Numerical characteristics of a stoichiometric matrix

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During this tutorial, you will learn how to determine and explore the numerical properties of a stoichiometric matrix. The numerical properties are key to analyzing the metabolic reconstruction at hand, to select the appropriate solver, or to determine incoherences in the network.

First, we must initialise The COBRA Toolbox after having followed the installation instructions carefully:

```
% initialise The COBRA Toolbox
initCobraToolbox
```

```
     _____   _____   _____   _____     _____      |
    /  ___| /  _  \ |  _  \ |  _  \   / ___ \     |   COnstraint-Based Reconstruction and Analysis
    | |     | | | | | |_| | | |_| |   | |___| |   |   The COBRA Toolbox - 2017
    | |     | | | | |  _  { |  _  /   |  ___  |   |
    | |___  | |_| | | |_| | | | \ \   | |   | |   |   Documentation:
    \_____| \_____/ |_____/ |_|  \_\ |_|   |_|   |   http://opencobra.github.io/cobratoolbox
                                                  |

> Checking if git is installed ...  Done.
> 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 ... Done.
> Adding all the files of The COBRA Toolbox ...  Done.
> Define CB map output... set to svg.
> Retrieving models ...   Done.
> TranslateSBML is installed and working properly.
> Configuring solver environment variables ...
  - [---*] ILOG_CPLEX_PATH: /Applications/IBM/ILOG/CPLEX_Studio1271/cplex/matlab/x86-64_osx
  - [---*] GUROBI_PATH: /Library/gurobi702/mac64/matlab
  - [----] TOMLAB_PATH :  --> set this path manually after installing the solver ( see instructions )
  - [---*] MOSEK_PATH: /Applications/mosek/8/
  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
-----------------------------------------------------------------------
cplex_direct  full              0      0      0      0      -
dqqMinos      full              1      -      -      -      -
glpk          full              1      1      -      -      -
gurobi        full              1      1      1      1      -
ibm_cplex     full              1      1      1      1      -
matlab        full              1      -      -      -      1
mosek         full              1      1      1      -      -
pdco          full              1      -      1      -      1
quadMinos     full              1      -      -      -      1
tomlab_cplex  full              0      0      0      0      -
qpng          experimental      -      -      1      -      -
tomlab_snopt  experimental      -      -      -      -      0
gurobi_mex    legacy            0      0      0      0      -
lindo_old     legacy            0      -      -      -      -
lindo_legacy  legacy            0      -      -      -      -
lp_solve      legacy            1      -      -      -      -
```

```
opti          legacy             0      0      0      0      0
-------------------------------------------------------------------
Total         -                  9      4      5      2      3

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


> You can solve LP problems using: 'dqqMinos' - 'glpk' - 'gurobi' - 'ibm_cplex' - 'matlab' - 'mosek' -
> You can solve MILP problems using: 'glpk' - 'gurobi' - 'ibm_cplex' - 'mosek'
> You can solve QP problems using: 'gurobi' - 'ibm_cplex' - 'mosek' - 'pdco' - 'qpng'
> You can solve MIQP problems using: 'gurobi' - 'ibm_cplex'
> You can solve NLP problems using: 'matlab' - 'pdco' - 'quadMinos'

> Checking for available updates ...
--> You cannot update your fork using updateCobraToolbox(). [2d59af @ tutorial-numCharact].
    Please use the MATLAB.devTools (https://github.com/opencobra/MATLAB.devTools).
```

Define the name of the model

Throughout this tutorial, we will use the *E.coli core* model [1]. It is generally good practice to define the name of the file that contains the model, the variable that contains the model structure, as well as the name of the stoichiometric matrix as separate variables. We here suppose that within the *modelFile*, there is a structure named *modelName* with a field *matrixName* that contains the stoichiometric matrix *S* (or *A*).

```
% define the filename of the model
modelFile = 'ecoli_core_model.mat';

% define the name of model structure
modelName = 'model';

% define the fieldname of the stoichiometric matrix
matrixName = 'S';
```

Load the stoichiometric matrix

In order to use the model, we need to load the *modelFile* first:

```
% load the modelName structure from the modelFile
load(modelFile, modelName);
```

Some models contain stoichiometric matrices with a different name (commonly coupled models). By default, the stoichiometric matrix is denoted *S*.

```
% select the matrix
S = model.S;
if isfield(model, matrixName) == 1 && strcmp(matrixName, 'A') == 1
    S = model.A;
end
```

Basic numerical characteristics

The **number of elements** represents the total number of entries in the stoichiometric matrix (including zero elements). This number is equivalent to the product of the number of reactions and the number of metabolites.

The number of rows is equivalent to the **number of metabolites** in the metabolic network. The number of columns corresponds to the **number of biochemical reactions** in the network.

```
% determine the number of reactions and metabolites in A
[nMets, nRxns] = size(S)
```

```
nMets = 72
nRxns = 95
```

```
% determine the number of elements in A
nElem = numel(S)  % Nmets * Nrxns
```

```
nElem = 6840
```

The total number of nonzero elements corresponds to the total number of nonzero entries in the stoichiometric matrix (excluding zero elements).

```
% determine the number of nonzero elements in A
nNz = nnz(S)
```

```
nNz = 360
```

Sparsity and Density

The **sparsity ratio** corresponds to the ratio of the number of zero elements and the total number of elements. Similarly, the **complementary sparsity ratio** is calculated as the difference of one and the sparsity ratio, and is the ratio of the number of nonzero elements and the total number of elements.

```
% determine the sparsity ratio of S (in percent)
sparsityRatio = (1 - nNz / nElem) * 100.0  % [%]
```

```
sparsityRatio = 94.7368
```

```
% determine the complementary sparsity ratio (in percent)
compSparsityRatio = 100.0 - sparsityRatio  % [%]
```

```
compSparsityRatio = 5.2632
```

The **average column density** corresponds to the ratio of the number of nonzero elements in each column and the total number of metabolites. The average column density corresponds to the arithmetic average of all the column densities (sum of all the column densities divided by the number of reactions).

```
% add the number of non-zeros in each column (reaction)
colDensityAv = 0;
for i = 1:nRxns
    colDensityAv = colDensityAv + nnz(S(:,i));
end

% calculate the arithmetic average number of non-zeros in each column
colDensityAv = colDensityAv / nRxns   % [-]
```

```
colDensityAv = 3.7895
```

The average column density provides a measure of how many stoichiometric coefficients participate in each biochemical reaction in average.

The **relative column density** corresponds to the ratio of the number of nonzero elements in each column and the total number of metabolites. The relative column density corresponds to the average column density divided by the total number of metabolites (expressed in parts-per-million [ppm]).

```
% determine the density proportional to the length of the column
colDensityRel = colDensityAv / nMets * 1e6  % [ppm]
```

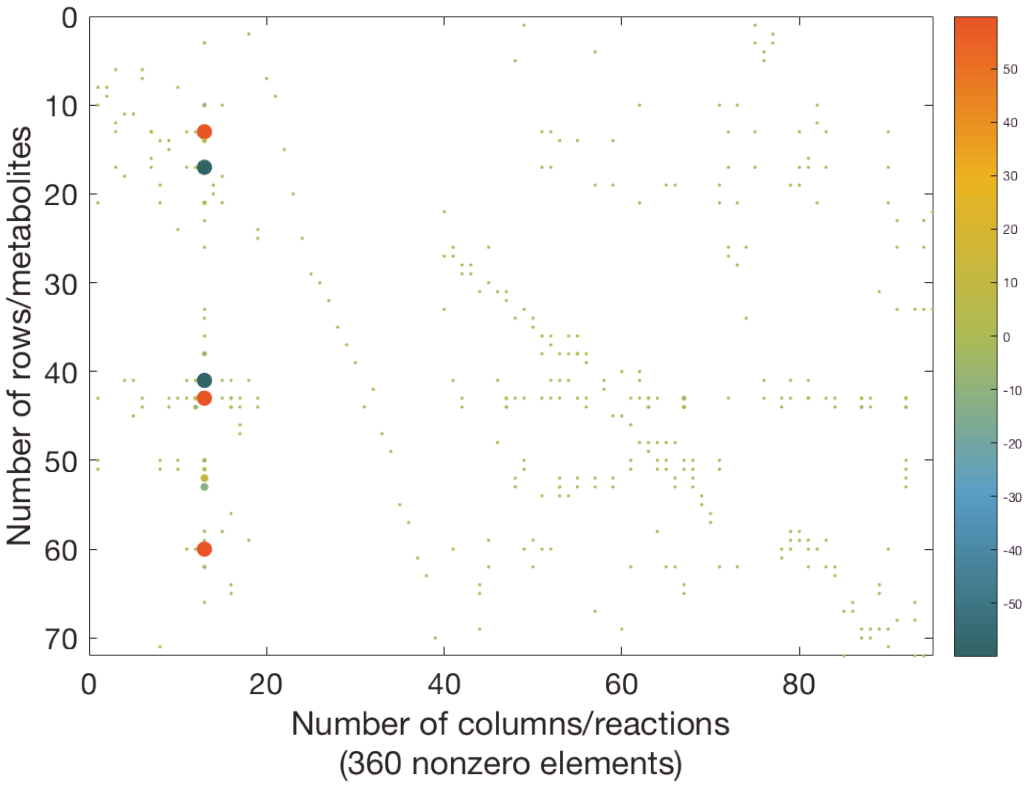
```
colDensityRel = 5.2632e+04
```

The relative column density indicates how many metabolites are being used in average in each reaction relative to the total number of metabolites in the metabolic network.

Sparsity Pattern (spy plot)

The visualisation of the sparsity pattern is useful to explore the matrix, spot inconsistencies, or identify patterns visually. In addition to the standard sparsity pattern, the magnitude of the elements of the stoichiometric matrix (stoichiometric coefficients) is shown as proportional to the size of the dot.

```
% print a colorful spy map of the S matrix
spyc(S, colormap(advancedColormap('proposal')));

% set the font size of the current figure axes
set(gca, 'fontsize', 14);
```



Rank

The **rank** of a stoichiometric matrix is the maximum number of linearly independent rows and is equivalent to the number of linearly independent columns. The rank is a measurement of how many reactions and metabolites are linearly independent. The rank is preferably calculated using the LUSOL solver [2].

```
% determine the rank of the stoichiometric matrix
rankS = getRankLUSOL(S)
```

```
rankS = 67
```

The **rank deficiency** of the stoichiometric matrix is a measure of how many reactions and metabolites are not linearly dependent, and expressed as the ratio of the rank of the stoichiometric matrix to the theoretical full rank.

```
% calculate the rank deficiency (in percent)
rankDeficiencyS = (1 - rankS / min(nMets, nRxns)) * 100  % [%]
```

```
rankDeficiencyS = 6.9444
```

Singular Values and Condition Number

A singular value decomposition of the stoichiometric matrix is the decomposition into orthonormal matrices U (of dimension *nMets* by *nMets*) and V (of dimension *nRxns* by *nRxns*), and a matrix with diagonal elements D such that $\mathrm{S} = \mathrm{U}\mathrm{D}V^T$.

Note that the calculation of singular values is numerically expensive, especially for large stoichiometric matrices.

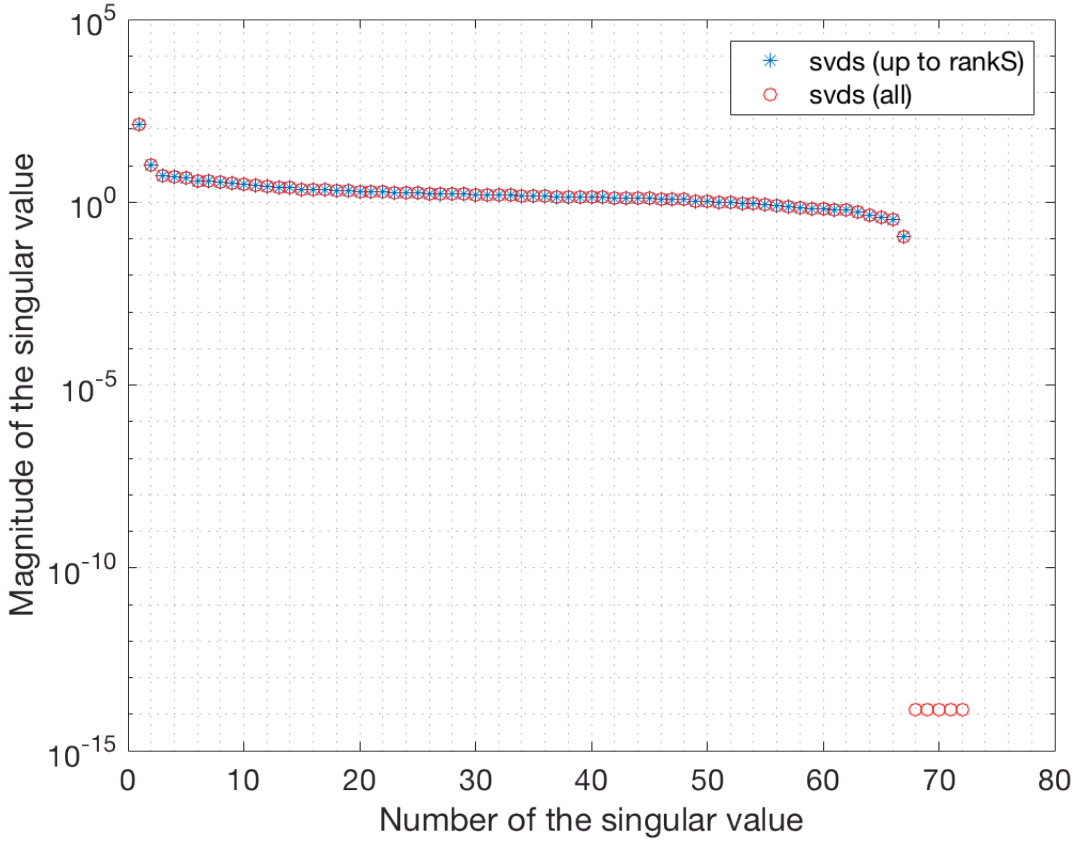
```
% calculate the singular values
svVect = svds(S, rankS);
```

The *svds()* function returns the number of singular values specified in the second argument of the function. As most stoichiometric matrices are rank deficient, some singular values are zero (or within numerical tolerances). The cut-off is located at the rank of the stoichiometric matrix.

```
% determine the vector with all singular values (including zeros)
svVectAll = svds(S, min(nMets, nRxns));
```

The singular values and their cut-off can be illustrated as follows:

```
% plot the singular values
figure;

% plot singular values obtained using svdsecon
semilogy(linspace(1, length(svVect), length(svVect)), svVect, '*');

% plot
hold on;
semilogy(linspace(1, length(svVectAll), length(svVectAll)), svVectAll, 'ro');

% set the font size of the current figure axes, show a legend and minor grid axes
set(gca, 'fontsize', 14);
legend('svds (up to rankS)', 'svds (all)')
grid minor;

% set the label
xlabel('Number of the singular value');
ylabel('Magnitude of the singular value');

hold off;
```



The **maximum singular** value is the square root of the largest element on the diagonal matrix obtained from singular value decomposition. The **minimum singular value** is the square root of the smallest element on the diagonal matrix obtained from singular value decomposition.

```
% determine the maximum and minimum singular values
maxSingVal = svVect(1) % first value of the vector with singular values
```

```
maxSingVal = 135.5764
```

```
minSingVal = svVect(rankS) % smallest non-zero singular value
```

```
minSingVal = 0.1161
```

Alternatively, if the rank of the stoichiometric matrix S is not known, the built-in functions can also be used:

```
maxSingValBuiltIn = svds(S, 1)
```

```
maxSingValBuiltIn = 135.5764
```

```
minSingValBuiltIn = svds(S, 1, 'smallestnz')
```

```
minSingValBuiltIn = 0.1161
```

The condition number of the stoichiometric matrix is the ratio of the maximum and minimum singular values. The higher this ratio, the more ill-conditioned the stoichiometric matrix is (numerical issues).

```
% determine the condition number
condNumber = maxSingVal / minSingVal
```

```
condNumber = 1.1676e+03
```

Scaling

The scaling estimate is based on the order of magnitude of the ratio of the maximum and minimum scaling coefficients, which are determined such that the scaled stoichiometric matrix has entries close to unity. In order to investigate the scaling of the stoichiometric matrix and provide an estimate of the most appropriate precision of the solver to be used, the following quantities should be calculated:

- **Estimation level:** The estimation level, defined by the parameter scltol provides a measure of how accurate the estimation is. The estimation level can be *crude*, *medium*, or *fine*.
- **Size of the matrix:** The size of the matrix indicates the size of the metabolic network, and is broken down into number of metabolites and number of reactions.
- **Stoichiometric coefficients:** The maximum and minimum values of the stoichiometric matrix provide a range of the stoichiometric coefficients and are determined based on all elements of the stoichiometric matrix. Their ratio (and its order of magnitude) provides valuable information on the numerical difficulty to solve a linear program.
- **Lower bound coefficients:** The maximum and minimum values of the lower bound vector provide a range of the coefficients of the lower bound vector. Their ratio (and its order of magnitude) provides valuable information on the numerical difficulty to solve a linear program.
- **Upper bound coefficients:** The maximum and minimum values of the upper bound vector provide a range of the coefficients of the upper bound vector. Their ratio (and its order of magnitude) provides valuable information on the numerical difficulty to solve a linear program.
- **Row scaling coefficients:** The row scaling coefficients are the scaling coefficients required to scale each row closer to unity. The maximum and minimum row scaling coefficients provide a range of row scaling coefficients required to scale the stoichiometric matrix row-wise. Their ratio (and its order of magnitude) provides valuable information on the numerical difficulty to solve a linear program.
- **Column scaling coefficients:** The column scaling coefficients are the scaling coefficients required to scale each column closer to unity. The maximum and minimum column scaling coefficients provide a range of column scaling coefficients required to scale the stoichiometric matrix column-wise. Their ratio (and its order of magnitude) provides valuable information on the numerical difficulty to solve a linear program.

The scaling properties of the stoichiometric matrix can be determined using:

```
[solverRecommendation, scalingProperties] = checkScaling(model);
```

```
------------------------ Scaling summary report ------------------------

Name of model:                                  Ecoli_core_model
Estimation level:                               fine (scltol = 1.00)
Name of matrix:                                 S
Size of matrix:
       * metabolites:                           72
       * reactions:                             95
Stoichiometric coefficients:
       * Minimum:                               -59.81
       * Maximum:                               59.81
Lower bound coefficients:
       * Minimum:                               -1000.00
       * Maximum:                               8.39
Upper bound coefficients:
       * Minimum:                               1000.00
```

```
       * Maximum:                             1000.00
Row scaling coefficients:
       * Minimum:                             2.66e-01 (row #: 26)
       * Maximum:                             7.73e+00 (row #: 13)
Column scaling coefficients:
       * Minimum:                             1.29e-01 (column #: 11)
       * Maximum:                             7.73e+00 (column #: 13)

--------------------------------- Ratios ---------------------------------

Ratio of stoichiometric coefficients:         -1.00e+00
Order of magnitude diff. (stoich. coeff.):    0

Ratio of lower bounds:                        -8.39e-03
Order of magnitude diff. (lower bounds):      0

Ratio of upper bounds:                        1.00e+00
Order of magnitude diff. (upper bounds):      0

Ratio of row scaling coefficients:            2.90e+01
Order of magnitude diff. (row scaling):       1

Ratio of column scaling coefficients:         5.98e+01
Order of magnitude diff. (column scaling):    1

--------------------------------------------------------------------------

-> The model is well scaled. Double precision is recommended.
```

Summary of model characteristics

The following numerical properties have been calculated:

- **Number of elements**: represents the total number of entries in the stoichiometric matrix (including zero elements). This number is equivalent to the product of the number of reactions and the number of metabolites.
- **Number of nonzero elements**: represents the total number of nonzero entries in the stoichiometric matrix (excluding zero elements).
- **Sparsity ratio**: ratio of the number of zero elements and the total number of elements.
- **Complementary sparsity ratio**: calculated as the difference of one and the sparsity ratio, and is the ratio of the number of nonzero elements and the total number of elements.
- **Average column density**: corresponds to the ratio of the number of nonzero elements in each column and the total number of metabolites. The average column density corresponds to the arithmetic average of all the column densities (sum of all the column densities divided by the number of reactions).
- **Relative column density**: corresponds to the ratio of the number of nonzero elements in each column and the total number of metabolites. The relative column density corresponds to the average column density divided by the total number of metabolites (expressed in parts-per-million (ppm)).
- **Rank**: the rank of a stoichiometric matrix is the maximum number of linearly independent rows and is equivalent to the number of linearly independent columns. The rank is a measurement of how many reactions and metabolites are linearly independent.
- **Rank deficiency**: the rank deficiency of the stoichiometric matrix is a measure of how many reactions and metabolites are linearly dependent, and expressed as the ratio of the rank of the stoichiometric matrix to the theoretical full rank.
- **Maximum singular value**: the largest element on the diagonal matrix obtained from singular value decomposition.
- **Minimum singular value**: the smallest element on the diagonal matrix obtained from singular value decomposition.

- **Condition number**: the condition number of the stoichiometric matrix is the ratio of the maximum and minimum singular values. The higher this ratio, the more ill-conditioned the stoichiometric matrix is (numerical issues).

```
fprintf([' --- SUMMARY ---\n',...
        'Model file/Model name/Matrix name    %s/%s/%s\n',...
        'Size is [nMets, nRxns]               [%d, %d]\n',...
        'Number of elements:                  %d \n',...
        'Number of nonzero elements:          %d \n',...
        'Sparsity ratio [%%]:                  %1.2f \n',...
        'Complementary sparsity ratio [%%]     %1.2f \n', ...
        'Average column density [ppm]:        %1.2f \n',...
        'Relative column density [ppm]:       %1.2f \n',...
        'Rank:                                %d \n',...
        'Rank deficiency [%%]:                 %1.2f \n',...
        'Maximum singular value:              %1.2f \n',...
        'Minimum singular value:              %1.2f \n',...
        'Condition number:                    %1.2f \n',...
        ],...
        modelFile, modelName, matrixName, nMets, nRxns, nElem, nNz, sparsityRatio, ...
        compSparsityRatio, colDensityAv, colDensityRel, rankS, rankDeficiencyS, ...
        maxSingVal, minSingVal, condNumber);
```

```
 --- SUMMARY ---
Model file/Model name/Matrix name    ecoli_core_model.mat/model/S
Size is [nMets, nRxns]               [72, 95]
Number of elements:                  6840
Number of nonzero elements:          360
Sparsity ratio [%]:                  94.74
Complementary sparsity ratio [%]     5.26
Average column density [ppm]:        3.79
Relative column density [ppm]:       52631.58
Rank:                                67
Rank deficiency [%]:                 6.94
Maximum singular value:              135.58
Minimum singular value:              0.12
Condition number:                    1167.63
```

References

[1] Reconstruction and Use of Microbial Metabolic Networks: the Core Escherichia coli Metabolic Model as an Educational Guide by Orth, Fleming, and Palsson (2010)

[2] P. E. Gill, W. Murray, M. A. Saunders and M. H. Wright (1987). Maintaining LU factors of a general sparse matrix, Linear Algebra and its Applications 88/89, 239-270.