

# Structural Equation Modeling of In silico Perturbations

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*Submitted to Journal:*  
Frontiers in Genetics

*Specialty Section:*  
Computational Genomics

*Article type:*  
Technology and Code Article

*Manuscript ID:*  
727532

*Received on:*  
18 Jun 2021

*Journal website link:*  
[www.frontiersin.org](http://www.frontiersin.org)

### *Conflict of interest statement*

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest

### *Author contribution statement*

JL and PB designed the framework, performed the analyses and drafted the paper. LL provided the guidance on SEM, KD developed and draft the R shiny code, TW provided essential components for T-Score calculation and prepared gene signatures and processed public data, FD, SW and JL conceived the idea, provided overall guidance and oversaw the project progression.

### *Keywords*

Structural Equation Modeling, Gene Expression, In silico perturbation, molecular interaction, r, Shiny

### *Abstract*

Word count: 142

Structural Equation Modeling (SEM) is a statistical approach for studying complex cause-effect hypotheses in a “closed system” of latent (hidden) endogenous variables. SEM has been widely used in various fields involving perturbations and measurable outcomes. We developed an R Shiny application, termed “Structural Equation Modeling of In silico Perturbations (SEMIPs)” to aid in the transfer of perturbations in gene expression pathways from one system to another for determining casual inference of molecular interactions in silico. SEMIPs computes a two-sided t-statistic (T score) to rank signature gene activities for modeling. It implements a basic SEM model and then performs bootstrap random sampling for statistical significance. As a use case example for SEMIPs, we showed that putative direct downstream genes of the GATA2 transcription factor are sufficient to infer GATA2’s activities in silico for the conserved PGR-GATA2-SOX17 genetic network in the human uterine endometrium.

### *Contribution to the field*

This manuscript described an R Shiny application, termed “Structural Equation Modeling of In silico Perturbations (SEMIPs)” that allows the transfer of perturbations in gene expression pathways from one system to another for determining causal inference of molecular interactions in silico. It provides a convenient interface to allow bench scientists to explore the expression data and generate testable hypotheses. SEMIPs computes a two-sided t-statistic (T score), applies a basic SEM model, and performs bootstrap random sampling for statistical significance. It has the capability to calculate response activities using large datasets representative of biological systems, to leverage the power of SEM to test the relationship among end points in a study, to provide users with the flexibility for testing new hypotheses, and to integrate a non-parametric testing procedure for assessing statistical significance. Overall, SEMIPs enables researchers to rapidly examine a given gene signature across systems and generate the functional hypothesis. This tool will be of broad interest to the translational research community.

### *Funding statement*

This research was supported by the Intramural Research Program of the National Institute of Environmental Health Sciences Z1AES103311 (FJD), Z99-ES999999 (SPW), Z01-ES102345 (PRB) and by the Gaine Research Foundation GRF-2018-01 (LL).

### *Ethics statements*

#### *Studies involving animal subjects*

Generated Statement: No animal studies are presented in this manuscript.

#### *Studies involving human subjects*

Generated Statement: No human studies are presented in this manuscript.

#### *Inclusion of identifiable human data*

Generated Statement: No potentially identifiable human images or data is presented in this study.

### *Data availability statement*

Generated Statement: Publicly available datasets were analyzed in this study. This data can be found here:  
<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE40659> <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE58144> <https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE39920>.

In review

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Running Title: Structural Equation Modeling In silico

**Keywords:** Structural Equation Modeling, gene expression, *in silico* perturbation, molecular interaction, R, Shiny

Word count: 2249

Number of Figures: 2                      Number of Supplementary Figures: 4

Number of Tables: 0                      Number of Supplementary Tables: 2

## 27 **Abstract**

28 Structural Equation Modeling (SEM) is a statistical approach for studying complex cause-effect  
29 hypotheses in a “closed system” of latent (hidden) endogenous variables. SEM has been widely used  
30 in various fields involving perturbations and measurable outcomes. We developed an R Shiny  
31 application, termed “Structural Equation Modeling of In silico Perturbations (SEMIPs)” to aid in the  
32 transfer of perturbations in gene expression pathways from one system to another for determining  
33 casual inference of molecular interactions *in silico*. SEMIPs computes a two-sided t-statistic (T  
34 score) to rank signature gene activities for modeling. It implements a basic SEM model and then  
35 performs bootstrap random sampling for statistical significance. As a use case example for SEMIPs,  
36 we showed that putative direct downstream genes of the GATA2 transcription factor are sufficient to  
37 infer GATA2’s activities *in silico* for the conserved PGR-GATA2-SOX17 genetic network in the  
38 human uterine endometrium.

## 39 **Introduction**

40 Although gene expression data in public repositories provide a valuable resource for investigators to  
41 infer regulatory processes (Edgar et al. 2002), the variables of interest are not always directly  
42 measurable in a causal response model system. Moreover, it is challenging to test the knowledge  
43 obtained from experimental model systems in humans due to undetermined clinical outcomes and  
44 ethical considerations. Structural equation modeling (SEM) offers a statistical framework to make  
45 casual inferences about the causality of latent (hidden) endogenous variables in a system (Grace  
46 2006). We were motivated to develop a Structural Equation Modeling of In silico Perturbations  
47 (SEMIPs) Shiny application to facilitate casual inference from *in silico* alterations of gene expression  
48 pathways. SEMIPs enables quantification of a projected activity metric (two-sided t-statistic, i.e. T  
49 score) calculated from gene expression activity upon exposure to a perturbation (Wu et al. 2015),  
50 thus allowing users to fit desired SEM models using selected endogenous and exogenous variables.

This application also provides two different bootstrap random sampling procedures (elimination with or without replacement) for testing the significance of a model based a non-parametric distribution. Previously, SEM was applied to gene expression data to evaluate an alteration of latent gene interactions that disrupts the progesterone receptor pathway in the uterus of pregnant mice and the model was then transferred *in silico* to a human reproductive system (Rubel et al. 2016). SEMIPs streamlines this process and allows bench scientists to perform the computations and analysis through a user-friendly interface.

## **Materials and Methods**

### **Overview of SEMIPs**

This SEMIPs RShiny App allows users to compute a two-sided t-statistic (T score) from gene expression data to infer the activities of genes of interest in a quantitative manner. Shown in Figure 1, SEMIPs App, which is highlighted in the orange dotted rectangle, facilitates the hypothesis generation and testing framework, this app also provides a 3-node model fitting function using structural equation modeling to test the joint regulation of a target gene by two upstream regulators *in silico*. In addition, for hypothesis generation purposes, a two-way bootstrap method, elimination with replacement or elimination without replacement, is included in the app to examine the impact of removing genes that belong to the same signaling cascade from the downstream targets of the gene of interest.

### **T-score Calculation**

The biological hypothesis generation relies on results obtained from the model animal perturbation system, normally with experimental mice or rats, then projects into human or other animal systems when either direct perturbation is not possible or the variables of interest are not directly measurable. Under an experimental perturbation, the genomics system response was measured and exemplified through the significantly changed gene set. Such an information was projected into another system via gene orthologues and the activities of genes of interest will be calculated by a two-side t-statistic

(T-score) (Rubel et al. 2016). The SEMIPs RShiny App provides an automated route to calculate such T-score with a separated tab “T-Scores” shown in Figure 2. It requires two components: (1) A list of gene signature (in Entrez gene symbol format) obtained from a study of interest; and (2) A gene expression data matrix that consists of gene expression profiles in a given context. The application will conduct the analysis and produce inferred activity results reflected as T scores that can be used in subsequent downstream analyses.

### **Structural Equation Modeling**

The second feature of SEMIPs App is the structural equation modeling (SEM). SEM is a statistical modeling approach that focuses on the study of complex cause-effect hypotheses about the mechanisms operating in systems, it useful when some variables are not directly measurable often used in clinical psychology research (Lin et al. 2013). We implement the SEM with lavaan package (Rosseel 2018) to provide a 3-node model fitting function using structural equation modeling to test the joint regulation of a target gene by two upstream regulators *in silico*. The app comes with a sample data file “app\_installation\_dir/dataSEM/sampleDAT.txt”. When the SEM tab is selected (Figure 2), this data will be loaded, users can select three variables from the drop-down list to test the SEM model. The SEMIPs App also provides a data file template “app\_installation\_dir/dataSEM/\_sampleDAT.txt” that users can modify and save as “sampleDAT.txt” to overwrite the default data. As a result, users’ data will be loaded when the App is launched next time. Users can save the modeling figure and all fitting statistics from the app.

### **Bootstrap Simulation**

The third feature (the bootstrap tab shown in Figure 2) assesses the potential impact from a perturbation on any downstream system. We implemented a two-class (elimination with or without replacement) bootstrap resampling for statistical inference (Supplementary Figure 1), which eliminates unrelated signatures and provides statistical significance to the SEM fitting. For this feature, it is assumed that the users have successfully run a T score analysis. The users also need to

enter the signatures associated with the downstream system of interest to evaluate. To improve the rigor of the statistical test, it is recommended to run the bootstrap a minimum of 1,000 times. This feature involves bootstrapping simulation, it needs multicore hardware and can take more times depending on how many iterations users choose.

## **Sample Data**

The SEMIPs App comes with four sets of testing data and data templates for user to use the application and further modify their own data for any customized research projects. They are located at `app_installation_dir/testData`.

## **Hardware and Software Requirement**

SEMIPs was written in R with the Shiny package (Rstudio 2014) that is known for its light weight web development framework with shiny-related features. The lavaan package (Rosseel 2018) was used for the SEM, other depending packages will be checked at the installation and need to be installed if not already available. The application requires modern multicore CPUs for the backend parallel processes. SEMIPs was developed under Linux CentOS7 and has been successfully tested on MacOS (v. 10.14.6) and Windows10. To install and run this application, users can follow the detailed instructions provided in the README.txt file. The SEMIPs Shiny app and source code are freely available at <https://github.com/NIEHS/SEMIPs> under the MIT license.

## **Results**

### **An Integrated Hypothesis Generation and Testing Framework**

As shown in Figure 1, the SEMIPs workflow depicts a biological question initially tested in an animal model and then applied to a human system. A biological hypothesis is tested in a model animal system (mouse) on relationship between two interacting factors (Fac1 & Fac2) and their endpoints. The hypothesis is translated to another species (i.e. human in our research) via T-score computation and verified with SEM model. Based on the SEM model, a presumed relationship can



be tested in humans by determining the significance of the inference via a non-parametric bootstrap resampling framework. The resulting perturbed pathways can be eventually tested in the animal model. These workflow steps are shown within the dotted rectangle on the right side of Figure 1 with three major features implemented in the SEMPIPs App as the function tabs when the Shiny App is launched (Figure 2).

### **T-Score Calculation Assisted Translational Research**

The Signature Analysis component conducts the T-Score calculation that ultimately helps to translate the knowledge obtained from the experimental animal study, as an example into human system.

Users can test this feature by uploading: (1) A list of gene signature (in Entrez gene symbol format) obtained from a study of interest (i.e. Human Sig.xlsx); and (2) A gene expression data matrix that consists of gene expression profiles in a given context (i.e. HumanArray2Shiny.xlsx) located under “/app\_installation\_dir/testData/t-score/”. Once successfully uploaded, top few lines of data will be visible for preview (Figure 2). For illustration purposes, we provide both mouse signature (i.e. Mouse Sig.xlsx) and human signature files, the proper matched specie needs to be selected. T-scores will be calculated by clicking the green “Go!” button, the top 10 rows of the T-scores will be shown for preview. The users are encouraged to download the T-Scores for further analysis. Since the T-Scores are calculated from two-side T-test, the corresponding p-values are also reported (the second column in T-Scores results shown in Figure 2).

### **Flexible Structural Equation Modeling**

A three-node structural equation model can be hypothesized by selecting the desired endogenous and exogenous variables. Once the SEM tab is selected, the default data (“app\_installation\_dir/dataSEM/sampleDAT.txt”) will be loaded, and all features are available for users to choose from the drop-down windows. Two variables are hypothesized as “causal variable” and one variable will be the “endpoint”. The tool reports model fitting statistics in a compressed (zipped) file that can be downloaded, the three-node SEM figure can also be downloaded. This

feature also allows users to test a separate system by uploading their relevant dataset. The dataset requires the same format as the example data. As shown in Figure 1, the SEM model fitting results especially those important statistics will provide valuable information to the hypothesis of interest, which can be further validated from the bench experiment. Sometime, the results can help researchers to proposed new hypothesis.

### **Two-class Bootstrap Simulation**

This feature was designed to assesses the potential impact from a perturbation on any downstream system. For a gene signature list obtained from the perturbation, any gene or gene sets that are biologically associated can be tested with this two-class (elimination with or without replacement) bootstrap resampling for statistical inference (Supplementary Figure 1). In the test data folder “/app\_installation\_dir/testData/bootstrap/”, four downstream gene sets are available. Under the “Bootstrap” tab, users can navigate to this location and run the bootstrap simulation analysis. The impact on the downstream system can be assessed by either elimination without replacement or with replacement. To ensure the rigor of the statistical test, it is recommended to run the bootstrap a minimum of 1,000 times. Depending on the hardware configuration, this analysis can take a considerable amount of time. Users can download the zipped results after the analysis is completed.

### **A User Case Application**

Previously we demonstrated that the mouse gene signatures of GATA2 and PGR allow inference of the interaction between GATA2 and PGR for regulation of SOX17 expression in the human endometrial tissues (Rubel et al. 2016). The full GATA2 gene signature consists of both direct and indirect downstream genes of GATA2 in the uterus (Rubel et al. 2016). Since GATA2 is known as a transcription factor that occupies cis-acting elements and confers genomic actions, we hypothesize that expression levels of GATA2’s direct downstream targets reflect its activities *in silico*. Here, a GATA2 direct downstream target is defined as a GATA2 regulated gene with GATA2 genome occupancy within 2-kilobase vicinity of the said gene’s transcription start site in the uterus (Gene Expression

Omnibus (GEO) accession: GSE40659, (Rubel et al. 2016)). This stringent criterion led to the identification of 634 genes (Supplementary Table 1), which is termed “GATA2 direct signature”. The GATA2 activity, as represented by the GATA2 direct signature in a T-score, was quantified by the SEMIPs app from gene expression data of the endometrium tissue for each individual human subject (GEO accession: GSE58144, (Koot et al. 2016)). T scores for the uterine GATA2 in all 115 patients were calculated by the app with the GATA2 direct signature and the data matrix of GEO accession: GSE58144 (Supplementary Table 2). Similarly, T scores for the uterine PGR (termed PGR signature) were obtained using the GEO accession: GSE39920 dataset (Rubel et al. 2016) on the same data matrix via the application’s T score calculation function. To test whether the GATA2 direct signature fits the model of the 3-node PGR-GATA2-SOX17 genetic network, the application was fed with T scores of GATA2 direct signature and PGR signature as exogenous variables and the SOX17 expression levels as the endogenous variable under the “SEM” function. The output data shows that, with GATA2 direct signature in place of the full gene signature, the model significantly fits the GEO accession: GSE58144 dataset with all proposed paths (Supplementary Figure 2) and this model is considered not rejected by the human data. This finding suggests that the expression levels of GATA2 direct downstream targets, a subset of the full GATA2 regulated genes, can mathematically serve as surrogate reporters of the GATA2 activities in the human endometrium tissues, which supports our hypothesis. Results of this analysis not only reduce the number of reporter genes for GATA2 activities to 634, but also implicate possibilities of a further reduction with additional filtering criteria on the gene list. A small and manageable panel of markers for GATA2 activities could serve as a future diagnostic tool for pregnancy failure (Díaz-Gimeno et al. 2011).

## Discussion

The SEMIPs R Shiny app offers an easy to use *in silico* perturbation testing system with several advantages. First, it has capability to calculate response activities using large datasets representative

of biological systems. Second, it leverages the power of SEM to test the relationship among end points in a study and provides users with the flexibility for testing new hypotheses. Lastly, it integrates a non-parametric testing procedure for assessing statistical significance.

This user-friendly app allows quick assessments on genetic interactions and subsequent hypothesis generation without the requirement of extensive knowledge on computation languages and statistical analyses. Due to its simplicity in design, this app is limited to a 3-node model fitting capability. Models of higher complexity can be tested using the R package MplusAutomation that focuses on automating the SEM modeling which was originally implemented in Mplus (Hallquist and Wiley 2018), a commercial software.

Currently, the two-class bootstrap analysis can only be conducted separately. Integration of these into the SEMIPs methodology for formulation into a single test will be investigated for future design, development and implementation. As noted in the manuscript and mentioned previously, the SEMIPs app has been adopted by researchers in the field with a few papers published recently (Liu et al. 2019, Wetendorf et al. 2020). We hope that it can serve a wider research community to address additional scientific questions.

### **Author Contributions**

JL and PB designed the framework, performed the analyses and drafted the paper. LL provided the guidance on SEM, KD developed and draft the Rshiny code, TW provided essential components for T-Score calculation and prepared gene signatures and processed public data, FD, SW and JL conceived the idea, provided overall guidance and oversaw the project progression.

### **Funding**

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## Acknowledgments

The authors would like to thank our colleagues Drs. Hamed Bostan, Eric Thomson, James Ward and Matt Wheeler for kindly testing SEMIPs and for providing valuable feedbacks to improve the application. We also thank for Drs. John House and Rong Li for their critique of the draft of this manuscript.

## Conflict of Interest

The authors would declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Figure Legends

**Figure 1.** The workflow and application of SEMIPs. The left four rectangles and arrows indicate our hypothesis testing and generation schema. A biological hypothesis is tested in a model animal model system (mouse) on relationship between two interacting factors (Fac1 & Fac2) and their endpoints. The hypothesis is translated to another species (i.e. human in our research) via T-score computation and verified with SEM model. This process is accomplished with our shinyapp indicated by two curved arrows.  $\gamma_{11}$  and  $\gamma_{21}$  are correlation efficient and  $\xi$  are model residuals. The two-class bootstrap analysis is shown in the red rectangle box. Hypothesis generating and exploring steps are explained by the bottom two rectangles.

**Figure 2.** The user interface is shown when it is launched. The main panel contains four tabs: “T-Scores”, “SEM”, “Bootstrap”, and “Instruction”. The right panel shows the screen when the “T-scores” is selected and generated. In the left panel, the application accepts two inputs, 1) a list of signatures (in Entrez gene symbol format) and 2) a data matrix of expression measurement with the top lines shown for viewing. The green “Go!” button is clicked to launch the T-score generation and grayed out to denote the process is running. The first 10 rows of the T-scores matrix are shown, which can be downloaded by clicking the “Download T-Scores” button.

Figure 1.TIF

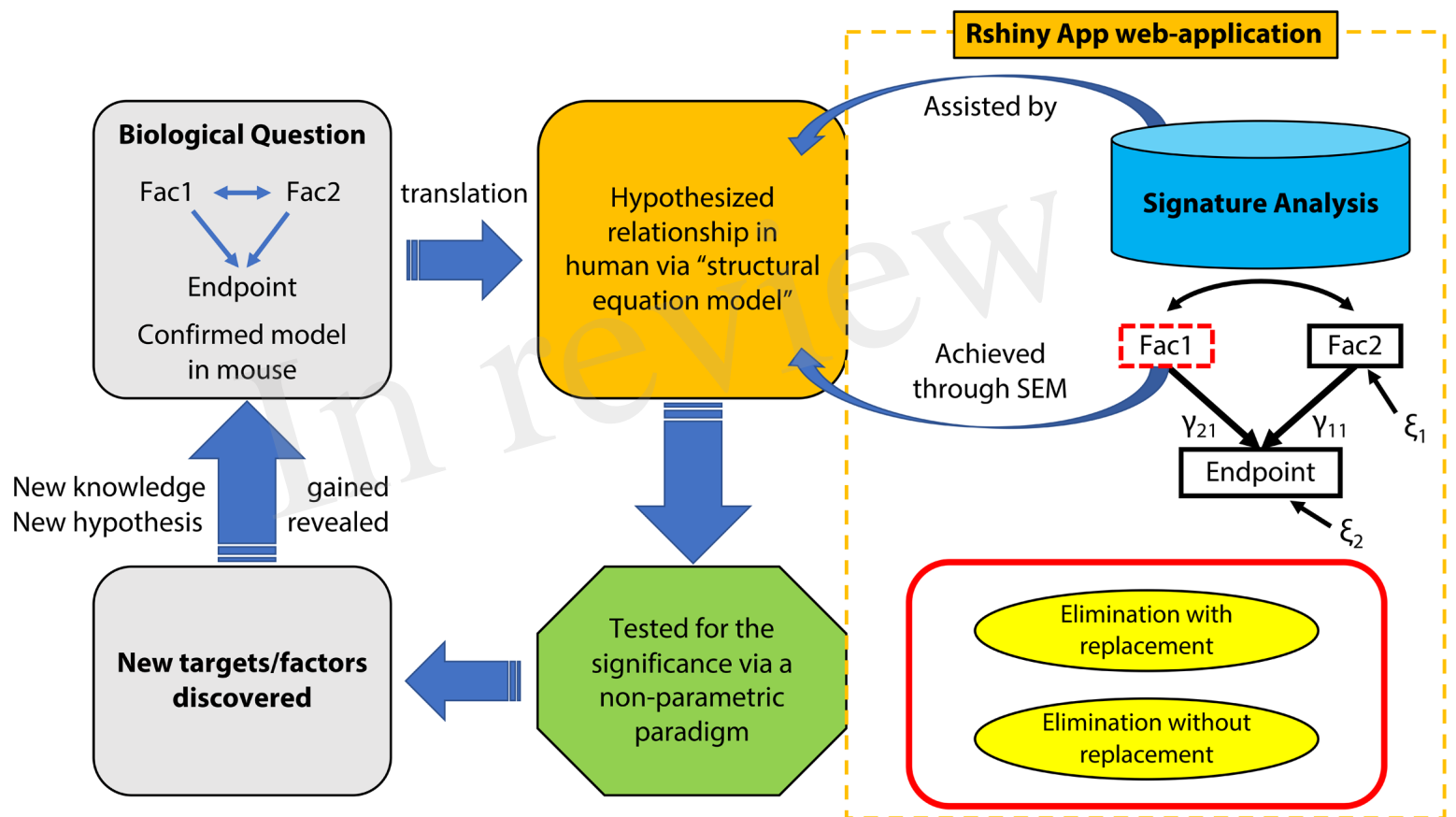


Figure 2.TIF

SEMIPs

Upload the signature file

Browse...

Mouse Sig.xlsx

Upload complete

Gene Type

☒ Mouse

☐ Human

Gene-mouse-Final	Signature
Pate4	High
Lrp2	High
Acta1	High
Lrp2	High

Upload the human check data

Browse...

HumanArray4Shiny.xlsx

Upload complete

Comment[GENE_SYMBOL]	Probe	GS
ATP5G2	Probe-1	
C7orf40	Probe-2	
OR9Q2	Probe-4	
C2CD4A	Probe-5	
AC063977.1	Probe-6	

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4356

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Go!

Tabs:

T-Scores

Bootstrap

SEM

Instructions

Download T-Scores

Show 10 entries

Search:

Variable	p-value	T-score
GSM 1402321	0.002095215	-3.081437
GSM 1402322	0.0311795	2.156678
GSM 1402323	2.358263e-8	5.611653
GSM 1402324	0.001645494	3.1531
GSM 1402325	0.000001096668	4.892383
GSM 1402326	0.03800382	2.076537
GSM 1402327	2.356422e-7	5.191265
GSM 1402328	8.351213e-37	-13.00026
GSM 1402329	0.004960278	-2.813516
GSM 1402330	0.7557735	-0.311089

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