Robust Metabolic Transformation Analysis - rMTA

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Reviewer(s):

INTRODUCTION

Metabolic Transformation Algorithm (MTA) [1] aims to identify targets that transform a disease metabolic state back into a healthy state, with potential application in any disease where a clear metabolic alteration is observed.

Robust Metabolic Transformation Algorithm (rMTA) [2] is the natural evolution of such an algorithm, removing the induced bias and studying all the possible outputs of metabolic perturbations; to discover how easy is for a perturbation to drive the metabolism into target or in the opposite direction. This can be seen in Figure 1. Our desired case is (**Figure 1A**), in which MTA and MTA targeting the opposte direction can only drive the metabolism into the desired direction. This is produced when the Transformation Scores (TSs) after gene knockout are skewed to the healthy direction in both the best-case (bTS) and worst-case scenario (wTS); (**Figure 1B**) TSs are similar in value and skewed to the opposite direction in the best-case and worst-case scenario and, therefore, under-determination arises; (**Figure 1C**) The same as (**Figure 1B**), but TS is higher in the best-case scenario and skewed to the healthy direction when MOMA is applied (mTS > 0). Under-determination is resolved here using mTS (MOMA TS), which generates the perturbation without any prior knowledge of the desired flux change direction.

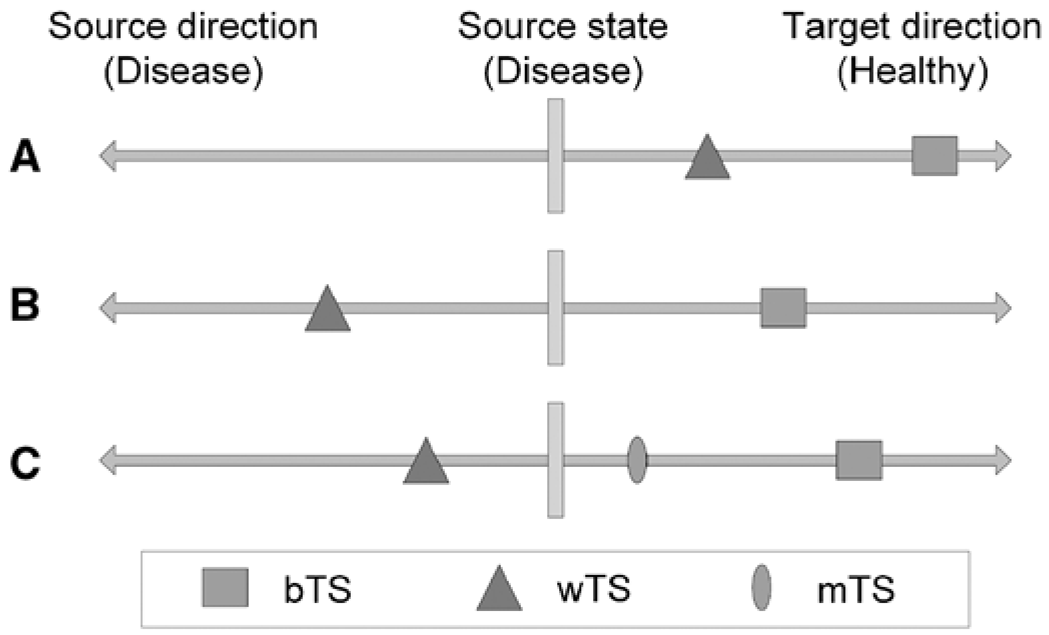

Figure 1. Illustration of the problem addressed by rMTA.

In order to show the use of the tool, we are going to use data from controlled gene knockout (*RRM1*) experiment in a human cell line with RPMI cultture media. The experiment reference is GSE9345 [3]. In such experiment, we are going to predict that *RRM1* drives the source state(WT) into the target (RRM1-knockout) state. This case is shown in table 2 of the rMTA article.

EQUIPMENT SETUP

Initialize The Cobra Toolbox and select the solver (~25 sec)

If necessary, initialise the Cobra Toolbox:

```
clear

initCobraToolbox(false) % false, as we don't want to update
```

```
      _____   _____   _____   _____     _____     |
     /  ___| /  _  \ |  _  \ |  _  \   / ___ \    |   COnstraint-Based Reconstruction and Analysis
     | |     | | | | | |_| | | |_| |  | |___| |   |   The COBRA Toolbox - 2021
     | |     | | | | |  _  { |  _  /  |  ___  |   |
     | |___  | |_| | | |_| | | | \ \  | |   | |   |   Documentation:
     \_____| \_____/ |_____/ |_|  \_\ |_|   |_|   |   http://opencobra.github.io/cobratoolbox
                                                  |

 > Checking if git is installed ...  Done (version: 2.13.3).
 > Checking if the repository is tracked using git ...  Done.
 > Checking if curl is installed ...  Done.
 > Checking if remote can be reached ...  Done.
 > Initializing and updating submodules (this may take a while)... Done.
 > Adding all the files of The COBRA Toolbox ...  Done.
 > Define CB map output... set to svg.
 > TranslateSBML is installed and working properly.
 > Configuring solver environment variables ...
   - [*---] ILOG_CPLEX_PATH: C:\Program Files\ibm\ILOG\CPLEX_Studio1210\cplex\matlab\x64_win64
   - [*---] GUROBI_PATH: C:\gurobi911\win64\matlab
   - [----] TOMLAB_PATH: --> set this path manually after installing the solver ( see instructions )
   - [----] MOSEK_PATH: --> set this path manually after installing the solver ( see instructions )
   Done.
 > Checking available solvers and solver interfaces ... Done.
 > Setting default solvers ... Done.
 > Saving the MATLAB path ... Done.
   - The MATLAB path was saved in the default location.

 > Summary of available solvers and solver interfaces

                  Support          LP      MILP        QP      MIQP       NLP        EP
    ------------------------------------------------------------------------------
    gurobi          active             1         1         1         1         -         -
    ibm_cplex       active             1         1         1         1         -         -
    tomlab_cplex    active             0         0         0         0         -         -
    glpk            active             1         1         -         -         -         -
    mosek           active             0         -         0         -         -         0
    matlab          active             1         -         -         -         1         -
    pdco            active             1         -         1         -         -         1
    quadMinos       active             0         -         -         -         -         -
    dqqMinos        active             0         -         0         -         -         -
    cplex_direct    active             0         0         0         -         -         -
    cplexlp         active             1         -         -         -         -         -
    qpng            passive            -         -         1         -         -         -
    tomlab_snopt    passive            -         -         -         -         0         -
    lp_solve        legacy             1         -         -         -         -         -
    -----------------------------------------------------------------------------
    Total           -                    7         3         4         2         1         1

 + Legend: - = not applicable, 0 = solver not compatible or not installed, 1 = solver installed.


 > You can solve LP problems using: 'gurobi' - 'ibm_cplex' - 'glpk' - 'matlab' - 'pdco' - 'cplexlp'
 > You can solve MILP problems using: 'gurobi' - 'ibm_cplex' - 'glpk'
 > You can solve QP problems using: 'gurobi' - 'ibm_cplex' - 'pdco'
 > You can solve MIQP problems using: 'gurobi' - 'ibm_cplex'
 > You can solve NLP problems using: 'matlab'
 > You can solve EP problems using: 'pdco'

> Checking for available updates ... skipped
```

Note that the approaches to calculate MTA and rMTA scores it is necessary to solve problems that are based on Mixed Integer Quadratic Programming (MIQP). The solver selected will be Cplex, althought it has also been tested with gurobi.

```
changeCobraSolver('ibm_cplex', 'all');
```

```
 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
 > The solver compatibility is not tested with MATLAB R2018b.
 > changeCobraSolver: Solver for LP problems has been set to ibm_cplex.

 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
 > The solver compatibility is not tested with MATLAB R2018b.
 > changeCobraSolver: Solver for MILP problems has been set to ibm_cplex.

 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
 > The solver compatibility is not tested with MATLAB R2018b.
 > changeCobraSolver: Solver for QP problems has been set to ibm_cplex.

 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
 > The solver compatibility is not tested with MATLAB R2018b.
 > changeCobraSolver: Solver for MIQP problems has been set to ibm_cplex.
 > changeCobraSolver: Solver ibm_cplex not supported for problems of type EP. No solver set for this probl
 > changeCobraSolver: Solver ibm_cplex not supported for problems of type NLP. Currently used: matlab
```

STEP 1: load the information to generate the reference flux

The first step of rMTA algorithm is the reconstruction of the model for a specific tissue and sample the feasible flux space to calculate a reference flux.

For this study we have used Recon1, using the RPMI-1640 culture media. We have used FVA to find all blocked reactions and remove them.

```
filename_metabolic_model = 'Recon1_RPMI1640_FVA.mat';
model = readCbModel(fullfile('Data',filename_metabolic_model))
```

```
Each model.subSystems{x} has been changed to a character array.
model = struct with fields:
                      S: [1239×1913 double]
                   mets: {1239×1 cell}
                      b: [1239×1 double]
                 csense: [1239×1 char]
                   rxns: {1913×1 cell}
                     lb: [1913×1 double]
                     ub: [1913×1 double]
```

```
                  c: [1913×1 double]
         osenseStr: 'max'
             genes: {1905×1 cell}
             rules: {1913×1 cell}
         metKEGGID: {1239×1 cell}
           grRules: {1913×1 cell}
        rxnGeneMat: [1913×1905 double]
rxnConfidenceScores: [1913×1 double]
        subSystems: {1913×1 cell}
       description: 'Recon1_RPMI1640_FVA.mat'
           modelID: 'Network'
                 C: [0×1913 double]
              ctrs: {0×1 cell}
                 d: [0×1 double]
            dsense: [0×1 char]
           ChEBIID: {1239×1 cell}
         ECNumbers: {1913×1 cell}
       InChIString: {1239×1 cell}
         PubChemID: {1239×1 cell}
            charge: [1239×1 int32]
           formula: {1239×1 cell}
              name: {1239×1 cell}
             notes: {1913×1 cell}
        references: {1913×1 cell}
             rever: [1913×1 double]
```

```
% transcript separator: there are some models (as Recon X) in which genes are
% used at transcript level, not in gene level. Transcript separator is a variable
% to join all transcripts of the gene and work at gene level.
transcript_separator = '.';

fprintf('\tMetabolic model uploaded\n');
```

```
Metabolic model uploaded
```

Then we import the gene expression data and reconstruct the model, using iMAT. This data has been obtaind in R using GEO accesion tools and performing the data preprocessing proposed for the Affymetrix Human Genome U133A 2.0 Array, using ARIMA, and the discretization into Highly , medium or lowly expressed proposed by the authors of iMAT[4]. This is explained in detail in the rMTA article in detail [2].

```
filename_onmics = 'GSE93425_Recon1_discret_iMAT_07_100.txt';
onmic_data = readtable(['Data',filesep,filename_onmics],'ReadVariableNames',true);

% Traduce onmic data from gene level to reaction level
aux_table = table(strtok(model.genes,transcript_separator),model.genes,'VariableNames',
onmic_data = outerjoin(aux_table, onmic_data, 'Keys','ENTREZ_ID');
head(onmic_data)
```

ans = 8×6 table

	ENTREZ_ID_aux_table	transcript	ENTREZ_ID_onmic_data	scramble	siRRM1	siRRM2
1	'100'	'100.1'	'100'	1	1	1
2	'10005'	'10005.1'	'10005'	0	0	0
3	'10005'	'10005.2'	'10005'	0	0	0
4	'10005'	'10005.3'	'10005'	0	0	0

	ENTREZ_ID_aux_table	transcript	ENTREZ_ID_onmic_data	scramble	siRRM1	siRRM2
5	'10007'	'10007.1'	'10007'	1	1	1
6	'10020'	'10020.1'	'10020'	0	1	0
7	'10026'	'10026.1'	'10026'	0	0	0
8	'10050'	'10050.1'	'10050'	-1	-1	-1

```
% prepare data for iMAT algorithm
expressionData = struct();
expressionData.gene = onmic_data.transcript;
expressionData.value = onmic_data.scramble*2;
[onmic_rxn_data.expression, onmic_rxn_data.parsedGPR] = mapExpressionToReactions(model,
onmic_rxn_data.expression(onmic_rxn_data.expression == -1) = 0; % not mapped reactions
fprintf('\tOmnic data transformed from gene level to reaction level\n');
```

```
    Omnic data transformed from gene level to reaction level
```

In the original formulation of the paper and in our implementation, the algorithm selected for tissue reconstruction is iMAT. iMAT is computationally expensive and it's solution is not unique, so we provide the result of iMAT implementation.

```
% code for iMAT solver
options  =struct();
options.solver = 'iMAT';
options.threshold_lb = + 1;
options.threshold_ub = - 1;
options.expressionRxns = onmic_rxn_data.expression;
options.timelimit = 30;
options.printLevel = 1;
options.numWorkers = 2;
options.numThreads = 2;

% run iMAT
tic
%tissueModel_scramble = createTissueSpecificModel(model, options, 1);
load(['Data' filesep 'tissueModel_scramble.mat'])
TIME.iMAT = toc
```

```
TIME = struct with fields:
    iMAT: 0.0792
```

The reconstructed model is sampled to obtain 2000 possible flux states, which can define a reference flux state. Sampling is computationaly expensive and stocastic, so we provide the solution of the article

```
% Sampling Method and options
sampling_method = 'ACHR';    %{('CHRR'), 'ACHR'}
sampling_options = struct();
sampling_options.nWarmupPoints = 5000;           % (default)
sampling_options.nPointsReturned  = 2000;        % (default)
sampling_options.nStepsPerPoint  = 500;        % (default = 200)
```

```
% Now COBRAtoolbox include sampler
tic
%[modelSampling,samples] = sampleCbModel(tissueModel_scramble,'sampleFiles',sampling_me
load(['Data' filesep 'Sampling_results.mat']);
TIME.sampling = toc;

sampleStats = calcSampleStats(samples);
```

```
Processing sample 1
```

```
% from reduced index to model.rxns index
idx = zeros(size(samples,1),1);
for i = 1:numel(idx)
    try
        idx(i) = find(strcmp(model.rxns,modelSampling.rxns{i}));
    catch
        idx(i) = find(cellfun(@length,strfind(model.rxns,modelSampling.rxns{i})));
        sampleStats.mean(i)=-1*sampleStats.mean(i) %Those reactions are reversed;
    end
end
rxnInactive = setdiff(1:length(model.rxns),idx); % inactive reactions
fields = fieldnames(sampleStats);
for i = 1:numel(fields)
    aux = sampleStats.(fields{i});
    sampleStats.(fields{i}) = zeros(size(model.rxns));
    sampleStats.(fields{i})(idx) = aux;
    clear aux
end

% resize the samples matrix
aux = samples;
samples = zeros(size(model.rxns,1),sampling_options.nPointsReturned);
samples (idx,:) = aux;
clear aux;
```

Finally we can set a reference flux

```
Vref = sampleStats.mean;
```

STEP 2: load the information of the differentially expressed genes and calculate upregulated and downregulated reactions

Once we have defined the source genotype, in most of the applications the disease state, we need to calculate the required changes in order to reach the objective state, in most of the cases the healthy state.

This is a particular case, in which we start in a Wild Type / scramble state (source) and try to calculate the gene Knock-out which reaches the mutant state (target). This is a controlled KO which allows us to evaluate the use of rMTA.

The differential expression of Scramble vs siRRM1 has done in R, using GEO accession tool ARIMA and limma, with the default parameters (this is explained in detail in the rMTA article in detail [2]).

```
% Differentially expressed genes
% Neccesary variables: 'gene','logFC','pval'
% 'Gene_ID' must be the same nomenclature as the metabolic model
% Study must be uploaded as DISEASE VS HEALTHY/CONTROL
filename_differentially_expressed_genes = 'scramble-siRRM1_differ_exp_met_genes.txt';
logFC_requiered = 0; % change if necesary
pval_requiered = 0.1; % change if necesary

differ_genes = readtable(fullfile('Data',filename_differentially_expressed_genes),...
    'ReadVariableNames',true);

differ_genes.pval = differ_genes.adj_P_Val; % requiered variable by code
differ_genes.gene = differ_genes.ENTREZ_ID; % requiered variable by code

% Here we should obtain an array similar to rxnHML, in which we have the
% information of whatever an expresion should increase, decrease or nothing
% (+1)R_f    (-1)R_b     (0)unchanged
% This vector is called rxnFBS (Forward, Backward, Unchanged)

rxnFBS = diffexprs2rxnFBS(model, differ_genes, Vref, ...
    'SeparateTranscript', transcript_separator, 'logFC', logFC_requiered, 'pval', pval_
```

```
Gene expression changes calculated
There are 204 trainscripts that are differentially expressed
There are 161 genes that are differentially expressed
Reaction expression changes calculated
There are 159 reactions that are differentially expressed
```

```

% change in rxnFBS all those reactions that are not active
%  it is not possible to predict the direction of the change
rxnFBS(rxnInactive) = 0;
fprintf('\tThere are %u reactions that are differentially expressed after curation\n',s
```

```
There are 76 reactions that are differentially expressed after curation
```

STEP 3: run rMTA algorithm, implemented in a function available in COBRA toolbox

Both MTA and rMTA use the same parameters: epsilon and alpha:

```
% Define alpha values to calculate rMTA
alpha_values = [0.66];  % (default range of values) % better to have more values
%  It has been included 0.66 as it is the original value used in the
%  original paper ('Yizhak et al, 2013')
num_alphas = length(alpha_values);

% Calculate epsilon, different for each reaction and with a minimum required change of
epsilon = calculateEPSILON(samples, rxnFBS);
```

One we have defined the parameters required by rMTA/MTA, we can use the COBRA function to calculate the transformation score (TS score):

```
changeCobraSolver('ibm_cplex', 'all')
```

```
 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
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 > changeCobraSolver: Solver for LP problems has been set to ibm_cplex.

 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
 > The solver compatibility is not tested with MATLAB R2018b.
 > changeCobraSolver: Solver for MILP problems has been set to ibm_cplex.

 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
 > The solver compatibility is not tested with MATLAB R2018b.
 > changeCobraSolver: Solver for QP problems has been set to ibm_cplex.

 > changeCobraSolver: IBM ILOG CPLEX interface added to MATLAB path.
 > The solver compatibility is not tested with MATLAB R2018b.
 > changeCobraSolver: Solver for MIQP problems has been set to ibm_cplex.
 > changeCobraSolver: Solver ibm_cplex not supported for problems of type EP. No solver set for this probl
 > changeCobraSolver: Solver ibm_cplex not supported for problems of type NLP. Currently used: matlab
ans = logical
   1
```

```
% execute the code
tic
[TSscore, deletedGenes, Vres] = rMTA(model, rxnFBS, Vref, alpha_values, epsilon, ...
    'timelimit', 60, 'SeparateTranscript', transcript_separator, 'printLevel', 1);
```

```
===================================
========  rMTA algorithm  =========
===================================
Step 0: preprocessing:
Calculate Gene Knock-out matrix
100%    [.........................................]
    GeneKOMatrix calculated
-------------------
Step 1 in progress: the best scenario
    Start rMTA best scenario case for alpha = 0.66
    cplex model for MTA built
    MIQP Iterations for bMTA
100%    [.........................................]
    All MIQP problems performed
    Step 1 time: 119.66 seconds = 1.99 minutes
-------------------
Step 2 in progress: MOMA
    QPproblem model for MOMA built
    QP Iterations for MTA
100%    [.........................................]
    All MOMA problems performed
    Step 2 time: 35.68 seconds = 0.59 minutes
-------------------
Step 3 in progress: the worst scenario
    Start rMTA worst scenario case for alpha = 0.66
    cplex model for MTA built
    MIQP Iterations for wMTA
100%    [.........................................]
    All MIQP problems performed
    Step 3 time: 120.45 seconds = 2.01 minutes
-------------------
```

```
TIME.rMTA = toc
```

```
TIME = struct with fields:
        iMAT: 0.0792
    sampling: 0.1070
        rMTA: 293.3228
```

STEP 4: save results in an Excel for study

First of all, we are going to clean the Results folder and save the results from this tutorial

```
delete(['Results' filesep 'H929_siRRM1_case.mat'])
delete(['Results' filesep 'H929_siRRM1_case.xlsx'])
save(['Results' filesep 'H929_siRRM1_case.mat'])
```

Secondly, we can use information from Biomart to provide additional information of the genes, like the ENSEMBL ID, gene name, symbol,...

```
% gene information
filename3 = 'Data\GeneInfo_HomoSapiens_ENSEMBL_103.txt';
biomart_genes = readtable(filename3,'ReadVariableNames',true);
```

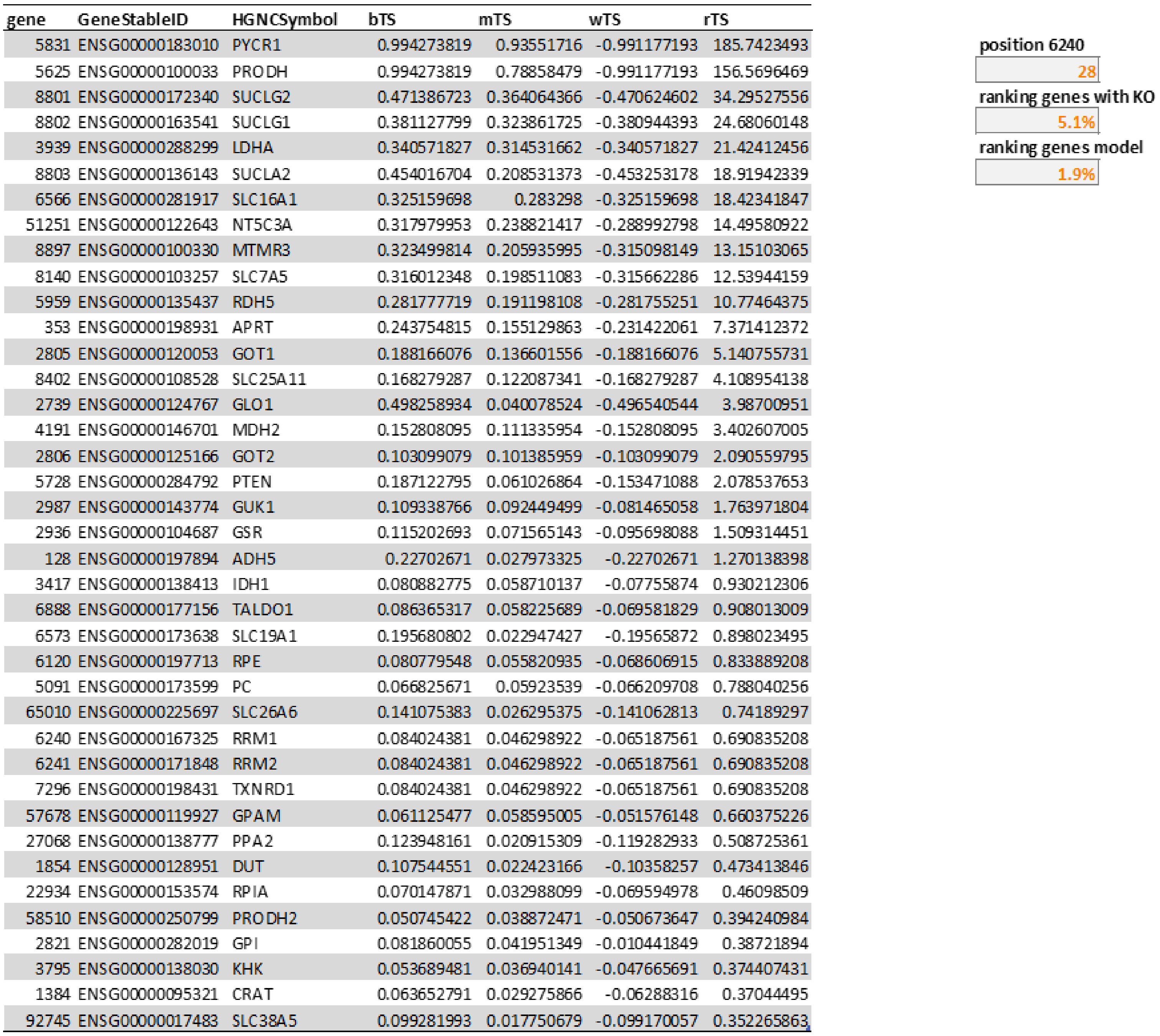
```
Warning: Variable names were modified to make them valid MATLAB identifiers. The original names are
saved in the VariableDescriptions property.
```

```
biomart_genes.NCBIGene_formerlyEntrezgene_ID = cellfun(@num2str, num2cell(biomart_genes
[~, idx] = ismember(deletedGenes, biomart_genes.NCBIGene_formerlyEntrezgene_ID);
idx = idx (idx>0);
gene_info = biomart_genes(idx,:);
gene_info.gene = gene_info.NCBIGene_formerlyEntrezgene_ID;
geneID=table(deletedGenes, 'VariableNames', {'gene'});
gene_info = outerjoin(geneID,gene_info,'MergeKeys',true);


rMTAsaveInExcel(['Results' filesep 'H929_siRRM1_case.xlsx'], TSscore, deletedGenes, alp
    'differ_genes', differ_genes,'gene_info', gene_info, 'RankingGeneID' ,'6240')
```

```
    Process results for alpha = 0.66
    Selected the "550" best solutions
    Write xls for alpha = 0.66
Warning: Added specified worksheet.
    Write selection of best genes
Warning: Added specified worksheet.
Warning: Added specified worksheet.
    SUMMARY
Warning: Added specified worksheet.
DONE
```

Obtained results should show that RRM1 has been predicted number 28 in the ranking, using an alpha of 0.66



gene	GeneStableID	HGNCSymbol	bTS	mTS	wTS	rTS
5831	ENSG00000183010	PYCR1	0.994273819	0.93551716	-0.991177193	185.7423493
5625	ENSG00000100033	PRODH	0.994273819	0.78858479	-0.991177193	156.5696469
8801	ENSG00000172340	SUCLG2	0.471386723	0.364064366	-0.470624602	34.29527556
8802	ENSG00000163541	SUCLG1	0.381127799	0.323861725	-0.380944393	24.68060148
3939	ENSG00000288299	LDHA	0.340571827	0.314531662	-0.340571827	21.42412456
8803	ENSG00000136143	SUCLA2	0.454016704	0.208531373	-0.453253178	18.91942339
6566	ENSG00000281917	SLC16A1	0.325159698	0.283298	-0.325159698	18.42341847
51251	ENSG00000122643	NT5C3A	0.317979953	0.238821417	-0.288992798	14.49580922
8897	ENSG00000100330	MTMR3	0.323499814	0.205935995	-0.315098149	13.15103065
8140	ENSG00000103257	SLC7A5	0.316012348	0.198511083	-0.315662286	12.53944159
5959	ENSG00000135437	RDH5	0.281777719	0.191198108	-0.281755251	10.77464375
353	ENSG00000198931	APRT	0.243754815	0.155129863	-0.231422061	7.371412372
2805	ENSG00000120053	GOT1	0.188166076	0.136601556	-0.188166076	5.140755731
8402	ENSG00000108528	SLC25A11	0.168279287	0.122087341	-0.168279287	4.108954138
2739	ENSG00000124767	GLO1	0.498258934	0.040078524	-0.496540544	3.98700951
4191	ENSG00000146701	MDH2	0.152808095	0.111335954	-0.152808095	3.402607005
2806	ENSG00000125166	GOT2	0.103099079	0.101385959	-0.103099079	2.090559795
5728	ENSG00000284792	PTEN	0.187122795	0.061026864	-0.153471088	2.078537653
2987	ENSG00000143774	GUK1	0.109338766	0.092449499	-0.081465058	1.763971804
2936	ENSG00000104687	GSR	0.115202693	0.071565143	-0.095698088	1.509314451
128	ENSG00000197894	ADH5	0.22702671	0.027973325	-0.22702671	1.270138398
3417	ENSG00000138413	IDH1	0.080882775	0.058710137	-0.07755874	0.930212306
6888	ENSG00000177156	TALDO1	0.086365317	0.058225689	-0.069581829	0.908013009
6573	ENSG00000173638	SLC19A1	0.195680802	0.022947427	-0.19565872	0.898023495
6120	ENSG00000197713	RPE	0.080779548	0.055820935	-0.068606915	0.833889208
5091	ENSG00000173599	PC	0.066825671	0.05923539	-0.066209708	0.788040256
65010	ENSG00000225697	SLC26A6	0.141075383	0.026295375	-0.141062813	0.74189297
6240	ENSG00000167325	RRM1	0.084024381	0.046298922	-0.065187561	0.690835208
6241	ENSG00000171848	RRM2	0.084024381	0.046298922	-0.065187561	0.690835208
7296	ENSG00000198431	TXNRD1	0.084024381	0.046298922	-0.065187561	0.690835208
57678	ENSG00000119927	GPAM	0.061125477	0.058595005	-0.051576148	0.660375226
27068	ENSG00000138777	PPA2	0.123948161	0.020915309	-0.119282933	0.508725361
1854	ENSG00000128951	DUT	0.107544551	0.022423166	-0.10358257	0.473413846
22934	ENSG00000153574	RPIA	0.070147871	0.032988099	-0.069594978	0.46098509
58510	ENSG00000250799	PRODH2	0.050745422	0.038872471	-0.050673647	0.394240984
2821	ENSG00000282019	GPI	0.081860055	0.041951349	-0.010441849	0.38721894
3795	ENSG00000138030	KHK	0.053689481	0.036940141	-0.047665691	0.374407431
1384	ENSG00000095321	CRAT	0.063652791	0.029275866	-0.06288316	0.37044495
92745	ENSG00000017483	SLC38A5	0.099281993	0.017750679	-0.099170057	0.352265863

position 6240	28
ranking genes with KO	5.1%
ranking genes model	1.9%

TIMING

1. Equipment Setup: ~25 sec.
2. Load the information and process it: ~5 sec.
3. Reconstruction: ~1-5 min.
4. Sampling: ~15 min.
5. rMTA: ~5 min

```
TIME
```

```
TIME = struct with fields:
```

```
         iMAT: 0.0792
     sampling: 0.1070
         rMTA: 293.3228
```

Note that it is advisable to have EXCEL installed, in order to save all the results in an easily understandable format.

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