) are a sif representation of our model and it can be easily loaded and used by Cytoscape for visualization.
* For a nicer visualization of our resulting network we assign the node attributes to each of the kinases/phosphosites present in our model. Then, by "Import Table from File" in cytoscape, you import the resulting nodesAttributes.txt file by making sure that the column containing the attributes is named nodesP.
* Then by “Import Styles” you import the visual properties by selecting the PHONEMeS\_vizmap.props which can be found on the Results folder.
* Select default\_0 on Styles and then you will get a nice visualization of the network.

**NOTE:** The example shared represent a simple case when we consider a single experimental condition with one target. However veryeasily we could as well consider and run PHONEMeS for multiple conditions for the case when we are targeting multiple kinases. For that we can do is just readapt the **targets.P** and **conditions** in the script like i.e. for the case when we have two conditions and also considering off-target effects on the second condition:

targets.P <- list(cond1=c("MTOR\_HUMAN"), cond2=c(“PK3CA\_HUMAN”, “AKT1\_HUMAN)

conditions <- list(c("cond1", “cond2”)) names(conditions) <- c("MTOR - Control", “PK3CA - Control)